Drug Class Review

Newer Drugs for Insomnia

Preliminary Scan Report #6

February 2017

Last Report: Update #2: October 2008

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Scan conducted by:
Brittany H. Lazur, MPH
Ryan Stoner, PhD

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

Oregon Health & Science University

OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses on new randomized controlled trials and comparative effectiveness reviews as well as actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

Update #2: October 2008 (searches through January 2008)

Date of Last Preliminary Update Scan Report

July 2015

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of newer drugs for insomnia in treating patients with insomnia?
2. What is the comparative tolerability and safety of newer drugs for insomnia when used to treat patients with insomnia?
3. Are there subgroups of patients for which one newer drug for insomnia is more effective or associated with fewer adverse events based on
    a. demographics (age, racial groups, and gender)?
    b. other medications (e.g., stimulants)?
    c. co-morbidities (including obstructive sleep apnea, other mental disorders)?
    d. pregnancy?
    e. history of substance abuse?

Inclusion Criteria

Populations

Adults and children with insomnia, including (DSM-IV-TR diagnoses):

- Primary insomnia
- Breathing-related sleep disorder (e.g., obstructive sleep apnea)
- Insomnia related to another mental disorder
- Substance-induced sleep disorder, insomnia type
- Sleep disorder due to a general medical condition, insomnia type

Table 1. Interventions

Generic name	Trade name	Dosage form
Doxepin	Silenor®	Oral tablet
Eszopiclone	Lunesta®	Oral tablet
Ramelteon	Rozerem®	Oral tablet
Suvorexant	Belsomra®	Oral tablet
Tasimelteon	Hetlioz®	Oral capsule
Zaleplon	Sonata®	Oral capsule
Zolpidem	Ambien®	Oral tablet
	Ambien CR®	Extended release oral tablet
	Edluar®	Sublingual tablet
	Zolpimist®	Oral metered spray
	Intermezzo®	Sublingual tablet

Effectiveness outcomes

- Sleep latency
- Sleep duration
- Number of awakenings
- Sleep quality
- Wake time after sleep onset
- Daytime alertness
- Tolerance
- Rebound

Wherever possible, data on duration of therapy (time to tolerance) will be evaluated within the context of comparative effectiveness.

Safety outcomes

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events
- Specific adverse events including, but not limited to:
    - Abuse potential
    - Withdrawal symptoms
    - Dependency
    - Impairment of memory/daytime functioning

Study designs (from last report)

Effectiveness:

- Controlled clinical trials of an included drug versus placebo or versus any active comparator (including, but not limited to, another included drug, benzodiazepines, trazodone, diphenhydramine, and amitriptyline).
- Good-quality systematic reviews

Adverse Events (dependency and withdrawal symptoms):

- Controlled clinical trials
- Observational studies (case-control, case series, case reports, cohort studies, surveys).

METHODS FOR SCAN

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® and Ovid MEDLINE® In-Process & Other Non-Indexed Citations from May 2015 through January 2017 using terms for specific included drugs and limits for English language and humans. Literature searches included any new drugs identified in the present scan in addition to those included in Table 1. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, new populations, and new serious harms (e.g., boxed warnings). To identify new drugs, we also searched CenterWatch (http://www.centerwatch.com), a privately-owned database of clinical trials information, and conducted a limited internet search. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm - "Our Publications" and "Our Databases"). All citations were imported into an electronic database (EndNote X7) and duplicate citations were removed.

Study Selection

We included only potentially relevant randomized controlled trials and comparative effectiveness reviews. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scans
New Drugs
Suvorexant (Belsomra®): orexin receptor antagonist approved on 8/13/2014 in oral tablet form and indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Tasimelteon (Hetlioz®): oral capsule approved on 1/31/2014 for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24).

Doxepin hydrochloride (Silenor®): oral tablet approved on 3/17/2010 for the treatment of insomnia characterized by difficulties with sleep maintenance.

New Formulations
Zolpidem tartrate (Intermezzo®): sublingual tablet approved on 11/23/2011 for the use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep.

Zolpidem tartrate (Edluar®): sublingual tablet approved on 3/13/2009 for the short-term treatment of insomnia characterized by difficulties with sleep initiation.

Zolpidem tartrate (Zolpimist®): oral spray approved on 12/19/2008 for the short-term treatment of insomnia characterized by difficulties with sleep initiation.

New Serious Harms (e.g., Boxed Warnings)

Identified in this Preliminary Update Scan
None.

Identified in previous Preliminary Update Scans
A drug safety communication was issued on 5/15/2014 for eszopiclone-containing sleep aids (including Lunesta® and generics), which warns of next-day impairment of driving and other activities that require alertness. The full drug safety communication can be found in Appendix A, which is published in a separate document.

Comparative Effectiveness Reviews

Identified in this Preliminary Update Scan
We identified 1 potentially relevant comparative effectiveness review published by the Agency for Healthcare Research & Quality in December 2015. This review could possibly answer parts of a DERP update report, as it covers all drugs included in the scope of this scan except tasimelteon. It also includes a broad range of drugs not included in the DERP report and non-

drug interventions, and their findings note that they did not find comparative evidence for the drugs. The citation for this review is listed below and the abstract is located in Appendix B, which is published in a separate document.

Brasure M, MacDonald R, Fuchs E, Olson CM, Carlyle M, Diem S, Koffel E, Khawaja IS, Ouellette J, Butler M, Kane RL, Wilt TJ. Management of Insomnia Disorder. Comparative Effectiveness Review No. 159. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00016-I). AHRQ Publication No.15(16)-EHC027- EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2015. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Identified in previous Preliminary Update Scans

None.

Randomized Controlled Trials

Medline searches for this scan resulted in 42 citations. Of those, 5 placebo-controlled trials (2 of eszopiclone, 1 of ramelteon, and 2 of suvorexant) in 4 publications and 1 post-hoc analysis of a placebo-controlled trial studying zolpidem were considered relevant to this scan.

Cumulatively, we have identified a total of 3 potentially relevant head-to-head trials and 40 potentially relevant placebo-controlled trials published since the last update report on this topic. Head-to-head trials were small, ranging in size from 48 to 72 participants. All head-to-head trials compared zolpidem to another included insomnia drug (N=2) or to another formulation of zolpidem (N=1). In terms of placebo-controlled evidence, 28% of trials studied eszopiclone, 25% studied zolpidem, 23% studied ramelteon, 10% studied doxepin (new drug since last report), 8% studied suvorexant (new drug since last report), and 2% each studied tasimelteon (new drug since last report), zaleplon, and zopiclone.

Characteristics of the head-to-head trials are listed to Table 2 and characteristics of the placebo-controlled trials are listed in Table 3, below. Abstracts of head-to-head trials are included in Appendix C and abstracts of placebo-controlled trials are included in Appendix D, both of which are published in a separate document.

Table 2. Potentially relevant head-to-head trials (N=3)

Author, Year	Drugs/Comparison	Focus
Huang, 2011	Zolpidem, zaleplon	N=48, efficacy, harms
Staner, 2010	Sublingual zolpidem, oral zolpidem	N=70, efficacy, harms
Uchimura, 2012	Zolpidem, eszopiclone	N=72, efficacy, harms, Japanese patients

Table 3. Potentially relevant placebo-controlled trials* (N=40)

Author, Year	Intervention	Focus
Krystal, 2010	Doxepin	Elderly patients
Krystal, 2011	Doxepin	Chronic primary insomnia
Lankford, 2012	Doxepin	Elderly patients
Rios Romenets, 2013	Doxepin	Parkinson's disease
Ancoli-Israel, 2010	Eszopiclone	Elderly patients
Joffe, 2010	Eszopiclone	Peri/postmenopausal women with insomnia
McCall, 2010	Eszopiclone	Depressed patients
Menza, 2010	Eszopiclone	Parkinson's disease
Fava, 2011	Eszopiclone (pooled analysis)	Anxious depression

Author, Year	Intervention	Focus
Pollack, 2011	Eszopiclone	Post-traumatic stress disorder
Krystal, 2012	Eszopiclone (subgroup analysis)	Wake time after sleep onset
Goforth, 2014	Eszopiclone	Chronic low-back pain
Sangal, 2014	Eszopiclone	Attention-deficit/hyperactivity disorder
Spierings, 2015	Eszopiclone	Migraineurs
Tek, 2014	Eszopiclone	Schizophrenia
Mayer, 2009	Ramelteon	Chronic primary insomnia
Wang-Weigand, 2009	Ramelteon (pooled analysis)	Chronic insomnia
Goonaratne, 2010	Ramelteon	Older patients with obstructive sleep apnea
Kohsaka, 2011	Ramelteon	Japanese patients
McElroy, 2011	Ramelteon	Bipolar 1 disorder with manic symptoms
Uchimura, 2011	Ramelteon	Japanese patients
Uchiyama, 2011	Ramelteon	Japanese patients
Uchiyama, 2011	Ramelteon	Japanese patients
Lequerica, 2015	Ramelteon	Traumatic brain injury
Michelson, 2014	Suvorexant	Primary insomnia
Herring, 2016 (2 trials)	Suvorexant	Non-elderly (18-64 years) and elderly (>64 years) patients with insomnia
Rajaratnam, 2009	Tasimelteon	Sleep-time shift
Park, 2013	Zaleplon	Obstructive sleep apnea
Omvik,2008	Zopiclone	Insomnia in patients ≥55 years
Roth, 2008	Zolpidem (sublingual)	Primary insomnia and history of prolonged middle of the night awakenings
Blumer, 2009	Zolpidem	Children
Hajak, 2009	Zolpidem	Menopausal women with depression and anxiety
Morin, 2009	Zolpidem	Persistent insomnia
Randall, 2012	Zolpidem	Chronic primary insomnia;
Roehrs, 2016 (subgroup analysis)		Gender differences in efficacy and safety
Roehrs, 2012	Zolpidem	Rebound insomnia
Roth, 2013	Zolpidem	Low-dose sublingual
Roth, 2014	Zolpidem	Sublingual, gender differences
Fava, 2009	Zolpidem ER	Generalized anxiety disorder
Fava, 2011	Zolpidem ER	Major depressive disorder

*Shading indicates trials identified in this scan. Others were identified in previous preliminary update scans.

SUMMARY

Since the last update report, we have identified 3 new drugs (doxepin hydrochloride (Silenor®), tasimelteon [Hetlioz®], and suvorexant [Belsomra®]), and 3 new drug formulations of zolpidem tartrate (sublingual tablet [Intermezzo® and Edluar®] and oral spray [Zolpimist®]). We have identified no new populations since the last update report. We have identified 1 new serious harm, pertaining to next day impairment of driving and other activities with eszopiclone-containing sleep aids (including Lunesta® and generics), since the last update report. We have identified 1 newly published AHRQ comparative effectiveness review pertaining to the management of insomnia disorder that could answer parts of a DERP update report. Since the last update report, we have identified 3 new head-to-head trials (all from previous scans) and 40 new placebo-controlled trials (5 in current scan).

APPENDIX A. NEW SERIOUS HARMS

ESZOPICLONE CONTAINING SLEEP AIDS: DRUG SAFETY COMMUNICATION - CAN CAUSE NEXT-DAY IMPAIRMENT

Including Lunesta and generics

[Posted 05/15/2014]

AUDIENCE: Pharmacy, Primary Care Medicine

ISSUE: FDA has notified health professionals and their medical care organizations of a new warning that the insomnia drug Lunesta (eszopiclone) can cause next-day impairment of driving and other activities that require alertness. FDA recommends a decreased starting dose of Lunesta to 1 mg at bedtime. Women and men are equally susceptible to impairment from Lunesta, so the recommended starting dose of 1 mg is the same for both. FDA approved changes to the Lunesta prescribing information and the patient Medication Guide to include these new recommendations. The drug labels for generic eszopiclone products will also be updated to include these changes.

BACKGROUND: A study of Lunesta found that the previously recommended dose of 3 mg can cause impairment to driving skills, memory, and coordination that can last more than 11 hours after receiving an evening dose (see Data Summary). Despite these driving and other problems, patients were often unaware they were impaired. The new lower recommended starting dose of 1 mg at bedtime will result in less drug in the blood the next day.

