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Month/Year of Review: March 2012
PDL Class: Sedative Hypnotics

Date of Last Review: October 2008
Source Document: DERP

Current Preferred Agents:
Zolpidem tartrate
Trazodone
Mirtazapine
Diphenydramine
Tricyclic Antidepressants

Current Non-Preferred Agents:

Benzodiazepines	Non-Benzodiazepines
Flurazepam	Zolpidem tartrate (Ambien CR®)
Temazepam	Zolpidem tartrate (Zolpimist spray®)
Quazapam (Doral®)	Zolpidem sublingual (Edluar®)
Estazolam	Zaleplon
Triazolam	Eszopiclone (Lunesta®)
	Ramelteon (Rozerem®)

Previous Recommendations:
- There is good quality evidence that zaleplon and zolpidem are similarly effective for subjective sleep latency .
- There is no comparative evidence in children.
- There is fair quality evidence that there is no significant difference between zolpidem and eszopiclone on measured sleep outcomes.
- There is fair quality evidence that there is no difference in rates of withdrawals due to adverse events between the newer sedative hypnotics.
- There is no comparative evidence about long-term safety.
- There is fair to poor quality evidence that the efficacy of zolpidem and zaleplon was similar in older and younger adults, although somnolence was more common with zolpidem in older adults.
- The risk of hip fracture in older women was increased with the use of zolpidem compared to both non-use and use of benzodiazepines.
- No evidence that one newer insomnia drug is safer or more effective in any subgroup based on gender or race was found.

PA Criteria: Treatment of uncomplicated insomnia is not covered, but insomnia contributing to a covered comorbid condition is. A benzodiazepine quantity limit PA is required for a quantity exceeding 15 doses/30 days. A prior authorization is in place to prevent duplicate sedative use requiring PA when a client is receiving two oral sedative medications at the same time.

Methods
Two scans were completed by the Oregon Evidence-based Practice Center Drug Effectiveness Review project which included a literature search through September 2010. The 2009 scan identified 5 potentially relevant new trials (Appendix A). None of these were head-to-head trials. The 2010 DERP scan resulted in another 5 potentially relevant new trials (Appendix B). These included placebo-controlled trials of eszopiclone in elderly patients, patients with comorbid depression, and women with menopausal symptoms; and one placebo-controlled trial of zolpidem compared to placebo. A head-to-head trial of sublingual zolpidem compared to oral zolpidem was also identified. A MEDLINE OVID search was conducted using all treatments for insomnia and limited to randomized controlled trials and meta-analysis, English language, and conducted in humans from October 2010 (date from last DERP scan) to current. The Agency for

Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Trials:

A total of 25 citations resulted from initial literature search. After inclusion for further review, 18 were evaluated further and nine potentially relevant randomized trials were identified (Appendix C). These trials are briefly described in table 1.

