Efficacy and safety of non-benzodiazepine and non-Z-drug hypnotic medication for insomnia in older people: a systematic literature review.

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ABSTRACT

Purpose: Insomnia is highly prevalent in older persons and significantly impacts quality of life, functional abilities and health status. It is frequently treated with benzodiazepines or Z-drugs. Due to adverse events, an increased use of alternative sedative medications has been observed in older adults. We aimed to study the efficacy and safety of alternative sedative medications for treating insomnia in older people, excluding benzodiazepines and Z-drugs.

Methods: We conducted a systematic search of MEDLINE (Pubmed), EMBASE and the Cochrane Central register of Controlled Trials databases. We included randomized controlled trials and prospective and retrospective quasi-experimental studies, conducted in patients older than 65 years, without psychiatric or neurological comorbidities.

Results: The systematic search yielded 9483 articles, of which 24 were included in this review, describing nine different sleep medications in total. No clear beneficial impact on sleep could be demonstrated in studies investigating the impact of melatonin (n=10), paroxetine (n=1), diphenhydramine (n=1), tiagabine (n=2) and valerian (n=1). Ramelteon slightly improved sleep latency (n=4), while doxepin was found to provide a sustained sleep improvement with a safety profile that was comparable to placebo (n=3). Suvorexant showed an improved sleep maintenance with only mild side effects (n=1). One study detected increased adverse effects of trazodone after three months, but did not evaluate the effect on sleep.

Conclusions: The overall level of evidence was limited, making it difficult to draw robust conclusions. Preliminary evidence points towards suvorexant, doxepin and possibly ramelteon as effective and safe pharmacological alternatives for treating insomnia in older adults.

KEY WORDS

Insomnia, older adults, aged, hypnotics and sedatives, antidepressant, sleep

INTRODUCTION

Insomnia affects approximately 20% to 58% of adults aged 65 years or older and its prevalence increases with age [1-4]. Insomnia is characterized by difficulties regarding initiating or maintaining sleep, or by waking too early in the morning and being unable to return to sleep. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM, Edition 5), patients are required to suffer from clinically significant distress or impairments in functioning to receive an insomnia diagnosis [5]. Insomnia causes downstream impairments such as daytime sleepiness, impairments in memory and concentration, and decreased functional performance. These symptoms may be misinterpreted as symptoms of dementia or mild cognitive impairment [6-8]. In addition, insomnia increases the risk of falls [9-11], as well as depression, anxiety disorders, and substance abuse [6]. It is also associated with a higher risk of incident Alzheimer dementia [12]. Most importantly, mortality risk has been observed to be increased up to twofold in older persons with sleep disorders [6,13].

Normal sleep architecture is composed of three segments which most people will cycle through four to five times per night. The first segment is characterized by light sleep and the second by deep sleep or delta sleep, which has restorative capacities. The third segment is the rapid eye movement (REM) sleep or "dream sleep". As a person ages, the duration of light sleep increases, deep sleep decreases, REM sleep decreases and sleep cycles are fewer and shorter. The total sleep time (TST) decreases from a mean of eight hours to five to seven hours of sleep per night. In older adults sleep becomes more susceptible to external influences, signified by increased arousability, increased wake after sleep onset (WASO) and also decreased sleep efficiency (SE, the percentage of time asleep/time in bed) [14,15]. These physiological changes contribute to the increasing incidence of insomnia with age. [16]

Psychological and behavioral therapies, particularly Cognitive Behavioral Therapy for Insomnia (CBT-I), are considered first-line treatments for insomnia [15]. CBT is however not widely available, costly and time-consuming. As a result pharmacotherapy remains to be commonly prescribed to treat disordered sleep [17]. Multiple medications have been approved by the US Food and Drug Administration for insomnia such as benzodiazepines (BZD's), Z-drugs, the orexin receptor antagonist suvorexant, the melatonin receptor agonists ramelteon and tasimelteon, the antidepressant doxepin and barbiturates.

