

## Appendix A. Search Strategy

Database: Ovid MEDLINE(R) <1946 to February Week 1 2013> Search Strategy:

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- 1 exp \*"Sleep Initiation and Maintenance Disorders"/ (5552)
- 2 insomnia.ti. (3462)
- 3 1 or 2 (5740)
- 4 exp Review Literature as Topic/ (6543)
- 5 Meta-Analysis/ (37251)
- 6 Meta-Analysis as Topic/ (12410)
- 7 Randomized Controlled Trials as Topic/ (83071)
- 8 randomized controlled trial/ (339841)
- 9 Random Allocation/ (76254)
- 10 clinical trial/ (473513)
- 11 clinical trial, phase i.pt. (12623)
- 12 clinical trial, phase ii.pt. (20260)
- 13 clinical trial, phase iii.pt. (7497)
- 14 clinical trial, phase iv.pt. (765)
- 15 controlled clinical trial.pt. (85159)
- 16 randomized controlled trial.pt. (339841)
- 17 multicenter study.pt. (150617)
- 18 clinical trial.pt. (473513)
- 19 exp Clinical Trials as topic/ (261069)
- 20 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (965823)
- 21 3 and 20 (1353)

Database: Embase <1974 to 2013 October 04> Search Strategy:

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- 1 retracted article/ (6992)
  - 2 (random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab. (964574)
  - 3 (animal\$ not human\$).sh,hw. (3893182)
  - 4 (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/  
(4027061)
  - 5 1 or 2 (971416)
  - 6 5 not (3 or 4) (788461)
  - 7 exp cohort analysis/ (159907)
  - 8 exp longitudinal study/ (65140)
  - 9 exp prospective study/ (251281)
  - 10 exp follow up/ (749189)
  - 11 cohort\$.tw. (363952)
  - 12 7 or 8 or 9 or 10 or 11 (1281955)
  - 13 exp case-control study/ (90182)
  - 14 (case\$ and control\$).tw. (421121)
  - 15 13 or 14 (455401)
  - 16 (case\$ and series).tw. (156716)
  - 17 exp review/ (2051906)
  - 18 (literature adj3 review\$).ti,ab. (210256)
  - 19 exp meta analysis/ (76138)
  - 20 exp "Systematic Review"/ (64808)
  - 21 17 or 18 or 19 or 20 (2235446)
  - 22 (medline or embase or pubmed or cinahl or amed or psychlit or psychinfo or scisearch or  
cochrane).ti,ab. (99548)
  - 23 retracted article/ (6992)
  - 24 22 or 23 (106493)
  - 25 21 and 24 (78872)
  - 26 (systematic\$ adj2 (review\$ or overview)).ti,ab. (66334)
  - 27 (meta?anal\$ or meta anal\$ or metaanal\$ or metanal\$).ti,ab. (75213)
  - 28 25 or 26 or 27 (159414)
  - 29 (ae or si or to or co).fs. (3025811)
  - 30 (safe or safety).ti,ab. (597679)
  - 31 side effect\$.ti,ab. (238469)
  - 32 ((adverse or undesireable or harm\$ or serious or toxic) adj3 (effect\$ or reaction\$ or event\$ or  
outcome\$)).ti,ab.  
(406840)
  - 33 exp adverse drug reaction/ (358500)
  - 34 exp drug toxicity/ (77733)
  - 35 exp intoxication/ (328807)
  - 36 exp drug safety/ (221088)
  - 37 exp drug monitoring/ (40455)
  - 38 exp drug hypersensitivity/ (49261)
  - 39 exp postmarketing surveillance/ (22411)
  - 40 exp phase iv clinical trial/ (1496)
  - 41 (toxicity or complication\$ or noxious or tolerability).ti,ab. (1146601)
  - 42 exp postoperative complication/ (478900)

43 exp peroperative complication/ (19583)  
44 or/29-43 (4748365)  
45 6 or 12 or 28 or 44 (6056103)  
46 insomnia.ti. (5775)  
47 exp \*insomnia/ (10897)  
48 46 or 47 (11163)  
49 45 and 48 (5674)  
50 limit 49 to (book or book series or conference abstract or conference proceeding or "conference review" or editorial or erratum or letter or note or short survey or trade journal) (768)  
51 49 not 50 (4906)  
52 limit 51 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) (316)  
53 limit 52 to (adult <18 to 64 years> or aged <65+ years>) (162)  
54 51 not 52 (4590)  
55 54 or 53 (4752)  
56 55 and 28 (181) **SRs**  
57 55 and 6 (1745) **rcts**

**Appendix B. Excluded Studies** Appendix C. Excluded Studies<sup>1-250, 251-414</sup>

1. Abramowitz EG, Barak Y, Ben-Avi I, et al. Hypnotherapy in the treatment of chronic combat-related PTSD patients suffering from insomnia: a randomized, zolpidem-controlled clinical trial. *International Journal of Clinical & Experimental Hypnosis*. 2008 Jul;56(3):270-80. PMID 18569138. *Excluded Population*
2. Al-Shamma HA, Anderson C, Chuang E, et al. Nelotanserin, a novel selective human 5-hydroxytryptamine<sub>2A</sub> inverse agonist for the treatment of insomnia. *Journal of Pharmacology & Experimental Therapeutics*. 2010 Jan;332(1):281-90. PMID 19841476. *Not Insomnia Disorder*
3. Altena E, Van Der Werf YD, Sanz-Arigita EJ, et al. Prefrontal hypoactivation and recovery in insomnia. *Sleep*. 2008 01 Sep;31(9):1271-6. PMID 2008427985. *Not RCT*
4. Ancolio C, Tardieu S, Soubrouillard C, et al. A randomized clinical trial comparing doses and efficacy of lormetazepam tablets or oral solution for insomnia in a general practice setting. *Human Psychopharmacology*. 2004 Mar;19(2):129-34. PMID 14994324. *Interventions not available in the U.S.*
5. Anonymous. Ambien CR for insomnia. *Obstetrics & Gynecology*. 2006 Apr;107(4):944-6. PMID 16582137. *Not RCT*
6. Anonymous. [Sleep disorder as alarm symptom]. *MMW Fortschritte der Medizin*. 2007 Oct 25;149(43):54-5. PMID 17992908. *Not Insomnia Disorder*
7. Anonymous. Optimal treatment for persistent insomnia. *Journal of the National Medical Association*. 2009 August;101(8):821-2. PMID 2009468758. *Not RCT*
8. Anonymous. [Melatonin agonist causes amplitude increase of the internal clock: for a productive day after a good night]. *MMW Fortschritte der Medizin*. 2009 Mar 26;151(13):85. PMID 19504828. *Not Available in English*
9. Anonymous. Low-dose sublingual zolpidem (Intermezzo) for insomnia due to middle-of-the-night awakening. *Medical Letter on Drugs & Therapeutics*. 2012 Apr 2;54(1387):25-6. PMID 22469649. *Not RCT*
10. Anonymous. [Valerian and hops complement each other well]. *MMW Fortschritte der Medizin*. 2012 Jan 19;154(1):59. PMID 22642008. *Not Available in English*
11. Arigo D, Smyth JM. The benefits of expressive writing on sleep difficulty and appearance concerns for college women. *Psychology & Health*. 2012;27(2):210-26. PMID 21678167. *Not Insomnia Disorder*

12. Arnedt JT, Conroy DA, Armitage R, et al. Cognitive-behavioral therapy for insomnia in alcohol dependent patients: a randomized controlled pilot trial. *Behaviour Research & Therapy*. 2011 Apr;49(4):227-33. PMID 21377144. *Excluded Population*
13. Baier PC. [How well do Z-substances help in insomnia?]. *MMW Fortschritte der Medizin*. 2013 Jun 27;155(12):30. PMID 23923306. *Not Available in English*
14. Baron KG, Corden M, Jin L, et al. Impact of psychotherapy on insomnia symptoms in patients with depression and multiple sclerosis. *Journal of Behavioral Medicine*. 2011 Apr;34(2):92-101. PMID 20809354. *Excluded Population*
15. Bazil CW, Dave J, Cole J, et al. Pregabalin increases slow-wave sleep and may improve attention in patients with partial epilepsy and insomnia. *Epilepsy & Behavior*. 2012 Apr;23(4):422-5. PMID 22424859. *Excluded Population*
16. Belanger L, Morin CM, Bastien C, et al. Self-efficacy and compliance with benzodiazepine taper in older adults with chronic insomnia. *Health Psychology*. 2005 May;24(3):281-7. PMID 15898864. *Excluded Population*
17. Bell IR, Howerter A, Jackson N, et al. Effects of homeopathic medicines on polysomnographic sleep of young adults with histories of coffee-related insomnia. *Sleep Medicine*. 2011 May;12(5):505-11. PMID 20673648. *Excluded Population*
18. Bell IR, Howerter A, Jackson N, et al. Nonlinear dynamical systems effects of homeopathic remedies on multiscale entropy and correlation dimension of slow wave sleep EEG in young adults with histories of coffee-induced insomnia. *Homeopathy: the Journal of the Faculty of Homeopathy*. 2012 Jul;101(3):182-92. PMID 22818237. *Not Insomnia Disorder*
19. Belleville G, Guay C, Guay B, et al. Hypnotic taper with or without self-help treatment of insomnia: a randomized clinical trial. *Journal of Consulting & Clinical Psychology*. 2007 Apr;75(2):325-35. PMID 17469890. *Excluded Population*
20. Belleville G, Morin CM. Hypnotic discontinuation in chronic insomnia: impact of psychological distress, readiness to change, and self-efficacy. *Health Psychology*. 2008 Mar;27(2):239-48. PMID 18377143. *Not RCT*
21. Berger AM, Kuhn BR, Farr LA, et al. Behavioral therapy intervention trial to improve sleep quality and cancer-related fatigue. *Psycho-Oncology*. 2009 Jun;18(6):634-46. PMID 19090531. *Excluded Population*
22. Berry RB, Patel PB. Effect of zolpidem on the efficacy of continuous positive airway pressure as treatment for obstructive sleep apnea. *Sleep*. 2006 Aug;29(8):1052-6. PMID 16944674. *Excluded Population*

23. Bettica P, Squassante L, Groeger JA, et al. Differential effects of a dual orexin receptor antagonist (SB-649868) and zolpidem on sleep initiation and consolidation, SWS, REM sleep, and EEG power spectra in a model of situational insomnia. *Neuropsychopharmacology*. 2012 Apr;37(5):1224-33. PMID 22237311. *Interventions not available in the U.S.*
24. Bettica P, Squassante L, Zamuner S, et al. The orexin antagonist SB-649868 promotes and maintains sleep in men with primary insomnia. *Sleep*. 2012 01 Aug;35(8):1097-104. PMID 2012457085. *Interventions not available in the U.S.*
25. Blin O, Micallef J, Audebert C, et al. A double-blind, placebo- and flurazepam-controlled investigation of the residual psychomotor and cognitive effects of modified release zolpidem in young healthy volunteers. *Journal of Clinical Psychopharmacology*. 2006 June;26(3):284-9. PMID 2006257349. *Inadequate Duration*
26. Bliwise DL. The pit (of sleeplessness) and the pendulum (of regulation). *Sleep Medicine*. 2010 Jan;11(1):7-8. PMID 19945339. *Not RCT*
27. Bon O. Low-dose Trazodone Effective in Insomnia. *Pharmacopsychiatry*. 2005 Sep;38(5):226. *Inadequate Duration*
28. Botteman MF, Ozminkowski RJ, Wang S, et al. Cost effectiveness of long-term treatment with eszopiclone for primary insomnia in adults: A decision analytical model. *CNS Drugs*. 2007;21(4):319-34. PMID 2007187656. *Not RCT*
29. Botteman MF, Ozminkowski RJ, Wang S, et al. Cost effectiveness of long-term treatment with eszopiclone for primary insomnia in adults: a decision analytical model.[Erratum appears in *CNS Drugs*. 2006;21(5):405]. *CNS Drugs*. 2007;21(4):319-34. PMID 17381185. *Not RCT*
30. Boyle J, Danjou P, Alexander R, et al. Tolerability, pharmacokinetics and night-time effects on postural sway and critical flicker fusion of gaboxadol and zolpidem in elderly subjects. *British Journal of Clinical Pharmacology*. 2009 February;67(2):180-90. PMID 2009098251. *Inadequate Duration*
31. Boyle J, Trick L, Johnsen S, et al. Next-day cognition, psychomotor function, and driving-related skills following nighttime administration of eszopiclone. *Human Psychopharmacology*. 2008 Jul;23(5):385-97. PMID 18350566. *Inadequate Duration*
32. Brandao LC, Hachul H, Bittencourt LR, et al. Effects of isoflavone on oxidative stress parameters and homocysteine in postmenopausal women complaining of insomnia. *Biological Research*. 2009;42(3):281-7. PMID 19915736. *No outcomes of interest*
33. Britton WB, Haynes PL, Fridel KW, et al. Mindfulness-based cognitive therapy improves polysomnographic and subjective sleep profiles in antidepressant users with sleep complaints. *Psychotherapy & Psychosomatics*. 2012;81(5):296-304. PMID 22832540. *Not Insomnia Disorder*