RECOMMENDATION: Health care professionals should follow the new dosing recommendations when starting patients on Lunesta. Patients should continue taking their prescribed dose of Lunesta and contact their health care professionals to ask about the most appropriate dose for them. FDA is continuing to evaluate the risk of impaired mental alertness with the entire class of sleep aid drugs, including over-the-counter drugs available without a prescription, and will update the public as new information becomes available.

APPENDIX B. NEW COMPARATIVE EFFECTIVENESS REVIEWS

Title: Management of Insomnia Disorder

Structured Abstract

Objective. To assess the efficacy, comparative effectiveness, and harms of treatments for insomnia disorder in the general adult population and older adults.

Data sources. Ovid MEDLINE®, the Cochrane Central Register of Controlled Trials, Embase®, and PsycINFO® bibliographic databases; hand searches of references of relevant studies.

Review methods. Two investigators screened abstracts and full-text articles of identified references for eligibility. Eligible studies included systematic reviews, randomized controlled trials (RCTs), and long-term observational pharmacologic studies enrolling participants with insomnia disorder. We analyzed data for global outcomes (measures that assess both sleep and daytime functioning associated with sleep), sleep parameters, and harms. We assessed risk of bias for RCTs, extracted data, assessed quality of relevant systematic reviews, and evaluated strength of evidence for comparisons and outcomes. Pooled estimates were analyzed to assess the efficacy and comparative effectiveness of treatments.

Results. We searched bibliographic databases through January 2015 for studies evaluating psychological, pharmacologic, and complementary and alternative medicine interventions for insomnia disorder. We synthesized evidence from 181 unique studies (data from 128 unique RCTs and 3 systematic reviews that synthesize data from 42 unique RCTs) and 12 observational studies. Sample sizes and enrollment criteria varied; most trials were short in duration. Outcome reporting and intervention effect sizes varied, and a large placebo response was often observed. Cognitive behavioral therapy for insomnia (CBT-I) improved global outcomes and nearly all sleep parameters in the general adult population, older adults, and adults with pain. We found insufficient evidence on adverse effects of these interventions. Evidence was less robust for psychological interventions other than CBT-I, but low-strength evidence shows that some interventions improve some sleep outcomes. Low- to moderate-strength evidence indicated that the nonbenzodiazepine hypnotics eszopiclone and zolpidem, and the orexin receptor antagonist suvorexant, improved short-term global and sleep outcomes in general adult populations. Doxepin improved sleep outcomes. The absolute mean effect was small. Evidence for benzodiazepine hypnotics, melatonin agonists, and antidepressants in general populations and for most pharmacologic interventions in older adults was generally insufficient. Evidence on adverse effects from RCT data was generally insufficient or low strength. Observational studies suggest that hypnotics may be associated with dementia, fractures, and major injury. Food and Drug Administration (FDA) labels warn about cognitive and behavioral changes, including driving impairment, and other harms, and advise lower doses for females and older/debilitated adults. Evidence on complementary and alternative medicine was insufficient. Evidence was insufficient to compare hypnotic medications within or across classes or versus CBT-I.

Conclusions. CBT-I or medical therapy with eszopiclone, zolpidem, and suvorexant improve global and sleep outcomes for insomnia disorder. Clinical significance, applicability,

comparative effectiveness, and long-term efficacy, especially among older adults, are less well known. Effect sizes vary, and a large placebo response is sometimes observed. Observational viii studies suggest an association of hypnotics with infrequent but serious harms. FDA labels provide specific warnings and precautions for drugs approved for insomnia.

APPENDIX C. NEW POTENTIALLY RELEVANT HEAD-TO-HEAD TRIALS (N=3)

Huang, Y.-S., S.-C. Hsu, et al. (2011). "A double-blind, randomized, comparative study to evaluate the efficacy and safety of zaleplon versus zolpidem in shortening sleep latency in primary insomnia." Chang Gung Medical Journal **34**(1): 50-56.

BACKGROUND: Benzodiazepines cause a high proportion of adverse effects while non-benzodiazepine compounds have demonstrated high efficacy and less adverse effects in patients with insomnia. The objective of this study was to compare the effectiveness and safety of non-BZ zaleplon and zolpidem in primary insomnia.

METHODS: This was a randomized, double-blind, active-controlled, double-dummy, comparative study. A total of 48 patients were enrolled, of which 45 patients completed the study. Patients who entered the study were required to take the study drug orally once daily at bedtime for two weeks. Each patient kept a sleep diary and answered a questionnaire. We used these documents to measure and evaluate changes from baseline to Week 2 in sleep latency, duration and quality of sleep, the number of awakenings and incidence of rebound insomnia.

RESULTS: The data revealed a significant decrease in sleep latency from baseline to Week 2 for patients receiving zaleplon 10 mg and zolpidem 10 mg. Patients receiving zaleplon exhibited a marginally greater, but not statistically significant, reduction in sleep latency than those who received zolpidem. There was no significant difference in the frequency of adverse effects between the zaleplon and zolpidem groups; however, during this clinical trial there was one lethal event caused by a traffic accident in the zaleplon group.

CONCLUSION: There was no significant difference between zaleplon and zolpidem in the efficacy of reducing sleep latency or adverse effects. A large pharmacovigilance study is needed before concluding that either zolpidem or zaleplon is free from next-day residual effects.

Staner, C., F. Joly, et al. (2010). "Sublingual zolpidem in early onset of sleep compared to oral zolpidem: polysomnographic study in patients with primary insomnia." Current Medical Research & Opinion **26**(6): 1423-1431.

OBJECTIVE: To compare the hypnotic effects of a single dose of a sublingual formulation of zolpidem (Edluar*) 10 mg vs oral formulation (Ambien dagger) 10 mg by polysomnography (PSG) in DSM-IV primary insomnia patients. Primary objective was to compare the two formulations on sleep induction, measured by latency to persistent sleep (LPS), sleep onset latency (SOL) and latency to stage 1 (ST1L). RESEARCH AND METHODS: This was a randomized, double-blind, two-period, cross-over multi-centre study in which each period comprised two successive PSG recording nights. Treatment was administered when PSG recordings started. Subjective sleep and residual effects were assessed the next morning. RESULTS: Seventy female and male patients aged 19-64 were analysed. Sublingual zolpidem significantly shortened LPS by 34% or 10.3 minutes as compared to oral zolpidem (95% CI: -4.3 min to -16.2 min, $p = 0.001$). SOL and ST1L were also significantly shortened ($p < 0.01$). Furthermore the two formulations were comparable in terms of sleep maintenance properties based on total sleep time (TST). The improvement in subjective sleep and next-day residual effects did not differ between the two treatments. Both routes of administration were well tolerated.

CONCLUSIONS: The results demonstrate that sublingual zolpidem is superior to an equivalent dose of oral zolpidem in terms of sleep inducing properties in a carefully selected sample of primary insomnia patients.

Uchimura, N., A. Kamijo, et al. (2012). "A randomized placebo-controlled polysomnographic study of eszopiclone in Japanese patients with primary insomnia." Sleep Medicine **13**(10): 1247-1253.

OBJECTIVES: To evaluate the efficacy and dose-response effect of eszopiclone on sleep latency and sleep maintenance in Japanese patients with primary insomnia.

METHODS: In this randomized, double-blind, five-way crossover study, 72 patients received placebo, eszopiclone 1mg, 2mg, and 3mg, and zolpidem 10mg in random order for two consecutive nights with a washout period between treatments. Objective sleep measures from polysomnography (PSG) and subjective patient reports were collected.

RESULTS: All active treatments produced significant improvement in objective and subjective sleep latency compared with placebo ($P<0.05$ for all comparisons); linear dose-response relationships were observed for eszopiclone. PSG-determined wake time after sleep onset (WASO), sleep efficiency, and number of awakenings (NA), and patient-reported measures of WASO, NA, sleep quality, sleep depth, and daytime functioning significantly improved following treatment with eszopiclone 2mg and 3mg and zolpidem 10mg versus placebo ($P<0.05$). Eszopiclone at all doses increased total sleep time and stage 2 sleep time ($P<0.001$ for both comparisons), but did not alter REM or slow-wave sleep. Eszopiclone was generally well tolerated; the most frequently reported adverse event was mild dysgeusia.

CONCLUSIONS: In Japanese patients with primary insomnia, eszopiclone 2mg and 3mg significantly improved PSG-determined and patient-reported sleep latency and sleep maintenance relative to placebo.

APPENDIX D. NEW POTENTIALLY RELEVANT PLACEBO-CONTROLLED TRIALS* (N=40)

Ancoli-Israel, S., A. D. Krystal, et al. (2010). "A 12-week, randomized, double-blind, placebo-controlled study evaluating the effect of eszopiclone 2 mg on sleep/wake function in older adults with primary and comorbid insomnia." Sleep **33**(2): 225-234.

BACKGROUND: Longer-term pharmacologic studies for insomnia in older individuals are sparse.

OBJECTIVE: To evaluate the efficacy and safety of 12 weeks of nightly eszopiclone in elderly outpatients with insomnia.

METHODS: Participants (65-85 years) met DSM-IV-TR criteria for insomnia with total sleep times (TST) < or = 6 h, and wake time after sleep onset (WASO) > or = 45 min. Participants were randomized to 12 weeks of eszopiclone 2 mg (n = 194) or placebo (n = 194), followed by a 2-week single-blind placebo run-out. Subject-reported measures of sleep (sTST, sleep latency [sSL], sWASO) and daytime function (alertness, concentration, wellbeing, ability to function) were assessed. AEs were monitored.

RESULTS: Subjects treated with 2 mg eszopiclone slept longer at night on average and at every individual time point compared to baseline than placebo subjects, as measured by TST over the 12-week double-blind period (P < 0.0001). Mean sTST over the double-blind period for eszopiclone-treated subjects was 360.08 min compared to 297.86 min at baseline, a mean change of 63.24 min. Over the double-blind period, eszopiclone-treated subjects also experienced a significantly greater improvement in sSL compared to placebo, with a mean decrease of 24.62 min versus a mean decrease of 19.92 min, respectively (P = 0.0014). Eszopiclone subjects also experienced a significantly greater decrease in WASO (mean decrease of 36.4 min) compared to placebo subjects (decrease of 14.8 min) (P < 0.0001). Post-discontinuation, sleep parameters were statistically improved versus baseline for eszopiclone (P-values < or = 0.01), indicating no rebound. The most common AEs (> or = 5%) were headache (eszopiclone 13.9%, placebo 12.4%), unpleasant taste (12.4%, 1.5%), and nasopharyngitis (5.7%, 6.2%).

CONCLUSION: In this Phase IV trial of older adults with insomnia, eszopiclone significantly improved patient-reported sleep and daytime function relative to placebo. Improvements occurred within the first week and were maintained for 3 months, with no evidence of rebound insomnia following discontinuation. The 12 weeks of treatment were well tolerated.

Clinical Trial Information: A Long-Term Safety and Efficacy Study of Eszopiclone in Elderly Subjects With Primary Chronic Insomnia; Registration #NCT00386334; URL - http://www.clinicaltrials.gov/ct2/show/NCT00386334?term=eszopiclone&rank=24

Blumer, J. L., R. L. Findling, et al. (2009). "Controlled clinical trial of zolpidem for the treatment of insomnia associated with attention-deficit/ hyperactivity disorder in children 6 to 17 years of age." Pediatrics **123**(5): e770-776.

OBJECTIVE: The goal was to evaluate the hypnotic efficacy of zolpidem at 0.25 mg/kg per day (maximum of 10 mg/day), compared with placebo, in children 6 through 17 years of age who were experiencing insomnia associated with attention-deficit/hyperactivity disorder.

METHODS: An 8-week, North American, multicenter, double-blind, placebo-controlled, parallel-group study was conducted. Patients underwent stratification according to age (6-

11 years [N = 111] or 12-17 years [N = 90]) and were assigned randomly to receive treatment with the study drug or placebo (in a 2:1 ratio). The primary efficacy variable was latency to persistent sleep between weeks 3 and 6. Secondary efficacy variables also were assessed, and behavioral and cognitive components of attention-deficit/hyperactivity disorder were monitored. Safety was assessed on the basis of reports of adverse events, abnormal laboratory data, vital signs, and physical examination findings. The potential for next-day residual effects also was assessed.

