Table 3.2.10 *Randomised controlled trials of treatment of insomnia with zolpidem, zopiclone, zaleplon and triazolam.*

First author Year Reference Country	Study design Blinding Patient characteristics	Interventions Number of individuals Withdrawal/ Drop outs	Method of measurement Baseline values	Results (1)	Results (2)	Study quality and relevance Comments
Allain 2001 [11] France	RCT, DB, PG, MC (58) ITT 3–7 nights SB P baseline 2 nights DB 26 nights DB intermittent Primary efficacy variable: subjective TST Primary insomnia DSM-IV ESS 7–15 ≥2 of the following: SOL >30 min TST 3–6 h WASO >30 min	Zolpidem 10 mg (Zol) Placebo (P) Intermittent administration ("as needed") Zol: 121/7 (5.7%) P: 124/3 (2.4%)	Efficacy: Sleep diary, MOS, CGI, SF-36 Compliance: Returned blister pack Safety: Spontaneous reports of AE, vital signs Female/male: 77%/23% Age: ~46±10 years Insomnia: ~80±90 min Zol / P ESS: 9.3 / 8.8 SD: 1.7 / 1.6 TST (min): 333 / 329 SD: 79 / 84 SOL: 52.6 / 61.2 SD: 39.5 / 40.3 SD: 1.3 / 1.3 WASO: 62.0 / 74.5 SD: 36.7 / 53.8	*Drug administration frequency* Zol: 67.6% P: 64.3% Zol / P TST (all nights): +74.6 / +63.2 SD: 77.7 / 69.9 TST (drug nights): +82.7* / +62.8 SD: 80.4 / 77.2 SQ: +20.6* / +14.1 SD: 22.3 / 17.4 SOL: –23.0 / –18.8 SD: 38.7 / 35.4 WASO: –32.8 / –31.4 SD: 37.7 / 37.1 Numbers represent changes from baseline	Statistically significant benefits for Zol over P on CGI and MOS No significant differences between groups for any domain of the SF-36 questionnaire TEAE's: Zol / P Any TEAE: 19% / 15% Anxiety: 4% Headache: 3.2% Rhinitis: / 3.3%	Moderate Differences in ESS and WASO at baseline Data on drug-free nights should have been reported in order to ascertain that the magnitude of rebound insomnia does not negate the benefit of the drug

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Table 3.2.10 *continued*

First author Year Reference Country	Study design Blinding Patient characteristics	Interventions Number of individuals Withdrawal/ Drop outs	Method of measurement Baseline values	Results (1)	Results (2)	Study quality and relevance Comments
Asnis 1999 [9] USA	RCT, DB, PG, MC (14) Quasi-ITT[1] 1 week SB P 4 weeks DB 1 week SB P DSM-IV diagnosis of major depressive disorder, dysthymic disorder or minor depressive disorder with mild or moderate symptomatology AND treated for ≥2 weeks with a stable dose of SSRI AND persistent insomnia defined by the following criteria: SOL >39 min or TST <6.5 h or NAW >2 and daytime complaints [1] Statistics based on pts that provided data after randomisation, Zol=94, P=96. Note the difference	Zolpidem 10 mg (Zol) Placebo (P) Zol: 94/21 (22%) P: 96/16 (17%) (4 pts lost before providing data after baseline, and are not included in the analysis)	Morning questionnaire (SOL, TST, NAW, WASO, SQ, ATC). MS, RF evaluated by VAS (0–100) SQ: 1=excellent, 4=poor	*Short-term effects (week 1)* *Medium-term effects (week 4)* [1] Change from baseline, approximated from diagram	*Discontinuation (night 1)* *Discontinuation (night 3)* Underlined numbers indicate a significant within-group change from baseline. No evidence of sedative/ hypnotic withdrawal syndrome (DSM-IV) in any group. Any TEAE: Zol 83%, P 74% during treatment, Zol 39%, P 43% during post-treatment week. Most prevalent AE: Headache	Moderate Shows that zol is effective for most studied parameters, and that withdrawal symptoms are mild and transient after 4 treatment in pts with affective disorder co-morbidity

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Table 3.2.10 continued

First author Year Reference Country	Study design Blinding Patient characteristics	Interventions Number of individuals Withdrawal/ Drop outs	Method of measurement Baseline values	Results (1)	Results (2)	Study quality and relevance Comments
Dorsey 2004 [10] USA	RCT, DB, PG, MC (9) ITT 6–14 nights preran-domisation screen/ baseline 4 weeks DB Women with peri-menopausal and postmenopausal insomnia Insomnia ≥6 months duration TST ≤6 h or WASO ≥1 h and daytime complaints	Zolpidem 10 mg (Zol) Placebo (P) Zol: 68/11 P: 73/5 n=141	Morning and evening questionnaires (SOL, NAW, WASO, TST, SRDDF). Weekly clinical inter-views (safety). PGI Female/male: 100%/0%	*Short-term effects (week 1)* *Medium-term effects (week 4)*	Safety 75.2% reported AE's	Moderate Zol appears effective for TST, WASO, NAW. No apparent effect on SOL. Significant but not clinically relevant effect on SRDDF. Higher inci-dence of AE's for zol

[1] TST data approximated from graph

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Table 3.2.10 *continued*

First author Year Reference Country	Study design Blinding Patient characteristics	Interventions Number of individuals Withdrawal/ Drop outs	Method of measurement Baseline values	Results (1)	Results (2)	Study quality and relevance Comments
Drake 2000 [46] USA	RCT, DB, CO, MC PP Dose-response study of zal. Combined report of 2 individual studies with different populations. Only study 1 used relevant doses of zal 2 nights DB treatment 5–12 days washout Primary insomnia DSM-III and ≥2 of the following: SOL >30 min NAW ≥3 TST 4–6 h	n=47 (PP population) *Study 1* Zaleplon 10 mg (Zal10) Zaleplon 40 mg (Zal40) Triazolam 0.25 mg (Tri) Placebo (P) *Study 2* Zaleplon 20 mg (Zal20) Zaleplon 60 mg (Zal60) Triazolam 0.25 mg (Tri) Placebo (P)	PSG (LPS, TST) Sleep diary (SOL, sTST, SQ) DSST, DCT, DST (residual sedative effects, cognitive impairment) Female/male: 23/24 Age: 41.6±9.5 years Baseline values not presented, but as the study has a crossover design, P values may be used as a substitute for baseline data	*Short-term effects (2 nights)* SQ: 1=poor, 4=excellent [1] As TRI is lower and has a smaller variation, it is reasonable to assume that it too should be significant	Zal shows dose-response effects on LPS *Residual impairment* No significant differences between relevant treatments for scores on DSST, DCT or DST. However, data is not presented adequately *Safety* No serious AE's reported. Most frequently reported AE's were headache, dizziness and somnolence	Moderate The reason for pooling two separate studies is not clear

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Table 3.2.10 *continued*

First author Year Reference Country	Study design Blinding Patient characteristics	Interventions Number of individuals Withdrawal/ Drop outs	Method of measurement Baseline values	Results (1)	Results (2)	Study quality and relevance Comments
Hajak 2002 [12] Europe	RCT, DB, PG, MC (105) PP for primary efficacy variable (CGI; not deemed a valid variable by the review group) ITT for secondary variables (TST, NAW) 3–7 nights SB P 14 nights DB Focus on intermittent use Chronic insomnia ≥1 months defined as sleeping difficulties AND daytime complaints AND TST 4–6 h AND ≥1 of the following: SOL ≥30 min NAW ≥3 WASO ≥30 min	Zolpidem 10 mg continuous (Zol-c) Zolpidem 10 mg discontinuous (Zol-d) Zol-c received 1 tablet/night, Zol-d received either Zol or placebo (P), Zol 10 nights and P 4 nights Zol-c: 386/22 (5.7%) Zol-d: 403/26 (6.4%) 7 pts excluded from ITT population as they were not assessed for the primary efficacy variable	Morning questionnaire (TST, NAW) SF-36 (QOL) Safety assessed by spontaneous reports or observed by investigator, vital signs at each visit Female/male: 66%/34% Age: 46.5±10 years Duration of insomnia: 4.5±6.5 years TST: 4.7± 0.7 h SOL: 61.4±48.3 min NAW: 3.1±1.7 min	*Medium-term effects (week 2)* [1] "Much improved" or "very much improved" Non-inferiority of Zol-d vs Zol-c could not be statistically proven No significant difference between groups on the 8 items on the SF-36 health survey		Moderate Data on SOL not extractable The study indicates that intermittent use might be as effective as continuous use

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Table 3.2.10 *continued*

First author Year Reference Country	Study design Blinding Patient characteristics	Interventions Number of individuals Withdrawal/ Drop outs	Method of measurement Baseline values	Results (1)	Results (2)	Study quality and relevance Comments
Lahmeyer 1997 [3] USA	RCT, DB, MC ITT 3 days P 31 days DB 4 days P ≥3 months disturbed sleep TST 4–6 h SOL ≥30 min Daytime complaints	Placebo (P) Zolpidem 10 mg (Zol10) Zolpidem 15 mg (Zol15)[1] P: 54/10 (18%) Zol10: 45/8 (18%) Zol15: 46/35 (19%) [1] Suprathera-peutic dose, data therefore not shown here	Efficacy: Sleep diary Female/male: 81/64 Mean age: 45±11.6 years *Baseline data* QOS: 1=excellent, 4=poor	*Short-term effects (week 1)* *Medium-term effects (week 4)* *Post-treatment (mean of 4 days)*	*Safety* *AE leading to discontinuation* Dry mouth, mental confusion, headache and lightheadedness, anxiety, panic attack, mild, un-controlled crying	Moderate No data for daytime symp-toms

QOS: 1=excellent, 4=poor

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Table 3.2.10 *continued*

First author Year Reference Country	Study design Blinding Patient characteristics	Interventions Number of individuals Withdrawal/ Drop outs	Method of measurement Baseline values	Results (1)	Results (2)	Study quality and relevance Comments
Leppik 1997 [21] USA	RCT, DB, PG, MC PP 1 week SB P 4 weeks DB 4 nights SB P Elderly pts with chronic insomnia DSM-III-R Duration >3 months TST 4–6 h SOL ≥30 min Impaired daytime functioning Primary endpoints: Subjective SOL and TST	Placebo (P) Zolpidem 5 mg (Zol) Triazolam 0.125 mg (Tri)[1] Temazepam 15 mg (Tem)[2] P: 84/10 (12%) Zol: 82/6 (7%) Tri: 85/14 (16%) [1] The dose of Tri is lower than the recommended (0.25 mg) [2] Tem is not approved for treatment of insomnia in Sweden, and data are for that reason omitted from this presentation	Efficacy: Sleep diary Safety: Spontaneous reports of AE's, Physical examination with electrocardiogram, laboratory evaluation Mean age: 69 years (59–85) Mean weight: 74.3 kg (39–134) Female/male: 63%/37% *Baseline*	*Short-term effects (week 1)* *Medium-term effects (week 4)* Post-treatment effects studied but not adequately reported. [1] Indicates that SOL and TST are presented as 'change to baseline'	*Safety* Any TEAE (no sign diff) P: 56% Zol: 63.4% Tri: 63.5% *Discontinuations due to AE's* P: 6 pts (groin pain, bursitis, hip fracture, ear infection, drowsiness and nausea) Zol: 2 pts (heart palpitations, drugged feeling) Tri: 5 pts (headache, lethargy, chest pain, loos stool, drowsiness) No indication of development of tolerance over the treatment period	Moderate Subclinical dose of Tri? Due to differences in baseline values the authors chose to present the results both as absolute values and as "change to baseline"

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First author Year Reference Country	Study design Blinding Patient characteristics	Interventions Number of individuals Withdrawal/ Drop outs	Method of measurement Baseline values	Results (1)	Results (2)	Study quality and relevance Comments
Scharf 1994 [8] USA	RCT, DB, PG, MC (4) PP 4 nights SB P (screening) 1 week SB P (baseline) 5 weeks DB 3 nights SB P Chronic insomnia defined as ≥3 months duration TST 4–6 h SOL ≥30 min Daytime complaints Primary efficacy variables: LPS: and SE measured by PSG	Zolpidem 10 mg[1] (Zol10) Zolpidem 15 mg[1] (Zol15) Placebo (P) 178 patients Zol10: 26/4 Zol15: 25/3 P: 42/1 [1] The recommended dose is 10 mg	PSG (primary efficacy variables) Evening and morning questionnaires, Global impression scale, DSST, DSCT SQ: 1=excellent, 4=poor	*Short-term effects (DB week 1)* *Long-term effects (DB week 5)*	*Post-treatment (mean 3 nights)* *Any TEAE's (%)* P: 58 Zol10: 50 Zol15: 52 2 pts withdrawn from Zol15 due to AE's: drowsiness, dizziness, nausea, oversedation, visual disturbance No evidence of tolerance after 5 weeks treatment. No evidence of impaired day-time functioning based on DSST or DSCT scores	High The study suggests that zol, at the recommended dose, is effective only when objective parameters are considered