34. Brooks AJ, Bell IR, Howerter A, et al. Effects of homeopathic medicines on mood of adults with histories of coffee-related insomnia. *Forschende Komplementarmedizin* (2006). 2010 Oct;17(5):250-7. PMID 20980764. *Excluded Population*
35. Brower KJ, Myra Kim H, Strobbe S, et al. A randomized double-blind pilot trial of gabapentin versus placebo to treat alcohol dependence and comorbid insomnia. *Alcoholism: Clinical & Experimental Research*. 2008 Aug;32(8):1429-38. PMID 18540923. *Excluded Population*
36. Buckley T, Duggal V, Schatzberg AF. The acute and post-discontinuation effects of a glucocorticoid receptor (GR) antagonist probe on sleep and the HPA axis in chronic insomnia: a pilot study. *Journal of Clinical Sleep Medicine*. 2008 Jun 15;4(3):235-41. PMID 18595436. *Not a valid comparison*
37. Bush AL, Armento ME, Weiss BJ, et al. The Pittsburgh Sleep Quality Index in older primary care patients with generalized anxiety disorder: psychometrics and outcomes following cognitive behavioral therapy. *Psychiatry Research*. 2012 Aug 30;199(1):24-30. PMID 22503380. *Not Insomnia Disorder*
38. Buysse D, Bate G, Kirkpatrick P. Fresh from the pipeline: Ramelteon. *Nature Reviews. Drug Discovery*. 2005 Nov;4(11):881-2. PMID 16299918. *Not RCT*
39. Campana LM, Clifford GD, Trinder J, et al. A possible method to predict response to non-pharmacological insomnia therapy. *Journal of Clinical Sleep Medicine*. 2011 Aug 15;7(4):370-5. PMID 21897773. *Not Insomnia Disorder*
40. Cappelleri JC, Bushmakin AG, McDermott AM, et al. Psychometric properties of a single-item scale to assess sleep quality among individuals with fibromyalgia. *Health & Quality of Life Outcomes*. 2009;7:54. PMID 19534799. *Not RCT*
41. Carney CE, Edinger JD. Identifying critical beliefs about sleep in primary insomnia.[Republished in *Sleep*. 2006 Apr;29(4):444-53; PMID: 16676777]. *Sleep*. 2006 Mar;29(3):342-50. PMID 16553020. *Not RCT*
42. Carney CE, Edinger JD. Identifying critical beliefs about sleep in primary insomnia.[Republished from *Sleep*. 2006 Mar;29(3):342-50; PMID: 16553020]. *Sleep*. 2006 Apr;29(4):444-53. PMID 16676777. *No outcomes of interest*
43. Chan AS, Wong QY, Sze SL, et al. A Chinese chan-based mind-body intervention improves sleep on patients with depression: a randomized controlled trial. *TheScientificWorldJournal*. 2012;2012:235206. PMID 22623888. *Excluded Population*
44. Chang E-T, Lai H-L, Chen P-W, et al. The effects of music on the sleep quality of adults with chronic insomnia using evidence from polysomnographic and self-reported analysis: A randomized control trial. *International Journal of Nursing Studies*. 2012 Aug;49(8):921-30. *Inadequate Duration*

45. Chang Y, Liu YP, Liu CF. The effect on serotonin and MDA levels in depressed patients with insomnia when far-infrared rays are applied to acupoints. *American Journal of Chinese Medicine*. 2009;37(5):837-42. PMID 19885944. *Not Insomnia Disorder*
46. Chen YL, Ye FZ, Tang W, et al. Efficacy of dexzopiclone in the treatment of insomnia. [Chinese]. *Chinese Journal of New Drugs*. 2011 30 Jul;20(14):1305-7+13. PMID 2012203694. *Not Available in English*
47. Coe HV, Hong IS. Safety of low doses of quetiapine when used for insomnia  
La seguridad de dosis bajas de quetiapina cuando se utiliza para insomnio. *Annals of Pharmacotherapy*. 2012 May;46(5):718-22. PMID 2012276458. *Not RCT*
48. Coe HV, Hong IS. Safety of low doses of quetiapine when used for insomnia. *Annals of Pharmacotherapy*. 2012 May;46(5):718-22. PMID 22510671. *Not RCT*
49. Cortoos A, De Valck E, Arns M, et al. An exploratory study on the effects of tele-neurofeedback and tele-biofeedback on objective and subjective sleep in patients with primary insomnia. *Applied Psychophysiology & Biofeedback*. 2010 Jun;35(2):125-34. PMID 19826944. *High Risk of Bias*
50. Cotroneo A, Gareri P, Nicoletti N, et al. Effectiveness and safety of hypnotic drugs in the treatment of insomnia in over 70-year old people. *Archives of Gerontology and Geriatrics*. 2007;44(Suppl 1):121-4. *Not RCT*
51. Currie SR, Clark S, Hodgins DC, et al. Randomized controlled trial of brief cognitive-behavioural interventions for insomnia in recovering alcoholics. *Addiction*. 2004 Sep;99(9):1121-32. PMID 15317632. *Excluded Population*
52. da Silva JB, Nakamura MU, Cordeiro JA, et al. Acupuncture for insomnia in pregnancy--a prospective, quasi-randomised, controlled study. *Acupuncture in Medicine*. 2005 Jun;23(2):47-51. PMID 16025784. *Excluded Population*
53. Davis JL, Wright DC. Randomized clinical trial for treatment of chronic nightmares in trauma-exposed adults. *Journal of Traumatic Stress*. 2007 Apr;20(2):123-33. PMID 17427914. *Not Insomnia Disorder*
54. Dijk DJ, Stanley N, Lundahl J, et al. Enhanced slow wave sleep and improved sleep maintenance after gaboxadol administration during seven nights of exposure to a traffic noise model of transient insomnia. *Journal of Psychopharmacology*. 2012 Aug;26(8):1096-107. PMID 22002961. *Excluded Population*
55. Dirksen SR, Epstein DR. Efficacy of an insomnia intervention on fatigue, mood and quality of life in breast cancer survivors. *Journal of Advanced Nursing*. 2008 Mar;61(6):664-75. PMID 18302607. *Excluded Population*

56. Dixon S, Morgan K, Mathers N, et al. Impact of cognitive behavior therapy on health-related quality of life among adult hypnotic users with chronic insomnia. *Behavioral Sleep Medicine*. 2006;4(2):71-84. PMID 16579717. *Not RCT*
57. Dong JP, Wang S, Sun WY, et al. [Randomized controlled observation on head point-through-point therapy for treatment of insomnia]. *Zhongguo Zhenjiu*. 2008 Mar;28(3):159-62. PMID 18447210. *Not Available in English*
58. Dopke CA, Lehner RK, Wells AM. Cognitive-behavioral group therapy for insomnia in individuals with serious mental illnesses: A preliminary evaluation. *Psychiatric Rehabilitation Journal*. 2004 Win;27(3):235-42. *Excluded Population*
59. Dorsey CM, Lee KA, Scharf MB. Effect of zolpidem on sleep in women with perimenopausal and postmenopausal insomnia: a 4-week, randomized, multicenter, double-blind, placebo-controlled study. *Clinical Therapeutics*. 2004 Oct;26(10):1578-86. PMID 15598474. *Excluded Population*
60. Edinger JD, Carney CE, Wohlgemuth WK. Pretherapy cognitive dispositions and treatment outcome in cognitive behavior therapy for insomnia. *Behavior Therapy*. 2008 Dec;39(4):406-16. PMID 19027437. *Not RCT*
61. Edinger JD, Wohlgemuth WK, Krystal AD, et al. Behavioral insomnia therapy for fibromyalgia patients: a randomized clinical trial. *Archives of Internal Medicine*. 2005 Nov 28;165(21):2527-35. PMID 16314551. *Excluded Population*
62. Edinger JD, Wohlgemuth WK, Radtke RA, et al. Dose-response effects of cognitive-behavioral insomnia therapy: a randomized clinical trial. *Sleep*. 2007 Feb;30(2):203-12. PMID 17326546. *Not RCT*
63. Elavsky S, McAuley E. Lack of perceived sleep improvement after 4-month structured exercise programs. *Menopause*. 2007 May-Jun;14(3 Pt 1):535-40. PMID 17224851. *Excluded Population*
64. Ensrud KE, Joffe H, Guthrie KA, et al. Effect of escitalopram on insomnia symptoms and subjective sleep quality in healthy perimenopausal and postmenopausal women with hot flashes: a randomized controlled trial. *Menopause*. 2012 Aug;19(8):848-55. PMID 22433978. *Excluded Population*
65. Epstein DR, Dirksen SR. Randomized trial of a cognitive-behavioral intervention for insomnia in breast cancer survivors. *Oncology Nursing Forum*. 2007 Sep;34(5):E51-9. PMID 17878117. *Excluded Population*
66. Erman M, Guiraud A, Joish VN, et al. Zolpidem extended-release 12.5 mg associated with improvements in work performance in a 6-month randomized, placebo-controlled trial. *Sleep*. 2008 Oct;31(10):1371-8. PMID 18853934. *Not RCT*

67. Erman M, Seiden D, Zammit G, et al. An efficacy, safety, and dose-response study of Ramelteon in patients with chronic primary insomnia. *Sleep Medicine*. 2006 Jan;7(1):17-24. PMID 16309958. *Inadequate Duration*
68. Erman MK, Loewy D, Scharf MB. Comparison of temazepam 7.5 mg with temazepam 15 mg for the treatment of transient insomnia. *Current Medical Research & Opinion*. 2004 Apr;20(4):441-9. PMID 15119980. *Not Insomnia Disorder*
69. Erman MK, Loewy DB, Scharf MB. Effects of temazepam 7.5 mg and temazepam 15 mg on sleep maintenance and sleep architecture in a model of transient insomnia. *Current Medical Research & Opinion*. 2005 Feb;21(2):223-30. PMID 15801993. *Not Insomnia Disorder*
70. Erman MK, Zammit G, Rubens R, et al. A polysomnographic placebo-controlled evaluation of the efficacy and safety of eszopiclone relative to placebo and zolpidem in the treatment of primary insomnia. *Journal of Clinical Sleep Medicine*. 2008 Jun 15;4(3):229-34. PMID 18595435. *Inadequate Duration*
71. Espie CA, Fleming L, Cassidy J, et al. Randomized controlled clinical effectiveness trial of cognitive behavior therapy compared with treatment as usual for persistent insomnia in patients with cancer. *Journal of Clinical Oncology*. 2008 01 Oct;26(28):4651-8. PMID 2008479844. *Excluded Population*
72. Espie CA, Fleming L, Cassidy J, et al. Randomized controlled clinical effectiveness trial of cognitive behavior therapy compared with treatment as usual for persistent insomnia in patients with cancer.[Erratum appears in *J Clin Oncol*. 2010 Jul 1;28(19):3205]. *Journal of Clinical Oncology*. 2008 Oct 1;26(28):4651-8. PMID 18591549. *Not RCT*
73. Farber RH, Burke PJ. Post-bedtime dosing with indiplon in adults and the elderly: results from two placebo-controlled, active comparator crossover studies in healthy volunteers. *Current Medical Research & Opinion*. 2008 Mar;24(3):837-46. PMID 18257978. *Interventions not available in the U.S.*
74. Fargason RE, Gamble K, Avis KT, et al. Ramelteon for insomnia related to attention-deficit/hyperactivity disorder (ADHD). *Psychopharmacology Bulletin*. 2011;44(2) PMID 2012087033. *Excluded Population*
75. Fava M, Asnis GM, Shrivastava R, et al. Zolpidem extended-release improves sleep and next-day symptoms in comorbid insomnia and generalized anxiety disorder. *Journal of Clinical Psychopharmacology*. 2009 Jun;29(3):222-30. PMID 19440075. *High Risk of Bias*
76. Fava M, Asnis GM, Shrivastava RK, et al. 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*. 2011 Jul;72(7):914-28. PMID 21208597. *Excluded Population*