RESULTS: The baseline-adjusted mean change in latency to persistent sleep at week 4 did not differ significantly between the zolpidem and placebo groups (-20.28 vs -21.27 minutes). However, differences favoring zolpidem were observed for the older age group in Clinical Global Impression scores at weeks 4 and 8. No next-day residual effects of treatment were associated with zolpidem, and no rebound phenomena occurred after treatment discontinuation. Central nervous system and psychiatric disorders were the most-frequent treatment-emergent adverse events (>5%) that were observed more frequently with zolpidem than with placebo; these included dizziness, headache, and hallucinations. Ten (7.4%) patients discontinued zolpidem treatment because of adverse events.

CONCLUSION: Zolpidem at a dose of 0.25 mg/kg per day to a maximum of 10 mg failed to reduce the latency to persistent sleep on polysomnographic recordings after 4 weeks of treatment in children and adolescents 6 through 17 years of age who had attention-deficit/hyperactivity disorder-associated insomnia.

Fava, M., G. M. Asnis, et al. (2009). "Zolpidem extended-release improves sleep and next-day symptoms in comorbid insomnia and generalized anxiety disorder." Journal of Clinical Psychopharmacology **29**(3): 222-230.

A multicenter, double-blind, parallel-group study was designed to assess the efficacy and safety of zolpidem extended-release coadministered with escitalopram in patients with insomnia and comorbid generalized anxiety disorder. Patients (N = 383) received open-label escitalopram 10 mg/d and were randomized to either adjunct zolpidem extended-release 12.5 mg or placebo. The primary efficacy measure was change from baseline to week 8 in subjective total sleep time. Secondary efficacy measures included subjective sleep onset latency, number of awakenings, wake time after sleep onset, sleep quality, the Hamilton Rating Scale for Anxiety, the Beck Anxiety Inventory, the Sleep Impact Scale, the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, and the Sheehan Disability Scale. The last-observation-carried-forward method was used to impute missing values for most efficacy measures. Safety was monitored at each visit. At week 8 and all time points, there was a significant improvement in the zolpidem extended-release/escitalopram group compared with placebo/escitalopram for total sleep time ($P < 0.0001$). Most of the secondary efficacy measures also significantly favored zolpidem at most visits ($P < 0.0001$). The most common treatment-emergent adverse events in both groups were nausea, dizziness, headache, fatigue, and dry mouth. Concurrent zolpidem extended-release/escitalopram, compared with placebo/escitalopram, significantly improved insomnia and sleep-related next-day symptoms, but not anxiety symptoms, in patients with comorbid insomnia and generalized anxiety disorder.

Fava, M., G. M. Asnis, et al. (2011). "Improved insomnia symptoms and sleep-related next-day functioning in patients with comorbid major depressive disorder and insomnia following concomitant zolpidem extended-release 12.5 mg and escitalopram treatment: a randomized controlled trial." Journal of Clinical Psychiatry **72**(7): 914-928.

OBJECTIVE: This investigation was performed to assess the efficacy and safety of zolpidem extended-release in patients with insomnia associated with major depressive disorder (MDD).

METHOD: Patients (N = 385) received open-label escitalopram 10 mg/d and were randomized to concomitant zolpidem extended-release 12.5 mg/night or placebo for 8 weeks (phase 1) in a randomized, parallel-group, multicenter trial. Responders (>= 50% in 17-item Hamilton Depression Rating Scale [HDRS(17)] score) continued 16 weeks of double-blind treatment (phase 2); escitalopram only was given during a 2-week run-out period. The study was conducted between February 2006 and June 2007. The primary efficacy measure was change from baseline in subjective total sleep time. Secondary efficacy measures included subjective sleep-onset latency, number of awakenings, wake time after sleep onset, sleep quality, sleep-related next-day functioning, HDRS(17), Sleep Impact Scale score, Patient and Clinical Global Impressions of Insomnia Treatment, the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, and the Quality of Life Enjoyment and Satisfaction Questionnaire. Adverse events were recorded throughout the study; sleep measures were also evaluated during the run-out period.

RESULTS: Throughout phase 1, zolpidem extended-release led to significantly greater improvements in total sleep time (P < .0001), wake time after sleep onset, sleep onset latency, number of awakenings, and sleep quality (P <= .0003), and some measures of sleep-related next-day functioning but not in depressive symptoms or quality of life. During phase 2, improvements with the zolpidem extended-release/escitalopram group occurred for total sleep time (significant [P < .05] at weeks 12 and 16), as well as for a few other secondary efficacy measures but not in depressive symptoms or quality of life. The most common adverse events associated with combination treatment included nausea, somnolence, dry mouth, dizziness, fatigue, and amnesia.

CONCLUSIONS: Zolpidem extended-release administered concomitantly with escitalopram for up to 24 weeks was well tolerated and improved insomnia and some sleep-related next-day symptoms and next-day functioning in patients with MDD but did not significantly augment the antidepressant response of escitalopram.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00296179. Copyright 2011 Physicians Postgraduate Press, Inc.

Fava, M., K. Schaefer, et al. (2011). "A post hoc analysis of the effect of nightly administration of eszopiclone and a selective serotonin reuptake inhibitor in patients with insomnia and anxious depression." Journal of Clinical Psychiatry **72**(4): 473-479.

OBJECTIVE: Patients with major depressive disorder (MDD) and significant anxiety are less responsive to antidepressants than those without anxiety. In this post hoc analysis of patients with insomnia and comorbid anxious depression, eszopiclone cotherapy with a selective serotonin reuptake inhibitor (SSRI) was compared with placebo cotherapy.

METHOD: Data were pooled from 2 randomized, double-blind, 8-week trials. One trial (conducted from January 2004 to October 2004) included patients with DSM-IV

insomnia and comorbid MDD treated with fluoxetine concurrently with eszopiclone 3 mg/d or placebo. The other trial (conducted from July 2005 to April 2006) included patients with DSM-IV-TR insomnia and comorbid generalized anxiety disorder treated with escitalopram concurrently with eszopiclone 3 mg/d or placebo. Anxious depression was defined as a baseline 17-item Hamilton Depression Rating Scale (HDRS-17) score >= 14 (excluding insomnia items) and an anxiety/somatization factor score >= 7. Treatment group differences were determined for mean changes in HDRS-17 scores (with and without insomnia items), HDRS anxiety/somatization scores, and response and remission rates. Severity of insomnia was assessed by the Insomnia Severity Index (ISI).

RESULTS: In the combined dataset, 347 of 1,136 patients (30.5%) had insomnia and comorbid anxious depression. Significant improvements in insomnia were observed for eszopiclone cotherapy relative to placebo cotherapy (mean change from baseline on the ISI: -11.0 vs -7.8, respectively; P < .001). There were greater reductions in HDRS-17 scores at week 8 following cotherapy with eszopiclone compared with placebo when the insomnia items were included (mean change: -14.1 vs -11.2, respectively; P < .01) or excluded (-10.6 vs -8.9; P < .01), but not for anxiety/somatization (-4.3 vs -4.1; P = .23). Response rates were greater for eszopiclone cotherapy than for placebo cotherapy (55.6% vs 42.0%, respectively; P = .01; 50.0% vs 44.4% when insomnia items were removed; P = .3). Remission rates were not significantly different (32.6% vs 27.2%, respectively; P = .28).

CONCLUSIONS: In this post hoc analysis of patients with insomnia and comorbid anxious depression derived from 2 trials, 8 weeks of eszopiclone therapy coadministered with an SSRI resulted in significantly greater improvements in insomnia, significantly greater reductions in HDRS-17 total score, and significantly greater HDRS-17 response rates compared with placebo coadministration. There were no significant differences in response rates (when insomnia items were excluded) and remission rates, as well as in anxiety/somatization scores. Further research is warranted to determine whether these modest antidepressant effects can be replicated, and anxiolytic effects demonstrated, when evaluated in a prospective manner. Copyright 2011 Physicians Postgraduate Press, Inc.

Goforth, H. W., et al. (2014). "A randomized, double-blind, placebo-controlled trial of eszopiclone for the treatment of insomnia in patients with chronic low back pain." Sleep **37**(6): 1053-1060.

STUDY OBJECTIVES: Insomnia, which is very common in patients with chronic low back pain (LBP), has long been viewed as a pain symptom that did not merit specific treatment. Recent data suggest that adding insomnia therapy to pain-targeted treatment should improve outcome; however, this has not been empirically tested in LBP or in any pain condition treated with a standardized pain medication regimen. We sought to test the hypothesis that adding insomnia therapy to pain-targeted treatment might improve sleep and pain in LBP.

DESIGN: Double-blind, placebo-controlled, parallel-group, 1-mo trial.

SETTING: Duke University Medical Center Outpatient Sleep Clinic.

PATIENTS: Fifty-two adult volunteers with LBP of at least 3 mo duration who met diagnostic criteria for insomnia (mean age: 42.5 y; 63% females).

INTERVENTIONS: Subjects were randomized to eszopiclone (ESZ) 3 mg plus naproxen 500 mg BID or matching placebo plus naproxen 500 mg twice a day.

MEASUREMENTS AND RESULTS: ESZ SIGNIFICANTLY IMPROVED TOTAL SLEEP TIME (MEAN INCREASE: ESZ, 95 min; placebo, 9 min) (primary outcome) and nearly all sleep measures as well as visual analog scale pain (mean decrease: ESZ, 17 mm; placebo, 2 mm) (primary pain outcome), and depression (mean Hamilton Depression Rating Scale improvement ESZ, 3.8; placebo, 0.4) compared with placebo. Changes in pain ratings were significantly correlated with changes in sleep.

CONCLUSIONS: The addition of insomnia-specific therapy to a standardized naproxen pain regimen significantly improves sleep, pain, and depression in patients with chronic low back pain (LBP). The findings indicate the importance of administering both sleep and pain-directed therapies to patients with LBP in clinical practice and provide strong evidence that improving sleep disturbance may improve pain.

TRIAL REGISTRATION: clinicaltrials.gov identifier: NCT00365976.

Gooneratne, N. S., P. Gehrman, et al. (2010). "Effectiveness of ramelteon for insomnia symptoms in older adults with obstructive sleep apnea: a randomized placebo-controlled pilot study." Journal of Clinical Sleep Medicine **6**(6): 572-580.

STUDY OBJECTIVES: To evaluate the effectiveness of ramelteon, a melatonin receptor agonist, for the treatment of insomnia in older adults starting auto-titrating positive airway pressure (APAP) therapy for sleep apnea.

METHODS: A parallel group, randomized, double-blind, placebo-controlled pilot effectiveness clinical trial. The study enrolled 21 research study participants who were >= 60 years old and had obstructive sleep apnea, defined by an apnea-hypopnea index (AHI) >= 5 events/h, with complaints of insomnia. The primary outcome measure was change in sleep onset latency determined from polysomnography at 4 weeks. Research study participants, all of whom were starting on APAP, were randomized to ramelteon 8 mg (n = 8) or placebo (n = 13).

RESULTS: Ramelteon treatment was associated with a statistically significant difference in sleep onset latency (SOL) as measured by polysomnography of 28.5 min (+/- 16.2 min) compared to placebo (95% C.I. 8.5 min to 48.6 min, effect size 1.35, p = 0.008). This was due to a 10.7 (+/- 17.0) min SOL reduction in the ramelteon arm and a 17.8 (+/- 23.5) min SOL increase in the placebo arm. No change was noted in subjective sleep onset latency (-1.3 min, +/- 19.3 min, 95% C.I.: -21.4 min to 18.7 min). No statistically significant changes were noted in the AHI, sleep efficiency (polysomnography and self-report), APAP adherence, Pittsburgh Sleep Quality Index global score, or Epworth Sleepiness Scale score when comparing ramelteon vs. placebo. Four adverse events occurred in the ramelteon arm and 2 in the placebo arm; none were considered to be related to treatment.

CONCLUSIONS: Ramelteon was effective in improving objective, but not subjective, sleep onset latency even in older adults who were starting APAP therapy for sleep apnea. Further research is warranted in examining the role of ramelteon in the care of older adults with insomnia symptoms and sleep apnea.

Hajak, G., J. Hedner, et al. (2009). "A 2-week efficacy and safety study of gaboxadol and zolpidem using electronic diaries in primary insomnia outpatients." Sleep Medicine **10**(7): 705-712.

OBJECTIVES: To evaluate the efficacy and safety profile of gaboxadol, a selective

extrasynaptic GABA(A) agonist (SEGA) previously in development for the treatment of insomnia.