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Table 3.2.10 continued

First author Year Reference Country	Study design Blinding Patient characteristics	Interventions Number of individuals Withdrawal/ Drop outs	Method of measurement Baseline values	Results (1)	Results (2)	Study quality and relevance Comments
Walsh 2000 [13] USA Supported by Lorex Pharma-ceuticals	RCT, DB, PG, MC (6) ITT (LOCF) 7 nights baseline 8 weeks DB 7 nights discontinuations Primary insomnia (DSM-IV) AND SOL ≥45 min OR TST ≤6.5 h AND daytime com-plaints Primary efficacy variable IGR and PGR (not deemed to be valid variables by the review group)	Zolpidem 10 mg (Zol) Placebo (P) Intermittent use, 3–5 nights/ week (mean 7.7 nights during the 14 nights DB treatment period) Zol: 82/19 (23%) P: 81/10 (12%)	IGR, PGR (primary efficacy variables) Morning questionnaire (secondary efficacy variables) SF-36, Profile of Mood States (QOL, Mood) Several neurocognitive tests, recording of AE's, vital signs (safety) Female/male: 71%/29% Age 44±1.2 years (mean±sem) TST: Approximated from diagram	*Short-term effects (week 1–2)* *Medium-term effects (week 3–4)*	*Long-term effects (week 7–8)* No difference in SF-36 or Profile of Mood States between groups at any visit Rebound insomnia observed in zol group only week 1–2 Safety data not adequately reported, but the higher drop out rate in the Zol group might reflect a higher incidence of AE's in this group	Moderate Baseline data not adequately reported On drug taking nights, zol is favourable vs P Comparative statistics for drug-free nights not ade-quately repor-ted, although there appear to be differen-ces favouring P. Possibly, rebound effects on drug-free nights could negate the positive effect on drug taking nights

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Table 3.2.10 *continued*

First author Year Reference Country	Study design Blinding Patient characteristics	Interventions Number of individuals Withdrawal/ Drop outs	Method of measurement Baseline values	Results (1)	Results (2)	Study quality and relevance Comments
Ware 1997 [2] USA	RCT, DB, PG PP 2 nights SB P baseline 28 nights DB 3 nights SB P Focus on rebound insomnia Primary efficacy variable: Changes in LPS and SE from baseline (PSG). Secondary variables: NAW, WASO (subjective measures) Chronic insomnia defined as: ≥3 months duration TST 4–6 h SOL ≥30 min Daytime complaints	Zolpidem 10 mg (Zol) Triazolam 0.5 mg (Tri)[1] Placebo (P) Zol: 37/3 Tri: 36/6 P: 37/2 [1] Dose of Tri higher than the recommended (normal dose 0.125–0.25 mg)	PSG at baseline, night 1–2, night 27–28 and 3 nights post-treatment (LPS, SE, NAW, WASO) Morning questionnaires (SOL, TST etc) Physical examinations, laboratory tests, spontaneous reports (safety) Female/male: 58%/42%	*Short-term effects (night 1–2)* *Medium-term effects (night 27–28)*	*Discontinuation (night 1)* *Discontinuation (night 3)*	Moderate Data on NAW were deemed to be erroneously reported, and therefore not included in this presentation No between-group comparisons were made, only changes from baseline

Table 3.2.10 *continued*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis	Intervention Number of individuals Withdrawal/ drop outs	Intervention Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention/Control Effects/side effects	Study quality and relevance Comments
Ancoli-Israel 1999 [22] USA	RCT, DB, MC. Zaleplon 5 mg (Zal5), zaleplon 10 mg (Zal10), zolpidem 5 mg (Zol5), placebo (P). 1 week SB P, 2 weeks of active treatment, 1 week of SB P	Pts aged 65 years or more who met DSM-IV criteria for primary insomnia. Requirements: SOL >30 minutes, and either WASO >3 or TST <6.5 h. Anxiety and depression were ruled out using Zung scales. 1 224 pts were screened, 551 pts met criteria, 2 were lost due to protocol violation. 549 pts received at least 1 dose of medication and were included in efficacy and safety analyses	166 pts received Zal5. Female/male: 58%/42%, mean age 71 years, range 65–86 165 pts received Zal10. Female/male: 58%/42%, mean age 71 years, range 65–92 111 pts received Zol5. Female/male: 57%/43%, mean age 72 years, range 64–85	107 pts received P. Female/male: 60%/40%, mean age 71 years, range 65–91. No sign differences between treatment groups in sex, age, weight, ethnic origin or Zung anxiety and depression scores	Daily post-sleep questionnaires. Safety assessments	SOL: Zal5 30, P 55; Zal10 30, P 55; Zol5 42, P 55 TST: Zal5 348, P 325; Zal10 345, P 325; Zol5 358, P 325 SQ: Zal5 3.75, P 4.0; Zal10 3.63, P 4.0; Zol5 3.5, P 4.0 SOL sign improved with Zal10 compared to placebo during both weeks. Zal5 did not differ from P during 1st week but reduced SOL sign during 2nd week compared to P. Zol5 sign reduced SOL both weeks. Zal10 was sign superior to Zol in reducing SOL during both weeks. TST improved sign with Zol5 during both weeks, with Zal10 during 1st week. No difference for Zal5 compared to placebo. Zol5 sign improved SQ during both weeks, Zal10 only during 1st week. Sign more rebound insomnia with Zol5, no difference for Zal5 or 10. No sign difference in side effects	Moderate Large patient material, home-living old clinically representative pts Zal10 and Zol5 about equal, more rebound insomnia after withdrawal of Zol5

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First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis	Intervention Number of individuals Withdrawal/ drop outs	Intervention Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention/Control Effects/side effects	Study quality and relevance Comments
Chaudoir 1983 [30] England	RCT, DB, cross-over design. Zopiclone 7.5 mg (Zop7.5), placebo (P). Wash-out 1 week, 7 days with Zop7.5 or P	At least one of the following: SOL >45 minutes, >2 nocturnal awakenings, TST <6 hours. History of insomnia, characterists of insomnia, previous hypnotic therapy, additional diagnosis, concomitant medication: no difference between groups. Mean age not stated; age range 35–65 years	30 pts randomised, 5 pts withdraw (2 Zop7.5, 3 P)	Crossover design	Patient diary, symptoms check-list, mood assessment scale	SOL decreased in zop group compared to P; number of awakenings decreased (1.5 vs 2.1), SQ increased. TST not assessed. No difference for the mood scale. Bitter taste more common in zop group	Moderate Zop improved SOL, reduced awakenings and improved TST

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First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis	Intervention Number of individuals Withdrawal/ drop outs	Intervention Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention/Control Effects/side effects	Study quality and relevance Comments
Dockhorn 1996 [5] USA	RCT, DB, MC. Zolpidem 10 mg (Zol10), placebo (P). 7–10 nights study. All had acute insomnia	DSM-III R, TST 4–6 hours, SOL >30 minutes, daytime complaints. Insomnia was due to situational stress (marriage, work, family, financial matters). All had experienced acute insomnia for 3–9 days. 139 pts randomised, mean age 32 years (range 20–55). 1 patient never received treatment, 138 pts remained for safety analysis. 2 pts had no efficacy follow-up data. Both groups were comparable with respect to age, race, weight, SOL ,TST and type of situational stress	68 pts received Zol10, 3 pts discontinued before completing the study, 3 more due to adverse events	68 pts received P, 6 pts discontinued before completing the study, 2 more due to adverse events	Both groups homogeneous as regards baseline sleep data. Subjective data. Morning questionnaire, Clinical Global Impression Questionnaire, POMS (mood scale)	*Day 1–2* *Day 3–10* Zol sign improved SOL (45.7 and 20.8 min on days 1–2 and 3–10), ease of falling asleep, and SQ compared to P both at ratings nights 1 and 2 and nights 3–10. WASO and NAW were also improved at nights 3–10. TST increased significant nights 1–2 (44.2 min) and nights 3–10 (33.2 min) compared to P. No difference between treatments for morning effects (concentration, sleepiness). All 6 items in the Clinical Global Impression Questionnaire improved sign compared to placebo. AE's events: headache and drowsiness were slightly more prevalent in the Zol10	Moderate Acute insomnia, 3–9 nights, due to psychosocial factors. Zol10 sign better than placebo during short-term treatment

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Table 3.2.10 *continued*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis	Intervention Number of individuals Withdrawal/ drop outs	Intervention Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention/Control Effects/side effects	Study quality and relevance Comments
Elie 1999 [6] Canada	RCT, DB, MC. Zaleplon 5 mg (Zal5), zaleplon 10 mg (Zal10), zaleplon 20 mg (Zal20), zolpidem 10 mg (Zol10), placebo (P). 1 week SB P run-in, 4 active treatment, 3 SB P. Data for Zal20 not shown	Pts aged 18–65 years, insomnia according to DSM-III-R. Symptoms required the last month: SOL >30 minutes, daytime impairment due to insomnia, and either TST <6.5 h or prolonged (>30 min) or frequent (>3) nocturnal awakenings. 615 pts randomised. 2 never got the medication, 39 lacked adequate documentation, 574 pts included in efficacy analysis	113 pts received Zal5. Female/male: 58%/42%, mean age 42 years. 112 pts received Zal 10 mg. Female/male: 64%/36%, mean age 42 years. (116 pts received Zal20, Female/male: 67%/33%, mean age 42 years). 115 pts received Zol10. Female/male: 67%/33%, mean age 44 years	118 pts received P. Female/male: 63%/37%, mean age 42 years	Sleep questionnaires	*Week 2* SOL: Zal5 35, P 48; Zal10 32, P 48; Zol10 37, P 48. TST: Zal5 359, P 359; Zal10 368, P 359; Zol10 387, P 359. SQ: Zal5 4.0 P 3.9; Zal10 3.9, P 3.9; Zol10 3.6, P 3.9. No difference for any WASQ values *Week 4* SOL: Zal5 31, P 37; Zal10 28, P 37; Zol10 37, P 37. TST: Zal5 372, P 377; Zal10 384, P 377; Zol10 400, P 377. SQ: Zal5 3.8, P 3.8; Zal10 3.7, P 3.8; Zol10 3.4, P 3.8. SOL sign improved for Zal10 during week 1–4, for Zal5 and Zol10 during week 1–3, all compared to P, which also improved from week 1 to 4 TST improved sign for Zol10 all 4 weeks, compared to P. No sign difference in TST for Zal5 and 10 compared to P. SQ improved sign for Zal10 during week 1 and for Zol10 during all weeks. Rebound insomnia and withdrawal symptoms sign more frequent for Zol10, compared to P, but not for the other drugs. Side effects about equal	Moderate Zol10 equal or better than Zal10, but with more rebound insomnia 1st discontinuation night and more withdrawal symptoms

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First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis	Intervention Number of individuals Withdrawal/ drop outs	Intervention Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention/Control Effects/side effects	Study quality and relevance Comments
Elie 1990 [28] Canada	RCT, DB, 3 group parallel study. Zopiclone 5 mg (Zop5), zopiclone 7.5 mg (Zop7.5), triazolam 0.125 (Tri0.125), triazolam 0.25 mg (Tri0.25), placebo (P). 3 day SB washout, P responders were excluded; P, triazolam or zopiclone for 3 weeks, 4 days placebo	After P-responder exclusion, 44 pts remained. Female/male: 75%/25%, mean age 76 years. No drop outs. Chronic insomnia, 84% had insomnia for >1 year. Pre-treatment data: Average TST 4.6 h, average SOL 1.57 h, WASO >3, no pts felt rested in the morning. SQ poor in 84%	15 pts received Zop5, after first week dose was increased to 7.5 mg (provided no side effects). 14 pts received Tri0.125, efter first week dose was increased to 0.25 mg (provided no side effects)	15 pts received placebo	Interview, questionnaire, side effects reporting. No sign difference between groups for various sleep variables at baseline. Arbitrary values	Only arbitraty units, no measurements in minutes Tri SOL and SQ improved compared to P for both active drugs for the entire period of 3 weeks. No differences for morning-wake-up or hangover. At discontinuation of drugs the tri group showed sign increase in SOL and decreased QOS. Changes in the zop group were not statistically sign. AE's were sign more frequent in the zop group. Hypnotic activity was maximal at 7.5 mg of zop and 0.25 mg of tri	Moderate Efficacy maintained for 3 weeks for both drugs. The higher doses, Zop7.5 and Tri0.25 were most effective