77. Fava M, McCall WV, Krystal A, et al. Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. *Biological Psychiatry*. 2006 Jun 1;59(11):1052-60. PMID 16581036. *High Risk of Bias*
78. Fava M, Schaefer K, Huang H, et al. 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*. 2011 Apr;72(4):473-9. PMID 21208574. *Excluded Population*
79. Feng Y, Wang XY, Li SD, et al. Clinical research of acupuncture on malignant tumor patients for improving depression and sleep quality. *Journal of Traditional Chinese Medicine*. 2011 September;31(3):199-202. PMID 2011550651. *Excluded Population*
80. Fernando A, 3rd, Arroll B, Falloon K. A double-blind randomised controlled study of a brief intervention of bedtime restriction for adult patients with primary insomnia. *Journal of Primary Health Care*. 2013 Mar;5(1):5-10. PMID 23457689. *Not Insomnia Disorder*
81. Fishbain DA, Hall J, Meyers AL, et al. Does pain mediate the pain interference with sleep problem in chronic pain? Findings from studies for management of diabetic peripheral neuropathic pain with duloxetine. *Journal of Pain & Symptom Management*. 2008 Dec;36(6):639-47. PMID 18504092. *Not RCT*
82. Fiss E, Guelere Paris E, De Castro Brandao D, et al. Passiflora, Crataegus and Erythrina combination efficacy and tolerability clinical evaluation compared to Passiflora, Crataegus and Salix combination in the treatment of patients suffering from insomnia and mild anxiety. [Portuguese]
- Avaliacao clinica da eficacia e tolerabilidade do uso da associacao de Passiflora alata, Crataegus oxyacantha L. e Erythrina mulungu comparado a associacao de Passiflora incarnata, Crataegus oxyacantha L. e Salix alba L. em portadores de insonia e ansiedade leves. *Revista Brasileira de Medicina*. 2006 September;63(9):489-96. PMID 2006513360. *Not Available in English*
83. Gan JG, Tian GQ, Qin GX. Study on efficacy of Zaoren Anshen capsules in treating senile insomnia and changes in its hemorheology. [Chinese]. *Zhongguo Zhongyao Zazhi*. 2013 15 Jan;38(2):273-5. PMID 2013283812. *Not Available in English*
84. Gao X, Xu C, Wang P, et al. Curative effect of acupuncture and moxibustion on insomnia: a randomized clinical trial. *Journal of Traditional Chinese Medicine*. 2013 August;33(4):428-32. PMID 2013535925. *Inadequate Duration*
85. Gao XY, Wei YL, Shao SJ, et al. [Multiple central clinical studies on the needling method for regulating wei and strengthening brain for treatment of insomnia]. *Zhongguo Zhenjiu*. 2007 Aug;27(8):623-5. PMID 17853766. *Not Available in English*

86. Geler Kulcu D, Gulsen G. Effect of physical therapy program on insomnia severity in a patient population with fibromyalgia syndrome. [Turkish]  
Fibromiyalji sendromlu bir grup hastada fizik tedavi programının uykusuzluk siddeti uzerine etkisi. *Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi*. 2009 June;55(2):64-7. PMID 2009573518. *Excluded Population*
87. Gellis LA, Arigo D, Elliott JC. Cognitive refocusing treatment for insomnia: a randomized controlled trial in university students. *Behavior Therapy*. 2013 Mar;44(1):100-10. PMID 23312430. *Not Insomnia Disorder*
88. Germain A, Shear K, Monk TH, et al. Treating complicated grief: effects on sleep quality. *Behavioral Sleep Medicine*. 2006;4(3):152-63. PMID 16879079. *Not Insomnia Disorder*
89. Glass JR, Sproule BA, Herrmann N, et al. Effects of 2-week treatment with temazepam and diphenhydramine in elderly insomniacs: a randomized, placebo-controlled trial. *Journal of Clinical Psychopharmacology*. 2008 Apr;28(2):182-8. PMID 18344728. *Inadequate Duration*
90. Gong YL, Zhang YB, Han C, et al. [Clinical observation on therapeutic effect of the pressing plantar reflex area with wooden needle for treatment of patients with insomnia]. *Zhongguo Zhenjiu*. 2009 Nov;29(11):935-7. PMID 19994698. *Not Available in English*
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## Appendix C

### Evidence Tables:

#### Psychological / Behavioral Interventions

**Table C1. Psychological Studies for Insomnia Disorder: Risk of Bias Assessment:**

| <b>Study</b>                          | <b>Risk of Bias Assessment</b>  |
|---------------------------------------|---|
| Arnedt, 2013 <sup>3</sup>             | Low-moderate: no ITT analysis; low attrition; multiple comparisons correction unclear; blinding, randomization method NR  |
| Pech, 2013 <sup>6</sup>               | Moderate: ITT analysis; multiple comparisons correction unclear.  |
| Vitiello, 2013 <sup>7</sup>           | Low-moderate: Participants and assessors blinded; modified ITT analysis; low attrition; no adjustment for multiple comparisons; did not discuss treatment fidelity.   |
| Epstein, 2012 <sup>8</sup>            | Low-moderate: no blinding; high attrition for 3-month and 1-year F/U.   |
| Espie, 2012 <sup>9</sup>              | Low: controlled for unequal baseline values in analyses; ITT analysis   |
| Jansson-Frojmark, 2012a <sup>10</sup> | Low-moderate: ITT analysis; multiple comparisons correction unclear; randomization method unclear; analysis blinded.  |
| Jansson-Frojmark, 2012b <sup>11</sup> | Low-Moderate: ITT analysis (one exception, a randomized participant who was excluded due to unstable medication use); Multiple comparisons correction unclear; randomization method unclear; analysis blinded.  |
| Morgan, 2012 <sup>12</sup>            | Moderate: Very high attrition; No mention of correcting for multiple comparisons for reported outcomes (only for exploratory analyses).   |
| Pigeon, 2012 <sup>13</sup>            | Low-moderate: Blinding unclear; no attrition.   |
| Bjorvatn, 2011 <sup>16</sup>          | Moderate: ITT analysis; blinding unclear; did not describe randomization process or compare baseline characteristics; attrition higher 20% for control group and did not explain missing data   |
| Buysee, 2011 <sup>17</sup>            | Moderate: Blinding unclear; multiple comparisons correction unclear; no sample size calculation   |
| Rybarczyk, 2011 <sup>21</sup>         | Low: Participants recruited at the same time as another study and were basically those who chose not to participate in that study. ITT analysis for 8 week analysis only, completers only for 1 year analysis. Multiple comparisons correction unclear. |
| Riley, 2010 <sup>22</sup>             | Moderate: No ITT analysis; two groups of intervention participants were combined for analyses; research assistants not blinded; did not adjust for multiple comparisons.no fidelity checks  |
| Edinger, 2009 <sup>23</sup>           | Low/moderate: Not ITT analysis; unclear about multiple comparisons corrections  |
| Friedman, 2009 <sup>24</sup>          | Moderate: high attrition, no reporting of population characteristics by group.  |
| Ritterband, 2009 <sup>25</sup>        | Low-moderate: ITT analysis; multiple comparisons correction unclear; no fidelity checks   |
| van Straten, 2009 <sup>26</sup>       | Low: ITT analysis; blinding, multiple comparisons adjustment, and fidelity checks unclear.  |
| Vincent, 2009 <sup>27</sup>           | Low-moderate: Multiple comparisons correction unclear;high attrition  |
| Vitiello, 2009 <sup>28</sup>          | Moderate: Not ITT analysis; multiple comparisons correction unclear; did not discuss attrition or compare completers to non-completers  |
| Soeffing, 2008 <sup>29</sup>          | Moderate-high: Discussed fidelity checks and treatment fidelity, but not attrition; did not report all scale outcomes; did not report methods for analyzing missing data  |
| Espie, 2007 <sup>30</sup>             | Low-moderate: High attrition  |
| Lack, 2007 <sup>31</sup>              | Moderate: Small sample size; attrition unclear.   |
| McCrae, 2007 <sup>32</sup>            | Moderate: Reporting bias, small n; one participant not included in analyses due to withdrawal; unclear blinding and multiple comparisons correction   |
| Germain, 2006 <sup>33</sup>           | Moderate: Unclear whether all participants analyzed, missing data, and multiple comparisons; no between-group analysis.   |
| Wu, 2006                              | Moderate: Blinding only for medications; not ITT analysis; multiple comparisons correction unclear; low statistical power   |
| Jansson, 2005 <sup>35</sup>           | Moderate: Did not mention blinding; few details about intervention; did not appear to correct for multiple comparisons; no explanation of attrition, completer analysis   |
| Morin, 2005 <sup>36</sup>             | Low-moderate: Says ITT analysis, but how drop-outs were handled NR; low attrition; randomization concealed; no sample size calculation; multiple comparisons correction unclear. Confusing as some "good sleepers" included despite requiring insomnia  |
| Rybarczyk, 2005 <sup>37</sup>         | Low-moderate: Multiple comparisons correction unclear; didn't discuss who was delivering interventions or fidelity checks   |
| Bastien, 2004 <sup>38</sup>           | Low-moderate: Data was missing for blinding, randomization process; attrition high at 6 months, unclear how missing data were handled   |

|                               |  |
|-------------------------------|--|
| Kirisoglu, 2004 <sup>39</sup> | Low-moderate: low attrition; randomization method unclear.   |
| Strom, 2004 <sup>40</sup>     | Moderate: attrition over 20%, mostly in the treatment group; completer analysis; multiple comparisons correction unclear.  |
| Edinger, 2003 <sup>41</sup>   | Low-moderate: Low attrition; ITT analysis; did not adjust for multiple comparisons   |
| Morgan, 2003                  | Moderate: high attrition but reasonably powered and well randomized.   |
| Rybarczyk, 2002 <sup>44</sup> | Moderate-high: high attrition; no consistent outcome across measure; randomized before final exclusion; did not correct for multiple comparisons for non-clinical significance measures; blinding unclear; outcome timing may not have been the same at post-treatment in all groups |
| Edinger, 2001 <sup>45</sup>   | Low: ITT analyses, though placebo group not included in 6 month analyses as they were re-randomized after first follow-up; otherwise low risk in all categories  |
| Espie, 2001 <sup>46</sup>     | Moderate/-high: Unclear about differences at baseline, blinding, multiple comparisons correction; no ITT analysis; no comparison of baseline characteristics   |
| Lichstein, 2001 <sup>47</sup> | Moderate: Completer-only analysis, reasonable sample size; multiple comparisons problem  |
| Friedman, 2000 <sup>48</sup>  | Low-moderate: therapist unblinded; ITT analysis; low attrition; possibly underpowered.   |
| Mimeault, 1999 <sup>49</sup>  | Moderate: Small sample size; no justification for clinical significance; completer-only analysis; While authors describe 4 LTFs during treatment, they do not describe the 9 they lost before follow-up (3 months).  |
| Morin, 1999 <sup>50</sup>     | Moderate: Analyses do not include drop outs. Blinding for PCT and PCT part of combined. No mention of correcting for multiple comparisons. Select outcomes reported, but justified. Placebo group has treatment after 3 months.  |
| Riedel, 1998 <sup>51</sup>    | Moderate-high: Small sample size and no power calculation, subjective outcome measure, participants motivated to quit sleep meds   |
| Riedel, 1995 <sup>54</sup>    | Moderate-high: Poor randomization; , blinding unclear, no detailed description of baseline characteristics; possibly underpowered  |
| Morin, 1993 <sup>56</sup>     | Low-moderate: Efficacy of randomization unclear; seemingly ITT analysis; multiple comparisons correction unclear; low attrition  |
| Espie, 1989 <sup>59</sup>     | Moderate-high: No sample size calculation and 4 treatment groups; unclear analysis, whether participants were analyzed per ITT, multiple comparisons, and what "experimental drop outs" means. Care provider for all groups was senior author  |
| Morawetz, 1989 <sup>60</sup>  | Moderate: Low attrition; ITT analysis; single investigator/author led therapy sessions; non-standard scales; small subgroups; not true 3-way randomization   |
| Morin, 1988 <sup>61</sup>     | Moderate: Blinding unclear; attrition unclear; ITT analysis unclear; possibly underpowered   |
| Schoicket, 1988 <sup>63</sup> | Moderate-high: randomization suspect (differing baseline characteristics); blinding unclear; no ITT analysis; low attrition; possibly underpowered   |
| Morin, 1987 <sup>64</sup>     | High: High dropouts, small n, possible reporting bias  |
| Lacks, 1983 <sup>67</sup>     | Moderate: Did not appear to analyze all participants (stated some were uncooperative, etc.); blinding unclear; small sample size for 4 treatment arms  |
| Puder, 1983                   | Moderate-High  |
| Woolfolk, 1983 <sup>71</sup>  | Moderate: Lack of statistical power  |
| Davies, 1977                  | Moderate-high: Small n, reporting bias, inconsistent sample sizes  |
| Lick, 1977 <sup>75</sup>      | Moderate-high: Small n, reporting bias, inconsistent sample sizes  |