Benzodiazepines and Z-drugs, often considered as the first choice pharmacologic therapy in adults, have shown to be effective in the short-term treatment of insomnia (<2-4 weeks). In contrast, these hypnotic agents have been associated with significant side effects when used chronically, especially in older

people. Prolonged use of benzodiazepines is associated with dependence, ataxia, sedation, falls, fractures, cognitive decline and dementia [13,18,19]. Also, Z-drugs have been linked to dementia, delirium, sleepwalking, fractures and increase in motor vehicle accidents [20-24]. For that reason, many physicians are inclined to prescribe alternative sedative medications.

Off-label psychotropic medication use for insomnia is prevalent in adults [25]. In older adults, antidepressants (trazodone, paroxetine, mirtazapine), antihistamines (diphenhydramine), antipsychotic agents, anticonvulsants (gabapentin, tiagabine) and herbal therapies (valerian and melatonin) are regularly prescribed [26,17]. There is however no specific recommendation on which therapies should be preferred in older adults. In this review we therefore focus on the efficacy and safety of frequently used both on- and off-label medications for treating insomnia, with exclusion of the 'classic' hypnotic drugs benzodiazepines and Z-drugs.

METHODS

Search strategy

A search string (Supplementary material 1) was co-developed with a library information specialist and was piloted by two reviewers (JS and SVC). MEDLINE (Pubmed), EMBASE and the Cochrane Central register of Controlled Trials were searched from inception of the database to September 1st 2019. Reference lists in retrieved articles and systematic reviews were also scanned to identify any relevant studies not captured.

Study selection

The search included randomized controlled trials, non-randomized controlled studies with parallel groups, prospective or retrospective cohort studies with control groups and observational studies. Articles published in English, French and Dutch were evaluated. Studies were included if the mean age was 65 years or older or if they analyzed a subgroup in this age cohort. Studies had to report either on the efficacy of a non-benzodiazepine or non-Z-drug in terms of sleep duration, subjective sleep quality or on the safety profile, being type and number of adverse drug events. Studies with antidepressants, antipsychotics, anticonvulsive medications, antihistamines, herbal therapies, melatonin receptor agonists and orexin receptor antagonists were included. Studies describing non-pharmacological interventions or including patients with dementia, Parkinson's disease or depression were excluded, as well as case reports, letters and abstracts.

Two reviewers (JS and SVC) piloted and performed the selection process independently. All articles were first screened on title and abstract. Of the remaining articles, the full text was read and articles fulfilling the criteria were included upon reaching consensus among the reviewers.

Data extraction and synthesis

Data were extracted independently by two reviewers (JS and SVC) and included study characteristics, intervention components, outcome measures and follow-up period. The efficacy of the medications was assessed by variables as shorter latency to sleep onset (LSO) or sleep latency (SL), longer total sleep time (TST), improved sleep efficiency (SE=total sleep time/time in bed) and fewer awakenings after sleep onset (WASO). Safety data evaluated were next-day residual effects, effects on cognition and reported adverse events. Studies and outcome measures were reported separately, no meta-analysis was performed due to the heterogeneity of both the studied medications and reported outcome measures.

Quality appraisal of included studies

Assessment of methodological quality was based on MINORS (methodological index for non-randomized studies), a standardized instrument in which each study is scored on twelve items (Supplementary material 3) [27]. The items were scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The maximum score is 16 for non-comparative studies and 24 for comparative studies.

RESULTS

Characteristics of the included studies

The search strategy resulted in 9483 publications, of which 155 were considered relevant after removing duplicates and screening title and abstract. Twenty-four studies were included after assessing the full text, totaling 450100 patients. Most studies were published post-2005 (n=21) and conducted in the United States of America (n=13) and the United Kingdom (n=4). The majority of studies were randomized controlled trials (n=21). All patients were 65 years and older in 18 of the studies. In other studies also younger patients (≥55 years) participated, with the mean age in these studies varying between 65.7 and 74.0 years. Patients had primary insomnia or sleeping complaints in 18 of studies. Nine interventional agents were identified: melatonin (10 studies, 1250 patients in total), ramelteon (4 studies, 2492 patients in total), doxepin (3 studies, 570 patients in total), trazodone (1 retrospective cohort study, 443359 patients), paroxetine (1 study, 27 patients), diphenhydramine (1 study, 19 patients),

tiagabine (2 studies, 207 patients), suvorexant (1 study, 2137 patients) and valerian (1 study, 16 patients). Duration of the intervention varied between 2 days and 48 weeks. The study characteristics and intervention are represented in Table 1.