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First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis	Intervention Number of individuals Withdrawal/ drop outs	Intervention Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention/Control Effects/side effects	Study quality and relevance Comments
Elie 1983 [27] Canada	DB, 5x5 latin square designs. Zopiclone 5 mg (Zop5), zopiclone 7.5 mg (Zop7.5), zopiclone 10 mg (Zop10), flurazepam 15 mg (Flu15), placebo (P). 5 balanced random drug orders, 5 groups of 6 pts each. Drug treatment 4 nights per week during 5 weeks. Data only shown for Zop5 and Zop7.5	Insomniacs for >1 year, suffering from at least one of the following: SOL (mean 1.1 h), WASO >3/night, insufficient TST (mean 4.3 h). No patient felt rested in the morning. Types of insomnia: sleep onset 5, midnight 7, late night 1, mixed 17 pts. 30 pts. Female/male: 74%/26%, mean age 75 years (range 60–93 years)	30 pts received at random Zop5, Zop7.5, Zop10, Flu15, P 4 nights a week during 5 weeks. No patient lost to follow-up	All 30 pts received P during the study	Interviews and questionnaires for sleep and side effects every morning	Both Zop5 and Zop7.5 increased SOL, increased TST and increased SQ. Wakenings not assessed. Zop effect increased linearly with dose for SOL and TST. Zop7.5 sign maximal for SQ, soundness and morning waking up quality. No sign difference between zop doses for sleep onset quality, duration of morning awakening and hangover index. P pts required sign more supportive medication during discontinuation compared to zop pts. Side effects: sign more coated tongue, dizziness, tension, faintness with Zop5, sign more well-being with Zop7.5. Data extraction impossible	Moderate No sign difference between Flu15 and Zop7.5 and Zop10. Less withdrawal effects with Flu15. More side effects with Zop5

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Table 3.2.10 *continued*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis	Intervention Number of individuals Withdrawal/ drop outs	Intervention Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention/Control Effects/side effects	Study quality and relevance Comments
Fleming 1995 [4] Canada, USA	RCT, DB, MC. Zolpidem 10 mg (Zol10), zolpidem 20 mg (Zol20), flurazepam 30 mg (Flu), placebo (P). Residual effects + short term efficacy. 1 night SB P, 3 nights DB active drugs + P treatment. Data only reported for Zol10	Chronic insomniacs: subjective TST 4–6 hours, SOL >30 minutes/night, daytime symptoms; all 3 symptoms had to be present for >6 months. 222 pts screened, 144 were randomised. 3 pts dropped out, efficacy analysis based on 141 pts, 133 pts completed study	35 pts received Zol10. No difference between groups for gender (females 43–57%) or age (mean age 33–37 years, range 21–60)	35 pts received P. 36 pts received Flu (positive control). No difference between groups for gender (females 43–57%) or age (mean age 33–37 years, range 21–60). 1 patient in Flu group dropped out	PSG, psychomotor tests (DSST + Symbol Copying Test, SCT), questionnaire, mood state. No sign baseline differences between any groups for any efficacy parameters	SOL (PSG) was sign reduced: 15 minutes (Zol10), mean change from baseline, but not in P (8 minutes) the first night. Similar sign changes occurred in subjective SOL. Sleep efficiency (PSG data) sign better for active drug compared to placebo *SQ* Zol 2.2/0.2, P 2.9/0.1. Residual effects: No sign difference in DSST from placebo for Zol10 and Zol20; sign impairment for Flu. Likewise no sign difference for SCT compared to P for Zol10 and Zol20 but a sign impairment in the Flu group. More adverse events in Zol20 group	Moderate No psychomotor impairment with Zol10 and Zol20 whereas Flu group deteriorated sign. More adverse events in Zol20 group

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Table 3.2.10 *continued*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis	Intervention Number of individuals Withdrawal/ drop outs	Intervention Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention/Control Effects/side effects	Study quality and relevance Comments
Fry 2000 [7] USA	RCT, DB, MC. Zaleplon 5 mg (Zal5), zaleplon 10 mg (Zal10), zaleplon 20 mg (Zal20), zolpidem 10 mg (Zol10), placebo (P). 1–3 weeks wash-out, 1 week SB P run-in, 4 weeks DB treatment, 3 nights placebo run-out. Data for Zal20 not shown	Pts aged 18–65 years, primary insomnia according to DSM-III-R. At least 3 times/week SOL >30 minutes Daytime impairment due to insomnia, and TST <6.5 h or WASO >3. 830 pts were screened, 595 pts qualified and were randomised	118 pts received Zal5. Female/male: 69%/31%, mean age 43 years. 20 pts dropped out, of whom 5 due to lack of efficacy. 120 pts received Zal10. Female/male: 54%/46%, mean age 40 years. 10 pts dropped out, of whom 5 due to lack of efficacy. 121 pts received Zal20. Female/male: 61%/39%, mean age 41 years. 17 pts dropped out, of whom 1 due to lack of efficacy	119 pts received P. Female/male: 64%/36%, mean age 43 years. 24 pts dropped out, of whom 3 due to lack of efficacy. 117 pts received Zol10 (active control). Female/male: 54%/46%, mean age 42 years. 20 pts dropped out, of whom 6 due to lack of efficacy	Sleep questionnaires. Rebound insomnia defined as worsening from baseline of symptoms. Withdrawal effects questionnaire. Data for SOL extracted from graph	*Week 2* SOL: Zal5 45, P 58; Zal10 36, P 50; Zol10 47, P 50 WASO: Zal5 1.67, P 2.0; Zal10 1.69, P 2.0; Zol10 1.5, P 2.0. TST: Zal5 366.4, P 360; Zal10 364.3, P 360; Zol10 384.4, P 360 *Week 4* SOL: Zal5 47, P 49; Zal10 35, P 56; Zol10 36, P 48 WASO: Zal5 1.71, P 1.71; Zal10 1.57, P 1.71; Zol10 1.67, P 1.71. TST: Zal5 360, P 364.3; Zal10 376.3, P 364.3; Zol10 392.9, P 364.3 SOL improved sign for Zal10 at week 1, 3 and 4, for Zal5 at 1, for Zol10 at week 1, compared to P. TST improved sign for Zol10 in all 4 weeks. No difference to P for Zal5 and Zal10. NAW sign less for Zol10 at week 1 and 3. SQ sign improved for Zol10 at all weeks. No pharmacological tolerance for any drug. Zol10 showed sign more rebound insomnia and withdrawal effects compared to the other treatments. No sign difference in AE's	Moderate Zal20 is a high dose. Zol10 slightly superior to Zal10. More rebound insomnia with Zol 10

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Table 3.2.10 *continued*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis	Intervention Number of individuals Withdrawal/ drop outs	Intervention Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention/Control Effects/side effects	Study quality and relevance Comments
Monchesky 1986 [29] Canada	RCT, DB, MC. Zopiclone 7.5 mg (Zop7.5), placebo (P). One week no-placebo wash-out, then 4 weeks study in 2 groups: design zop-placebo-zop-zop (group A) and zop-zop-placebo-zop (group B)	Insomnia at least 3 months + at least 2 of the following: SOL >45 min, >3 WASO, early morning awakening, TST usually <5 h and always <6 h. 99 pts were enrollad, 91 pts completed the study. 8 drop outs: 5 due to intercurrent illness, 2 lost to follow-up, 1 did not meet inclusion criteria	Group A 46 pts. Female/male: 1%/99%, mean age 46 years, mean duration of insomnia 77 months *Group B* 45 pts. Female/male: 71%/29%, mean age 47 years, mean duration of sleep 83 months	All pts received placebo during 2nd (group A) or 3rd (group B) week	Presleep and postsleep questionnaires. Daytime SQ, SOL, TST, WASO, SQ, soundness of sleep, morning state of rest. Likert 1–7 scales. SOL Group A: 72 min, Group B: 106 min Usual TST Group A: 281 min, Group B: 262 min Nightly awakenings Group A: 3.4 Group B: 3.1 All differences nonsignificant	Sign differences in favour of Zop7.5 compared to P for sleepiness during the day. Percentages of improvement were (group A and B, respectively): SOL 48 and 50; TST 26 and 28; WASO 29 and 35; superior SQ 40 and 51; sounder sleep 41 and 43; more rested in the morning 42 and 41. No sign differences in reported side effects	Moderate Zop7.5 sign superior to P. Relatively great improvements percentually in the subjective sleep parameters in zop group compared to P

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Table 3.2.10 *continued*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis	Intervention Number of individuals Withdrawal/ drop outs	Intervention Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention/Control Effects/side effects	Study quality and relevance Comments
Perlis 2004 [14] USA	RCT, DB, MC. Zolpidem 10 mg (Zol10), placebo (P). Non-nightly (3–5 doses/ week) treatment during 12 weeks	Pts with insomnia according to DSM-IV criteria. Requirements: SOL >45 min, or TST <6 h, + impaired daytime function due to insomnia, at least 3/7 nights. 322 pts screened. 123 not randomised: failed entry criteria (78), non-compliance (18), use of other medication (12), other (15). 199 pts randomised. Of 199 pts efficacy data were available for 192 pts. Female/male: 71%/29%, mean age 41 years, range 18–64	98 pts received Zol10. Female/male: 61%/39%, mean age 41 years. Efficacy data available for 95 pts, 18 pts discontinued during treatment, 80 pts completed study	101 pts received P. Female/male: 81%/19%, mean age 40 years. Efficacy data available for 97 pts, 21 pts discontinued during treatment, 80 pts completed study	Sleep diaries. Biweekly clinic visits	Medication nights: SOL, NAW, WASO and TST all sign improved at all ratings compared to P. No-pill nights: No difference between Zol10 and P. All nights (pill and no-pill nights): SOL sign improved at week 10, NAW sign improved at week 2, WASO sign improved at week 2, TST sign improved at all ratings. Global outcome measure sign better for Zol10 at all ratings. A trend for dose escalation in both groups over time. Side effects: 7 pts in zol group discontinued due to side effects, 3 in P group	Moderate Few studies on non-nightly medication. Sign differences between Zol10 and P during pill nights, no difference during non-pill nights (as could be expected)

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Table 3.2.10 *continued*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis	Intervention Number of individuals Withdrawal/ drop outs	Intervention Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention/Control Effects/side effects	Study quality and relevance Comments
Walsh 2000 [45] USA	RCT, DB, MC (6 centers). Zaleplon 2 mg (Zal2), zaleplon 5 mg (Zal5), zaleplon 10 mg (Zal10), placebo (P). 2 consecutive nights in sleep laboratory, followed by 5 or 12 days wash-out with sleep at home. Data for Zal2 not shown	SOL subjective >30 min, >3 WASO, TST 180–360 minutes. Of 311 pts, 92 pts screened out on clinical exclusion criteria, remaining 219 pts screened with PSG and 54 pts qualified for study. 6 pts lost and 48 pts entered and completed study. Female/male: 35%/65%, mean age 67 years, range 60–79	4 groups of pts, each holding 12 pts, received randomly each Zal2; 12 pts Zal5, 12 pts Zal10 and 12 pts P No drop outs	All 4 groups received placebo as 1 of 4 treatment arms	PSG for 2 consecutive nights. Sleep questionnaire, psychomotor tests	<u>*PSG data*</u> Both drugs (Zal5, Zal10) sign reduced SOL compared to placebo No effect on total NAW for any drug <u>*Subjective sleep data.*</u> SOL decreased sign for Zal10 and Zal5. TST increased sign only for Zal10. Median SOL was 45 minutes for P, and Zal5 and Zal10 30 and 25 minutes, respectively. Reaction time sign longer with Zal10	Moderate Median total sleep times 20 to 30 minutes longer for zal than P. Zal dose of 2 mg too low