**Table C2. Efficacy of Psychological Interventions in the general adult population: strength of evidence assessments**

| Outcome                             | Intervention     | # Trials (n) | Summary statistics, [95% CI]    | Risk of Bias | Directness | Precision | Consistency | Reporting Bias | Evidence Rating |
|-------------------------------------|------------------|--------------|---------------------------------|--------------|------------|-----------|-------------|----------------|-----------------|
| <b>Global</b>                       |                  |              |                                 |              |            |           |             |                |                 |
| Remission                           | CBT              | 4 (115)      | RR= 2.06<br>[1.03 to 4.12]      | Medium       | Direct     | Imprecise | Consistent  | Undetected     | Moderate        |
|                                     | BBT              | NR           | NA                              | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Stimulus Control | NR           | NA                              | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Relaxation       | NR           | NA                              | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     |                  |              |                                 |              |            |           |             |                |                 |
|                                     |                  |              |                                 |              |            |           |             |                |                 |
| Responder (ISI score change of 7/8) | CBT              | 2 (62)       | RR= 4.56<br>[0.54 to 38.50]     | Medium       | Direct     | Imprecise | Consistent  | Undetected     | Low             |
|                                     | BBT              | NR           | NA                              | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Stimulus Control | NR           | NA                              | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Relaxation       | NR           | NA                              | NA           | NA         | NA        | NA          | NA             | Insufficient    |
| ISI score                           | CBT              | 4 (190)      | WMD=-4.63<br>[-6.42 to -2.85]   | Medium       | Direct     | Precise   | Consistent  | Undetected     | Moderate        |
|                                     | BBT              | NR           | NA                              | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Stimulus Control | NR           | NA                              | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Relaxation       | NR           | NA                              | NA           | NA         | NA        | NA          | NA             | Insufficient    |
| PSQI score                          | Individual CBT   | 4 (307)      | WMD=-2.86<br>[-3.69 to -2.02]   | Medium       | Direct     | Precise   | Consistent  | Undetected     | Moderate        |
|                                     | BBT              | NR           | NA                              | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Stimulus Control | NR           | NA                              | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Relaxation       | NR           | NA                              | NA           | NA         | NA        | NA          | NA             | Insufficient    |
| CGI=very much improved              | CBT              | 1 (60)       | RR= 8.08<br>[1.13 to 57.73]     | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
|                                     | BBT              | NR           | NA                              | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Stimulus Control | NR           | NA                              | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Relaxation       | NR           | NA                              | NA           | NA         | NA        | NA          | NA             | Insufficient    |
| <b>Sleep</b>                        |                  |              |                                 |              |            |           |             |                |                 |
| Subjective sleep onset latency      | CBT              | 11 (1049)    | WMD=-11.34<br>[-18.00 to -4.68] | Medium       | Direct     | Precise   | Consistent  | Undetected     | Moderate        |
|                                     | BBT              | 2 (50)       | WMD=-23.38                      | Medium       | Direct     | Precise   | Consistent  | Undetected     | Low             |

| Outcome                                | Intervention     | # Trials (n) | Summary statistics, [95% CI]      | Risk of Bias | Directness | Precision | Consistency  | Reporting Bias | Evidence Rating |
|--|------------------|--------------|-----------------------------------|--------------|------------|-----------|--------------|----------------|-----------------|
| (minutes)*                             |                  |              | [-36.29 to -9.85]                 |              |            |           |              |                |                 |
|  | Stimulus Control | 2 (47)       | WMD= -35.45<br>[-89.35 to 18.45]  | Medium       | Direct     | Imprecise | Inconsistent | Undetected     | Insufficient    |
|  | Relaxation       | 2 (42)       | WMD=-38.65<br>[-73.61 to -3.69]   | Medium       | Direct     | Imprecise | Consistent   | Undetected     | Low             |
| Subjective total sleep time (minutes)* | CBT              | 13 (1091)    | WMD= 11.24<br>[1.45 to 21.03]     | Medium       | Direct     | Imprecise | Consistent   | Undetected     | Moderate        |
|  | BBT              | 1 (9)        | MD=1.10<br>[.38 to 1.82]          | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Insufficient    |
|  | Stimulus Control | 2 (47)       | WMD= 43.19<br>[3.26 to 83.12]     | Medium       | Direct     | Imprecise | Consistent   | Undetected     | Low             |
|  | Relaxation       | 1 (27)       | WMD= 34.20<br>[-24.66 to 93.06]   | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Insufficient    |
| Wake time after sleep onset            | CBT              | 9 (734)      | WMD= -26.41<br>[-40.97 to -11.84] | Medium       | Direct     | Precise   | Inconsistent | Undetected     | Low             |
|  | BBT              | 1 (19)       | MD=-29.00<br>[-53.74 to -4.26]    | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Insufficient    |
|  | Stimulus Control | 3 (97)       | WMD= -3.38<br>[-19.09 to 12.34]   | Medium       | Direct     | Imprecise | Inconsistent | Undetected     | Low             |
|  | Relaxation       | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
| Sleep efficiency                       | CBT              | 12 (1059)    | WMD=6.13<br>[3.23 to 9.03]        | Medium       | Direct     | Precise   | Consistent   | Undetected     | Moderate        |
|  | BBT              | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
|  | Stimulus Control | 1 (20)       | WMD= 0.80<br>[-7.55 to 9.15]      | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Insufficient    |
|  | Relaxation       | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
| Sleep quality                          | CBT              | 10 (840)     | WMD=0.43<br>[0.20 to 0.67]        | Medium       | Direct     |           |              | Undetected     | Moderate        |
|  | BBT              | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
|  | Stimulus Control | 1 (20)       | WMD= 0.30<br>[-0.54 to 1.14]      | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Insufficient    |
|  | Relaxation       | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio

\* As a rule, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org)*)

**Table C3. Efficacy of Psychological Interventions in older adults: Strength of Evidence Assessments**

| Outcome                             | Type              | # Trials (n) | Summary statistics, [95% CI]   | Risk of Bias | Directness | Precision | Consistency | Reporting Bias | Evidence Rating |
|-------------------------------------|-------------------|--------------|--------------------------------|--------------|------------|-----------|-------------|----------------|-----------------|
| Remission (ISI <sub>≤</sub> 7)      | CBT               | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | BBT               | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Sleep restriction | 1 (94)       | RR = 5.68<br>[1.32 to 24.54]   | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
|                                     | Stimulus Control  | 1 (94)       | RR = 7.39<br>[1.76 to 30.94]   | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
| Remission (PSQI <sub>≤</sub> 5)     | CBT               | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | BBT               | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Sleep restriction | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Stimulus Control  | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
| Responder (ISI score change of 7/8) | CBT               | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | BBT               | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Sleep restriction | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Stimulus Control  | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
| Remitters                           | CBT               | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | BBT               | 1 (26)       | RR: 4.20<br>[1.76 to 10.01]    | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
|                                     | Sleep restriction | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Stimulus Control  | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
| ISI score                           | CBT               | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | BBT               | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Sleep restriction | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Stimulus Control  | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
| ISI mean change                     | CBT               | 1 (125)      | MD= 2.10<br>[0.55 to 2.65]     | Medium       | Direct     | Precise   | Unknown     | Undetected     | Insufficient    |
|                                     | BBT               | NR           | NA                             | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|                                     | Sleep restriction | 1 (94)       | MD= -5.00<br>[-6.94 to -3.06]  | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
|                                     | Stimulus Control  | 1 (94)       | MD= -5.10<br>[-7.02 to -3.18]  | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
| PSQI score                          | CBT               | 1 (125)      | MD=-2.80<br>{-5.28 to -0.41}   | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
|                                     | BBT               | 2 (114)      | WMD= -3.02<br>[-4.13 to -1.91] | Medium       | Direct     | Precise   | Consistent  | Undetected     | Low             |

| Outcome                                   | Type              | # Trials (n) | Summary statistics, [95% CI]      | Risk of Bias | Directness | Precision | Consistency  | Reporting Bias | Evidence Rating |
|---|-------------------|--------------|-----------------------------------|--------------|------------|-----------|--------------|----------------|-----------------|
|   | Sleep restriction | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
|   | Stimulus Control  | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
| PSQI mean change                          | CBT               | 1 (129)      | MD=-2.20<br>[1.40 to 3.36]        | Medium       | Direct     | Precise   | Unknown      | Undetected     | Insufficient    |
|   | BBT               | 1 (26)       | RR= 4.20<br>[1.76 to 10.01]       | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Insufficient    |
|   | Sleep restriction | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
|   | Stimulus Control  | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
| ISS                                       | CBT               | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
|   | BBT               | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
|   | Sleep restriction | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
|   | Stimulus Control  | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
| CGI=very much improved                    | CBT               | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
|   | BBT               | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
|   | Sleep restriction | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
|   | Stimulus Control  | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
| Subjective sleep onset latency (minutes)* | CBT               | 2 (48)       | WMD=-1.44<br>[-24.05 to 1.78]     | Medium       | Direct     | Imprecise | Inconsistent | Undetected     | Insufficient    |
|   | BBT               | 4 (181)      | WMD=-10.36<br>[-15.57 to -5.15]   | Low          | Direct     | Precise   | Consistent   | Undetected     | Moderate        |
|   | Sleep restriction | 3 (171)      | WMD= -9.67<br>[-25.51 to 6.18]    | Medium       | Direct     | Imprecise | Inconsistent | Undetected     | Insufficient    |
|   | Stimulus Control  | 3 (129)      | WMD= -16.16<br>[-37.14 to 4.83]   | Medium       | Direct     | Imprecise | Inconsistent | Undetected     | Insufficient    |
| Subjective total sleep time (minutes)*    | CBT               | 3(77)        | WMD= -1.44<br>[-26.04 to 28.93]   | Medium       | Direct     | Imprecise | Inconsistent | Undetected     | Insufficient    |
|   | BBT               | 4 (181)      | WMD= -27.75<br>[-56.06 to 0.63]   | Medium       | Direct     | Imprecise | Inconsistent | Undetected     | Low             |
|   | Sleep restriction | 3 (171)      | WMD= 3.12<br>[-28.54 to 34.79]    | Medium       | Direct     | Imprecise | Inconsistent | Undetected     | Insufficient    |
|   | Stimulus Control  | 2 (113)      | WMD= 40.37<br>[23.47 to 57.27]    | Medium       | Direct     | Imprecise | Inconsistent | Undetected     | Low             |
| Wake time after sleep onset               | CBT               | 3 (77)       | WMD= -48.34<br>[-78.88 to -17.80] | Medium       | Direct     | Precise   | Consistent   | Undetected     | Moderate        |
|   | BBT               | 4 (181)      | WMD= -13.91<br>[-21.11 to -6.71]  | Medium       | Direct     | Precise   | Consistent   | Undetected     | Moderate        |

| Outcome                      | Type              | # Trials (n) | Summary statistics, [95% CI]      | Risk of Bias | Directness | Precision | Consistency  | Reporting Bias | Evidence Rating |
|------------------------------|-------------------|--------------|-----------------------------------|--------------|------------|-----------|--------------|----------------|-----------------|
|                              | Sleep restriction | 3 (171)      | WMD= -24.47<br>[-40.98 to -7.96]  | Medium       | Direct     | Imprecise | Consistent   | Undetected     | Moderate        |
|                              | Stimulus Control  | 1 (94)       | WMD= -26.60<br>[-38.11 to -15.09] | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Insufficient    |
| Sleep efficiency             | CBT               | 3 (77)       | WMD= 12.44<br>[7.62 to 17.26]     | Medium       | Direct     | Precise   | Consistent   | Undetected     | Low             |
|                              | BBT               | 4 (181)      | WMD= 5.11<br>[2.47 to 7.75]       | Medium       | Direct     | Precise   | Consistent   | Undetected     | Moderate        |
|                              | Sleep restriction | 3 (171)      | 6.61 [2.48 to 15.70]              | Moderate     | Direct     | Imprecise | Inconsistent | Undetected     | Insufficient    |
|                              | Stimulus Control  | 1 (94)       | WMD= 13.20<br>[9.92 to 16.48]     | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Insufficient    |
| Sleep efficiency-mean change | CBT               | 1 (123)      | WMD= 11.20<br>[6.25 to 16.15]     | Medium       | Direct     | Precise   | Unknown      | Undetected     | Insufficient    |
|                              | BBT               | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
|                              | Sleep restriction | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
|                              | Stimulus Control  | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
| Sleep quality                | CBT               | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
|                              | BBT               | NR           | NA                                | NA           | NA         | NA        | NA           | NA             | Insufficient    |
|                              | Sleep restriction | 1 (94)       | SMD= 0.74<br>[0.32 to 1.16]       | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Insufficient    |
|                              | Stimulus Control  | 1 (94)       | WMD= 13.20<br>[9.92 to 16.48]     | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Insufficient    |

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio

\* As a rule of thumb, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org*)