METHODS: This was a randomised, double-blind, placebo-controlled, parallel-group, 2-week, Phase III study of gaboxadol 5, 10 and 15mg in outpatients meeting the DSM-IV criteria of primary insomnia (N=742). Zolpidem 10mg was used as active reference.

RESULTS: At weeks 1 and 2, significant improvement in total sleep time (sTST) compared to placebo was seen for all doses of gaboxadol (all $p<0.05$). In addition, gaboxadol 10 and 15mg decreased the number of awakenings (sNAW) ($p<0.05$) while only gaboxadol 15mg improved wakefulness after sleep onset (sWASO) ($p<0.05$). At week 1, all doses of gaboxadol significantly improved time-to-sleep onset (sTSO) ($p<0.05$). At week 2, a sustained effect on sTSO was observed for gaboxadol 15mg. Zolpidem also showed effect on all of these variables. Gaboxadol and zolpidem improved sleep quality, freshness after sleep, daytime function and energy at both weeks. Transient rebound insomnia was observed following discontinuation of treatment with zolpidem, but not gaboxadol.

CONCLUSIONS: Gaboxadol 15mg treatment for 2 weeks significantly improved sleep onset and maintenance variables as well as sleep quality and daytime function, as did zolpidem. Gaboxadol 5 and 10mg also showed benefits on most efficacy variables. Gaboxadol was generally safe and well tolerated, with no evidence of withdrawal symptoms or rebound insomnia after discontinuation of short-term treatment. For zolpidem, transient rebound insomnia was observed.

Herring, W. J., et al. (2016). "Suvorexant in Patients With Insomnia: Results From Two 3-Month Randomized Controlled Clinical Trials." Biological Psychiatry 79(2): 136-148.

BACKGROUND: Suvorexant is an orexin receptor antagonist for treatment of insomnia. We report results from two pivotal phase 3 trials.

METHODS: Two randomized, double-blind, placebo-controlled, parallel-group, 3-month trials in nonelderly (18-64 years) and elderly (>65 years) patients with insomnia. Suvorexant doses of 40/30 mg (nonelderly/elderly) and 20/15 mg (nonelderly/elderly) were evaluated. The primary focus was 40/30 mg, with fewer patients randomized to 20/15 mg. There was an optional 3-month double-blind extension in trial 1. Each trial included a 1-week, randomized, double-blind run-out after double-blind treatment to assess withdrawal/rebound. Efficacy was assessed at week 1, month 1, and month 3 by patient-reported subjective total sleep time and time to sleep onset and in a subset of patients at night 1, month 1, and month 3 by polysomnography end points of wakefulness after persistent sleep onset and latency to onset of persistent sleep (LPS). One thousand twenty-one patients were randomized in trial 1 and 1019 patients in trial 2.

RESULTS: Suvorexant 40/30 mg was superior to placebo on all subjective and polysomnography end points at night 1/week 1, month 1, and month 3 in both trials, except for LPS at month 3 in trial 2. Suvorexant 20/15 mg was superior to placebo on subjective total sleep time and wakefulness after persistent sleep onset at night 1/week 1, month 1, and month 3 in both trials and at most individual time points for subjective time to sleep onset and LPS in each trial. Both doses of suvorexant were generally well tolerated, with <5% of patients discontinuing due to adverse events over 3 months. The results did not suggest the emergence of marked rebound or withdrawal signs or symptoms when suvorexant was discontinued.

CONCLUSIONS: Suvorexant improved sleep onset and maintenance over 3 months of nightly treatment and was generally safe and well tolerated.

Joffe, H., L. Petrillo, et al. (2010). "Eszopiclone improves insomnia and depressive and anxious symptoms in perimenopausal and postmenopausal women with hot flashes: a randomized, double-blinded, placebo-controlled crossover trial." American Journal of Obstetrics & Gynecology **202**(2): 171.e171-171.e111.

OBJECTIVE: Menopause-associated insomnia is commonly associated with other symptoms (hot flashes, depression, anxiety). Given frequent symptom cooccurrence, therapies targeting sleep may provide an important approach to treatment during midlife.

STUDY DESIGN: Peri/postmenopausal women (40-65 years old) with sleep-onset and/or sleep-maintenance insomnia cooccurring with hot flashes and depressive and/or anxiety symptoms were randomized to eszopiclone 3 mg orally or placebo in a double-blinded, crossover 11 week trial. Changes in the Insomnia Severity Index (ISI) scale and secondary outcomes (diary-based sleep parameters, depression/anxiety, hot flashes, quality of life) were analyzed using repeated-measure linear models.

RESULTS: Of 59 women, 46 (78%) completed the study. Eszopiclone reduced ISI scores by 8.7 + or - 1.4 more points than placebo ($P < .0001$). Eszopiclone improved ($P < .05$) all sleep parameters, depressive symptoms, anxiety symptoms, quality of life, and nighttime but not daytime hot flashes.

CONCLUSION: Eszopiclone treats insomnia and cooccurring menopause-related symptoms. Our results provide evidence that hypnotic therapies may improve multiple domains of well-being during midlife.

Kohsaka, M., T. Kanemura, et al. (2011). "Efficacy and tolerability of ramelteon in a double-blind, placebo-controlled, crossover study in Japanese patients with chronic primary insomnia." Expert Review of Neurotherapeutics **11**(10): 1389-1397.

The aim of this study was to evaluate the efficacy and safety of ramelteon 4, 8, 16 or 32 mg and placebo in Japanese patients with chronic insomnia using a randomized, double-blind, five-period crossover design. A total of 65 Japanese patients with chronic primary insomnia received ramelteon or placebo for two nights each in sleep laboratories. Changes in sleep parameters were assessed objectively by polysomnography and subjectively by postsleep questionnaires. Safety and tolerability was evaluated by assessment of the occurrence of adverse events, next-day residual effects and laboratory and ECG investigations. Ramelteon 8 and 32 mg significantly shortened the mean latency to persistent sleep in comparison with placebo, and there was a statistically significant trend for linear dose-response for this sleep parameter. Overall changes in sleep architecture were modest (<3% changes vs placebo), with increases in stage 1 and decreases in stage 3/4. Ramelteon was well tolerated, the most common adverse effect being somnolence, which was similar to placebo at doses up to 8 mg, but increased with higher doses. Next-day residual effects occurred no more frequently with ramelteon at any dose than with placebo. When compared with sleep latency data from a similarly-designed US study, there was no evidence of any ethnic differences in the efficacy of ramelteon between Japanese and US patients. Overall, ramelteon 8 mg showed the most favorable balance between sleep-promoting effects and tolerability. The unique efficacy

profile of ramelteon, promoting sleep initiation without affecting other sleep parameters, may be due to its circadian shifting effect.

Krystal, A. D., H. H. Durrence, et al. (2010). "Efficacy and Safety of Doxepin 1 mg and 3 mg in a 12-week Sleep Laboratory and Outpatient Trial of Elderly Subjects with Chronic Primary Insomnia." Sleep **33**(11): 1553-1561.

STUDY OBJECTIVES: to evaluate the efficacy and safety of doxepin 1 mg and 3 mg in elderly subjects with chronic primary insomnia.

DESIGN AND METHODS: the study was a randomized, double-blind, parallel-group, placebo-controlled trial. Subjects meeting DSM-IV-TR criteria for primary insomnia were randomized to 12 weeks of nightly treatment with doxepin (DXP) 1 mg (n = 77) or 3 mg (n = 82), or placebo (PBO; n = 81). Efficacy was assessed using polysomnography (PSG), patient reports, and clinician ratings. Objective efficacy data are reported for Nights (N) 1, 29, and 85; subjective efficacy data during Weeks 1, 4, and 12; and Clinical Global Impression (CGI) scale and Patient Global Impression (PGI) scale data after Weeks 2, 4, and 12 of treatment. Safety assessments were conducted throughout the study.

RESULTS: DXP 3 mg led to significant improvement versus PBO on N1 in wake time after sleep onset (WASO; $P < 0.0001$; primary endpoint), total sleep time (TST; $P < 0.0001$), overall sleep efficiency (SE; $P < 0.0001$), SE in the last quarter of the night ($P < 0.0001$), and SE in Hour 8 ($P < 0.0001$). These improvements were sustained at N85 for all variables, with significance maintained for WASO, TST, overall SE, and SE in the last quarter of the night. DXP 3 mg significantly improved patient-reported latency to sleep onset (Weeks 1, 4, and 12), subjective TST (Weeks 1, 4, and 12), and sleep quality (Weeks 1, 4, and 12). Several global outcome-related variables were significantly improved, including the severity and improvement items of the CGI (Weeks 2, 4, and 12), and all 5 items of the PGI (Week 12; 4 items after Weeks 2 and 4). Significant improvements were observed for DXP 1 mg for several measures including WASO, TST, overall SE, and SE in the last quarter of the night at several time points. Rates of discontinuation were low, and the safety profiles were comparable across the 3 treatment groups. There were no significant next-day residual effects; additionally, there were no reports of memory impairment, complex sleep behaviors, anticholinergic effects, weight gain, or increased appetite.

CONCLUSIONS: DXP 1 mg and 3 mg administered nightly to elderly chronic insomnia patients for 12 weeks resulted in significant and sustained improvements in most endpoints. These improvements were not accompanied by evidence of next-day residual sedation or other significant adverse effects. DXP also demonstrated improvements in both patient- and physician-based ratings of global insomnia outcome. The efficacy of DXP at the doses used in this study is noteworthy with respect to sleep maintenance and early morning awakenings given that these are the primary sleep complaints of the elderly. This study, the longest placebo-controlled, double-blind, polysomnographic trial of nightly pharmacotherapy for insomnia in the elderly, provides the best evidence to date of the sustained efficacy and safety of an insomnia medication in older adults.

Krystal, A. D., H. Huang, et al. (2012). "A WASO sub-group analysis of a 6-month study of eszopiclone 3 mg." Sleep Medicine **13**(6): 691-696.

BACKGROUND: Insomnia marked by sleep maintenance difficulty is extremely prevalent. Yet, problems staying asleep have been relatively neglected as a research focus compared to problems falling asleep. Insomnia treatment studies typically have not required participants to have a problem specifically with sleep maintenance. It is possible that exclusion of such subjects limits the detection of treatment effects in the overall trial in general, and of effects on sleep maintenance specifically. In order to address these issues we conducted a post hoc analysis of a 6-month placebo-controlled trial in which there were no inclusion criteria that specified sleep maintenance difficulties to assess the variable effects of baseline wake time after sleep onset (WASO - the primary maintenance measure) on the efficacy of eszopiclone 3mg.

METHODS: Patients diagnosed with chronic primary insomnia were randomized to eszopiclone 3mg (n=593) or placebo (n=195) nightly for six months. The present analyses of this study consisted of: (1) determination of the distribution of baseline WASO; (2) continuous analysis of the relationship between baseline WASO severity and drug-placebo difference at month 1 and 6; and (3) categorical efficacy analyses of subgroups delimited by the following WASO thresholds: 0, 30, 45, 60, and 90 min.

RESULTS: The baseline WASO distribution was: <= 30=32.2%; >0 to <= 45=41.5%; >30 to <= 90=33.0%; >45 to <= 90=23.7%; >90=22.6%. A relationship between greater baseline WASO severity and a significantly greater drug-placebo difference in efficacy for WASO was evident in both continuous and categorical analyses. Eszopiclone was found to have significant sleep maintenance efficacy at each time point across the entire range of WASO severity studied.

CONCLUSIONS: As illustrated in this analysis, a significant proportion of chronic insomnia patients in efficacy trials that select on the basis of sleep onset latency and total sleep time criteria may have normative-range WASO. However, even in the subgroup with minimal WASO there was a significant sleep maintenance effect. The absence of any sleep maintenance effect in a drug trial may reflect the inclusion of relatively many insomnia patients with no baseline WASO abnormality. However, treatments with therapeutic effects on sleep maintenance, can still demonstrate improvement in sleep maintenance, even in a population not selected for this type of sleep problem, if adequately powered. Future clinical trials intending to examine sleep maintenance should employ WASO selection criteria that would ensure sufficient power to detect a sleep maintenance effect. Drug-placebo difference increased as a function of baseline WASO severity, suggesting that eszopiclone's clinical effectiveness for insomnia may be enhanced in patients with more severe sleep maintenance symptoms.