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Table 3.2.10 *continued*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis	Intervention Number of individuals Withdrawal/ drop outs	Intervention Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention/Control Effects/side effects	Study quality and relevance Comments
Walsh 1998 [44] USA	RCT, DB, MC (10 centers). Zaleplon 5 mg (Zal5), zaleplon 10 mg (Zal10), triazolam 0.25 mg (Tri0.25), placebo (P). Study duration 19 nights: 3 P, 14 nights of treatment, 2 nights on P	DSM III-R and 2 of 4 of the following: Subjective SOL <45 min, WASO >3, TST <6.5 h, daytime sleep-related symptoms. 673 pts screened (clinical and PSG), 456 failed criteria, 85 pts refused/ violated protocol. 132 pts were randomised in 4 groups	34 pts got Zal5. Female/male: 62%/38%, mean age 39 years; 33 pts got Zal10. Female/male: 64%/36%, mean age 40 years. Zal5 3 drop outs Zal10 1 drop out	31 got Tri0.25. Female/male: 50%/50%, mean age 39 years, 34 pts got P. Female/male: 55%/45%, mean age 43 years. P: 3 drop outs	Sleep laboratory study. PSG (nights 1–5 and 15–19), questionnaires, psychomotor tests	125 pts completed the study. SOL sign shorter for Zal5 vs P (mean 17 vs 25 min) and Zal10 (mean 18 vs 25 min) on night 4/5 but not on night 16/17; for Zal5 18 vs 20 min; for Zal10 16 vs 20 min. No difference between any zal dose and P for TST on any night. SOL Tri0.25 18 vs 25 min day 4–5, 23 vs 20 min day 16–17. TST increased sign for Tri0.25 compared to P, day 4–5 431 vs 400 min, day 16–17 420 vs 411 min (ns). Subjective data were consistent with PSG data. No difference in psychomotor data between groups. Adverse events were reported in 35% (Zal5), 42% (Zal10), 55% (Tri0.25) and 38% (P)	High quality Placebo pts improved spontaneously during later phase of study. SOL mean reduction was 5–8 min night 4/5, TST mean increase was 2–31 min night 4/5 for the various drugs

* Statistical significance $p<0.05$.
** Significant vs Tri.
d Drugs.
nd No drugs.

ATC = Ability to concentrate (1 = excellent, 4 = poor); C = Control; CGI = Clinical global improvement scale; CO = Crossover; DB = Double-blind; DCT = Digit copying; DF = Day functioning, difficulty doing activities during the prior 24 hours due to sleep problems (1 = not at all, 5 = could not do daily work); DIMS = Difficulty in initiating or maintaining sleep; DST = Digit span; DSST = Digit symbol substitution; ESS = Epworth Sleepiness Scale; h = Hours; I = Intervention; IGR = Investigator global rating; ITT = Intention to treat; LOCF = Last observation carried forward; LPC = Latence to persistent sleep; MC = Multicenter study; min = Minutes; MOS = Medical Outcome Study; MS = Morning sleepiness (0 = very sleepy, 100 = not at all sleepy); NS = Non significant; P = Placebo; PGI = Patient global impression; PGR = Patient global rating, (+) indicates nights when pill was taken, (–) indicates nights when no pill was taken; PSG = Polysomnography; Pts = Patients; RCT = Randomised controlled trial; RF = Refreshed feeling (VAS, 0 = Very refreshed, 100 = Not at all refreshed); SB = Single blind; SE = Sleep efficiency; SOL = Sleep onset latency; SOL/B = SOL presented as change from baseline; SQ = Sleep quality (1 = excellent, 4 = poor); SRDDF = Sleep-related difficulty with daytime functioning (assessed by evening questionnaire); SSL = Self-reported subjective sleep latency; SST = Self-reported subjective total sleep time; STST = Subjected total sleeptime; TEAE = Treatment emergency adverse events; TST = total sleep time; TST/B = TST presented as change from baseline; URTI = Upper respiratory tract infection; WASO = Wake after sleep onset

Table 3.4.2 *Randomised controlled trials of Melatonine treatment in insomnia.*

First author Year Reference Country	Study design, Diagnoses, Male/Female, Blinding Inclusion criteria	Intervention Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results 1 Effects/side effects	Results 2	Study quality and relevance Comments
Haimov 1995 [13] Israel	RCT DB Crossover 3 x 7 days 2 week wash out (not tabled – lacks control) Primary insomnia. ICSD-elderly (in or outside institutions). 6 months insomnia – problems ≥3 nights/ week + reduced daytime functioning. Extended 2 months without control (not tabelled). Insomniacs had lower melatonin peak Female/male: 16/10 Mean age 73.1 and 81.1 years in two subgroups	2 mg melatonin. Sustained release 1 week (S) n=26 2 mg melatonin. Fast release, 1 week (F) n=26 (1 mg sustained release 2 months n=17, Not tabelled – lack of control) No drop outs	Actigraphy No baseline (crossover)	*TST* No effect *Sleep latency (min)* S: 37±11 F: 32±7 P: 54±13 *Efficiency (%)* S: 80.4±1.8* F: 78.8±1.7 P: 77.4±1.9 *Activity (number)* S: 23.0±2.5 F: 25.8±3.8 P: 26.9±2.6	No difference in side effects between groups	Moderate Clear effect of sustained release on latency and efficiency, but not TST. Some unclarities in loss of subjects. No difference in adverse effects between groups

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Table 3.4.2 *continued*

First author Year Reference Country	Study design, Diagnoses, Male/Female, Blinding Inclusion criteria	Intervention Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results 1 Effects/side effects	Results 2	Study quality and relevance Comments
Lemoine 2007 [26] France	RTC, DB, PG 3 weeks one dose 2 weeks runout Primary insomnia ≥1 month ≥55 years exclusion of other diseases n= 170 Age: 68.5 Female/male: 66/34	Sustained release *2 mg (2)* n=82 Drop outs: 4 (5%) Age: 68.5 years *Placebo (P)* n=88 Drop outs: 2 (2.5%) Age: 68.5 years	Sleep diary, (Leeds), Quality of night (QON), Quality of day (QOD), Tyler–Burton benzodiazepine withdrawal symptom questionnaire (BWSQ Leeds quality)* No baseline values for several variables– only change values	*Leeds quality of sleep (estimated from figure)* 2: +22 P: +17 *Leeds morning alertness BFW* 2: +16 P: +7 *Sleep diary quality* 2: +0.88* P: +0.45 n = Values above indicate improvement from baseline *QoS basel-change* Base Treat 2: 69±13 –27±21 P: 69±12 –18±17 *BWSQ* Base Treat 2: 59±14 64±14 P: –6±16 –18±20 No difference in adverse effect – low levels	No difference in adverse effects	Moderate Effects on subjective quality, but standard measures on sleep latency and TST are lacking. No polysomnography. Only partial baseline data. No differences between groups on adverse effects

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Table 3.4.2 *continued*

First author Year Reference Country	Study design, Diagnoses, Male/Female, Blinding Inclusion criteria	Intervention Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results 1 Effects/side effects	Results 2	Study quality and relevance Comments
Wade 2007 [25] United Kingdom	RCT, PG, DB 3 weeks One dose Primary insomnia DSM-IV-IR Age: 55–80 years Exhaustion or other disorders *2 mg (2)* Female/male: 60%/40% *Placebo (P)* Female/male: 34.7%/65.3%	Melatonin, sustained release *2 mg (2)* n=177 Age: 66 Drop outs: 8 *Placebo (P)* n=177 Drop outs: 12	Subjective ratings No baseline results	10 mm improvement on SQ and BFW *Melatonin* *Placebo* 26% 15% *Base* *Treatment* *(mean±SD)* Leeds qual of sleep 2: 54±9 46±16 P: 54±10 50±15 Morning alertness (BFW) 2: 52±11 45±15 P: 52±12 48±14 Diffic fall asleep 2: 53±8 46±14 P: 52±5 48±11 Sleep latency (min) 2: 65±70 41±55 P: 58±65 45±59 Sign refers to difference in base-treat between placebo and 2 mg Also PSQI was improved as was WHO quality of life scale	No effects on number of awakenings or TST, CGI No difference in adverse events	Moderate Effects of Circadin on many variables, however, final sleep latency was very long and TST was not affected

* Statistical significant.

BFW = Behaviour following wakefulness; CGI = Clinical global improvement scale; DB = Double-blind, n = Number; P = Placebo; PG = Parallel group; PSQI = Pittsburgh Sleep Quality Index; RCT = Randomised controlled trial; SQ = Sleep quality; TST = Total sleep time; WHO = World Health Organisation

Table 3.5.6 *Randomised controlled trials of psychological treatments of insomnia.*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal/ drop outs	Control Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention Effects/ side effects	Results Control Effects/ side effects	Study quality and relevance Comments
Currie 2000 [1] Canada	RCT	Insomnia (DSM-IV) secondary to non-malignant chronic pain. Exclusion of major medical and psychiatric co-morbidity Female/male: 55%/45% Age: 45 years (29–59)	I: CBT (group, 7 sessions, 2 h each); n=32 Treatment drop outs: 1 FU drop outs: 3	C: Wait list (self-monitoring and weekly therapist support, 7 weeks) n=28 Treatment drop outs: 2 FU drop outs: 3 Offered CBT after FU	Sleep diary (SOL, WASO, TST), PSQI *Baseline (I)* SOL: 54.7±34.4 min WASO: 88.9±74 min TST: 5.8±1.5 h PSQI: 13.6±3.7 *Baseline (C)* SOL: 44.6±40.8 min WASO: 100±57.5 min TST: 5.4±1.2 h PSQI: 14.2±2.7	*Post-treatment (I)* SOL: 28.1±19 min (I>C) WASO: 40.2±40.6 min (I>C) TST: 6.1±1.6 h (I=C) PSQI: 8.8±3.5 (I>C) *3 months FU (I)* SOL: 27.8±16.7 min (I>C) WASO: 51.6±50.1 min (I>C) TST: 6.4±1.4 h (I=C) PSQI: 7.9±3.7 (I>C)	*Post-treatment (C)* SOL: 58.2±54.7 min WASO: 91.5±67.1 min TST: 5.5±1.4 h PSQI: 12.7±3.4 *3 months FU (C)* SOL: 46.8±38.1 min WASO: 97.5±60.1 min TST: 5.6±1.2 h PSQI: 13.5±3.6	Moderate Several strengths. Weaknesses: eg description of randomisation, no blinding Study drop out: 15%
Dirksen 2008 [13] Same study as Epstein 2007 [6]	See Epstein 2007 [6]	See Epstein 2007 [6]	See Epstein 2007 [6]	See Epstein 2007 [6]	*Questionnaires (I)* ISI: 23.9±4.3 *Questionnaires (C)* ISI: 22.7±4.0	*Post-treatment* ISI: 14.4±5.3 (I=C, between groups)	*Post-treatment* ISI: 16.3±5.0	Moderate

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Table 3.5.6 *continued*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal/ drop outs	Control Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention Effects/ side effects	Results Control Effects/ side effects	Study quality and relevance Comments
Edinger 2001 [11] USA	RCT Double blind (patients and therapists to hypotheses and placebo), placebo-controlled	DSM-III insomnia + WASO: ≥60 min + duration: ≥6 months + onset after age 10 + 1 sleep disruptive practice. Exclusion of psychiatric, medical and other sleep disorders Female/male: 46.7%/53.3% Age: 55.3 years	I1: CBT (individual 6 sessions) n=25 Treatment drop outs: 2 FU drop outs: 7–9 I2: Relaxation (individual, 6 sessions); n=25 Treatment drop outs: 2 FU drop outs: 7–8	C: Placebo (individual 6 sessions) n=25 Treatment drop outs: 1 Randomised to CBT or relaxation after post-treatment (not included in analysis)	PSG (WASO, TST), sleep diary (TST, WASO, SQ), ISQ *Baseline (I1)* TST: 348±62 min WASO: 55±25 min SQ: 2.87±0.52 ISQ: 54.4±12.4 *Baseline (I2)* TST: 315±57 min WASO: 53±32 min SQ: 2.83±0.41 ISQ: 58.5±11.2 *Baseline (C)* TST: 347±68 min WASO: 61±33 min SQ: 2.83±0.52 ISQ: 51.7±14	*Post-treatment (I1)* TST: 360±8 min WASO: 28±4 min (I1>I2+C) SQ: 3.4±0.1 (I1>I2) ISQ: 41.9±2.5 (I1>C) *Post-treatment (I2)* TST: 362±9 min WASO: 44±4 min SQ: 2.9±0.1 ISQ: 47.6±2.6 *6 months FU (I1 and I2)* Results given in graphs; Maintained results from post-treatment I1>I2: WASO	*C post-treatment* TST: 361±8 min WASO: 47±4 min SQ: 3.1±0.1 ISQ: 52.9±2.6	Moderate Several strengths. Weaknesses: eg no placebo control at 6 months follow-up Study drop out: 25–29%