## Appendix D. Evidence Tables:

### Pharmacologic Interventions

**Table D1. Pharmacologic Interventions for insomnia disorder: risk of bias assessments**

| Study  | Risk of Bias Assessment   |
|--|---|
| Roth 2013 <sup>79</sup><br>Non-benzodiazepine hypnotic           | Low<br>Adjusted for multiple comparisons using hierarchy; 20/294 (7%) attrition; reporting bias, ie, data only for TST; outcomes for NOW, SL must be estimated from figure; no data for WASO  |
| Lankford 2012 <sup>80</sup><br>Antidepressants                   | Low<br>Computer-generated randomization; large enough sample size for adequate power ; 7% (17/254) attrition; Unclear if adjusted for multiple comparisons; Data for LSO and NAASO NR   |
| Roehrs 2012 <sup>81</sup><br>Non-benzodiazepine hypnotic         | High<br>Achieved sample size based on withdrawal symptoms; 25/58 (43%) attrition, reasons described; outcomes for completers and withdrawers reported separately; mall samples size, found NS difference in outcomes (ie, concluded no rebound); possible type II error, despite sample size/power calculation  |
| Krystal 2011 <sup>82</sup><br>Antidepressants                    | Low/moderate<br>229 randomized; 11% attrition; ITT analysis; double-blinded, PSG scorer blinded; unclear if adjusted for multiple comparisons; some outcome data NR.  |
| Uchimura 2011 <sup>83</sup><br>Ramelteon                         | Moderate<br>No sample size calculation, but large populations; 1-ary outcome adjusted for 2-point comparison; primary outcome analyzed on randomized and per-protocol population; 362/1443 (25%) attrition; data for SOL after week 2, for TST for week 1; no data for NAW, sleep quality, or PGI; forced escalation study  |
| Wade 2011 <sup>84</sup><br>Ramelteon                             | Low/Moderate<br>5% attrition for 3 weeks, 22% 26 week extension, reasons described; reports data for SL only; re-analysis of data from Wade 2010 by total cohort and different age subgroups  |
| Ancoli-Israel 2010 <sup>85</sup><br>Non-benzodiazepine hypnotics | Low/moderate<br>Internet-based randomization system; achieved sample size based on power calculation; addressed multiple comparisons using sequential comparisons; 26% attrition, similar between groups; reporting bias, ie, no data for NOW, quality, depth of sleep; data for TST, SL, WASO must be estimated from figures   |
| Krystal 2010 <sup>86</sup><br>Antidepressants                    | Low<br>Double-blinded, PSG scorer blinded; 11% attrition; ITT analysis; no mention of adjustment for multiple comparisons   |
| Wade 2010 <sup>87</sup><br>Ramelteon                             | Low<br>Achieved desired sample size for primary outcome; 5% attrition for 3 weeks, 22% 26 week extension  |
| Fava 2009 <sup>88</sup><br>Zolpidem                              | High<br>Patient population and attrition not described (only abstract states number of subjects (n=383), n does not appear anywhere else, or how many in each arm; power statement states that total of 260 subjects needed for 90% power but enrolled more; ITT and per-protocol analyses; no adjustment for multiple comparisons -despite making 200 secondary efficacy comparison; Most outcome data must be estimated from figures and are shown as change from baseline; no data for SDS or SIS, or MGH-CPFQ; no outcomes for Q-LES-Q or HRU |
| Mayer 2009 <sup>89</sup><br>Ramelteon                            | Low<br>No sample size calculation but large population; 116/451 (26%) discontinued over 6 months (reasons described), but all who were randomized were analyzed, using last observation carried forward   |
| Krystal 2008 <sup>90</sup><br>Non-benzodiazepine hypnotic        | Low/Moderate<br>Achieved sample size based on power calculation; 405/1018 (40%) attrition (over 24 weeks), reasons described; ITT analysis using last observation carried forward; no adjustment for multiple comparisons; outcome data must be estimated from figures  |

| Study  | Risk of Bias Assessment  |
|--|--|
| Walsh 2007 <sup>91</sup><br>Non-benzodiazepine hypnotic    | Low<br>Achieved sample size, having assumed 42% attrition in power calculations; 350/828 (42%) attrition over 6 months; attrition 52% among placebo, 37% among active drug; used last-observation-carried forward for missing values; results refer to 2 tables as online supplements, which could not be found  |
| Zammit 2007 <sup>92</sup><br>Ramelteon                     | Low/Moderate<br>Achieved sample size based on power calculation; 405/1018 (40%) attrition (over 24 weeks), reasons described; ITT analysis using last observation carried forward; no adjustment for multiple comparisons; outcome data must be estimated from figures   |
| Reynolds 2006 <sup>93</sup><br>Antidepressants             | High<br>26% (7/27) attrition; Analysis does not appear to be ITT although unclear; No adjustment for multiple comparisons; small sample size small n (27 started, 20 completed; no sample size calculation/power statement; all data must be derived from figures, which are impossible to read; data for sleep efficiency by PSG NR   |
| Roth 2006 <sup>94</sup><br>Ramelteon                       | Moderate<br>No sample size/power calculation, but large sample; 128/829 (15%) attrition, reasons described; no mention of how non-completers were handled, no n's in results; reporting bias (no outcome data for NOW, ease of falling back to sleep, sleep quality)   |
| Wu 2006 <sup>34</sup>                                      | Moderate<br>Small sample size, no small sample/ power calculation; moderate attrition rate; completer analysis   |
| Perlis 2004 <sup>95</sup>                                  | Low/Moderate<br>No power calculation or adjustment for multiple comparisons; 39/199 (20%) attrition (over 12 weeks), reasons described; ITT analysis using last observation carried forward  |
| Zammit 2004 <sup>97</sup>                                  | Low<br>Achieved sample size based on power calculation; addressed multiple comparisons using hierarchy; 16/308 (5%) attrition, between-group differences described; ITT analysis; consistent reporting   |
| Krystal 2003 <sup>98</sup><br>Non-benzodiazepine hypnotic  | Low<br>Achieved sample size based on power calculation (which assumed 50% attrition); adjusted for multiple comparison using Bonferroni correction; 320/791 (40%) attrition (over 6 month study), but lower than assumed in sample size calculation, reasons described; however, attrition twice as high in placebo group than active drug group; analyses: ITT (using last observation carried forward), observed cases, and completers |
| Walsh 2002 <sup>99</sup><br>Non-benzodiazepine hypnotic    | Moderate/High<br>no sample size calculation or adjustment for multiple comparisons; 28/163 (17%) attrition, reasons described; many outcomes in methods are not in results; other outcome data must be estimated from figures; very poorly reported methods, eg no patient inclusion/exclusion criteria (questions at end of report suggest this was transcribed from an oral presentation)  |
| Allain 2001 <sup>100</sup><br>Non-benzodiazepine hypnotics | Low<br>No sample size calculation, but found many significant differences; no adjustment for multiple comparisons; non-standard daytime outcome measures; attrition 10/245 (4%) unbalanced: more patients withdrew from the placebo arm than from the active treatment arm (5% vs 0%), citing lack of efficacy; ITT analysis with "observed cases procedure" and LOCF  |
| Hajak 2001 <sup>101</sup><br>Antidepressant                | Moderate<br>47 subjects total; 15% attrition; outcome analysis by completers only, AEs by ITT; no sample size calculation; did adjust for multiple comparisons   |
| Fry 2000 <sup>102</sup><br>Non-benzodiazepine hypnotic     | Low<br>More women in Zaleplon 5 mg group; adjusted for multiple comparisons between zaleplon doses & placebo using Dunnett distribution; no sample size calculation, but fairly large n; data for SOL must be estimated from figure; 9/595 (2%) attrition; reasons described; consistent reporting   |

| Study   | Risk of Bias Assessment  |
|---|--|
| Asnis 1999 <sup>103</sup><br>Non-benzodiazepine hypnotic    | High<br>No sample-size calculation, no adjustment for multiple comparisons; completer-only analysis; non-standard scales for daytime outcomes; 37/193 (19%) attrition; reporting bias, ie, no outcomes for ease of falling asleep, daytime concentration, activities, alertness, mood, concentration, or creativity, GIT, or QoL; much data must be estimated from figures |
| Elie 1999 <sup>104</sup><br>Non-benzodiazepine hypnotic     | Low<br>Adjusted for multiple comparisons using Dunnett distribution; no sample size calculation, but fairly large n; 41/615 (7%) not in efficacy analysis; reasons for attrition and attritions by treatment group NR (except for AEs); data for SOL must be estimated from figure; consistent reporting   |
| Morin 1999 <sup>50</sup><br>Benzodiazepine                  | Low –Moderate: Analyses do not include drop outs. Incomplete blinding; no mention of correcting for multiple comparisons. Select outcomes reported, but justified: low attrition.  |
| Lahmeyer 1997 <sup>105</sup><br>Non-benzodiazepine hypnotic | Moderate: no adjustment for multiple comparisons; moderate attrition; possible reporting bias.   |
| Leppik 1997 <sup>106</sup><br>Head to head                  | Low-Moderate: low attrition during active treatment; no ITT analyses; possible reporting bias;   |
| Scharf 1994 <sup>107</sup><br>Non-benzodiazepine hypnotic   | Low/Moderate<br>Double-blinded, PSG scoring blinded; some nonstandard scales: no details on components of Morning or Evening Questionnaire or Global Impression; no data for "refreshing" or number of awakenings ; no correction for multiple comparisons   |
| Minnekeer 1988 <sup>108</sup><br>Benzodiazepine             | Moderate<br>25.9% drop out rate, largest in placebo group; not ITT for efficacy; no adjustment for multiple comparisons; no standard outcomes scales; outcome data displayed in figures only; scales in figure 1 and 2 unclear; little correlation between outcomes in methods and in results  |
| Mittler 1984 <sup>109</sup><br>Benzodiazepine               | Low/high<br>Small sample size, n=21; no sample size/ power calculation; attrition NR; no mention of adjustment for multiple comparisons; non-standard scales; non-standard scales.   |
| Reeves 1977 <sup>110</sup><br>Benzodiazepine                | Moderate/high<br>Small sample size (n=41), 15% attrition; no small sample size/ power calculation; completer analysis; no adjustment for multiple comparisons; non-standard scales   |

**Table D2. Efficacy of nonbenzodiazepines in the general adult population: strength of evidence assessments**

| Outcome                                   | Type                 | # Trials (n) | Summary statistics, [95% CI]   | Risk of Bias | Directness | Precision | Consistency  | Reporting Bias | Evidence Rating |
|---|----------------------|--------------|--|--------------|------------|-----------|--------------|----------------|-----------------|
| <b>Global</b>                             |                      |              |  |              |            |           |              |                |                 |
| Clinical global outcome                   | Eszopiclone          | 1 (825)      | RR 2.7 [2.1, 3.4]  | Medium       | Direct     | Precise   | Unknown      | Undetected     | Low             |
|   | Zaleplon             | NR           |  |              |            |           |              |                | Insufficient    |
|   | Zolpidem             | NR           |  |              |            |           |              |                | Insufficient    |
|   | Zolpidem “as needed” | 1 (243)      | RR 2.2 [1.6, 3.2]  | Medium       | Direct     | Precise   | Unknown      | Undetected     | Low             |
|   | Zolpidem SL          | NR           |  |              |            |           |              |                | Insufficient    |
|   | Zolpidem ER          | 1 (1016)     | RR 1.8 [1.6, 2.0]  | Medium       | Direct     | Precise   | Unknown      | Undetected     | Low             |
| <b>Sleep</b>                              |                      |              |  |              |            |           |              |                |                 |
| Subjective sleep onset latency (minutes)* | Eszopiclone          | 3 (1820)     | WMD -19.1 [-24.1, -14.1]   | Medium       | Direct     | Precise   | Consistent   | Undetected     | Moderate        |
|   | Zaleplon 10mg        | 1 (209)      | MD -9.9 [-19.5, -0.4]  | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Insufficient    |
|   | Zaleplon 5 mg        | 1 (208)      | MD 2.5 [-9.0, 14.3]  | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Insufficient    |
|   | Zolpidem             | 2 (255)      | WMD -12.8 [-21.5, -4.2]  | Medium       | Direct     | Precise   | Consistent   | Undetected     | Moderate        |
|   | Zolpidem “as needed” | 2 (355)      | WMD -14.8 [-23.4, -6.2]  | Medium       | Direct     | Precise   | Consistent   | Undetected     | Moderate        |
|   | Zolpidem SL          | 1 (295)      | MD -18 [CI NR].  | Medium       | Direct     | Precise   | Unknown      | Undetected     | Insufficient    |
|   | Zolpidem ER          | 1 (1018)     | Greater with zolpidem ER (graphically displayed)   | Medium       | Direct     | Unknown   | Unknown      | Suspected      | Insufficient    |
| Subjective total sleep time (minutes)*    | Eszopiclone          | 3 (1820)     | WMD 44.8 [35.4, 54.2]  | Medium       | Direct     | Precise   | Consistent   |                | Moderate        |
|   | Zaleplon             | 2 (930)      | NA, not pooled<br>NS versus placebo  | Medium       | Direct     | Unclear   | Consistent   | Suspected      | Low             |
|   | Zolpidem             | 4 (704)      | NA, not pooled. mixed results versus placebo   | Medium       | Direct     | Imprecise | Inconsistent | Suspected      | Low             |
|   | Zolpidem “as needed” | 2 (355)      | WMD 48.1 [34.8, 61.5]  | Medium       | Direct     | Precise   | Consistent   | Undetected     | Moderate        |
|   | Zolpidem SL          | 1 (295)      | NS versus placebo, data NR   | Medium       | Direct     | Imprecise | Unknown      | Suspected      | Insufficient    |
|   | Zolpidem ER          | 1 (1018)     | Greater with zolpidem ER (graphically displayed)   | Medium       | Direct     | Unknown   | Unknown      | Suspected      | Insufficient    |
|   |                      |              |  |              |            |           |              |                |                 |
| Wake time after sleep onset               | Eszopiclone          | 3 (1820)     | WMD -10.8 [-19.8, -1.70];  | Medium       | Direct     | Precise   | Inconsistent | Undetected     | Low             |
|   | Zaleplon             | NR           |  |              |            |           |              |                | Insufficient    |
|   | Zolpidem             | NR           |  |              |            |           |              |                | Insufficient    |
|   | Zolpidem “as needed” | 2 (437)      | Score at endpoint (1 trial)<br>MD -22.80 [-36.98 to -8.62]<br>Mean change (1 trial)<br>MD -1.40 [-10.77 to 7.97] | Medium       | Direct     | Imprecise | Inconsistent | Undetected     | Low             |
|   | Zolpidem SL          | 1 (295)      |  | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Insufficient    |
|   | Zolpidem ER          | 1 (1018)     | Greater with zolpidem ER (graphically displayed)   | Medium       | Direct     | Unknown   | Unknown      | Suspected      | Insufficient    |