Outcomes to measure efficacy on sleep included subjective scores (sleep diaries, questionnaires) and objective measures (polysomnography, wrist actigraphy). Outcomes to measure safety included reported adverse events, delirium, "morning after" psychomotor impairment and memory impairment, determined by a variety of scales. (Table 2) Quality of included studies, assessed by MINORS varied from 12 to 23 for comparative studies and 7 to 12 for non-comparative studies. More information can be found in the Supplementary Table 2.

Melatonin

Ten studies investigated the effect of melatonin supplements in older persons [28-37]. Three studies assessed objective measures with wrist actigraphy, of which one in the hospital and two on an outpatient basis [32,29,34]. Both Jaiswal et al. (n=69) and Baskett et al. (n=40) could not demonstrate a significant improvement in TST. In the study by Garfinkel et al. (n=12), using a controlled release form of melatonin, an improvement in SE and WASO was observed, but there was no effect on TST [32].

Six studies evaluated subjective sleep parameters on an outpatient basis. An improvement in subjective sleep quality and number of awakenings was observed in five studies. Three of these investigations used extended-release melatonin 2 mg daily [35-37]. The study by Baskett et al, using a fast-release compound of melatonin, showed no effect [29].

Three studies evaluated the in-hospital use of melatonin in patients without primary insomnia and its effects on sleep and incidence of delirium [31,34,28]. Fan et al. found better postoperative subjective sleep quality and improved general well-being in surgical patients receiving melatonin [31]. Jaiswal et al. failed to show an effect on sleep (both subjective and on wrist actigraphy) and incidence of delirium in patients admitted to an internal medicine service [34]. An earlier study in internal medicine patients by Al Aama et al. showed a reduction (12% vs. 31% in placebo group, p=0.014) in delirium incidence with melatonin 0,5mg, but no effect on subjective sleep parameters [28]. None of the studies reported major side effects attributed to melatonin.

Ramelteon

Roth et al. showed a significant decrease in subjective SL for both ramelteon 4mg and 8mg over a 5 week period [38]. Subjective TST was increased at week 1 and week 3 but not at week 5. No significant rebound insomnia or adverse events were seen in this study. A subanalysis by Mini et al. showed a

sustained reduction in the SL in the subgroup with a subjective SL of >60 min [39]. Richardson et al. showed a sustained improvement of subjective SL and TST during 1 year in the group treated with ramelteon 8mg (values not reported)[40]. During a 3-day wash-out period, an increase in SL and reduction in TST was observed. No major adverse events were seen, except for a statistically significant decrease in free testosterone in older men. Also, authors noted a 57.7% drop-out over 1 year (144 out of 248 patients).

Roth et al. evaluated the effects of ramelteon 4 and 8 mg using polysomnography [41]. A significant reduction in latency to persistent sleep was found, as well as an improved TST and SE. Subjective sleep assessments showed no difference between placebo and ramelteon 8mg in this study. A cohort study by Avidan et al. (n=988) showed no increase in adverse events associated with ramelteon [42].

Doxepin

Three published trials have studied doxepin in older adults using doses of 1, 3 and 6 mg [43-45]. All three doxepin doses improved TST and SL at multiple time points. Clinical global impression scale improved during weeks 2 (for 3 and 6 mg), weeks 4 (for 3 mg) and weeks 12 (for 1 mg and 3 mg). Also, at least 4 of the 5 items of the Patient Global Impression scale improved with all 3 doses at all time points. The insomnia severity index improved with doxepin 3 mg and 6 mg at all time points compared to placebo.