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Table 3.5.6 *continued*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal/ drop outs	Control Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention Effects/ side effects	Results Control Effects/ side effects	Study quality and relevance Comments
Edinger 2009 [5] USA	RCT, parallel-group, stratification (gender, age group, use of sleep medication, insomnia severity, and type of insomnia: primary or co-morbid) Blinding: patients to hypotheses	Primary (n=40; PI) or co-morbid (n=41; CMI) insomnia (RDC criteria), total wake ≥60 min. Exclusion of unstable medical or psychiatric condition, suicide risk, acute pain/ sleep-interfering pain, apnea, PLMD Female/male: 30%/70% Age: 54.2 years	I: CBT (individual, 4 sessions, 1 h each); n=41 Treatment drop outs: 5 FU drop outs: 3	C: Sleep hygiene (individual, 4 sessions, 1 h each) n=40 Treatment drop outs: 7 FU drop outs: 0	Electronic sleep diary (SOL, WASO, TST), ISQ, PSQI *Baseline (PI/CMI) (I)* SOL: 43±7/52±7 min WASO: 66±10/ 73±9 min TST: 338±19/ 333±18 min ISQ: 46±4/50±4 PSQI: 11±1/14±1 *Baseline (PI/CMI) (C)* SOL: 38±7/36±8 min WASO: 76±10/ 65±10 min TST: 45±19/ 380±21 min ISQ: 36±4/46±4 PSQI: 12±1/12±1	*Post-treatment (PI/CMI) (I)* SOL: 23±5/28±5 min (I>C) WASO: 30±7/36±7 min I=C) TST: 372±22/345±20 min (I=C) ISQ: 24±5/29±4 (I>C) PSQI: 6±1/8±1 (I=C) *6 months FU (PI/CMI) (I)* SOL: 28±5/33±5 min (I=C) WASO: 35±7/39±6 min (I=C) TST: 397±19/341±18 min (I=C) ISQ: 18±5/33±5 (I>C) PSQI: 6±1/10±1 (I=C) No difference between PI+CMI on outcomes	*Post-treatment (PI/CMI) (C)* SOL: 28±4/32±5 min WASO: 49±7/45±7 min TST: 365±20/386±23 min ISQ: 28±5/32±5 PSQI: 8±1/8±1 *6 months FU (PI/CMI) (C)* SOL: 22±5/25±5 min WASO: 48±6/ 41±7 min TST: 398±18/ 395±20 min ISQ: 24±5/35±6 PSQI: 8±1/8±1	High quality Several strengths Weaknesses: no substantial Study drop out: 19%

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Table 3.5.6 continued

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal/ drop outs	Control Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention Effects/ side effects	Results Control Effects/ side effects	Study quality and relevance Comments
Epstein 2007 [6] USA	RCT Breast cancer survivors with treatment completed ≥3 months before entry. Recruitment from newspaper ads, physicians "referrals", support groups	DSM-IV and ICSD. SOL or WASO ≥30 min, 3 nights/week for 2 weeks Disturbed sleep complaint for ≥3 months 38% primary and 62% co-morbid insomnia	CBT-I multi-component (stimulus control, sleep restriction, sleep hygiene/ education) 6-weeks group treatment given by a psychiatric nurse n=34 Drop outs: I: 15% C: 7%	Single-component (sleep hygiene/ education) n=38	*Sleep diary 2-weeks (I)* SOL: 52±55 min WASO: 57.9±30.6 min TST: 362.8±55.5 min SQ: 2.6±0.4 *Sleep diary 2-weeks (C)* SOL: 49.0±42.7 min WASO: 54.3±34.3 min TST: 373.3±70.3 min SQ: 2.8±0.5	*Post-treatment* SOL: 21±17 min (I=C, between groups) WASO: 28.5±22.5 min (I=C, between groups) TST: 396.0±44.2 min (I=C, between groups) SQ: 2.8±0.6 (I=C) Sign differences within groups on SOL, WASO, TST and SQ	*Post-treatment* SOL: 28±25 min WASO: 32.6±31.4 min TST: 405.1±52.7 min SQ: 3.1±0.5	Moderate No control group without treatment

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Table 3.5.6 continued

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal/ drop outs	Control Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention Effects/ side effects	Results Control Effects/ side effects	Study quality and relevance Comments
Espie 2007 [7] United Kingdom	RCT Effectiveness study CBT vs TAU	Aged ≥18 years; Referred by GP; SOL ≥30 min and/or WASO ≥30 min ≥3 nights/week during ≥6 months; Complaint of insomnia impact Female/male: 68%/32% Age: 54 years	5 sessions, small groups, multi-component by primary care nurses n=107 Drop outs at post-treatment: 11.2% and at 6–month FU: 29.0%	TAU n=94 Drop outs at posttreatment: 11.7% and at 6-month FU: 28.7%	*Sleep diary (I)* SOL: 60±50 min WASO: 101.9±88.2 min TST: 5.54±1.69 h *Sleep diary (C)* SOL: 54±41 min WASO: 85.0±71.4 min TST: 5.93±1.46 h *Clinical outcomes (I)* PSQI: 12.7±3.75 *Clinical outcomes (C)* PSQI: 12.3±3.55	*Sleep diary* Post-treatment SOL: 37±43 min (I<C, between groups) WASO: 66.1±50.3 min (I=C, between groups) TST: 5.74±1.19 h (I=C) 6 months FU SOL: 42±45 min (I=C, between groups) WASO: 83.0±76.3 min (I=C, between groups) TST: 5.89±1.27 h (I=C) *Clinical outcomes* Post-treatment PSQI: 9.84±4.17 (I<C, between groups) 6 months FU PSQI: 8.40±4.14 (I<C, between groups)	*Sleep diary* Post-treatment SOL: 56 min WASO: 77 min TST: 5.91 h 6 months FU SOL: 51 min WASO: 93 min TST: 5.85 h *Clinical outcomes* Post-treatment PSQI: 11.3±3.68 6 months FU PSQI: 11.2±3.24	Moderate ITT Actigraph: no effects on SOL but sign effects on WASO

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Table 3.5.6 continued

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal/ drop outs	Control Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention Effects/ side effects	Results Control Effects/ side effects	Study quality and relevance Comments
Espie 2008 [8] United Kingdom	RCT Effectiveness study; Treatment delivered by oncology nurses Patients with cancer. CBT vs TAU	Cancer diagnosis; +18 years; DSM-IV criteria for chronic insomnia; mean SOL ≥30 min or WASO; >3 nights/week for ≥3 months; daytime dysfunction Female/male: 69%/31% Age: 59 years (52–70)	5 weekly group CBT-I sessions (in reality CBT plus TAU) n=100 Attrition to post-treatment 26% and to 6-month FU 33%	n=50 Attrition to post-treatment 18% and to 6-month FU 22%	Sleep diary *Median (interquartile range) (I)* SOL: 41 (20.3–64.8) min WASO: 62.0 (40.7–107.5) min TST: 399.0 (343.3–455.9) min *Median (interquartile range) (C)* SOL: 27.4 (22.4–50.0) min WASO: 51.0 (30.5–82.0) min TST: 392.0 (348.0–457.9) min	*Post-treatment* SOL: 19 (12–27) months (I<C) WASO: 27.0 (14.0–57.5) months (I<C) TST: 426.3 (370.1–456.8) months (I=C) *6-month F-U* SOL: 19 (11–28) months (I<C) WASO: 26.1 (12.6–59.4) months (I<C) TST: 438.7 (408.6–470.6) months (I=C) Actigraphy showed sign higher effect sizes post-treatment for SOL, WASO and TST in the treatment group but showed no differences at FU	*Post-treatment* SOL: 27 (16–53) months WASO: 51.0 (33.0–93.3) months TST: 409.0 (327.3–453.3) months *6-month FU* SOL: 22 (15–37) months WASO: 34.0 (22.5–78.0) months TST: 413.5 (354.0–493.0) months	Moderate Medians (Interquartile ranges) and standardized effects compared
Jansson 2005 [12] Sweden	RCT CBT-I vs. Self-help pamphlet. Recruitment through newspaper ads. Early intervention	SOL or WASO >30 min; >3 days/week; duration 3–12 months Female/male: 77%/23% Age: 49 years	CBT 6 group sessions, 6 weeks + booster session after 2 months n=64 Drop outs: 21.9%	Self-help 8-page pamphlet sent by mail n=72 Drop outs 15.3%	*Sleep diary 1-week (I)* SOL: 58±53 min WASO: 133±75 min TST: 4.8±1.0 h SQ: 1.5±0.7 *Sleep diary 1-week (C)* SOL: 68±55 min WASO: 114±83 min TST: 5.3±1.2 h SQ: 1.5±0.6	SOL: 34±32 months (I<C) WASO: 67±58 months (I<C) TST: 5.8±1.0 hours (I>C) SQ: 2.8±1.2 (I>C)	SOL: 62±57 months WASO: 90±61 months TST: 5.5±1.2 hours SQ: 2.2±1.0	Moderate Daytime dysfunction Post-treatment assessment after 1 year

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Table 3.5.6 *continued*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal/ drop outs	Control Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention Effects/ side effects	Results Control Effects/ side effects	Study quality and relevance Comments
Lichstein 2000 [2] USA	RCT	Insomnia secondary to medical (pain, prostate disease, neurologic disorder, or respiratory disease) or psychiatric (anxiety or depression) conditions. Exclusion of other sleep disorders Female/male: 48%/52% Age: 68.6 years (58–)	I: BT (individual, 4 sessions) n=24 Treatment drop outs: 1 FU drop outs: 0	C: Wait list n=25 Post-treatment or FU drop outs: 4 CBT after FU	Sleep diary (SOL, WASO, TST, SQ) *Baseline (I)* SOL: 48±42 min WASO: 87±61 min TST: 329±86 min SQ: 2.7±0.7 *Baseline (C)* SOL: 55±41 min WASO: 68±57 min TST: 343±99 min SQ 2.6±0.6	*Post-treatment (I)* SOL: 31±24 min (I=C) WASO: 61±64 min (I=C) TST: 374±115 min (I=C) SQ: 3.2±0.7 (I>C) *3 month FU (I)* SOL: 27±19 min (I=C), WASO: 56±41 min (I=C) TST: 373±67 min (I=C) SQ: 3.2±0.6 (I>C)	*Post-treatment (C)* SOL: 42±25 min WASO: 69±5 min TST: 374±11 min SQ: 2.7±0.6 *3 months FU (C)* SOL: 50±37 WASO: 61±5 min TST: 360±10 min SQ: 2.6±0.7	Moderate Several strengths Weaknesses: eg description of randomisation Study drop out: 10%

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Table 3.5.6 continued

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal/ drop outs	Control Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention Effects/ side effects	Results Control Effects/ side effects	Study quality and relevance Comments
Lichstein 2001 [14] USA	RCT, stratification (gender, sleep efficiency, and ISI score)	Psychophys. insomnia (primary), SOL or WASO ≥30 min, 3 times per week or more. Exclusion of other sleep disorders, medical or psychiatric disorders, and sleep medication Female/male: 74%/26% Age: 68 years (59–92)	I1: Relaxation (individual, 6 sessions) n=30 Treatment drop outs: 2 FU drop outs: 1 I2: Sleep compression (individual, 6 sessions) n=30 Treatment drop outs: 2 FU drop outs: 1 3 withdrawn at FU due to apnea	C: Placebo (individual, 6 sessions) n=29 Treatment drop outs: 2 FU drop outs: 3 1 withdrawn at FU due to apnea	Sleep diary (SOL, WASO, TST, SQ), PSG (baseline and FU) *Baseline (I1)* SOL: 32±20 min WASO: 66±37 min TST: 345±78 min SQ: 2.9±0.6 IIS: 100±23 *Baseline (I2)* SOL: 33±30 min WASO: 67±33 min TST: 328±58 min SQ: 2.8±0.6 IIS: 98±21 *Baseline (C)* SOL: 35±21 min WASO: 72±36 min TST: 332±71 min SQ: 2.9±0.5 IIS: 104±22	*Post-treatment (I1)* SOL: 22±15 min (I1=I2=C) WASO: 43±26 min (I1=I2=C) TST: 398±87 min (I1=I2=C) SQ: 3.5±0.6 (I1=I2=C) *Post-treatment (I2)* SOL: 21±16 min WASO: 42±32 min TST: 314±82 min SQ: 3.4±0.6 *12 months FU (I1)* SOL: 27±19 min (I1=I2=C) WASO: 52±46 min (I1=I2=C) TST: 404±88 min (I1=I2=C) SQ: 3.4±0.5 (I1=I2=C) *12 months FU (I2)* SOL: 23±17 min WASO: 38±28 min TST: 364±69 min SQ: 3.5±0.5	*Post-treatment (C)* SOL: 24±15 min WASO: 50±28 min TST: 377±55 min SQ: 3.3±0.6 IIS: 100±27 *2 months FU (C)* SOL: 37±27 min WASO: 58±29 min TST: 373±53 min SQ: 3.2±0.6 IIS: 97±18	Moderate Several strengths Weaknesses: eg withdrawals (n=4) due to apnea, no blinding, description of randomisation Study drop out: 12%