Krystal, A. D., A. Lankford, et al. (2011). "Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia." Sleep **34**(10): 1433-1442.

STUDY OBJECTIVES: To evaluate the efficacy and safety of doxepin (DXP) 3 mg and 6 mg in adults diagnosed with primary insomnia.

DESIGN AND METHODS: The study was a randomized, double-blind, parallel-group, placebo-controlled trial. Patients meeting DSM-IV-TR criteria for primary insomnia were randomized to 35 days of nightly treatment with DXP 3 mg (n=75), DXP 6 mg (n=73), or placebo (PBO; n=73), followed by 2 nights of single-blind PBO to evaluate discontinuation (DC) effects. Efficacy was assessed using polysomnography (PSG) and

patient reports. Efficacy data were examined for Night (N) 1, N15, and N29. Safety assessments were conducted throughout the study.

RESULTS: Compared with PBO, DXP 3 and 6 mg significantly improved wake time after sleep onset (WASO) on N1 (3 mg and 6 mg; P<0.0001), N15 (3 mg P=0.0025; 6 mg P=0.0009), and N29 (3 mg P=0.0248; 6 mg P=0.0009), latency to persistent sleep (LPS) on N1 (3 mg P=0.0047; 6 mg P=0.0007), and total sleep time (TST) on N1 (3 mg and 6 mg P<0.0001), N15 (6 mg P=0.0035), and N29 (3 mg P=0.0261; 6 mg P<0.0001). In terms of early morning awakenings, DXP 3 and 6 mg demonstrated significant improvements in SE in the final quarter of the night on N1, N15, and N29, with the exception of 3 mg on N29 (P=0.0691). Rates of discontinuation were low, and the safety profiles were comparable across the 3 treatment groups. There were no significant next-day residual effects, and there were no spontaneous reports of memory impairment, complex sleep behaviors, anticholinergic effects, weight gain, or increased appetite. Additionally, there was no evidence of rebound insomnia after DXP discontinuation.

CONCLUSIONS: Five weeks of nightly administration of DXP 3 mg and 6 mg to adults with chronic primary insomnia resulted in significant and sustained improvements in sleep maintenance and early morning awakenings (with the exception of SE in the final quarter of the night on N29 for 3 mg [P=0.0691]). These sleep improvements were not accompanied by next-day residual effects or followed by rebound insomnia or withdrawal effects upon discontinuation. These findings confirm the unique profile of sleep maintenance efficacy and safety of DXP observed in prior studies.

Lankford, A., R. Rogowski, et al. (2012). "Efficacy and safety of doxepin 6 mg in a four-week outpatient trial of elderly adults with chronic primary insomnia." Sleep Medicine **13**(2): 133-138.

INTRODUCTION: The efficacy and safety of doxepin (DXP), a histamine H(1) receptor antagonist, was evaluated in elderly adults with sleep maintenance insomnia.

METHODS: This was a randomized, double-blind, placebo-controlled outpatient trial. Elderly adults meeting DSM-IV-TR criteria for primary insomnia were randomized to four weeks of nightly treatment with either DXP 6 mg (N=130) or placebo (PBO; N=124). Efficacy was assessed using patient self-report instruments and clinician ratings. Patient-reported endpoints included subjective total sleep time (sTST), subjective wake after sleep onset (sWASO), latency to sleep onset (LSO), sleep quality, and a Patient Global Impression scale (PGI). The primary endpoint was sTST at week 1.

RESULTS: DXP 6 mg produced significantly more sTST and less sWASO at week 1 (both p-values <0.0001) than PBO. These significant improvements versus placebo were maintained at weeks 2-4 (all p-values <0.05). There were no significant differences in LSO for DXP 6 mg versus PBO. DXP 6 mg significantly improved sleep quality (weeks 1, 3, and 4, p<0.05) and several outcome-related parameters, including several items on the PGI, the severity and improvement items of the Clinician Global Impression scale (CGI; weeks 1 and 2) and the Insomnia Severity Index (ISI; weeks 1-4), all versus PBO. There were no reports of anticholinergic effects (e.g., dry mouth) or memory impairment. The safety profile of DXP 6 mg was comparable to that of PBO.

CONCLUSIONS: In elderly adults with insomnia, DXP 6 mg produced significant improvements in sleep maintenance, sleep duration, and sleep quality endpoints that were sustained throughout the trial. These data suggest that DXP 6 mg is effective for treating sleep maintenance insomnia and is well-tolerated in elderly adults with chronic primary

insomnia. Copyright 2011 Elsevier B.V. All rights reserved.

Lequerica, A., et al. (2015). "Pilot Study on the Effect of Ramelteon on Sleep Disturbance After Traumatic Brain Injury: Preliminary Evidence From a Clinical Trial." Archives of Physical Medicine & Rehabilitation 96(10): 1802-1809.

OBJECTIVE: To investigate the effect of ramelteon on sleep and daytime functioning among individuals with traumatic brain injury (TBI).
DESIGN: A double-blind, placebo-controlled study with a crossover design.
SETTING: A research facility attached to an acute rehabilitation hospital.
PARTICIPANTS: Individuals with TBI (N=13) complaining of sleep difficulties with a Pittsburgh Sleep Quality Index score >5.
INTERVENTIONS: A nightly dosage of ramelteon (8 mg) was given over a period of 3 weeks.
MAIN OUTCOME MEASURES: An actigraph and a daily sleep log were used to measure sleep/wake patterns. Daytime functioning was measured after 3 weeks of treatment using a computer-administrated neuropsychological test battery in conjunction with subjective questionnaires measuring mood, daytime sleepiness, and fatigue.
RESULTS: A significant increase in objectively measured total sleep time and a small increase in sleep latency were observed after 3 weeks of treatment compared with placebo. Treatment also showed a significant increase in standardized neuropsychological test scores, with a particular improvement on an index of executive functioning.
CONCLUSIONS: Preliminary evidence for the effectiveness of 8 mg of ramelteon taken nightly over a 3-week period was found in the treatment of sleep difficulties among individuals with TBI. Improvements in total sleep time and some aspects of cognitive functioning are discussed.Copyright © 2015 American Congress of Rehabilitation Medicine. Published by Elsevier Inc. All rights reserved.

Mayer, G., S. Wang-Weigand, et al. (2009). "Efficacy and safety of 6-month nightly ramelteon administration in adults with chronic primary insomnia." Sleep **32**(3): 351-360.

STUDY OBJECTIVES: Long-duration (> or = 6 months) polysomnographic studies of insomnia medications are lacking. This study evaluated the long-term efficacy of ramelteon, a selective MT1/MT2 melatonin-receptor agonist used for insomnia treatment.
DESIGN: Six-month, randomized, double-blind, placebo-controlled study. SETTING: Forty-six investigative sites in the United States, Europe, Russia, and Australia.
PARTICIPANTS: Four hundred fifty-one adults (age > or = 18 years) with chronic primary insomnia.
INTERVENTIONS: Ramelteon, 8 mg, or placebo 30 minutes before bedtime nightly for 6 months.
MEASUREMENTS: Sleep was evaluated by polysomnography and morning questionnaires on the first 2 nights of Week 1; the last 2 nights of Months 1, 3, 5, and 6; and Nights 1 and 2 of the placebo run-out. Next-morning residual effects as well as adverse effects and vital signs were recorded at each visit. Rebound insomnia and withdrawal effects were evaluated during placebo run-out.
RESULTS: Over the 6 months of treatment, ramelteon consistently reduced latency to persistent sleep compared with baseline and with placebo; significant decreases were observed at Week 1 and Months 1, 3, 5, and 6 ($P < 0.05$). Ramelteon significantly reduced subjective sleep latency relative to placebo at Week 1, Month 1, and Month 5 ($P < 0.05$), with

reductions nearing statistical significance at Months 3 and 6 (P < or = 0.08). No significant next-morning residual effects were detected during ramelteon treatment. No withdrawal symptoms or rebound insomnia were detected after ramelteon discontinuation. Most adverse events were mild or moderate in severity.
CONCLUSIONS: In adults with chronic insomnia, long-term ramelteon treatment consistently reduced sleep onset, with no next-morning residual effects or rebound insomnia or withdrawal symptoms upon discontinuation.

McCall, W. V., J. N. Blocker, et al. (2010). "Treatment of insomnia in depressed insomniacs: effects on health-related quality of life, objective and self-reported sleep, and depression." Journal of Clinical Sleep Medicine **6**(4): 322-329.
STUDY OBJECTIVES: Insomnia is associated with poor health related quality of life (HRQOL) in depressed patients. Prior clinical trials of hypnotic treatment of insomnia in depressed patients have shown improvement in HRQOL, but in these studies HRQOL was relegated to a secondary outcome, and objective measures of sleep were not undertaken.
DESIGN: Double-blind, randomized, placebo-controlled clinical trial.
SETTING: Outpatient clinic and sleep laboratory. PATIENTS: 60 depressed, insomniac outpatients.
INTERVENTIONS: One week of open-label fluoxetine (FLX), followed by 8 more weeks of FLX combined with either eszopiclone (ESZ) 3 mg or placebo at bedtime.
MEASUREMENTS: The primary HRQOL measure was the daily living and role functioning subscale (DLRF) of the Basis-32. Other measures included the Q-LES-Q, self-reported sleep, PSG, actigraphy, depression severity (HRSD).
RESULTS: At the end of randomized treatment, patients receiving ESZ had lower (better) DLRF scores (0.81 +/- 0.64) than those receiving placebo (1.2 +/- 0.72), p = 0.01. The effect size for DLRF was 0.62, indicating a moderate effect. An advantage for ESZ was also seen in other measures of HRQOL, and most assessments of antidepressant efficacy and sleep. Women reported better end of treatment HRQOL scores than men.
CONCLUSIONS: ESZ treatment of insomnia in depressed patients is associated with multiple favorable outcomes, including superior improvement in HRQOL, depression severity, and sleep.

McElroy, S. L., E. L. Winstanley, et al. (2011). "A randomized, placebo-controlled study of adjunctive ramelteon in ambulatory bipolar I disorder with manic symptoms and sleep disturbance." International Clinical Psychopharmacology **26**(1): 48-53.
This study evaluated the efficacy and tolerability of ramelteon in ambulatory bipolar I disorder with manic symptoms and insomnia. Twenty-one outpatients with bipolar I disorder by Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria with mild-to-moderate manic symptoms and sleep disturbance were randomized to receive either ramelteon (N=10) or placebo (N=11) in an 8-week, double-blind, fixed-dose (8 mg/day) study. Ramelteon and placebo had similar rates of reduction in ratings of symptoms of insomnia, mania, and global severity of illness. However, ramelteon was associated with improvement in a global rating of depressive symptoms. It was also well tolerated and associated with no serious adverse events. The small sample size may have limited the ability of the study to detect potentially clinically important drug-placebo differences. Further studies of ramelteon in subgroups of bipolar patients with sleep

disturbance, including those with depression or euthymia, seem indicated.

Menza, M., R. D. Dobkin, et al. (2010). "Treatment of insomnia in Parkinson's disease: a controlled trial of eszopiclone and placebo." Movement Disorders **25**(11): 1708-1714.

Parkinson's disease (PD) is a common neurodegenerative disease affecting up to 1 million individuals in the United States. Sleep disturbances, typically in sleep maintenance, are found in up to 88% of these individuals and are associated with a variety of poor outcomes. Despite being common and important, there are few data to guide clinical care. We conducted a 6-week, randomized, controlled trial of eszopiclone and placebo in 30 patients with PD and insomnia. Patients with other primary sleep disorders (PSG defined) were excluded. The primary outcome was total sleep time (TST), and secondary measures included wake after sleep onset (WASO), number of awakenings, and quality of sleep, among others. The groups did not significantly differ on TST, but significant differences, favoring eszopiclone, did emerge in number of awakenings (P = 0.035), quality of sleep (P = 0.018), and in physician-rated CGI improvement (P = 0.035). There was also a trend toward significance in WASO (P = 0.071). There were no significant differences between groups in measures of daytime functioning. The drug was well tolerated, with 33% of patients on eszopiclone and 27% of patients on placebo reporting adverse events. Although modest in size, this is the first controlled study of the treatment of insomnia in patients with PD. Eszopiclone did not increase TST significantly but was superior to placebo in improving quality of sleep and some measures of sleep maintenance, which is the most common sleep difficulty experienced by patients with PD. Definitive trials of the treatment of sleep disorders in this population are warranted.