| Outcome                                    | Type                 | # Trials (n) | Summary statistics, [95% CI]  | Risk of Bias | Directness | Precision | Consistency  | Reporting Bias | Evidence Rating |
|--|----------------------|--------------|---|--------------|------------|-----------|--------------|----------------|-----------------|
| Sleep efficiency                           | Eszopiclone          | NR           |   |              |            |           |              |                | Insufficient    |
|  | Zaleplon             | NR           |   |              |            |           |              |                | Insufficient    |
|  | Zolpidem             | NR           |   |              |            |           |              |                | Insufficient    |
|  | Zolpidem "as needed" | NR           |   |              |            |           |              |                | Insufficient    |
|  | Zolpidem SL          | NR           |   |              |            |           |              |                | Insufficient    |
|  | Zolpidem ER          | NR           |   |              |            |           |              |                | Insufficient    |
| Sleep quality                              | Eszopiclone          | 2 (992)      | SMD 0.47 [0.32, 0.61]   | Medium       | Direct     | Precise   | Consistent   | Undetected     | Moderate        |
|  | Zaleplon             | 2 (879)      | RR 1.19 [1.02 to 1.38]  | Medium       | Direct     | Precise   | Consistent   | Undetected     | Moderate        |
|  | Zolpidem             | 3 (557)      | RR 1.40 [1.20 to 1.65]  | Medium       | Direct     | Imprecise | Consistent   | Undetected     | Moderate        |
|  | Zolpidem "as needed" | 2 (408)      | Not pooled.<br>Mean change (1 trial)<br>SMD 0.32 [0.07 to 0.58];<br>"significant improvement vs. placebo (data not shown) (1 trial) | Medium       | Direct     | Precise   | Consistent   | Suspected      | Low             |
|  | Zolpidem SL          |              | SMD 0.38 [0.15, 0.61]   | Medium       | Direct     | Precise   | Unknown      | Undetected     | Insufficient    |
|  | Zolpidem ER          | NR           |   |              |            |           |              |                | Insufficient    |
| <b>Adverse Effects</b>                     |                      |              |   |              |            |           |              |                |                 |
| Study withdrawals                          | Eszopiclone          | 3 (1927)     | RR 0.81 [0.66 to 1.00]  | Medium       | Direct     | Imprecise | Inconsistent | Undetected     | Low             |
|  | Zaleplon             | 2 (971)      | RR 1.42 [0.89 to 2.26]  | Medium       | Direct     | Imprecise | Consistent   | Undetected     | Low             |
|  | Zolpidem             | 4 (704)      | RR 1.31 [0.86 to 2.01]  | Medium       | Direct     | Imprecise | Consistent   | Undetected     | Low             |
|  | Zolpidem "as needed" | 3 (607)      | RR 1.0 [0.5 to 2.0]   | Medium       | Direct     | Imprecise | Inconsistent | Undetected     | Low             |
|  | Zolpidem SL          | 1 (295)      | RR 1.44 [0.61, 3.42]  | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Insufficient    |
|  | Zolpidem ER          | 1 (1018)     | RR 0.74 [0.64, 0.86]  | Medium       | Direct     | Precise   | Unknown      | Undetected     | Low             |
| Study withdrawals due to an adverse effect | Eszopiclone          | 3 (1927)     | RR 1.4 [0.97 to 2.0]  | Medium       | Direct     | Imprecise | Consistent   | Undetected     | Low             |
|  | Zaleplon             | 2 (965)      | RR 1.63 [0.69 to 3.88]  | Medium       | Direct     | Imprecise | Consistent   | Undetected     | Low             |
|  | Zolpidem             | 4 (703)      | RR 2.65 [1.12 to 6.28]  | Medium       | Direct     | Precise   | Consistent   | Undetected     | Moderate        |
|  | Zolpidem "as needed" | 3 (607)      | RR 2.8 [0.95 to 8.0]  | Medium       | Direct     | Imprecise | Consistent   | Undetected     | Insufficient    |
|  | Zolpidem SL          | 1 (295)      | RR 0.32 [0.01, 7.79]  | Medium       | Direct     | Imprecise | Unknown t    | Undetected     | Insufficient    |
|  | Zolpidem ER          | 1 (1018)     | RR 1.79 [1.04, 3.08]  | Medium       | Direct     | Precise   | Unknown      | Undetected     | Low             |
| Patients with ≥1 adverse effect            | Eszopiclone          | 2 (1616)     | RR 1.2 [1.1 to 1.4]   | Medium       | Direct     | Precise   | Consistent   | Undetected     | Moderate        |
|  | Zaleplon             | 2 (688)      | RR 0.96 [0.89 to 1.05]  | Medium       | Direct     | Precise   | Consistent   | Undetected     | Moderate        |
|  | Zolpidem             | 4 (698)      | RR 1.05 [0.91 to 1.21]  | Medium       | Direct     | Precise   | Consistent   | Undetected     | Moderate        |
|  | Zolpidem "as         |              |   |              |            |           |              |                |                 |

| Outcome | Type        | # Trials (n) | Summary statistics, [95% CI] | Risk of Bias | Directness | Precision | Consistency | Reporting Bias | Evidence Rating |
|---------|-------------|--------------|------------------------------|--------------|------------|-----------|-------------|----------------|-----------------|
|         | needed"     | 1 (245)      | RR 1.3 [0.7, 2.2]            | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Low             |
|         | Zolpidem SL | NR           |                              |              |            |           |             |                | Insufficient    |
|         | Zolpidem ER | 1 (1018)     | RR 1.23 [1.10, 1.39]         | Medium       | Direct     | Precise   | Unknown     | Undetected     | Low             |

ER=extended release; MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio; SL=sublingual

**Table D3. Efficacy of nonbenzodiazepines in older adults: strength of evidence assessments**

| Outcome                                    | Type        | # Trials (n) | Summary statistics, [95% CI] | Risk of Bias | Directness | Precision | Consistency | Reporting Bias | Evidence Rating |
|--|-------------|--------------|------------------------------|--------------|------------|-----------|-------------|----------------|-----------------|
| <b>Global</b>                              |             |              |                              |              |            |           |             |                |                 |
| Clinical global outcome                    | Eszopiclone | 1 (386)      | RR 1.51 [1.11, 2.06]         | Medium       | Direct     | Precise   | Unknown     | Undetected     | Low             |
|  | Zolpidem    | NR           |                              |              |            |           |             |                | Insufficient    |
| <b>Sleep</b>                               |             |              |                              |              |            |           |             |                |                 |
| Subjective sleep onset latency (minutes)*  | Eszopiclone | 1 (382)      | MD -4.90 [-15.32, 5.52]      | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Low             |
|  | Zolpidem    | 1 (152)      | MD -18.3 [-31.2, -5.4]       | Medium       | Direct     | Precise   | Unknown     | Undetected     | Insufficient    |
| Subjective total sleep time (minutes)*     | Eszopiclone | 1 (382)      | MD 30.0 [19.7, 40.3]         | Medium       | Direct     | Precise   | Unknown     | Undetected     | Low             |
|  | Zolpidem    | 1 (152)      | MD 18.20 [-3.16, 39.56]      | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
| Wake time after sleep onset                | Eszopiclone | 1 (380)      | MD -21.6 [-29.6, -13.6]      | Medium       | Direct     | Precise   | Unknown     | Undetected     | Low             |
|  | Zolpidem    | NR           |                              |              |            |           |             |                | Insufficient    |
| Sleep efficiency                           | Eszopiclone | NR           |                              |              |            |           |             |                | Insufficient    |
|  | Zolpidem    | NR           |                              |              |            |           |             |                | Insufficient    |
| Sleep quality                              | Eszopiclone | 1 (388)      | SMD 0.24 [0.04, 0.44]        | Medium       | Direct     | Precise   | Unknown     | Undetected     | Low             |
|  | Zolpidem    | NR           |                              |              |            |           |             |                | Insufficient    |
| <b>Adverse Effects</b>                     |             |              |                              |              |            |           |             |                |                 |
| Study withdrawals                          | Eszopiclone | 1 (388)      | RR 1.02 [0.72, 1.46]         | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Low             |
|  | Zolpidem    | 1 (166)      | RR 0.61 [0.23, 1.61]         | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
| Study withdrawals due to an adverse effect | Eszopiclone | 1 (388)      | RR 1.56 [0.69, 3.51]         | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
|  | Zolpidem    | 1 (166)      | RR 0.34 [0.07, 1.64]         | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
| Patients with ≥1 adverse effect            | Eszopiclone | 1 (388)      | RR 1.17 [0.98, 1.41]         | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Low             |
|  | Zolpidem    | 1 (166)      | RR 1.13 [0.88, 1.46]         | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

**Table D4. Efficacy of melatonin and ramelteon in the general adult population: strength of evidence assessments**

| Outcome                                    | Type      | # Trials (n) | Summary statistics, [95% CI]                    | Risk of Bias | Directness | Precision | Consistency  | Reporting Bias | Evidence Rating |
|--|-----------|--------------|---|--------------|------------|-----------|--------------|----------------|-----------------|
| <b>Global</b>                              |           |              |   |              |            |           |              |                |                 |
| Clinical global outcome                    | Melatonin | 1 (700)      | MD -0.39 [-0.71 to -0.08]                       | Medium       | Direct     | Precise   | Unknown      | Suspected      | Insufficient    |
|  | Ramelteon | NR           |   |              |            |           |              |                | Insufficient    |
| <b>Sleep</b>                               |           |              |   |              |            |           |              |                |                 |
| Subjective sleep onset latency (minutes)*  | Melatonin | 1 (700)      | MD -6 [-10 to -2]                               | Medium       | Direct     | Precise   | Consistent   | Suspected      | Low             |
|  | Ramelteon | 5 (2972)     | WMD -3.1 [-7.4 to 1.2]                          | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Low             |
| Subjective total sleep time (minutes)*     | Melatonin | NR           |   |              |            |           |              |                | Insufficient    |
|  | Ramelteon | 5 (2781)     | WMD 0.08 [-10 to 10.1]                          | Medium       | Direct     | Imprecise | Inconsistent | Undetected     | Low             |
| Wake time after sleep onset                | Melatonin | NR           |   |              |            |           |              |                | Insufficient    |
|  | Ramelteon | 2 (721)      | WMD 5.9 [-6.1 to 17.9]                          | Medium       | Direct     | Imprecise | Consistent   | Undetected     | Low             |
| Sleep efficiency                           | Melatonin | NR           |   |              |            |           |              |                | Insufficient    |
|  | Ramelteon | NR           |   |              |            |           |              |                | Insufficient    |
| Sleep quality                              | Melatonin | NR           |   |              |            |           |              |                | Insufficient    |
|  | Ramelteon | 5 (2973)     | WMD -0.08 [-0.16 to -0.01]                      | Medium       | Direct     | Imprecise | Inconsistent | Undetected     | Low             |
| <b>Adverse Effects</b>                     |           |              |   |              |            |           |              |                |                 |
| Study withdrawals                          | Melatonin | 1 (711)      | RR 0.87 [0.64 to 1.18]                          | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Insufficient    |
|  | Ramelteon | 2 (1594)     | RR 1.47 [1.11 to 1.94]<br>RD 0.05 [-0.02, 0.12] | Medium       | Direct     | Imprecise | Consistent   | Undetected     | Low             |
| Study withdrawals due to an adverse effect | Melatonin | 1 (711)      | RR 0.86 [0.42 to 1.75]                          | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Insufficient    |
|  | Ramelteon | 3 (1999)     | RR 1.23 [0.47 to 3.25]                          | Medium       | Direct     | Imprecise | Consistent   | Undetected     | Low             |
| Patients with ≥1 adverse effect            | Melatonin | 1 (711)      | RR 0.77 [0.49 to 1.21]                          | Medium       | Direct     | Imprecise | Unknown      | Undetected     | Low             |
|  | Ramelteon | 3 (1999)     | RR 1.03 [0.93 to 1.13]                          | Medium       | Direct     | Precise   | Consistent   | Undetected     | Moderate        |