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Table 3.5.6 continued

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal/ drop outs	Control Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention Effects/ side effects	Results Control Effects/ side effects	Study quality and relevance Comments
Ritterband 2009 [3] USA	RCT	Primary insomnia, duration ≥6 months. Exclusion of other sleep disorders, medical or psychiatric conditions Female/male: 77%/23% Age: 44.9 years (11.0)	I: CBT via internet (6 cores during 9 weeks); n=22 Treatment drop outs: 0 Post-treatment drop outs: 1 FU drop out: 3	C: Wait list n=23 Post-treatment drop outs: 1 (began shift work) CBT via internet after post-treatment	Sleep diary (SOL, WASO, TST, restored, soundness (SQ)), ISI *Baseline (I)* SOL: 32±28 min WASO: 67±41 min TST: 350±88 min Restored: 2.7±0.7 Soundness: 2.8±0.6 ISI: 15.7 (14.1–17.4) *Baseline (C)* SOL: 35±21 min WASO: 56±19 min TST: 366±61 min Restored 2.7±0.6 Soundness: 2.8±0.6 ISI: 16.3 (14.6–17.9)	*Post-treatment (I)* SOL: 18±13 min (I=C) WASO: 30±20 min (I>C) TST: 405±61 min (I=C) Restored: 3.2±0.7 (I=C) Soundness: 3.2±0.6 (I=C) ISI: 6.6 (4.7–8.5) (I>C) *6 months FU (I)* ISI: 7.3 (5.1–9.6): maintained ISI	*Post-treatment (C)* SOL: 33±16 min WASO: 52±27 min TST: 380±60 min Restored: 2.9±0.7 Soundness: 2.9±0.7 ISI: 15.5 (13.6–17.4) No assessment after post-treatment	Moderate Several strengths Weaknesses: eg no blinding Study drop out: 9%

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Table 3.5.6 *continued*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal/ drop outs	Control Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention Effects/ side effects	Results Control Effects/ side effects	Study quality and relevance Comments
Rybarczyk 2005 [9] USA	RCT	Co-morbid insomnia (medical conditions: Osteoarthritis, coronary heart disease, or chronic obstructive pulmonary disease). Insomnia ≥3 times per week, 6 months duration. Exclusion of other sleep disorders, medical and psychiatric conditions I: Female/male: 61%/39% C: Female/male: 74%/26% Age I: 70.1 years Age C: 67.7 years	I: CBT (group, 8 sessions); n=46 Treatment drop outs: 2 FU drop outs: 0	C: Placebo (stress management and wellness, group, 8 sessions) n=46 Treatment drop outs: 2 FU drop outs: 0 CBT after post-treatment	Sleep diary (SOL, WASO, TST), PSQI, SII *Baseline (I)* SOL: 46±50 min WASO: 50±39 min TST: 339±68 min PSQI: 10.8±3.6 SII: 21.7±5 *Baseline (C)* SOL: 36±26 min WASO: 58±41 min TST: 345±76 min PSQI: 10.8±3.4 SII: 21.3±5.2	*Post-treatment (I)* SOL: 22±20 min (I>C) WASO: 22±18 min (I>C) TST: 372±60 min (I=C) PSQI: 6.8±3.9 (I>C) SII: 14.9±5.2 (I>C)	*Post-treatment (C)* SOL: 33±27 min WASO: 49±39 min TST: 371±67 min PSQI: 9.5±3.5 SII: 19.9±5.5 C after CBT: decreased SOL, WASO, PSQI, SII	High quality Several strengths. Weaknesses: no substantial Study drop out: 4%

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Table 3.5.6 *continued*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal/ drop outs	Control Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention Effects/ side effects	Results Control Effects/ side effects	Study quality and relevance Comments
Savard 2005 [4] Canada	RCT Insomnia secondary to breast cancer CBT-I vs waiting list until post-treatment/post-waiting. Thereafter analysis of pooled data within groups	ICSD and DSM-IV criteria. SOL and/or WASO >30 min; SE <85%; >3 nights/week for >6 months; marked distress or daytime dysfunction Female/male: 100%/0% Age: 54 years	8 weekly group sessions of CBT n=27 *Drop outs* Post-treatment: 14.3% 3-month: 25.0% 6-month: 25.0% 12-month: 42.9%	Wait list, n=30 *Drop outs* Post-treatment: 3.3% 3-month: 16.7% 6-month: 20.0% 12-month: 20.0%	*Mean (95% CI)* Sleep diary (I) SOL: 41 (34–49) min WASO: 114.4 (98.7–130.1) min TST: 351.0 (327.8–374.2) min ISI: 16.15 (14.25–18.05) Sleep diary (C) SOL: 44 (34–54) min WASO: 108.8 (89.6–128.1) min TST: 369.5 (346.1–392.9) min ISI: 16.13 (14.48–17.78)	*Sleep diary* Post-treatment SOL: 18 (10–26) min (I<C) WASO: 51.7 (35.3–68.1) min (I<C) TST: 379.2 (355.3–403.1) min (I=C) ISI: 7.57 (5.59–9.55) (I<C) Pooled data from post-treatment to FUs showed no sign difference within groups for SOL or WASO but TST improved sign ISI showed improvements (I<C)	*Sleep diary* Post-waiting SOL: 36 (29–43) min WASO: 96.8 (81.7–111.9) min TST: 387.1 (364.7–409.5) min ISI: 13.70 (11.88–15.52)	Moderate Pooled data from pre-treatment to post-treatment showed sign difference within groups for SOL, WASO and TST

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Table 3.5.6 *continued*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal/ drop outs	Control Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results Intervention Effects/ side effects	Results Control Effects/ side effects	Study quality and relevance Comments
Soeffing 2008 [10] USA	RCT	Chronic insomnia, sustained and frequent use of hypnotic medication for insomnia, interest in reducing sleep medication Exclusion: other sleep disorders (apnea and PLMD), seizures, sleep-interfering psychiatric or medical conditions, high substance-levels Female/male: 64%/36% Age: 64 years	I: BT (8 individual sessions); n=20	C: Placebo biofeedback (8 individual sessions); n=27	Sleep diary (SOL, WASO, TST, SQ) *Baseline (I)* SOL: 45±36 min WASO: 72±85 min TST: 353±81 min SQ: 2.7±0.7 *Baseline (C)* SOL: 41±23 min WASO: 58±28 min TST: 355±54 min SQ: 2.8±0.6	*Post-treatment (I)* SOL: 20±15 min (I>C) WASO: 27±19 min (I>C) TST: 408±50 min (I=C) SQ: 3.6±0.5 (I=C)	*Post-treatment (C)* SOL: 31±22 min WASO: 38±21 min TST: 405±52 min SQ: 3.3±0.6	Moderate Several strengths. Weaknesses: eg no blinding Drop-outs not reported

BT = Behaviour therapy; C = Control; CBT = Cognitive behaviour therapy; CMI = Co-morbid intervention; FU = Follow-up; h = Hours; I = Intervention; ISI = Insomnia Severity Index; ISQ = Insomnia Symptom Questionnaire; ITT = Intention to treat; min = Minutes; n = Number; P = Placebo; PI = Primary insomnia; PLMD = Periodic Limb Movement Disorder; PSG = Polysomnography; PSQI = Pittsburgh Sleep Quality Index; RCT = Randomised controlled trial; SII = Sleep Impairment Index; SOL = Sleep onset latency; SQ = Sleep quality; TAU = Treatment as usual; TST = Total sleep time; WASO = Wake after sleep onset

Table 3.6.1 *Randomised controlled studies of combined pharmacological and psychological treatment of insomnia.*

First author Reference Year Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal/ drop outs	Control Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results intervention Effects/side effects	Results control Effects/side effects	Study quality and relevance Comments
Baillargeon 2003 [16] Canada	RCT, no blinding	Insomnia (≥6 months and day time impairment), ≥50 years, daily use of BZ ≥3 months, either (1) inability to refrain from sleeping pills or (2) SE <80% Exclusion: Cognitive impairment, insomnia due to physical/psychiatric condition Age: 67.4 years Female/male: 58%/42%	I: CBT (8 sessions, group, booster session) + gradual tapering (see under Control) n=35 Treatment drop out: 1 PT drop out: 1 3-months FU drop out: 2 12-months FU drop out: 2	C: Gradual tapering (8 sessions, physician-led, manual) n=30 Treatment drop out: 6 PT drop out: 1 3-months FU drop out: 1 12-months FU drop out: 1	Sleep diary (BZ consumption), blood screening (BZ discontinuation) No baseline values	*PT (I)* BZ-free 77% (I>C) Dosage reduction ≥50%: 97% (I=C) *3-months FU (I)* BZ-free 67% (I>C) Dosage reduction ≥50%: 76% (I=C) *12-months FU (I)* BZ-free 70% (I>C). Dosage reduction ≥50%: 81% (I=C)	*PT (C)* BZ-free 38% Dosage reduction ≥50%: 69% *3-months FU (C)* BZ-free 34%, dosage reduction ≥50%: 66% *12-months FU (C)* BZ-free 24% Dosage reduction ≥50%: 52%	Moderate Several strengths. Weaknesses: eg no blinding. Adverse tapering events recorded: none reported Study drop out: 12%

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Table 3.6.1 *continued*

First author Reference Year Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal/ drop outs	Control Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results intervention Effects/side effects	Results control Effects/side effects	Study quality and relevance Comments
Belleville 2007 [17] Canada	RCT, no blinding	Insomnia (≥6 months, ≥3 nights/week, daytime impairment; specific criteria in the past or at assessment), ≥18 years, sleep medication use >3 nights at least 3 months Exclusion: Medical or psychological disorder related to sleep disorder, other sleep disorder, psychotropic medication for other than insomnia, current psychotherapy, sleep-disrupting medication Age: 55.3 years Female/male: 64%/36%	I: Tapering (see under Control) + self-help CBT (standard CBT components, 5 booklets during 8 weeks) n=28 Treatment drop out: 5 1-month FU drop out: 7 3-months FU drop out: 6 6-months FU drop out: 8	C: Tapering (withdrawal schedule, 2 sessions led by physician, weekly phone calls) n=25 Treatment drop out: 0 1-month FU drop out: 1 3-months FU drop out: 2 6-months FU drop out: 2	Sleep diary (TWT, TST, daily quantity and frequency of hypnotic medication use), ISI *Baseline (I)* TWT: 170±83 min TST: 348±83 min Hypnotic quantity: 1.8±1.5 mg Hypnotic frequency: 6.5±1 night/week ISI: 17.6±4.0 *Baseline (C)* TWT: 191±151 min TST: 325±91 min Hypnotic quantity: 1.3±1.1 mg Hypnotic frequency: 6.6±1.1 night/week ISI: 16.8±4.5	*PT (I)* TWT: 115±73 min (I=C) TST: 352±82 min (I=C) Hypnotic quantity: 0.2 mg±0.4 (I=C) Hypnotic frequency: 1±2.2 night/week (I=C) ISI: 11.7±5.1 (I=C) *1-months FU (I)* TWT: 102±49 min (I=C) TST: 365±84 min (I=C) Hypnotic quantity: 0.2±0.3 mg (I=C) Hypnotic frequency: 1.3±2.2 night/week (I=C) ISI: 11.7±5.4 (I=C) *3-months FU (I)* TWT: 108±70 min (I=C) TST: 374±88 min (I=C) Hypnotic quantity: 0.2±0.7 mg (I=C) Hypnotic frequency: 1.3±2.4 night/week (I=C) ISI: 11.1±5.4 (I=C) *6-months FU (I)* TWT: 121±106 min (C>I) TST: 372±88 min (I=C) Hypnotic quantity: 0.3±0.8 mg (I=C) Hypnotic frequency: 1.7±2.5 night/week (I=C) ISI: 10.7±5.9 (I=C)	*PT (C)* TWT: 196±145 min TST: 322±87 min Hypnotic quantity: 0.1±0.2 mg Hypnotic frequency: 1.1±2.1 night/week ISI: 14.3±6.1 *1-months FU (C)* TWT: 168±130 min TST: 346±97 min Hypnotic quantity: 0.2±0.5 mg Hypnotic frequency: 1.6±2.5 night/week ISI: 13.6±7.9 *3-months FU (C)* TWT: 159±121 min TST: 353±86 min Hypnotic quantity: 0.3±0.6 mg Hypnotic frequency: 1.8±2.7 night/week ISI: 11.6±6.8 *6-months FU (C)* TWT: 144±100 min TST: 354±83 min Hypnotic quantity: 0.4±0.6 mg Hypnotic frequency: 2.2±2.9 night/week ISI: 11.5±7.5	Moderate Several strengths. Weaknesses: eg no blinding. Adverse events recorded: none reported Study drop out: 17%