Using polysomnography to evaluate doxepin, all three doses improved WASO (-12.2min, $p<0.05$ for doxepin 1 mg; -33.5min, $p<0.001$ for doxepin 3 mg), TST (+30min, $p<0.001$ for doxepin 3 mg) and SE [44,45]. Significant effects were maintained up until night 85 [44].

The most common adverse effects in all studies were nausea, dizziness and somnolence and were comparable in frequency to placebo. There were no reports of memory impairment and no differences between placebo and doxepin in psychomotor function and daytime alertness.

Trazodone

In our search, no studies were found regarding the efficacy of trazodone on sleep in older adults, but one large retrospective cohort study observed an association between trazodone use for insomnia and accidental events [42]. In the three month period after its initiation, trazodone was found to be associated with a composite endpoint, consisting of falls, fractures and dislocations (odds ratio: 1.56, 95% CI 1.39 to 1.73) [42].

Paroxetine

One study in 27 patients evaluating the effect of paroxetine showed a subjective improvement in sleep quality, an increase in LSO and a reduction in WASO [46]. There was no effect on overall sleep efficiency. Given the lack of a clear effect, Reynolds et al. recommend to avoid the use of paroxetine in the treatment of insomnia in older people.

Tiagabine

Two RCTs showed no benefit of the anti-epileptic drug tiagabine on subjective sleep quality [47,48]. In terms of polysomnographic findings, Walsh et al. (n=24) found a significant increase in TST (+11.7 minutes, p=0.022) and a reduction in WASO (-12.3 minutes, p=0.019) in the tiagabine 4 mg group, as well as an increase in deep sleep in both the tiagabine 4 and 8 mg group [47]. The larger follow-up study by Roth et al. failed to show a benefit on TST and WASO. The 8 mg dose was associated with troublesome adverse events, residual effects and reduced alertness [48].

Diphenhydramine

Diphenhydramine showed a reduction in the number of awakenings (1.7 vs. 2.0, $p<0.05$) in one study, but there was no effect on TST, WASO and sleep quality [49]. No adverse events were reported in the diphenhydramine group in the two week treatment period.

Suvorexant

A pooled analysis of 2 RCTs showed that suvorexant 30 mg increased the subjective TST at week 1 ($+24.9 \pm 6.9$ min, $p<0.001$), while subjective LSO (-9.6 ± 4.7 min, $p<0.001$) and WASO (-10.3 ± 4.7 min, $p<0.001$) were reduced [50]. These effects were sustained at 1 month and 3 months. In the suvorexant 15 mg group a significant effect was seen on TST and WASO, but not on LSO at month 1 and 3.

On polysomnographic studies, suvorexant 30 mg improved the WASO and SL at each timepoint, though the effect diminished over time. In the suvorexant 15 mg group, there was a significant decrease in WASO at each time point. No significant decrease in SL was determined [50]. Adverse drug events were more frequent in the suvorexant 30mg group compared to placebo (23.8% vs 14.7%, $p<0.05$), with somnolence being most frequent.

Valerian

One RCT evaluated the effects of valerian on insomnia in 16 older women but found no significant differences between valerian and placebo on any of the researched variables [51]. Side effects were reported to be mild.

DISCUSSION

Despite insomnia being highly prevalent and health-impairing in older people, there are no specific clinical practice guidelines on what constitutes a best-choice medication therapy. In our review, we identified 24 studies involving nine different compounds used as hypnotics. Twenty-one studies concerned placebo controlled RCTs. None of the included studies compared medications head-to-head, except for a retrospective cohort study by Avidan et al [42]. The effect sizes on multiple sleep-related outcomes were rather small and studies were mostly limited in duration. The studies displayed a broad range of methodologies and employed a wide array of subjective (questionnaires, scales, diaries) and objective (polysomnography, actigraphy) outcome measures. The studies were performed in different settings and enrolled diverse patient groups. This large heterogeneity renders it difficult to compare results of different treatment strategies and rules out a meta-analysis.