Michelson, D., et al. (2014). "Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial." Lancet Neurology **13**(5): 461-471.

BACKGROUND: Suvorexant (MK-4305) is an orexin receptor antagonist shown to be efficacious for insomnia over 3 months. We aimed to assess its clinical profile during and after 1 year of treatment.

METHODS: We did a randomised, placebo-controlled, parallel-group trial at 106 investigational centres in the Americas, Australia, Europe, and South Africa from December, 2009, to August, 2011. Patients aged 18 years or older with primary insomnia by DSM-IV-TR criteria were assigned using a computer-generated randomised allocation schedule to receive nightly suvorexant (40 mg for patients younger than 65 years, 30 mg for patients aged 65 years or older) or placebo at a 2:1 ratio for 1 year with a subsequent 2-month randomised discontinuation phase in which patients on suvorexant either continued suvorexant or were abruptly switched to placebo while patients on placebo remained on placebo. Treatment assignment was masked from patients and investigators. The primary objective was to assess the safety and tolerability of suvorexant for up to 1 year. Secondary objectives were to assess the efficacy of suvorexant for improving patient-reported subjective total sleep time (sTST) and time to sleep onset (sTSO) over the first month of treatment. Efficacy endpoints over the first month were assessed with a mixed model with terms for baseline value of the response variable, age, sex, region, treatment,

time, and treatment by time interaction. This trial is registered with ClinicalTrials.gov, number NCT01021813.

FINDINGS: 322 (62%) of 522 patients randomly assigned to receive suvorexant and 162 (63%) of 259 assigned to receive placebo completed the 1-year phase. Over 1 year, 362 (69%) of 521 patients treated with suvorexant experienced any adverse events compared with 164 (64%) of 258 treated with placebo. Serious adverse events were recorded in 27 patients (5%) who received suvorexant and 17 (7%) who received placebo. The most common adverse event, somnolence, was reported for 69 patients (13%) who received suvorexant and seven (3%) who received placebo. At month 1, suvorexant (517 patients in the efficacy population) showed greater efficacy than placebo (254 in the efficacy population) in improving sTST (387 min vs 160 min; difference 227, 95% CI 164 to 290; p<00001) and sTSO (-180 min vs -84 min, difference -95, -146 to -45; p=00002).

INTERPRETATION: Our findings show that suvorexant was generally safe and well tolerated over 1 year of nightly treatment in patients with insomnia, with efficacy noted for subjective measures of sleep onset and maintenance.

Morin, C. M., A. Vallieres, et al. (2009). "Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial." JAMA : the journal of the American Medical Association **301**(19): 2005-2015.

CONTEXT: Cognitive behavioral therapy (CBT) and hypnotic medications are efficacious for short-term treatment of insomnia, but few patients achieve complete remission with any single treatment. It is unclear whether combined or maintenance therapies would enhance outcome.

OBJECTIVES: To evaluate the added value of medication over CBT alone for acute treatment of insomnia and the effects of maintenance therapies on long-term outcome.

DESIGN, SETTING, AND PATIENTS: Prospective, randomized controlled trial involving 2-stage therapy for 160 adults with persistent insomnia treated at a university hospital sleep center in Canada between January 2002 and April 2005.

INTERVENTIONS: Participants received CBT alone or CBT plus 10 mg/d (taken at bedtime) of zolpidem for an initial 6-week therapy, followed by extended 6-month therapy. Patients initially treated with CBT attended monthly maintenance CBT for 6 months or received no additional treatment and those initially treated with combined therapy (CBT plus 10 mg/d of zolpidem) continued with CBT plus intermittent use of zolpidem or CBT only.

MAIN OUTCOME MEASURES: Sleep onset latency, time awake after sleep onset, total sleep time, and sleep efficiency derived from daily diaries (primary outcomes); treatment response and remission rates derived from the Insomnia Severity Index (secondary outcomes).

RESULTS: Cognitive behavioral therapy used singly or in combination with zolpidem produced significant improvements in sleep latency, time awake after sleep onset, and sleep efficiency during initial therapy (all P<.001); a larger increase of sleep time was obtained with the combined approach (P = .04). Both CBT alone and CBT plus zolpidem produced similar rates of treatment responders (60% [45/75] vs 61% [45/74], respectively; P = .84) and treatment remissions (39% [29/75] vs 44% [33/74], respectively; P = .52) with the 6-week acute treatment, but combined therapy produced a higher remission rate compared with CBT alone during the 6-month extended therapy phase and the 6-month follow-up

period (56% [43/74 and 32/59] vs 43% [34/75 and 28/68]; P = .05). The best long-term outcome was obtained with patients treated with combined therapy initially, followed by CBT alone, as evidenced by higher remission rates at the 6-month follow-up compared with patients who continued to take zolpidem during extended therapy (68% [20/30] vs 42% [12/29]; P = .04).

CONCLUSION: In patients with persistent insomnia, the addition of medication to CBT produced added benefits during acute therapy, but long-term outcome was optimized when medication is discontinued during maintenance CBT. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00042146.

Omvik, S., B. Sivertsen, et al. (2008). "Daytime functioning in older patients suffering from chronic insomnia: treatment outcome in a randomized controlled trial comparing CBT with Zopiclone." Behaviour Research and Therapy **46**(5): 623-641.

The paper presents data from a randomized controlled trial comparing treatment effects of cognitive behavioural therapy (CBT), hypnotic treatment (Zopiclone), and placebo in a sample of insomnia patients. Data from the same trial have already demonstrated that CBT was more efficient in improving sleep than Zopiclone. The novel outcomes that are reported here concern daytime functioning. Forty-six older patients (age >or= 55) qualifying for a diagnosis of primary insomnia were recruited to participate. Assessments were completed at baseline, post-treatment, and at a 6-months follow-up, and measures of worry, anxiety, depression, interpersonal relationships, subjective alertness, vigilance, and quality of life were used. The participants in both treatment conditions scored within the normal range on the outcome measures at baseline with the exception of reporting less alertness, relative to a group of good sleepers. One interaction effect indicated that subjective alertness improved more in the Zopiclone group than the CBT group from baseline to post-treatment, and another that CBT was more effective than Zopiclone in reducing trait anxiety from baseline to follow-up. It was concluded that the treatments yielded only minor effects on the measures of daytime functioning, and that none of them was clearly superior to the other.

Park, J.G., E.J. Olson, et al. (2013). “Impact of zaleplon on continuous positive airway pressure therapy compliance.” Journal of Clinical Sleep Medicine **9**(5): 439-444.

STUDY OBJECTIVE: To determine whether pretreatment with zaleplon immediately before CPAP titration improves 1-month CPAP adherence in subjects newly diagnosed with OSA.

METHODS: Prospective, randomized, double-blinded, placebo-controlled trial of a single dose of zaleplon 10 mg or matching placebo at the start of CPAP titration during laboratory-based, split-night polysomnography (PSG). Baseline sleep symptoms were assessed with the Functional Outcomes of Sleep Questionnaire (FOSQ) and Epworth Sleepiness Scale (ESS). CPAP usage and change in symptom questionnaire responses were assessed at 1-month follow-up.

RESULTS: One hundred thirty-four newly diagnosed OSA patients undergoing their initial split-night PSG (49.8 + 11.3 years old with an apnea-hypopnea index of 16.5 (7, 32) [median (interquartile range)] were randomized to zaleplon (n = 73) or placebo (n = 63). Complete follow-up data were available in 83 subjects (44 zaleplon group; 39 placebo group).

CPAP was used for 6.5 (5, 7) h/day with zaleplon versus 6.5 (5, 8) h/ day with placebo (p = 0.64). Improvements in FOSQ and ESS scores did not differ between the two groups.
CONCLUSION: A single dose of zaleplon at the start of a split-night CPAP titration does not result in superior CPAP adherence or improvement in symptoms at 1-month compared to placebo. Our data show that zaleplon is safe and is associated with shorter sleep latency during CPAP titration, but it does not translate into improved short-term CPAP adherence.

Pollack, M. H., E. A. Hoge, et al. (2011). "Eszopiclone for the treatment of posttraumatic stress disorder and associated insomnia: a randomized, double-blind, placebo-controlled trial." Journal of Clinical Psychiatry **72**(7): 892-897.
OBJECTIVE: The development of novel strategies for the treatment of posttraumatic stress disorder (PTSD) represents a critical public health need. We present the first prospective, randomized, double-blind, placebo-controlled trial of a non-benzodiazepine hypnotic agent for the treatment of PTSD and associated insomnia.
METHOD: Twenty-four patients with PTSD by DSM-IV criteria and sleep disturbance were treated in a randomized, double-blind, placebo-controlled crossover study of 3 weeks of eszopiclone 3 mg at bedtime compared to placebo. The primary outcome measures were changes in scores on the Short PTSD Rating Interview (SPRINT) and the Pittsburgh Sleep Quality Index (PSQI). The data were collected from April 2006 to June 2008.
RESULTS: Three weeks of eszopiclone pharmacotherapy was associated with significantly greater improvement than placebo on PTSD symptom measures including the SPRINT (P = .032) and the Clinician-Administered PTSD Scale (P = .003), as well as on measures of sleep including the PSQI (P = .011) and sleep latency (P = .044). Greater improvement with eszopiclone on PTSD measures was present even when specific sleep-related items were excluded. Adverse events were consistent with the known profile of the drug.
CONCLUSIONS: This study provides initial evidence that pharmacotherapy with eszopiclone may be associated with short-term improvement in overall PTSD severity as well as associated sleep disturbance. Longer, more definitive study of eszopiclone in PTSD is warranted.
TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00120250. Copyright 2011 Physicians Postgraduate Press, Inc.

Rajaratnam, S.M., M.H. Polymeropoulos et al. (2009). “Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: two randomised controlled multicentre trials.[Erratum appears in Lancet. 2009 Apr 11;373(9671):1252].” Lancet **373**(9662): 482-491.
BACKGROUND: Circadian rhythm sleep disorders are common causes of insomnia for millions of individuals. We did a phase II study to establish efficacy and physiological mechanism, and a phase III study to confirm efficacy of the melatonin agonist tasimelteon (VEC-162) for treatment of transient insomnia associated with shifted sleep and wake time.
METHODS: We undertook phase II and phase III randomised, double-blind, placebo-controlled, parallel-group studies. In a phase II study, 39 healthy individuals from two US sites were randomly assigned to tasimelteon (10 [n=9], 20 [n=8], 50 [n=7], or 100 mg [n=7]) or placebo (n=8). We monitored individuals for 7 nights: 3 at baseline, 3 after a 5-h advance of sleep-wake schedule with treatment before sleep, and 1 after treatment; we measured

plasma melatonin concentration for circadian phase assessment. In a phase III study, 411 healthy individuals from 19 US sites, who had transient insomnia induced in a sleep clinic by a 5-h advance of the sleep-wake schedule and a first-night effect in a sleep clinic, were given tasimelteon (20 [n=100], 50 [n=102], or 100 mg [n=106]) or placebo (n=103) 30 min before bedtime. Prespecified primary efficacy outcomes were polysomnographic sleep efficiency (phase II study), latency to persistent sleep (phase III study), and circadian phase shifting (phase II study). Analysis was by intention to treat. Safety was assessed in both studies. These trials are registered with ClinicalTrials.gov, numbers NCT00490945 and NCT00291187.

FINDINGS: In the phase II study, tasimelteon reduced sleep latency and increased sleep efficiency compared with placebo. The shift in plasma melatonin rhythm to an earlier hour was dose dependent. In the phase III study, tasimelteon improved sleep latency, sleep efficiency, and wake after sleep onset (ie, sleep maintenance). The frequency of adverse events was similar between tasimelteon and placebo.

INTERPRETATION: After an abrupt advance in sleep time, tasimelteon improved sleep initiation and maintenance concurrently with a shift in endogenous circadian rhythms. Tasimelteon may have therapeutic potential for transient insomnia in circadian rhythm sleep disorders.

Randall, S., T. A. Roehrs, et al. (2012). "Efficacy of eight months of nightly zolpidem: a prospective placebo-controlled study." Sleep **35**(11): 1551-1557.