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Table 3.6.1 *continued*

First author Reference Year Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal/ drop outs	Control Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results intervention Effects/side effects	Results control Effects/side effects	Study quality and relevance Comments
Morin 2004 [18] Canada	RCT	BZ medication use at least 50% of nights at least 3 months, insomnia with daytime impairment, ≥55 years Exclusion: Medical or psychiatric disorder directly related to insomnia, apnea, PLMD, psychotherapy, psychotropic drugs, severe psychopathology, cognitive impairment Female/male: 50%/50% Age: 62.5 years	I: CBT + medication tapering (see under Control) n=27 Treatment drop out: 2 PT drop out: 0 3-months FU drop out: 4 12-months FU drop out: 4	C1: CBT (10 sessions in groups, led by psychologist) n=24 Treatment drop out: 2 PT drop out: 0 3-months FU drop out: 3 12-months FU drop out: 5 C2: Medication tapering (10 individual sessions led by physician) n=25 Treatment drop out: 3 PT drop out: 0 3-months FU drop out: 5 12-months FU drop out: 5	*Baseline (I)* BZ use/week: 64±6 mg Frequency: 6.8±0.4 night/week TWT: 126±11 min TST: 368±13 min SOL: 34±4 min WASO: 45±7 min *Baseline (C1)* BZ use/week: 71±7 mg Frequency 6.7±0.5 night/week TWT: 152±12 min TST: 352±14 min SOL: 32±5 min WASO: 50±7 min *Baseline (C2)* BZ use/week: 66±6 mg Frequency: 6.6±0.5 night/week TWT: 149±11 min TST: 355±14 min SOL: 39±5 min WASO: 58±7 min	*Post-treatment (I)* Quantity/week: 1.3±6.3 mg (I=C1=C2) Frequency: 0.2±0.4 night/week(I>C2) TWT: 92±12 min (I=C1=C2) TST: 328±14 min (I=C1=C2) SOL: 30±5 min (I=C1=C2) WASO: 37±7 min (I=C1=C2) *12-months FU (I)* Quantity/week: 4.4±6.6 mg (I=C1=C2) Frequency: 1.6±0.5 night/week (I=C1=C2) TWT: 99±12 min (I=C1=C2) TST: 360±14 min (I=C1=C2) SOL: 24±5 min (I=C1=C2) WASO 46±7 min (I=C1=C2)	*Post-treatment (C1)* Quantity/week: 7.5±6.8 mg Frequency: 1.5±0.5 night/week TWT: 95±12 min TST: 312±15 min SOL: 25±5 min WASO: 41±7 min *12-months FU (C1)* Quantity/week: 9.7±7.1 mg Frequency: 2.7±0.5 night/week TWT: 98±13 min TST: 362±15 min SOL: 25±5 min WASO: 35±8 min *Post-treatment (C2)* Quantity/week: 11.4±6.7 mg Frequency: 2.3±0.5 night/week TWT: 151±12 min TST: 338±14 min SOL: 42±5 min WASO: 61±7 min *12-months FU (C2)* Quantity/week: 13.3±7.1 mg Frequency: 2.7±0.5 night/week TWT: 120±13 min TST: 380±15 min SOL: 34±5 min WASO: 46±8 min	Moderate Several strengths. Weaknesses: eg poor randomisation description Study drop out: 18%

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Table 3.6.1 *continued*

First author Reference Year Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal/ drop outs	Control Number of individuals Withdrawal/ drop outs	Method of measurement Baseline values	Results intervention Effects/side effects	Results control Effects/side effects	Study quality and relevance Comments
Morin 2009 [10] Canada	RCT, randomisation in 2 phases, blinding (independent assessor and PSG)	Insomnia, duration ≥6 months, daytime impairment Exclusion: Medical illness affecting insomnia, lifetime psychotic/bipolar disorder, current depression or more than two previous depression episodes, suicide attempt history, apnea, RLS, PLMD, shift work/ irregular sleep pattern Female/male: 61%/39% Age: 50.3 (10.1)	*IA Phase 1* CBT (group, 6 weekly sessions) n=80 Treatment drop out: 5 *IB Phase 2* Extended CBT (group, 6 monthly sessions) n=38 Treatment drop out: 1 FU drop outs: 4 or (IC) no extension (6 months) n=37 Treatment drop out: 2	*CA Phase 1* CBT + zolpidem (6 weeks; same as phase 1 CBT; 10 mg, sessions by physician) n=80 Treatment drop out: 6 *CB Phase 2* CBT, no zolpidem (same as for extended CBT) n=37 Treatment drop out: 1 FU drop out: 6 or (CC) CBT + zolpidem (6 monthly sessions with physician; tapering) n=37 Treatment drop out: 4 FU drop out: 4	Sleep diary (SOL, WASO, TST), PSG, ISI *Baseline (IA)* SOL: 37±3 min WASO: 117±5 min TST: 344±7 min ISI: 17.3±0.5 *Baseline (CA)* SOL: 30±3 min WASO: 129±5 min TST: 349±7 min ISI: 17.6±0.5	*PT (IA) (end of Phase 1)* SOL: 17±3 min (I=C) WASO: 48±5 min (I=C) TST: 338±7 min (C>I): ISI 8.9±0.5 (I=C) *6-months FU (IB) (end of Phase 2)* SOL: 19±3 min WASO: 61.6±5 min TST: 363±8 min ISI: 8.7±0.7 *6-months FU (IC) (end of Phase 2)* SOL: 22±3 min WASO: 59±6 min TST: 385±9 min ISI: 8.1±0.7 *6-months FU (IB)* SOL: 16±2 min WASO: 56±6 min TST :383±10 min ISI: 8.9±0.7 *6-months FU (IC)* SOL: 18±2 min WASO: 63±5 min TST: 389±10 min ISI: 8.9±0.7	*PT (CA) (end of Phase 1)* SOL: 18±3 min WASO: 46±5 min TST: 359±7 min ISI: 8.8±0.5 *6-months FU (CB) (end of Phase 2)* SOL: 18±3 min WASO: 48±6 min TST: 391±9 min ISI: 7.0±1 min *6-months FU (CC) (end of Phase 2)* SOL: 15±3 min WASO: 66±6 min TST: 373±9 min ISI: 8.7±0.8 *6-months FU (CB)* SOL: 14±2 min WASO: 47±6 min TST: 399±10 min ISI: 5.8±0.7 *6-months FU (CC)* SOL: 16±2 min WASO: 64±6 min TST: 391±11 min ISI: 8.8±0.8	High Several strengths Weaknesses: no substantial Study drop out: 17%

BZ = Benzodiazepine; CA = Control phase 1 (CBT + zolpidem); CB = Control, phase 2 (CBT); CBT = Cognitive behaviour therapy; CC = Control, phase 2 (CBT + zolpidem); IA = Intervention, phase 1 (CBT); IB = Intervention, phase 2 (CBT); IC = Intervention, phase 2 (–); ISI = Insomnia Severity Index; FU = Follow-up; min = Minutes; PSG = Polysomnography; PLMD = Periodic limb movement disorder; PT = Post-treatment; RCT = Randomised controlled trial; RLS = Restless legs syndrome; SE = Sleep efficiency; SOL = Sleep onset latency; TST = Total sleep time; TWT = Total wake time; WASO = Wake after sleep onset

Table 4.2.3 *Studies of the association between treatment of insomnia and risk for falls.*

First author Year Reference Country	Study design	Inclusion criteria or diagnosis Female/male Age (mean, range)	Exposure Confounders	Number of individuals Number of lost to follow-up	Method of measurement of outcome	Results (OR, 95% CI)	Study quality and relevance Comments
Avidan 2005 [1] USA	150–210 days Prospective cohort of long term patients with 6 months data	437 nursing homes Residents ≥65 years Female/male: 76%/24% Mean age: 84,4±8 years	Insomnia Hypnotics/non-hypnotics within cohort Confounders age sex, burden of illness, proximity to death, functional and cognitive status Number of medications, emergency room visits and resource utilisation. (MDS Minimum data set) Excluded short term patients without data	n=74 232 n=34 163 evaluated 17 039 died 20 977 discharged before follow-up 2 053 lost to follow-up	Falls Hip fractures during 6 months from baseline to follow-up within 180 days Blinded evaluators	*Falls* Insomnia Yes/no OR (adjusted)=1.52 (1.38–1.66) Hypno use Yes/no OR=1.29 (1.13–1.48) Insomnia 1–5 nights/week/no insomnia OR=1.47 (1.33–1.63) Insomnia ≥6 nights/week/no insomnia OR=1.86 (1.44–2.39) Insomnia hypno use/ No insomnia no hypno OR=1.54 (1.21–1.97) Insomnia no hypno use/ No insomnia no hypno OR=1.96 (1.79–2.16) No insomnia hypno use/ No insomnia no hypno OR=1.27 (1.08–1.49) *Hip fractures* Insomnia Yes/no OR (adjusted)=1.45 (1.14–1.85) Hypno use Yes/no OR=1.46 (1.01–2.10) Insomnia hypno use/ No ins no hypno OR=1.65 (0.87–3.12) Insomnia no hypno use/ No insomnia no hypno OR=1.44 (1.11–1.87) No insomnia hypno use/ No insomnia no hypno OR=1.43 (0.92–2.23)	Moderate Very nice cohort study, detailed characterisation of risk factors. Classification and outcome measures tested between investigators

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Table 4.2.3 continued

First author Year Reference Country	Study design	Inclusion criteria or diagnosis Female/male Age (mean, range)	Exposure Confounders	Number of individuals Number of lost to follow-up	Method of measurement of outcome	Results (OR, 95% CI)	Study quality and relevance Comments
Glass 2005 [4] Canada	Metaanalysis of RCTs 1966–2003	Included studies, n=24 Patients >60 years with insomni, n=2 417	Benzodiazepines Zolpidem Zaleplone Zoplicone Antihistamines Diphenhydramine	Placebo or placebo run in scores	Sleep parameters	SQ, TST time, WASO	Moderate Long and short-acting drugs grouped together, run in placebo might overestimate effects. Falls or fractures not primary endpoint
					Psychomotor events	Increased psychomotor events (13 studies, 1 016 patients) OR=2.25 (0.93–5.41) p>0.05	
					Adverse cognitive events	Adverse cognitive events (10 studies, 712 patients) OR=4.78 (1.47–15.47) p<0.01	
					Daytime fatigue	Daytime fatigue (16 studies, 2 220 patients) OR=3.82 (1.88–7.80) p<0.001	