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

**Table D5. Efficacy of ramelteon in older adults: strength of evidence assessments**

| Outcome                                    | Type      | # Trials (n) | Summary statistics, [95% CI] | Risk of Bias | Directness | Precision | Consistency | Reporting Bias | Evidence Rating |
|--|-----------|--------------|------------------------------|--------------|------------|-----------|-------------|----------------|-----------------|
| <b>Global</b>                              |           |              |                              |              |            |           |             |                |                 |
| Clinical global outcome                    | Ramelteon | NR           |                              |              |            |           |             |                | Insufficient    |
| <b>Sleep</b>                               |           |              |                              |              |            |           |             |                |                 |
| Subjective sleep onset latency (minutes)*  | Ramelteon | 1 (826)      | MD -10.1 [-15.6, -4.6]       | Medium       | Direct     | Precise   | Unknown     | Undetected     | Low             |
| Subjective total sleep time (minutes)*     | Ramelteon | 1 (825)      | MD 5.90 [-1.95, 13.75]       | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Low             |
| Wake time after sleep onset                | Ramelteon | NR           |                              |              |            |           |             |                | Insufficient    |
| Sleep efficiency                           | Ramelteon | NR           |                              |              |            |           |             |                | Insufficient    |
| Sleep quality                              | Ramelteon | 1 (826)      | SMD -0.10 [-0.27, 0.07]      | Medium       | Direct     | Precise   | Unknown     | Undetected     | Low             |
| <b>Adverse Effects</b>                     |           |              |                              |              |            |           |             |                |                 |
| Study withdrawals                          | Ramelteon | 1 (829)      | RR 0.88 [0.63, 1.23]         | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Low             |
| Study withdrawals due to an adverse effect | Ramelteon | 1 (829)      | RR 0.93 [0.40, 2.16]         | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
| Patients with ≥1 adverse effect            | Ramelteon | 1 (829)      | RR 1.10 [0.96, 1.26]         | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Low             |

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

**Table D6. Efficacy of benzodiazepines in the general adult population: strength of evidence assessments**

| Outcome   | Benzodiazepine type | Number of trials | n   | Summary statistics, WMD or MD [95% CI] | Risk of bias | Directness | Precision | Consistency | Reporting bias | Evidence rating |
|---|---------------------|------------------|-----|--|--------------|------------|-----------|-------------|----------------|-----------------|
| <b>Global</b>   |                     |                  |     |  |              |            |           |             |                |                 |
| <b>Clinical Global Impression responders: (much-very much improved) or ISI score “clinically reduced” (percent reporting)</b> | Triazolam           | 0                | NA  | NR                                     | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Flurazepam          | 0                | NA  | NR                                     | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Quazepam            | 0                | NA  | NR                                     | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Temazepam           | 0                | NA  | NR                                     | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Temazepam           | 0                | NA  | NR                                     | NA           | NA         | NA        | NA          | NA             | Insufficient    |
| <b>Sleep</b>  |                     |                  |     |  |              |            |           |             |                |                 |
| <b>Subjective sleep latency (minutes)*</b>  | Triazolam           | 1                | 14  | NA <sup>a</sup>                        | Medium-high  | NA         | NA        | NA          | Suspected      | Insufficient    |
|   | Flurazepam          | 1                | 14  | NA <sup>a</sup>                        | Medium-high  | NA         | NA        | NA          | Suspected      | Insufficient    |
|   | Quazepam            | 1                | 108 | NA <sup>a</sup>                        | High         | NA         | NA        | NA          | Suspected      | Insufficient    |
|   | Temazepam           | 1                | 34  | MD: -30.9 (-51.20 to -10.60)           | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
| <b>Subjective total sleep time (minutes)*</b>   | Triazolam           | 1                | 14  | NA <sup>a</sup>                        | Medium-high  | NA         | NA        | NA          | Suspected      | Insufficient    |
|   | Flurazepam          | 1                | 14  | NA <sup>a</sup>                        | Medium-high  | NA         | NA        | NA          | Suspected      | Insufficient    |
|   | Quazepam            | 1                | 108 | NA <sup>a</sup>                        | High         | NA         | NA        | NA          | Suspected      | Insufficient    |
|   | Temazepam Morin     | 1                | 35  | MD: 33.2 (-8.77 to 75.17)              | Low          | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
|   | Temazepam Wu        | 1                | 34  | MD 93.5 min (45.84 to 141.16)          | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
| <b>Insomnia Severity Index (score)</b>  | Triazolam           | 0                | NA  | NR                                     | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Flurazepam          | 0                | NA  | NR                                     | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Quazepam            | 0                | NA  | NR                                     | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Temazepam           | 0                | NA  | NR                                     | NA           | NA         | NA        | NA          | NA             | Insufficient    |
| <b>Adverse Effects</b>  |                     |                  |     |  |              |            |           |             |                |                 |
| <b>Study withdrawals</b>  | Any benzodi-        | 2                | 147 | RR: 0.77 (0.47 to 1.25)                | Medium       | Direct     | Imprecise | Consistent  | Suspected      | Insufficient    |

| Outcome   | Benzodiazepine type | Number of trials | n   | Summary statistics, WMD or MD [95% CI] | Risk of bias | Directness | Precision | Consistency | Reporting bias | Evidence rating |
|---|---------------------|------------------|-----|--|--------------|------------|-----------|-------------|----------------|-----------------|
|   | azepine             |                  |     |  |              |            |           |             |                |                 |
| <b>Study withdrawals due to an adverse effect</b>       | Any benzodiazepine  | 2                | 147 | RR: 1.54 (0.42 to 5.63)                | Medium       | Direct     | Imprecise | Consistent  | Suspected      | Insufficient    |
| <b>Patients with <math>\geq 1</math> adverse effect</b> | Any benzodiazepine  | 0                | NA  |  | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |

MD=mean difference; NA=not applicable; NR=not reported; WMD-weighted mean difference

<sup>a</sup>Re summary statistics for sleep latency and TST: studies did not report a measure of variance so outcomes could not be calculated for specific doses or pooled.

**Table D7. Efficacy of antidepressants in the general adult population: strength of evidence assessments**

| Outcome  | Anti-depressant | Number of Trials | n   | Summary statistics, [95% CI] <sup>a</sup>            | Risk of Bias  | Directness | Precision | Consistency | Reporting Bias | Evidence Rating |
|--|-----------------|------------------|-----|--|---------------|------------|-----------|-------------|----------------|-----------------|
| <b>Global</b>  |                 |                  |     |  |               |            |           |             |                |                 |
| Clinical Global Impression responders: (much-very much improved) or ISI score “clinically reduced” (percent reporting) | Doxepin         | 1                | 40  | MD -0.58 (-1.05 to -0.12)                            | Medium        | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
|  | Trazodone       | 0                | 0   | NA   | NA            | NA         | NA        | NA          | NA             | Insufficient    |
| Insomnia Severity Index (score)  | Doxepin         | 0                | 0   | NA   | NA            | NA         | NA        | NA          | NA             | Insufficient    |
|  | Trazodone       | 1                | 20  | MD 0.9 (-3.14 to 4.94)                               | Moderate-High | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
| <b>Sleep</b>   |                 |                  |     |  |               |            |           |             |                |                 |
| Subjective sleep latency (minutes)   | Doxepin         | 0                | 0   | NA   | NA            | NA         | NA        | NA          | NA             | Insufficient    |
|  | Trazodone       | 0                | 0   | NA   | NA            | NA         | NA        | NA          | NA             | Insufficient    |
| Subjective total sleep time (minutes)  | Doxepin         | 1                | 221 | 3 mg: MD 11.9 (SE, 5.97)<br>6 mg: MD 17.3 (SE, 5.96) | Moderate      | Direct     | Precise   | Unknown     | Suspected      | Insufficient    |
|  | Trazodone       | 0                | 0   | NA   | NA            | NA         | NA        | NA          | NA             | Insufficient    |
| Insomnia Severity Index (score)  | Doxepin         | 0                | 0   | NA   | NA            | NA         | NA        | NA          | NA             | Insufficient    |
|  | Trazodone       | 1                | 20  | MD 0.9 (-3.14 to 4.94)                               | Moderate-High | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
| <b>Adverse Effects</b>   |                 |                  |     |  |               |            |           |             |                |                 |
| Study withdrawals  | Doxepin         | 2                | 276 | RR 1.01 (0.52 to 1.96)                               | Moderate      | Direct     | Precise   | Consistent  | Undetected     | Insufficient    |
|  | Trazodone       | 1                | 20  | RR 1.00 (0.02 to 46.06)                              | Moderate-High | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
| Study withdrawals due to an adverse event  | Doxepin         | 2                | 276 | RR 1.19 (0.36 to 3.93)                               | Moderate      | Direct     | Precise   | Consistent  | Undetected     | Insufficient    |
|  | Trazodone       | 1                | 20  | RR 1.00 (0.02 to 46.06)                              | Moderate-High | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
| Patients with ≥1 adverse event   | Doxepin         | 2                | 268 | RR 1.11 (0.96 to 1.27)                               | Moderate      | Direct     | Precise   | Consistent  | Undetected     | Low             |
|  | Trazodone       | 0                | 0   | NA   | NA            | N/A        | N/A       | N/A         | N/A            | Insufficient    |

CI=confidence interval; MD=mean difference; n=number of participants; RR = relative risk; SE=standard error

<sup>a</sup> Analyses based on outcomes measures only. In some cases, significance of outcomes differs from that in primary studies, which incorporated baseline values and/or center in analysis.

**Table D8. Efficacy of antidepressants in older adults: strength of evidence assessments**

| Outcome  | Antidepressant Age | Number of trials | n   | Summary statistics, [95% CI] <sup>a</sup>  | Risk of bias | Directness | Precision | Consistency  | Reporting bias | Evidence rating |
|--|--------------------|------------------|-----|--|--------------|------------|-----------|--------------|----------------|-----------------|
| <b>Global</b>  |                    |                  |     |  |              |            |           |              |                |                 |
| Clinical Global Impression responders: (much-very much improved) | Doxepin            | 2                | 494 | 4 weeks<br>1 mg MD: -0.2<br>(-0.53 to 0.13)<br>3 mg MD: -0.4<br>(-0.76 to -0.04)<br>6 mg MD: -0.3<br>(-0.57 to -0.03)        | Low          | Direct     | Precise   | Consistent   | Suspected      | Low             |
| Insomnia Severity Index (score)                                  | Doxepin            | 2                | 494 | 4 weeks<br>1 mg SMD: -0.36<br>(-0.67 to -0.05)<br>3 mg SMD: -0.42<br>(-0.73 to -0.11)<br>6 mg SMD: -0.26<br>(-0.51 to -0.02) | Low          | Direct     | Precise   | Consistent   | Suspected      | Low             |
| <b>Sleep Outcomes</b>  |                    |                  |     |  |              |            |           |              |                |                 |
| Subjective sleep latency (minutes)                               | Doxepin            | 1                | 240 | 4 weeks<br>1 mg MD: -11.30<br>(-21.75 to -0.85)<br>3 mg MD: -7.90<br>(-21.14 to 5.34)  | Low          | Direct     | Imprecise | Inconsistent | Undetected     | Insufficient    |
| Subjective total sleep time (minutes)                            | Doxepin            | 2                | 494 | 4 weeks<br>1 mg WMD: 31.30<br>(8.72 to 53.88)<br>3 mg WMD: 45.50<br>(22.51 to 68.49)<br>6 mg WMD: 9.70<br>(-6.42 to 25.82)   | Low          | Direct     | Imprecise | Inconsistent | Suspected      |                 |
| <b>Adverse Effects</b>   |                    |                  |     |  |              |            |           |              |                |                 |
| Study withdrawals  | Doxepin            | 2                | 495 | RR 0.63<br>(0.36 to 1.12)  | Low          | Direct     | Imprecise | Consistent   | Undetected     | Insufficient    |
| Study withdrawals due to an adverse event                        | Doxepin            | 2                | 495 | RR 0.73<br>(0.20 to 2.69)  | Low          | Direct     | Imprecise | Consistent   | Undetected     | Insufficient    |
| Patients with ≥ 1 adverse event                                  | Doxepin            | 2                | 494 | RR 0.87<br>(0.60 to 1.26)  | Low          | Direct     | Imprecise | Consistent   | Undetected     | Low             |

CI=confidence interval; MD=mean difference; n=number of participants; RR = relative risk; SMD = standardized mean difference; WMD = weighted mean difference

<sup>a</sup>Analyses based on outcome measures only. In some cases, significance of outcomes differs from that reported in RCT, which incorporated baseline values and/or center in analysis.