STUDY OBJECTIVES: To evaluate the long-term (8 months) efficacy of zolpidem in adults with chronic primary insomnia using polysomnography.

DESIGN: Randomized, double-blind, placebo-controlled clinical trial.

SETTING: Sleep disorders and research center.

PARTICIPANTS: Healthy participants (n = 91), ages 23-70, meeting DSM-IV-TR criteria for primary insomnia.

INTERVENTIONS: Nightly zolpidem, 10 mg (5 mg for patients > 60 yrs) or placebo 30 minutes before bedtime for 8 months.

MEASUREMENTS AND RESULTS: Polysomnographic sleep parameters and morning subject assessments of sleep on 2 nights in months 1 and 8. Relative to placebo, zolpidem significantly increased overall total sleep time and sleep efficiency, reduced sleep latency and wake after sleep onset when assessed at months 1 and 8. Overall, subjective evaluations of efficacy were not shown among treatment groups.

CONCLUSIONS: In adults with primary insomnia, nightly zolpidem administration remained efficacious across 8 months of nightly use.

CLINICAL TRIAL INFORMATION: ClinicalTrials.gov Identifier: NCT01006525; Trial Name: Safety and Efficacy of Chronic Hypnotic Use; http://clinicaltrials.gov/ct2/show/NCT01006525.

Rios Romenets, S., L. Creti, et al. (2013). “Doxepin and cognitive behavioural therapy for insomnia in patients with Parkinson's disease -- a randomized study.” Parkinsonism & Related Disorders **19**(7): 670-675.

INTRODUCTION: Although a variety of pharmacologic and non-pharmacologic treatments are effective for insomnia in the general population, insomnia in Parkinson's disease differs

in important ways and may need different treatments. No studies have conclusively demonstrated effective insomnia treatments in Parkinson's disease.

METHODS: We conducted a three-arm six-week randomized pilot study assessing non-pharmacologic treatment (cognitive behavioural therapy with bright light therapy) or doxepin (10 mg daily), compared to an inactive placebo in Parkinson's patients with insomnia. Sleep outcomes included insomnia scales, clinical global impression, sleep diaries and actigraphy. Secondary outcomes included motor severity, fatigue, depression and quality of life.

RESULTS: 18 patients were randomized, 6 to each group. Compared to placebo, doxepin improved the Insomnia Severity Index (-9 + 5.4 vs. -2 + 3.9, p = 0.03), the SCOPA-night score (-5.2 + 1.5 vs. -2.3 + 2.8, p = 0.049), the Pittsburgh Sleep Quality Index-sleep disturbances subscale (-0.5 + 0.5 vs 0.2 + 0.4, p = 0.02), and both patient and examiner-rated clinical global impression of change (1.7 + 0.8 vs. 0.5 + 0.8, p = 0.03 and 1.4 + 0.5 vs. 0.3 + 0.5, p = 0.003). On secondary outcomes doxepin reduced the fatigue severity scale (p = 0.02) and improved scores on the Montreal Cognitive Assessment (p = 0.007). Non-pharmacological treatment reduced the Insomnia Severity Index (-7.8 + 3.8 vs. -2.0 + 3.9, p = 0.03), and the examiner-reported clinical global impression of change (p = 0.006), but was associated with decline in Parkinson Disease Questionnaire-39. There were no changes in other primary and secondary outcomes, including actigraphy outcomes. Adverse events were comparable in all groups.

CONCLUSION: Doxepin and non-pharmacologic treatment substantially improved insomnia in Parkinson's disease. These potential benefits must be replicated in a full confirmatory randomized controlled trial. Crown Copyright 2013. Published by Elsevier Ltd. All rights reserved.

Roehrs, T. A., S. Randall, et al. (2012). "Twelve months of nightly zolpidem does not lead to rebound insomnia or withdrawal symptoms: a prospective placebo-controlled study." Journal of Psychopharmacology **26**(8): 1088-1095.

Rebound insomnia, worsened sleep when discontinuing use of a hypnotic, is reported in some short-term studies. No study has prospectively assessed, using patient reports or nocturnal polysomnography (NPSG), the likelihood of rebound insomnia with chronic hypnotic use. The objectives of this study was to assess in primary insomniacs the likelihood of experiencing rebound insomnia and a withdrawal syndrome on repeated placebo substitutions over 12 months of nightly zolpidem use. A group of 33 primary insomniacs, without psychiatric disorders or drug and alcohol abuse, 32-65 years old, 15 men and 18 women, were randomized to take zolpidem 10 mg (n = 17) or placebo (n = 16) nightly for 12 months. In probes during months 1, 4, and 12, placebo was substituted for 7 consecutive nights in both the zolpidem and placebo groups. NPSGs were collected and Tyrer Bezodiazepine Withdrawal Symptom Questionnaires were completed on the first two discontinuation nights. Rebound insomnia was not observed on the first two and the seventh discontinuation nights and its likelihood did not increase over the 12 months of nightly zolpidem use. Some individuals did show rebound insomnia, approximately 30-40% of participants, but the percentage of 'rebounders' did not differ between the placebo and zolpidem groups and did not increase across 12 months. No clinically significant withdrawal symptoms on the Tyrer were observed on the discontinuation nights over the 12 months of nightly use. Chronic nightly hypnotic use at therapeutic

doses by primary insomniacs does not lead to rebound insomnia or withdrawal symptoms.

Roehrs, T. A. and T. Roth (2016). "Gender Differences in the Efficacy and Safety of Chronic Nightly Zolpidem." Journal of Clinical Sleep Medicine 12(3): 319-325.

STUDY OBJECTIVES: Studies have shown pharmacokinetic differences for hypnotics in women compared to men, but few studies have assessed either short-or long-term differences in efficacy and safety.

METHODS: To evaluate gender differences in the efficacy and safety of chronic nightly zolpidem (10 mg), we did a post hoc assessment of a large clinical trial. In the trial, participants with primary insomnia (n = 89), ages 23-70, meeting DSM-IV-TR criteria for primary insomnia were randomized, double blind, to nightly zolpidem, 10 mg (n = 47) or placebo (n = 42) 30 minutes before bedtime nightly for 12 months. Polysomnographic sleep on 2 nights in months 1 and 8 and likelihood of next-day sleepiness, rebound insomnia, and dose escalation were evaluated in months 1, 4, and 12.

RESULTS: Relative to placebo, zolpidem significantly increased sleep efficiency and reduced sleep latency and wake after sleep onset assessed at months 1 and 8, with no differences in efficacy between women and men and no diminution of efficacy over months. On a next-day multiple sleep latency test (MSLT), no residual sedation was observed for either women or men. No rebound insomnia or dose escalation was seen with no gender differences in either.

CONCLUSIONS: In adults with primary insomnia, nightly zolpidem administration showed no gender differences in acute or chronic efficacy or in next-day sleepiness. Zolpidem remained efficacious and safe across 12 months. CLINCIAL TRIALS REGISTRATION: ClinicalTrials.gov Identifier: NCT01006525; Trial Name: Safety and Efficacy of Chronic Hypnotic Use; http://clinicaltrials.gov/ct2/show/NCT01006525.

Roth, T., S. G. Hull, et al. (2008). "Low-dose sublingual zolpidem tartrate is associated with dose-related improvement in sleep onset and duration in insomnia characterized by middle-of-the-night (MOTN) awakenings." Sleep **31**(9): 1277-1284.

STUDY OBJECTIVES: To evaluate the efficacy and safety of low-dose, sublingual zolpidem tartrate when taken during a scheduled middle-of-the-night (MOTN) awakening in subjects with insomnia characterized by difficulty returning to sleep following MOTN awakenings. DESIGN: Randomized, double-blind, placebo-controlled, 3-way crossover study.

METHODS: Each treatment period consisted of 2 consecutive nights of dosing separated by a washout of 5 to 12 days. Subjects were awakened 4 h after lights out, dosed with sublingual zolpidem tartrate (3.5 mg or 1.75 mg) or placebo, kept awake for 30 min, and then returned to bed for an additional 4 h. Sleep parameters were assessed by polysomnography (PSG) and post-sleep questionnaires. SETTING: Five sleep laboratories.

PARTICIPANTS: Adults (24 males, 58 females, mean age 45.9 y) with a diagnosis of DSM-IV primary insomnia and a history of prolonged MOTN awakenings. Baseline difficulties with MOTN awakenings were confirmed by a 10-day screening sleep diary and PSG screening.

RESULTS: Low-dose sublingual zolpidem tartrate demonstrated significant dose-related

decreases in latency to persistent sleep and total sleep time (P < 0.001) compared to placebo after MOTN dosing. All subject reports paralleled PSG observations. Neither dose showed next-morning impairment on the DSST or ratings of sleepiness. The 3.5-mg dose produced improvements in reports of sleep quality (P < 0.001), ability to function, and level of refreshed sleep (P < 0.05 for both dosages) compared to placebo. Sublingual zolpidem tartrate lozenges were generally safe and well tolerated.

CONCLUSIONS: Low-dose sublingual zolpidem tartrate may be suitable for treatment of patients who have difficulty resuming sleep after MOTN awakenings.

Roth, T., A. Krystal, et al. (2013). "Novel sublingual low-dose zolpidem tablet reduces latency to sleep onset following spontaneous middle-of-the-night awakening in insomnia in a randomized, double-blind, placebo-controlled, outpatient study." Sleep **36**(2): 189-196.

STUDY OBJECTIVES: To evaluate efficacy and safety of 3.5-mg zolpidem tartrate sublingual tablets (ZST) on latency to sleep onset after middle-of-the-night (MOTN) awakenings in patients with insomnia characterized by difficulty returning to sleep after MOTN awakenings.

DESIGN: Multicenter randomized, double-blind, placebo-controlled, parallel-group.

SETTING: Outpatient.

PATIENTS: There were 295 adults (median age 43 y; 68.1% female) with primary insomnia and difficulty returning to sleep after MOTN awakenings (three or more MOTN awakenings/wk during screening).

INTERVENTIONS: After a 2-wk, single-blind placebo eligibility period, participants were randomized 1:1 to as-needed MOTN dosing with 3.5 mg ZST or placebo for 28 nights. An interactive voice response system determined if the study drug could be taken and recorded sleep/wake efficacy measures.

RESULTS: ZST significantly (P < 0.0001) decreased latency to sleep onset over 4 wk (baseline 68.1 min; ZST 38.2 min) compared with placebo (baseline 69.4 min; placebo 56.4 min). Ratings of morning sleepiness/alertness significantly (P = 0.0041) favored the ZST group on nights medication was taken but not on other nights. Participants in the ZST group took the study drug on 62% of nights during the 4 wk; members of the placebo group took study medication on 64% of nights. Adverse events were generally mild and at the same rate (19.3% of participants) in both groups. There were no treatment-related serious adverse events (SAEs), and one adverse event-related study discontinuation from the placebo group. Dosing/week did not increase across the study.

CONCLUSIONS: 3.5 mg ZST used as needed significantly reduced latency to return to sleep in comparison with placebo in these patients with insomnia. Sleep quality was improved, and morning sleepiness/alertness scores also improved. ZST was well tolerated. These data demonstrate the utility of a sleep-promoting agent when used as needed in the MOTN.

CLINICAL TRIALS REGISTRATION: NCT00466193: "A Study of Zolpidem Tartrate Tablet in Adult Patients with Insomnia" http://www.clinicaltrials.gov/ct2/show/NCT00466193?spons=%22Transcept+Pharmaceuticals%22&spons_ex=Y&rank=2

Roth, T., et al. (2014). "Gender influences on efficacy and safety of sublingual zolpidem tartrate for middle-of-the-night awakening in insomnia." Human Psychopharmacology **29**(1): 25-30.