Strengths of our review are both the scope, featuring different medications and including studies evaluating efficacy and safety. Given the lack of large RCTs, we also included quasi-experimental studies. We included studies evaluating both objective and subjective sleep parameters, as well as trials both in hospital and on an outpatient basis. A weakness of our approach is the exclusion of neurological and psychiatric comorbidities. As most off-label medications used for insomnia are antidepressants or antipsychotics, these medications are studied mainly in patients with psychiatric comorbidities. Given the multifactorial etiology of insomnia on its own, we opted not to include these trials and only include trials evaluating the effect on older adults without significant neurological or psychiatric comorbidities. Trials evaluating patients with dementia were excluded on similar grounds. A Cochrane review in 2016 found six placebo-controlled RCTs studying the effects on insomnia in dementia [52]. In this review, McCleery et al. found a lack of evidence to guide drug treatment in dementia. It is possible that certain medications used off-label were not included in the search. We tried to correct for this by searching for different medication types as well as specific compounds. Also, while certainly important for treating insomnia, non-pharmacological therapies were excluded.

Most studies evaluated the effect of the medication on quantitative sleep measures such as TST, SL, WASO and sleep efficiency. Sleep medication was considered to be effective if (some of) these parameters improved. For example, while Glass et al. reported a decrease in the number of awakenings using diphenhydramine, there was no effect on other sleep parameters (sleep quality, TST and SL) [49]. In some studies, even small non clinical significant changes (e.g. of less than 10 minutes) were found to be statistically significant [38,41,45] hindering drawing robust conclusions about the efficacy of these

compounds. Although the DSM-V definition of insomnia mentions the sleep disturbance to be causing clinically significant distress or impairment in functioning, the impact on social, occupational or other areas of functioning is less well studied and/or not clearly mentioned in most articles. There were ten studies that did not evaluate the effects on next-day alertness, fatigue, psychomotor function, delirium or cognition, which is an important concern in older people. Moreover, we notice that the mean age was <75 years in 83.3% of our included studies, showing an important lack of data in the very old.

The most studied medication was melatonin. Three major observations were made. First, the use of melatonin in older persons appears to be safe. Second, we should take into account the large heterogeneity between the tested doses, tablet formulation (slow versus immediate release form) and outcome measures, which precluded making strong statements on its place in the management of insomnia in older adults. Third, inconsistent results were found for multiple outcomes across all studies included in our review. While three studies showed an improvement with the extended-release formulation on subjective sleep quality, no benefit on total sleep time using objective parameters was demonstrated, except for one small study (n=12) by Garfinkel et al. [32]. There are conflicting results regarding the effect on quality of life and morning alertness [29-31,33,35-37]. A potential role of melatonin to support benzodiazepine discontinuation in older people has been suggested, but only in small trials without a long-term follow-up [30,33]. In sum, there is insufficient evidence to recommend the use of melatonin for the management of sleep problems in hospital and evidence for its use in an outpatient setting seems equivocal.

Ramelteon, doxepin and suvorexant are approved in the United States but not in Europe for the treatment of insomnia [53]. Ramelteon is a selective melatonin (MT1/MT2) receptor agonist approved for insomnia and has shown a small but significant effect on sleep latency, both on subjective and objective measurements. Roth et al. evaluated next day alertness, but no effects on the downstream events of insomnia are studied, precluding a clear clinical benefit [41]. While an increase in subjective total sleep time after 1 year was reported by Richardson et al, given the large drop-out rate in this trial (57.7%) it is difficult to ascertain fully the benefit of ramelteon in insomnia management[40]. Richardson et al. also reported a reduction in free testosterone in older men, raising potential concerns for long-term safety. Importantly, the European Medicine Agency (EMA) advised against a marketing authorization in Europe because the difference in SL was considered too small to be clinically relevant and long-term effectiveness was furthermore not sufficiently demonstrated [54].