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Table 4.2.3 *continued*

First author Year Reference Country	Study design	Inclusion criteria or diagnosis Female/male Age (mean, range)	Exposure Confounders	Number of individuals Number of lost to follow-up	Method of measurement of outcome	Results (OR, 95% CI)	Study quality and relevance Comments
Vassallo 2006 [2] United Kingdom	Prospective observational study 17 months. Medium length of stay (observation) 17 days	Rehabilitation patients consecutively hospitalised. Benzodiazepines antipsychotic night medication. Anxiolytic Sedatives hypnotics Current use <1 year previous use	All Confused/tranq Confused/no tranq Non-confused/tranq Non-confused/no tranq	n=1 025 n=127 n=285 n=107 n=506 Number of lost to follow-up not stated	Blinded follow-up falls (hospital accident reporting system at discharge or after 30 days	*Falls* Non confused/confused OR=0.38 (0.29–0.49) p<0.0001 No tranq/tranq OR=0.63 (0.49–0.82) p=0.001 Confused no tranq/ confused tranq OR=0.79 (0.49–1.26) p=0.33 Non confused no tranq/ non confused tranq OR=0.58 (0.32–1.07) p=0.12 *Recurrent falls* Confused no tranq/ confused tranq OR=0.45 (0.23–0.87) p=0.026 Non-confused no tranq/ non-confused tranq OR=0.84 (0.23–3.03) p=0.73	Moderate Not insomnia but hypnotics. Small numbers in subgroups. Falls not fractures

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Table 4.2.3 *continued*

First author Year Reference Country	Study design	Inclusion criteria or diagnosis Female/male Age (mean, range)	Exposure Confounders	Number of individuals Number of lost to follow-up	Method of measurement of outcome	Results (OR, 95% CI)	Study quality and relevance Comments
Vestergaard 2008 [3] Denmark	Large register study	Any fracture in 2 000 n=124 655, Female/male: 48.2%/51.8% Age mean: 43.44 years (0–100)	Exposure to anxiolytics, sedatives and hypnotics current <1 yr and past >1 yr. Data from prescription database (refundable drugs) Adjustment for comorbid conditions (Charlson index), marital and occupational status, use of antidepressant and neuroleptic use and alcoholism	n=124 655 Controls from background population n=373 962 Age, gender matching	Any fracture in 2 000 Data from National hospital discharge register (All in and outpatients)	Risk for fracture >0.25 DDD *Alprazolam* Any: 1.15 (1.06–1.24) Hip dose-r: 1.26 (1.04–1.54) *Diazepam* Any dose-r: 1.22 (1.16–1.28) Hip dose-r: 1.61 (1.44–1.80) *Hydroxyzine* Any: 1.01 (0.76–1.36) Hip: 1.33 (0.72–2.47) *Flunitrazepam* Any: 1.11 (1.02–1.20) Hip: 1.08 (0.91–1.28) *Nitrazepam* Any: 0.97(0.93–1.01) Hip: 0.99 (0.91–1.08) *Oxazepam* Any: 1.12 (1.06–1.19) Hip: 1.42(1.26–1.59) *Triazolam* Any: 0.95 (0.88–1.03) Hip: 1.16 (0.99–1.36) *Zaleplone* Any: 1.09 (0.72–1.67) Hip: 0.59 (0.18–1.90) *Zolpidem* Any dose-r: 1.20 (1.14–1.26) Hip dose-r: 1.36 (1.23–1.52) *Zopiclone* Any dose-r: 1.14 (1.09–1.18) Hip dose-r: 1.40 (1.30–1.52) Dose response pattern for most drugs half life >24 h tendency to increased risk	Moderate Not insomnia but hypnotics, large, well designed study

DDD = Daily defined dose; n = Number; OR = Odds ratio; tranq = Tranquillizer, tranquillizing medication; RCT = Randomised controlled trial

Table 4.2.4 *Studies of the association between treatment of insomnia and risk for traffic accidents.*

First author Year Reference Country	Study design	Inclusion criteria or diagnosis Female/male Age (mean, range)	Exposure Confounders	Number of individuals	Method of measurement of outcome	Results (OR, 95% CI, p)	Study quality and relevance Comments
Barbone 1998 [11] Italy United Kingdom	Cohort study Design: "within person case cross over" Dispensed prescription by community health number	1992–1995 n=19 386 1 731 drug users >18 years	Use of drug on day of accident by ever use Tricyclic antidepressives SSRI Benzodiazepines Zopiclone	*Tricyclic anti-depressives* 189/30 038 *SSRI* 84/13 984 *Benzodiazepines* 235/40 402 *Zopiclone* 14/1 696	Road accident attended by police (paper records) sex age of driver, weekday, time of day, lighting condition, severity of injuries	*Tricyclic antidepressives* 0.93 (0.72–1.21) *SSRI* 0.85 (0.55–1.33) *Benzodiazepines* 1.62 (1.24–2.12) *Zopiclone* 4.0 (1.31–12.2) *Hypnotics* Short half-time (Zopiclone) 4.0 (1.31–12.2) Intermediate half-time (n=120) 1.10 (0.73–1.64) Long half-time (n=28) 0.88 (0.41–1.87) Highest risk associated with anxiolytics not hypnotics (test for difference p=0.01)	Moderate Not specific insomnia but hypnotics included in analysis. 95% of hypnotic benzodiazepines were used as single dose nightly. Few individuals in the subgroups

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Table 4.2.4 *continued*

First author Year Reference Country	Study design	Inclusion criteria or diagnosis Female/male Age (mean, range)	Exposure Confounders	Number of individuals	Method of measurement of outcome	Results (OR, 95% CI, p)	Study quality and relevance Comments
Neutel 1994 [12] Canada	Cohort study Saskatchewan Health database	2 months after benzodiazepine prescription triazolam, flurazepam	Cases Hypnotics n= 78 070 Anxiolytics n=147 726 n=97 862 Adjustment for concomitant drug use, alcohol abuse and social assistance		Risk of hospitalisation for injuries. Age adjusted incidence rates. Standard population sum of all categories	*Hypnotics* OR=3.9 (1.9–8.3) *Anxiolytics <2 weeks* OR=2.5 (1.2–5.2) *Hypnotics* OR=6.5 (1.9–22.4) *Anxiolytics <4 weeks* OR=5.6 (1.7–18.4) *Hypnotics/Anxiolytics <1 week* OR=9.1/13.5 *Hypnotics /Anxiolytics <2 weeks* OR=5.0/1.9 *Males more than female (hypnotics + axiolytics)* <2 weeks OR 4.2 (2.3–7.6) <4 weeks OR 3.5 (2.2–5.5) *Higher risk in young (hypnotics)* 20–39 years OR=8.3 40–59 years OR=4.6 60+ years OR=2.8	Moderate Only one hypnotic drug used in Sweden

DDD = Daily defined dose; n = Number; OR = Odds ratio

Table 5.2 *Studies of various methods to alleviate insomnia.*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal Drop outs	Control Number of individuals Withdrawal Drop outs	Method of measurement Baseline values	Results Intervention/Control Effects/side effects	Study quality and relevance Comments
Alessi 2005 [2] USA	RCT. Pts in 4 nursing homes. 5 days and nights intervention	Excessive daytime sleeping + nighttime sleep disruption. Out of 492 pts, 133 met criteria, 120 completed baseline assessments, 118 were randomised	62 pts. Female/male: 77%/33%, mean age 87 years. 4 dropped out, 58 completed behavioural observations, 54 completed actigraphy. Intervention: 30 min daily sunlight exposure, increased physical activity, structured bedtime routine, reduction of nightly noise and light	56 pts. Female/male: 76%/24%, mean age 85 years. 6 dropped out, 50 completed behavioural observations, 46 completed actigraphy	Actigraphy. Rating scales. Behavioural observations	No sign effect on percentage of nighttime sleep or number of awakenings. A sign but modest decrease in duration of nighttime awakenings in intervention group. A sign decrease in daytime sleeping in intervention group as well as a sign increase in social activities and conversation	Moderate Short intervention, 5 days/nights. Only minor effect on sleep parameters
Alessi 1999 [3] USA	RCT. Urinary incontinent nursing home residents	Of 127 residents, 79 were urinary incontinent. 64 met study criteria, informed consent from 58. 29 dropped out due to death, refusal or transfer. 29 pts were randomised	15 pts. Female/male: 86%/14%, mean age 88 years. Intervention: 14 week physical activity program + nighttime noise and light reduction and non-sleep disruptive nursing care program	14 pts. Female/male: 93%/7%, mean age 88 years. Nighttime noise reduction and non-sleep disruptive nursing care program	Actigraphy. Various rating scales	Intervention group had sign more nighttime sleep and less daytime in bed compared to control group. Intervention group also had sign less daytime agitation	Moderate Daytime physical activity + care program (noise, nursing care) effective in promoting sleep
LaReau 2008 [14] USA	Pts 65+ in acute medical and cardiology care. Mean duration of stay <5 days	70 pts included, 11 withdraw, 59 completed. Female/male: 57%/43%, mean age 79 years	29 pts, mean age 78 years. Intervention: noise reduction, light reduction, relaxation techniques, clustered nursing activities. Unnecessary interruptions (baths, weights) eliminated	30 pts, mean age 80 years	Sleep questionnaire. VAS	No effect on sleep questionnaire questions. Number of sleep medications sign less in intervention group, sleep quality sign improved and ability to remain asleep compared to control group	Moderate Only quality of sleep and ability to remain asleep improved. All other sleep parameters unchanged

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Table 5.2 *continued*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal Drop outs	Control Number of individuals Withdrawal Drop outs	Method of measurement Baseline values	Results Intervention/Control Effects/side effects	Study quality and relevance Comments
Martin 2007 [12] USA	RCT. Nursing home pts. 3 day baseline, 5 days intervention during 5 days or usual care (controls)	Daytime sleepiness and nighttime sleep disruption. 118 nursing home pts randomised, 10 died or withdraw after randomisation, 108 completed intervention phase, 58 intervention, 50 control. Valid actigraphy records for 54 interventions and 46 controls	54 pts. Female/male: 76%/24%, mean age 88 years. Intervention: Increased exposure to outdoor bright light, out-of-bed during the day, structured physical activity, a bedtime routine, reduction of light and noise in room	46 pts. Female/male: 80%/20%, mean age 86 years	Actigraphy. Behavioural observations. Noise and light monitoring. Activity rhythm measurements	Intervention patients spent 19%, less time in bed daytime, compared to controls. Increase of active period in the rest/activity rhythm	Moderate Short-term intervention, no clear-cut sleep data
Ouslander 2006 [15] USA	CT. One group got immediate intervention, the other delayed intervention. All eligible pts participated, no "pure" control group	Chronic nursing home residents aged 65+. Unable to walk unaided nighttime, no severe behavioural symptoms, maximum one roommate. 1 007 pts screened, 847 did not meet criteria/no consent/other failures. 230 completed baseline assessments. 107 allocated to intervention, 123 to delayed intervention (=controls)	107 pts. Female/male: 83%/17%, mean age 83 years. 30 pts dropped out, did not complete intervention. Intervention during 17 days: exercise protocol, out-of-bed daytime, late day bright light exposure, strict bedtime routine, noise abatement program	123 pts. Female/male: 67%/33%, mean age 82 years. 40 dropped out: did not complete control phase or delayed intervention. Those who got delayed intervention may be regarded as control group (before intervention)	Actigraphy, PSG in subsample. Primary outcomes: measures of sleep. Behavioural and mood assessments	No sign changes in any of the actigraphic measures of sleep, nor in the 45 pts that underwent PSG	Moderate No effect on sleep in this multi-intervention study

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Table 5.2 *continued*

First author Year Reference Country	Study design Blinding	Inclusion criteria or diagnosis Female/male Age (mean, range)	Intervention Number of individuals Withdrawal Drop outs	Control Number of individuals Withdrawal Drop outs	Method of measurement Baseline values	Results Intervention/Control Effects/side effects	Study quality and relevance Comments
Schnelle 1999 [13] USA	RCT. Urinary incontinent nursing home pts. Observations during at least 5 days (mean 5.3 days)	230 pts included, 46 pts withdraw or died or were hospitalised. Intervention: behavioural intervention to nursing staff to reduce noise and light nighttime, individualise nighttime incontinence care to reduce sleep disruption	90 pts. Female/male: 85%/15%, mean age 82 years	94 pts. Female/male: 79%/21%, mean age 85 years	Actigraphy. Behavioural observations	Despite noise and light reduction, only 2 night sleep measures were improved: awakenings associated with a com- bination of noise plus light and awakening associated with light. No other sleep variables were changed compared to control group	Moderate No impact on sleep measures

CT = Controlled trial; PSG = Polysomnography; Pts = Patients; RCT = Randomised controlled trial; VAS = Visual analogue scale