OBJECTIVE: Evaluate potential gender effects on efficacy and safety of a buffered zolpidem sublingual tablet (ZST) formulation.
METHODS: Post hoc analysis of the pivotal sleep laboratory and outpatient studies, per gender.
RESULTS: In the sleep laboratory study, polysomnography-derived latency to persistent sleep after middle-of-the-night was significantly improved for both genders at both 1.75mg and 3.5mg ZST (females: 15.7 and 8.6min, respectively, vs. 27.7min [placebo]; males: 19.0 and 12.7min vs. 29.0min [placebo]) with no significant gender differences. In the outpatient study, subjective sleep onset latency after middle-of-the-night was significantly shorter for both genders treated with ZST 3.5mg versus placebo over the 4-week average (females: 37.3 vs. 59.4min, $p<0.0001$; males: 38.6 vs. 55.1min, $p<0.01$). There were no gender differences in subjective sleep onset latency after middle-of-the-night awakening. In the outpatient study, weekly usage of ZST and placebo by both genders declined throughout the study. Morning alertness following dosing nights improved in both genders, although significant only in females. In both studies, there were no gender differences in adverse events.
CONCLUSION(S): Time to return to sleep after middle-of-the-night dosing with ZST improved in both genders, with no gender differences in efficacy and safety.

Sangal, R. B., et al. (2014). "Eszopiclone for insomnia associated with attention-deficit/hyperactivity disorder." Pediatrics **134**(4): e1095-1103.
OBJECTIVE: To evaluate efficacy and safety of eszopiclone compared with placebo in children and adolescents with insomnia associated with attention-deficit/hyperactivity disorder (ADHD).
METHODS: A 12-week, randomized, double-blind, placebo-controlled trial evaluated efficacy and safety of high- or low-dose eszopiclone (1 or 2 mg in children aged 6-11 years, 2 or 3 mg in children ages 12-17 years), given every evening, in 486 patients with ADHD-related insomnia. The primary efficacy variable was change in latency to persistent sleep from baseline to week 12, based on polysomnography. Key secondary measures were polysomnography-measured wake time after sleep onset, Clinical Global Impression Parent/Caregiver and Child scales, and the Conners' ADHD rating scales. The safety of eszopiclone was further studied over 1 year of open-label treatment in 55 patients who completed the double-blind study, and 249 patients with no previous eszopiclone exposure.
RESULTS: Neither low-dose nor high-dose eszopiclone significantly reduced latency to persistent sleep compared with placebo after 12 weeks of treatment. Secondary outcomes were considered nonsignificant based on the hierarchical statistical analysis plan. The most frequent treatment-emergent adverse events over 12 weeks with eszopiclone were headache, dysgeusia, and dizziness. The study results demonstrated that eszopiclone was well tolerated over 1 year of treatment, with 11.2% of patients discontinuing open-label treatment because of an adverse event.
CONCLUSIONS: Eszopiclone (up to 3 mg) failed to reduce latency to persistent sleep on polysomnography after 12 weeks in children aged 6 to 17 years with ADHD-related insomnia. Eszopiclone was well tolerated in the 1-year study.

Spierings, E. L., et al. (2015). "Efficacy of treatment of insomnia in migraineurs with eszopiclone (Lunesta) and its effect on total sleep time, headache frequency, and daytime functioning: A randomized, double-blind, placebo-controlled, parallel-group, pilot study." Cranio 33(2): 115-121.

AIMS: A review on headache and insomnia revealed that insomnia is a risk factor for increased headache frequency and headache intensity in migraineurs. The authors designed a randomized, double blind, placebo-controlled, parallel-group, pilot study in which migraineurs who also had insomnia were enrolled, to test this observation.
METHODOLOGY: In the study, the authors treated 79 subjects with IHS-II migraine with and/or without aura and with DSM-IV primary insomnia for 6 weeks with 3 mg eszopiclone (Lunesta()) or placebo at bedtime. The treatment was preceded by a 2-week baseline period and followed by a 2-week run-out period.
RESULTS: Of the 79 subjects treated, 75 were evaluable, 35 in the eszopiclone group, and 40 in the placebo group. At baseline, the groups were comparable except for sleep latency. Of the three remaining sleep variables, total sleep time, nighttime awakenings, and sleep quality, the number of nighttime awakenings during the 6-week treatment period was significantly lower in the eszopiclone group than in the placebo group (P = 0.03). Of the three daytime variables, alertness, fatigue, and functioning, this was also the case for fatigue (P = 005). The headache variables, frequency, duration, and intensity, did not show a difference from placebo during the 6-week treatment period.
CONCLUSIONS: The study did not meet primary endpoint, that is, the difference in total sleep time during the 6-week treatment period between eszopiclone and placebo was less than 40 minutes. Therefore, it failed to answer the question as to whether insomnia is, indeed, a risk factor for increased headache frequency and headache intensity in migraineurs.

Tek, C., et al. (2014). "The impact of eszopiclone on sleep and cognition in patients with schizophrenia and insomnia: a double-blind, randomized, placebo-controlled trial." Schizophrenia Research 160(1-3): 180-185.

BACKGROUND: Insomnia is frequent in schizophrenia and may contribute to cognitive impairment as well as overuse of weight inducing sedative antipsychotics. We investigated the effects of eszopiclone on sleep and cognition for patients with schizophrenia-related insomnia in a double-blind placebo controlled study, followed by a two-week, single-blind placebo phase.
METHODS: Thirty-nine clinically stable outpatients with schizophrenia or schizoaffective disorder and insomnia were randomized to either 3mg eszopiclone (n=20) or placebo (n=19). Primary outcome measure was change in Insomnia Severity Index (ISI) over 8 weeks. Secondary outcome measure was change in MATRICS Consensus Cognitive Battery (MATRICS). Sleep diaries, psychiatric symptoms, and quality of life were also monitored.
RESULTS: ISI significantly improved more in eszopiclone (mean=-10.7, 95% CI=-13.2; -8.2) than in placebo (mean=-6.9, 95% CI=-9.5; -4.3) with a between-group difference of -3.8 (95% CI=-7.5; -0.2). MATRICS score change did not differ between groups. On further analysis there was a significant improvement in the working memory test, letter-number span component of MATRICS (mean=9.8+/-9.2, z=-2.00, p=0.045) only for subjects with schizophrenia on eszopiclone. There were improvements in sleep diary items in both groups with no between-group differences. Psychiatric symptoms remained stable. Discontinuation rates were similar. Sleep remained improved during single-blind placebo phase after eszopiclone was stopped, but the working memory improvement in patients with schizophrenia was not durable.

CONCLUSIONS: Eszopiclone stands as a safe and effective alternative for the treatment of insomnia in patients with schizophrenia. Its effects on cognition require further study.

Uchimura, N., A. Ogawa, et al. (2011). "Efficacy and safety of ramelteon in Japanese adults with chronic insomnia: a randomized, double-blind, placebo-controlled study." Expert Review of Neurotherapeutics **11**(2): 215-224.

This randomized, double-blind, placebo-controlled study assessed the efficacy and safety of ramelteon 4 and 8 mg in Japanese adults with chronic insomnia. A secondary objective was to evaluate efficacy and safety when doses were uptitrated from placebo, ramelteon 4 and 8 mg to 4, 8 and 16 mg, respectively. Patient-reported sleep data were collected using sleep diaries. There was no statistically significant difference between ramelteon and placebo in the change in subjective sleep latency (sSL) in the full analysis set (n = 1130). Significant improvement was observed in the change in subjective total sleep time with ramelteon 8 mg at week 1. In post hoc analyses, ramelteon 8 mg reduced sSL in individuals with smaller fluctuations (within +/-30 min) of sSL at baseline, in those with a shorter (<1 year) history of insomnia and in individuals who had not used benzodiazepines. Ramelteon up to 16 mg nightly was safe and well tolerated.

Uchiyama, M., M. Hamamura, et al. (2011). "Long-term safety and efficacy of ramelteon in Japanese patients with chronic insomnia." Sleep Medicine **12**(2): 127-133.

OBJECTIVE: To evaluate the safety of ramelteon, a highly selective MT1/MT2 melatonin receptor agonist, during 24 weeks' treatment of Japanese patients with chronic insomnia.

METHODS: In a single-blind, flexible-titration, multicenter study incorporating placebo run-in and run-out periods, 190 adults with chronic insomnia received ramelteon 4 or 8 mg, titrated up to 16 mg if necessary, for 24 weeks. Primary endpoints included adverse events, residual effects, rebound insomnia, withdrawal symptoms, and dependence. Secondary endpoints included subjective sleep latency and total sleep time.

RESULTS: Drug-related adverse events occurred in 11.6% of patients. No clinically important changes occurred in biochemical, hematological or endocrine parameters. There were no signs of next-day residual effect, rebound insomnia, withdrawal symptoms or dependence. Mean subjective sleep latency decreased significantly, and total sleep time increased significantly; both reached a plateau by week 20 and were sustained thereafter ($P<0.0001$).

CONCLUSIONS: Ramelteon was well tolerated in adult Japanese patients with chronic insomnia and did not cause deterioration of efficacy, residual effects, rebound insomnia, withdrawal symptoms, or dependence after 24 weeks' treatment.

Uchiyama, M., M. Hamamura, et al. (2011). "Evaluation of subjective efficacy and safety of ramelteon in Japanese subjects with chronic insomnia." Sleep Medicine **12**(2): 119-126.

OBJECTIVE: To assess patient-reported efficacy and safety of ramelteon in Japanese patients with chronic insomnia.

METHODS: Randomized, double-blind, placebo-controlled, multicenter trial. After a placebo lead-in period, 987 adults with chronic insomnia received ramelteon 8 mg or placebo once daily for 2 weeks, followed by a placebo run-out period to monitor rebound

insomnia. Patient-reported sleep data were collected using sleep diaries.
RESULTS: Ramelteon significantly reduced mean patient-reported sleep latency (primary endpoint) compared with placebo during week 1 (-4.54 min; p=0.001). Ramelteon maintained greater efficacy in sleep latency than placebo at week 2, but the difference did not achieve statistical significance. In a subset of patients who adhered to treatment and completed their diaries as instructed, a statistically significant reduction in subjective sleep latency was sustained through week 2. Compared with placebo, ramelteon also significantly improved mean total sleep time and mean sleep quality during week 1, the number of awakenings during week 2, and overall patient global impression scores. There was no evidence of rebound insomnia. Adverse events were generally mild and transient.
CONCLUSIONS: In Japanese adults with chronic insomnia, ramelteon 8 mg significantly reduced patient-reported sleep latency, increased total sleep time and improved sleep quality after 1 week of treatment. Ramelteon was generally well tolerated with no rebound insomnia.

Wang-Weigand, S., M. McCue, et al. (2009). "Effects of ramelteon 8 mg on objective sleep latency in adults with chronic insomnia on nights 1 and 2: pooled analysis." Current Medical Research & Opinion **25**(5): 1209-1213.
OBJECTIVE: Ramelteon is an MT(1)/MT(2) melatonin receptor agonist indicated for the treatment of insomnia characterized by difficulty with sleep onset. In previous clinical studies, ramelteon reduced latency to persistent sleep (LPS) in subjects with chronic insomnia. The goal of the current analysis was to determine the average reduction in LPS and overall adverse event profile for subjects taking ramelteon 8 mg.
RESEARCH DESIGN AND METHODS: This pooled analysis examined four randomized, double-blind, placebo-controlled clinical trials of ramelteon in subjects with chronic insomnia. The analysis included adults (age 18-83 years) with chronic insomnia who took ramelteon 8 mg or placebo. The primary endpoint of each trial was mean LPS, measured by polysomnography (PSG) on nights 1 and 2. Adverse events were collected for all subjects for the duration of each trial.
RESULTS: Efficacy data were available for 566 subjects who took ramelteon 8 mg (mean age 46.7 years) and 556 subjects who took placebo (mean age 47.8 years). Mean LPS at baseline was 66.6 min for the placebo group and 66.9 min for the ramelteon group. At nights 1 and 2, mean LPS for the ramelteon 8 mg group (30.2 min) was significantly less than the mean LPS for the placebo group (43.3 min). The least squares mean difference from placebo was -13.1 min ($p < 0.001$). Headache (8.9% ramelteon 8 mg, 8.8% placebo) and somnolence (3.5% ramelteon 8 mg, 0.7% placebo) were the most common adverse events.
CONCLUSIONS: Ramelteon 8 mg, on average, reduced LPS by approximately 13 min more than placebo on nights 1 and 2 of treatment in adults with chronic insomnia. Ramelteon was well tolerated with a low incidence of adverse events. This mean reduction in LPS versus placebo is similar to what has been reported for other classes of insomnia medications. However, these results reflect nights 1 and 2 of treatment and may not be representative of longer treatments.

*Shading indicates trials identified in this scan. Others were identified in previous preliminary update scans.