The tricyclic antidepressant doxepin was used at low doses (1 mg, 3 mg and 6 mg), at which it inhibits histamine receptors without expected relevant actions on other pharmacological targets [13,26]. It is likely that this antihistamine action might explain the purported hypnotic effects. As a tricyclic antidepressant agent, it has however a potential for anticholinergic side effects and the AGS therefore advises against its use . While two trials evaluated memory impairment and found no increased risk after use of doxepin, the long term effects remain unclear as the longest follow-up was 12 week [43,44].

Suvorexant showed an improvement in both subjective and objective sleep parameters [50]. The effect was less pronounced when a lower dose (15mg) was used. The FDA approved suvorexant at a lower dose than the dose studied in these trials (10 mg, up to a maximum of 20 mg) and no trials were found evaluating the efficacy in older adults at the approved dose of 10mg.

While off-label use of antidepressants such as trazodone and mirtazapine has increased for sleep disorders [26], no studies were found supporting their use in older adults. Off-label use of trazodone for insomnia in healthy adults and patients with Alzheimer's disease has increased and several studies are supporting its use [55,56]. However, given an increase in adverse events [42] and no studies showing a benefit in older people without comorbidities, there seems to be insufficient evidence for its use in this population. Similarly, no trials were found studying the antidepressant mirtazapine in older people for the treatment of insomnia.

Other medications assessed were the herbal supplement valerian, the antihistaminic drug diphenhydramine, paroxetine and tiagabine [47-49,51,46]. None of the aforementioned medications showed a clear effect in the management of insomnia. Only one small trial with valerian in older people was conducted and systematic reviews of studies in younger patients showed conflicting results regarding its efficacy [57-59]. Use of tiagabine was associated with more side effects. Furthermore, in 2019 the American Geriatrics Society recommended to avoid diphenhydramine and doxepin in doses greater than 6 mg due to potential anticholinergic side effects [24].

Taken together, factors causing insomnia, such as an underlying medical condition, medication use or poor sleep hygiene, should always be ruled out before initiating pharmacological therapy in older adults. The choice of a hypnotic agent involves considering the symptom pattern, treatment goals, patient's preference, past treatment responses, comorbidity, contraindications, concurrent medication interactions, side effects, cost and availability of other treatments. In chronic insomnia, non-pharmacological therapies such as cognitive behavioural therapy are to be considered as first-line treatment options [60] . Based on the current evidence, no clear recommendation as to pharmacotherapy for insomnia in older adults can be made. Doxepin, suvorexant and ramelteon show promising results, but further trials evaluating long-term efficacy, safety and impact on daily functioning are required before clear recommendations as to their use can be made. Further research is necessary to evaluate the efficacy of both trazodone and mirtazapine, both commonly used off-label for the treatment of insomnia.

CONCLUSION

There is very limited evidence for suvorexant and doxepin as effective and safe sleep medications in older people. Studies evaluating paroxetine, diphenhydramine, tiagabine and valerian did not find a convincing effect on sleep. Evidence for melatonin and ramelteon seems more equivocal. Despite being frequently used off-label, no evidence was found to support using of mirtazapine or trazodone for the

treatment of insomnia in healthy older adults. The clinical relevance of small changes in quantitative measures remains unclear. Future research should more focus on the impact of sleep medication on global functioning and well-being.

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflicts of interest.

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Figure 1: Study selection flow diagram