Table 1: Potentially relevant new trials

Study	Comparison	Population	Primary Outcome	Results	
Krystal, 2011[1] RCT, DB, PG, PC	Doxepin 3mg, Doxepin 6mg, placebo	Primary Insomnia	Wake time after sleep onset (WASO)	<u>WASO at night 1</u> 3mg: 41 minutes 6mg: 36 minutes Pl: 67 minutes P<0.001 for both doses vs. placebo	<u>WASO at night 29</u> 3mg: 47 minutes 6mg: 41minutes Pl: 61 minutes P=0.0025 3mg P=0.0009 6mg
Pollack, 2011[2] RCT, DB, PC, CO	Eszoplicone 3mg vs. placebo	Post-traumatic stress disorder associated insomnia	Changes in scores on the Short PTSD Rating Interview and Pittsburgh Sleep Quality Index (PSQI)	<u>Reduction in PSQI score</u> E: -3.2 P: -0.87 P=0.011	
Fava, 2011[3] RCT, DB, PC, PG	Zolpidem ER 12.5mg vs. placebo + open label escitalopram 10mg	Insomnia associated with major depressive disorder	Change from baseline in subjective total sleep time at week 8	<u>Least Squares mean difference :</u> Z: 100 min P: 58 min P<0.001 The superiority of zolpidem ER (P<0.05) was maintained through week 16 but not at weeks 20 and 24.	
Fava, 2011[4] Post Hoc Analysis	Eszoplicone 3mg + SSRI vs. placebo + SSRI	Insomnia associated with anxious depression	Mean improvements from baseline Insomnia Severity Index (ISI) scores	<u>Mean improvement in ISI total score at week 8:</u> E + SSRI: -10.9 ± 6.8 P+ SSRI: -8.5 ± 7.4 P<0.001	
Roth, 2010[5] RCT, DB, PC, PG	Doxepin 6 mg versus placebo	Induced transient insomnia in healthy adults	Latency to persistent sleep	<u>Latency to persistent sleep:</u> D: 21 minutes P: 34 minutes P<0.001	
Huang, 2011[6] RCT, DB,	Zaleplon 10mg vs. zolpidem 10mg	Primary Insomnia	Change in sleep latency from baseline to week 2	No statistically significant difference was observed in sleep latency (p=0.084), sleep duration (p=0.868), or number of awakenings (p=0.637) at week 2.	
McElroy, 2011[7] RCT, PC, DB	Ramelteon 8mg vs. placebo	Bipolar 1 disorder with manic symptoms and sleep disturbance	Change in Pittsburgh Insomnia Rating Scale (PIRS)	patients receiving ramelteon had a similar rate of reduction in mean total PIRS scores compared to patients receiving placebo (p=0.59) *38% overall attrition rate	
Gooneratne, 2010[8] RCT, PG,	Ramelteon 8mg versus placebo	≥ 60 years old with obstructive sleep apnea	Change in sleep onset latency at 4 weeks.	<u>Sleep Onset Latency:</u> R: -10.7 min P: 17.8 min	

DB	N=27			P=0.008 Mean Difference 28.5 m 95% CI (8.5 to 48.6) * neither objective nor subjective sleep efficiency differed significantly between study arms.
Krystal, 2010[9] RCT, DB, PC, PG	Doxepin 1mg vs. doxepin 3mg vs. placebo N=240	Elderly patients with chronic primary insomnia	Wake time after sleep onset (WASO) on night 1	<u>Mean WASO at night 1</u> 1mg: 91.8 minutes 3mg: 74.5 minutes Pl: 108.9 minutes P=0.0053 for 1mg ; P<0.001 for 3mg vs. placebo

New drugs:
None

New Dosage forms/New Indications:
Doxepin hydrochloride (Silenor®) was FDA approved in March 2010 for the treatment of insomnia characterized by difficulties with sleep maintenance. Approved doses are 6 mg for adults and 3 mg for elderly patients. Doxepin was originally developed as a Tricyclic antidepressant but also exhibits sedative properties.

A sublingual form of zolpidem tartrate (Edluar®) was approved by the FDA in March 2009 for the treatment of insomnia characterized by difficulty with sleep initiation.

An oral spray form of zolpidem tartrate (Zolpimist®) was approved by the FDA in December 2008 for the treatment of insomnia characterized by difficulty with sleep initiation.

New FDA Indications:
None

New FDA safety alerts:
None

New Systematic Reviews:
None

Evidence-based Clinical Guidelines:
The American Academy of Sleep Medicine 2008 treatment guidelines for primary insomnia do not distinguish amongst the agents in this review.[10] There are considerations to be made for individual patients, but there is no clear agent for the population at large.

Recommendations:
1. No further research or review needed.
2. Make doxepin (Silenor) non-preferred due to lack of data showing doxepin to be superior to other agents in this class.
3. Maintain specialized formulations of zolpidem (Edluar and Zolpimist) non- preferred due to no significant clinical advantage over tablets.

Appendix A: potentially relevant trials from 2009 DERP Scan (n=5)

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): e770-6.
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): 222-30.
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.

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): 351-60.
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.

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): 2005-15.

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): 623-41.

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.

Appendix B: Potentially relevant new trials from 2010 DERP scan (n=5)

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): 225-34.

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

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): 705-12.

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.

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.e1-171.e11.
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.

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): 322-9.
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.

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): 1423-31.
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 patient

Appendix C : Relevant new trials from current scan (n=9)

1. **Krystal AD, Lankford A, Durrence HH, Ludington E, Jochelson P, Rogowski R, Roth T. Efficacy and safety of doxepin 3 and 6 mg in a 35-day sleep laboratory trial in adults with chronic primary insomnia. Sleep. 2011 Oct 1;34(10):1433-42.**

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

2. **Pollack MH, Hoge EA, Worthington JJ, Moshier SJ, Wechsler RS, Brandes M, Simon NM. Eszopiclone for the treatment of posttraumatic stress disorder and associated insomnia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2011 Jul;72(7):892-7. Epub 2011 Feb 22.**

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.