**Table D9. Comparative effectiveness of pharmaceutical treatments: strength of evidence assessments**

| Outcome                                    | Type                   | # Trials (n) | Summary statistics, [95% CI]  | Risk of Bias | Directness | Precision | Consistency | Reporting Bias | Evidence Rating |
|--|------------------------|--------------|---|--------------|------------|-----------|-------------|----------------|-----------------|
| <b>Global</b>                              |                        |              |   |              |            |           |             |                |                 |
| Clinical global outcome                    | Zolpidem vs. Temazepam | 1 (157)      |   | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
|  | Zaleplon vs. Zolpidem  | NR           |   |              |            |           |             |                | Insufficient    |
| <b>Sleep</b>                               |                        |              |   |              |            |           |             |                |                 |
| Subjective sleep onset latency (minutes)*  | Zolpidem vs. Temazepam | 1 (159)      | MD 0.00 [-10.43 to 10.43]   | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
|  | Zaleplon vs. Zolpidem  | 1 (301)      | MD -13.7 [-25.1 to -2.3] favoring zolpidem 10 mg vs. zaleplon 5 mg<br>NS zolpidem 10 mg versus zaleplon 10 mg | Medium       | Direct     | Precise   | Unknown     | Undetected     | Insufficient    |
| Subjective total sleep time (minutes)*     | Zolpidem vs. Temazepam | 1 (159)      | MD 27.0 [2.1 to 51.9] favoring zolpidem   | Medium       | Direct     | Precise   | Unknown     | Undetected     | Insufficient    |
|  | Zaleplon vs. Zolpidem  | 2 (965)      | No direct comparison and reported data does not allow analysis  |              |            |           |             | Suspected      | Insufficient    |
| Wake time after sleep onset                | Zolpidem vs. Temazepam | 1 (159)      | MD 1.00 [-10.51 to 12.51]   | Medium       | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
|  | Zaleplon vs. Zolpidem  | NR           |   |              |            |           |             |                | Insufficient    |
| Sleep efficiency                           | Zolpidem vs. Temazepam | NR           |   |              |            |           |             |                | Insufficient    |
|  | Zaleplon vs. Zolpidem  | NR           |   |              |            |           |             |                | Insufficient    |
| Sleep quality                              | Zolpidem vs. Temazepam | NR           |   |              |            |           |             |                | Insufficient    |
|  | Zaleplon vs. Zolpidem  | 2 (870)      | RR 0.90 [0.80 to 1.01]  | Medium       | Direct     | Precise   | Consistent  | Undetected     | Moderate        |
| <b>Adverse Effects</b>                     |                        |              |   |              |            |           |             |                |                 |
| Study withdrawals                          | Zolpidem vs. Temazepam | NR           |   |              |            |           |             |                | Insufficient    |
|  | Zaleplon vs. Zolpidem  | 2 (965)      | RR 0.98 [0.66 to 1.46]  | Medium       | Direct     | Imprecise | Consistent  | Undetected     | Low             |
| Study withdrawals due to an adverse effect | Zolpidem vs. Temazepam | NR           |   |              |            |           |             |                | Insufficient    |
|  | Zaleplon vs. Zolpidem  | 2 (958)      | RR 0.68 [0.36 to 1.27]  | Medium       | Direct     | Imprecise | Consistent  | Undetected     | Low             |

| Outcome                               | Type                   | # Trials (n) | Summary statistics, [95% CI] | Risk of Bias | Directness | Precision | Consistency | Reporting Bias | Evidence Rating |
|---------------------------------------|------------------------|--------------|------------------------------|--------------|------------|-----------|-------------|----------------|-----------------|
| Patients with $\geq 1$ adverse effect | Zolpidem vs. Temazepam | NR           |                              |              |            |           |             |                | Insufficient    |
|                                       | Zaleplon vs. Zolpidem  | 2 (958)      | RR 0.95 [0.87 to 1.03]       | Medium       | Direct     | Precise   | Consistent  | Undetected     | Moderate        |

MD=mean difference; NA=not applicable; NR=not reported; RR=risk ratio; WMD=weighted mean difference

Appendix E. Complementary and Alternative Medicine  
Interventions Supporting Tables:

**Table E1. Complementary and alternative health interventions: AMSTAR assessments of previous systematic reviews**

| Topic (Author, Year)                   | A <i>Priori</i> Design | Dual Review  | Search Strategy | Inclusion Criteria | Included/ Excluded/ Identified | Study Charac-teristics | Study RoB | SoE | Stat Analysis | Pub Bias | COI | Comments  | Overall Assessment |
|--|------------------------|--------------|-----------------|--------------------|--------------------------------|------------------------|-----------|-----|---------------|----------|-----|---|--------------------|
| Acupuncture Cheuk, 2012 <sup>113</sup> | Yes                    | Yes          | Yes             | Yes                | Yes                            | Yes                    | Yes       | Yes | Yes           | Yes      | No  |   | High               |
| Homeopathy Cooper, 2010 <sup>114</sup> | Yes                    | Can't answer | Yes             | Yes                | Yes                            | Yes                    | Yes       | Yes | No            | No       | No  | No mention of how many independent data extractors  | Fair               |
| Valerian Taibi, 2007 <sup>115</sup>    | Yes                    | Can't answer | Yes             | Yes                | Yes                            | Yes                    | Yes       | Yes | No            | No       | Yes | No mention of how many independent extractors, ?how homogeneity assessed, ?assessment of publication bias | Fair               |

Include abbreviations from table

**Table E2. Complementary and alternative medicine interventions for insomnia disorder: risk of bias assessments**

| <b>Study</b>                  | <b>Risk of Bias Assessment</b>   |
|-------------------------------|--|
| Hachul, 2013 <sup>116</sup>   | Moderate-High: (if pooled)/High (if unpooled): Underpowered/no sample size calculation; possible Type II error; Attrition NR; Multiple comparisons correction unclear; Only PSG sleep values.  |
| Harrison, 2013 <sup>117</sup> | Moderate-High: Blocked randomization: one of a pair of matched participants "randomly selected" a bottle from box A or box B; the other of the pair got the bottle from the other box; may have low power due to small sample size; no power/sample size calculation; 6/34 (18%) attrition; completer-only analyses; most data for SOL is presented as 5-point categorical scale; no ITT analysis. |
| Huo, 2013 <sup>118</sup>      | Moderate<br>Randomized based on random number table; no power analysis and sample size/power calculation, but found significant differences; 0/60 (0%) attrition; blinding unclear.  |
| Lin, 2013 <sup>119</sup>      | Low-Moderate: Not ITT analysis: computer-generated randomization; opaque envelopes; triple blinded with investigators, patients and statisticians blinded to treatment group; power analysis and sample size calculation; achieved desired sample size; 26/212 (12%) attrition; completer-only analyses  |
| Abbasi, 2012 <sup>120</sup>   | Moderate: Assessor blinding unclear. Not ITT analysis. No correction for multiple comparisons; randomization suspect; possibly underpowered.   |
| Afonso, 2012 <sup>121</sup>   | High: High attrition; No ITT analysis; Unblinded; no adjustment for multiple comparisons or 3-way comparisons  |
| Oliveira, 2012 <sup>122</sup> | Moderate-High: Blinding unclear. Doesn't appear to be ITT analysis; Blinding not mentioned; no adjustment for multiple comparisons; no sample size/power calculation; 8/52 (15%) attrition, reasons NR by treatment group; completer-only analysis; data for ISI must be estimated from figure   |
| Hachul, 2011 <sup>123</sup>   | Moderate<br>low attrition; no mention of how missing data were handled; possible reporting bias; no correction for multiple comparisons; possibly underpowered.  |
| Zick, 2011 <sup>124</sup>     | Low-Moderate:<br>blinding and randomization adequate; possibly underpowered.   |
| Zhang, 2010 <sup>126</sup>    | Moderate-High: blinding unclear; attrition unclear; no adjustment for multiple comparisons; possibly underpowered.   |

ISI= Insomnia Sleep Index; NS= not significant; PSG= polysomnography; SE= sleep efficiency; SOL= sleep onset latency; TST= total sleep time

**Table E3. Complementary and Alternative Medicine, Placebo-controlled Trials<sup>a</sup>: Strength of Evidence**

| Outcome   | CAM Intervention    | Number of trials | n                                       | Summary statistics, [95% CI] | Risk of bias | Directness | Precision | Consistency | Reporting bias | Evidence rating |
|---|---------------------|------------------|---|------------------------------|--------------|------------|-----------|-------------|----------------|-----------------|
| <b>Clinical Global Impression responders: (much-very much improved) or ISI score “clinically reduced” (percent reporting)</b> | Magnesium           | 0                | NA                                      | NA                           | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Isoflavone          | 0                | NA                                      | NA                           | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Homeopathic complex | 0                | NA                                      | NA                           | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Wuling capsule      | 0                | NA                                      | NA                           | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Simillimum          | 0                | NA                                      | NA                           | NA           | NA         | NA        | NA          | NA             | Insufficient    |
| Chamomile   | 0                   | NA               | NA                                      | NA                           | NA           | NA         | NA        | NA          | Insufficient   |                 |
| <b>Subjective sleep latency (minutes)</b>   | Magnesium           | 1                | 43                                      | MD: -18 (-29.60 to -6.40)    | Low          | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
|   | Isoflavone          | 0                | NA                                      | NA                           | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Homeopathic complex | 1                | 27                                      | MD: -1.3 <sup>bc</sup>       | Moderate     | Direct     | Unknown   | Unknown     | Undetected     | Insufficient    |
|   | Wuling capsule      | 0                | NA                                      | NA                           | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Simillimum          | 0                | NA                                      | NA                           | NA           | NA         | NA        | NA          | NA             | Insufficient    |
| Chamomile   | 1                   | 34               | MD: 1.3 (-2.59 to 5.19)                 | Low                          | Direct       | Imprecise  | Unknown   | Undetected  | Insufficient   |                 |
| <b>Subjective total sleep time (minutes)</b>  | Magnesium           | 1                | 43                                      | MD: 18 (-8.23 to 44.23)      | Low          | Direct     | Imprecise | Unknown     | Undetected     | Insufficient    |
|   | Isoflavone          | 0                | NA                                      | NA                           | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Homeopathic complex | 0                | NA                                      | NA                           | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Wuling capsule      | 0                | NA                                      | NA                           | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Simillimum          | 1                | 30                                      | 0.9 <sup>c</sup>             | High         | Direct     | Unknown   | Unknown     | Suspected      | Insufficient    |
| Chamomile   | 1                   | 34               | MD <sup>n</sup> : -24 (-70.30 to 22.30) | Low                          | Direct       | Imprecise  | Unknown   | Undetected  | Insufficient   |                 |
| <b>Insomnia Severity Index (score)</b>  | Magnesium           | 1                | 43                                      | MD: -1.63 (-3.06 to -.20)    | Low          | Direct     | Precise   | Unknown     | Undetected     | Insufficient    |
|   | Isoflavone          | 0                | NA                                      | NA                           | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Homeopathic complex | 0                | NA                                      | NA                           | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Wuling capsule      | 0                | NA                                      | NA                           | NA           | NA         | NA        | NA          | NA             | Insufficient    |
|   | Simillimum          | 0                | NA                                      | NA                           | NA           | NA         | NA        | NA          | Suspected      | Insufficient    |
| Chamomile   | 1                   | 34               | MD: 0.3 (-2.91 to 3.51)                 | Low                          | Direct       | Imprecise  | Unknown   | Undetected  | Insufficient   |                 |

| Outcome                                   | CAM Intervention | Number of trials | n   | Summary statistics, [95% CI]  | Risk of bias | Directness | Precision | Consistency  | Reporting bias | Evidence rating |
|---|------------------|------------------|-----|-------------------------------|--------------|------------|-----------|--------------|----------------|-----------------|
| Study withdrawals                         | Any CAM          | 4                | 313 | MD: 0.03<br>(-.04 to 0.10)    | Moderate     | Direct     | Precise   | Consistent   | Suspected      | Low             |
| Study withdrawals due to an adverse event | Any CAM          | 4                | 320 | MD: .006<br>(-0.006 to 0.018) | Low          | Direct     | Precise   | Consistent   | Suspected      | Moderate        |
| Patients with $\geq 1$ adverse event      | Any CAM          | 2                | 250 | MD: 0.024<br>(0-.034 to 0.08) | Moderate     | Direct     | Imprecise | Inconsistent | Suspected      | Low             |

CAM=complementary and alternative medicine; MD: mean difference; MP: mean proportion

<sup>a</sup> Other CAM studies did not have placebo control: Afonso et al 2012 compared passive stretching, yoga, and no treatment; Oliveira et al compared therapeutic massage, passive movement, and "control."

<sup>b</sup> On scale where 0 = 0-15 min; 1 = 15-30 min; 2 = 30-45 min; 3 = 45-60 min; and 4 = 60+ min; difference in medians reported as significant at 7.04 minutes.

<sup>c</sup> Measures of variance not reported and not calculable.

**Appendix F. Comparative Effectiveness Trials –  
Across Intervention Types Supporting Tables**

**Table F1. Previous Systematic reviews used in lieu of de novo data extraction: AMSTAR Assessments**

| Topic SR (Author year)                   | A priori design | Dual review | Search strategy | Inclusion Criteria | included/excluded/identified | Study characteristics | Study RoB | SoE | Stat analysis | Pub bias | COI |  | Overall Assessment |
|--|-----------------|-------------|-----------------|--------------------|------------------------------|-----------------------|-----------|-----|---------------|----------|-----|--|--------------------|
| CBT vs Drug Mitchell 2012 <sup>129</sup> | Yes             | Yes         | Yes             | No                 | Yes                          | Yes                   | Yes       | Yes | Can't answer  | No       | Yes | Fair, mainly because not sure if homogeneity assessed, publication bias not assessed | Fair               |

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