3. **Fava M, Asnis GM, Shrivastava RK, Lydiard B, Bastani B, Sheehan DV, Roth T. 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. J Clin Psychiatry. 2011 Jul;72(7):914-28. Epub 2010 Dec 28.**

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 ($P \leq .0003$), 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.

4. **Fava M, Schaefer K, Huang H, Wilson A, Iosifescu DV, Mischoulon D, Wessel TC. 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. J Clin Psychiatry. 2011 Apr;72(4):473-9. Epub 2010 Nov 2.**

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.

5. **Roth T, Heith Durrence H, Jochelson P, Peterson G, Ludington E, Rogowski R, Scharf M, Lankford A. Efficacy and safety of doxepin 6 mg in a model of transient insomnia. Sleep Med. 2010 Oct;11(9):843-7.**

INTRODUCTION: The efficacy and safety of doxepin (DXP) 6mg tablets were evaluated in healthy adults in a model of transient insomnia. METHODS: This was a randomized, double-blind, parallel-group, placebo-controlled study in healthy adults using a model of transient insomnia. A first-night effect combined with a 3-h phase advance was implemented to induce transient insomnia in healthy adults. Subjects received a single night time dose of placebo (PBO; N=282) or DXP 6mg (N=283) in a sleep laboratory. Efficacy was evaluated objectively (polysomnography; PSG) and subjectively (morning questionnaire). Consistent with the model utilized, the primary endpoint was latency to persistent sleep (LPS); secondary PSG endpoints included wake after sleep onset (WASO; key secondary endpoint), total sleep time (TST), wake time after sleep (WTAS) and sleep efficiency (SE; overall, by quarter of the night and hourly); secondary subjective endpoints included latency to sleep onset (LSO), subjective WASO (sWASO), subjective TST (sTST) and sleep quality. RESULTS: DXP 6mg demonstrated statistically significant improvements in LPS (13min decrease versus PBO; p<0.0001), WASO (39min less than PBO; p<0.0001), TST (51min more than PBO; p<0.0001), WTAS (p<0.0001), overall SE (p<0.0001), SE in each quarter of the night (p<0.0001) and SE in each of the 8h (p□0.0003), all versus PBO. Additionally, DXP 6mg significantly improved subjective variables including LSO (p<0.0001), sWASO (p=0.0063), sTST (p<0.0001), and sleep quality (p=0.0004), versus PBO. There was no consistent evidence of next-day residual sedation and also minor sleep stages alterations. The incidence of adverse events was comparable to placebo. CONCLUSIONS: In this model of transient insomnia, DXP 6mg demonstrated significant improvements in sleep onset, sleep maintenance, sleep duration and sleep quality, and also appeared to reduce early morning awakenings. These data suggest that DXP 6mg may be effective and well tolerated in adults experiencing transient insomnia.

6. **Huang YS, Hsu SC, Liu SI, Chen CK. 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 Med J. 2011 Jan-Feb;34(1):50-6.**

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.

7. **McElroy SL, Winstanley EL, Martens B, Patel NC, Mori N, Moeller D, McCoy J, Keck PE Jr. A randomized, placebo-controlled study of adjunctive ramelteon in ambulatory bipolar I disorder with manic symptoms and sleep disturbance. Int Clin Psychopharmacol. 2011 Jan;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.

8. **Gooneratne NS, Gehrman P, Gurubhagavatula I, Al-Shehabi E, Marie E, Schwab R. Effectiveness of ramelteon for insomnia symptoms in older adults with obstructive sleep apnea: a randomized placebo-controlled pilot study. J Clin Sleep Med. 2010 Dec 15;6(6):572-80.**

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.

9. **Krystal AD, Durrence HH, Scharf M, Jochelson P, Rogowski R, Ludington E, Roth T. 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. 2010 Nov;33(11):1553-61.**

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.

Additional References:

10. Schutte-Rodin S; Broch L; Buysse D; Dorsey C; Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008;4(5):487–504.