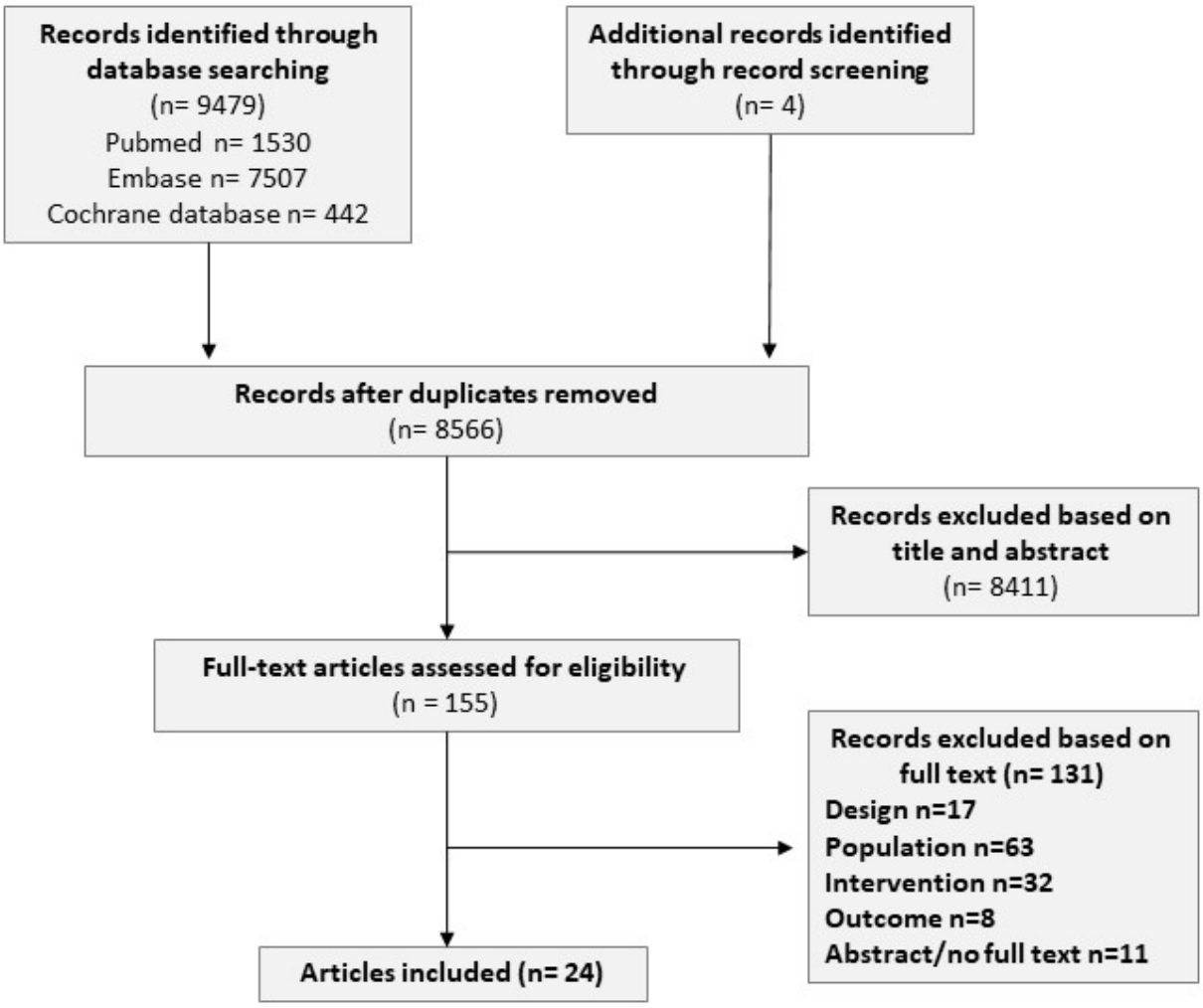

Table 1: Characteristics of included studies. *Abbreviations are alphabetically listed in Supplementary material 1.*

Study	Country + setting	Design	Sample	Inclusion criteria	Exclusion criteria	Intervention and duration of the intervention	Outcome	Follow-up period of outcome
Al-Aama et al, 2011	Canada, hospitalized patients	Single-center randomized, double-blind, placebo-controlled trial	n=122	>65y admitted to Internal Medicine units	-short hospitalization or life expectancy (<48h) -Intracranial bleeding or seizures -Abnormal coagulation tests	**Melatonin 0.5mg** or placebo once daily until discharge, death or up to 14 days.	-Delirium (CAM, MDAS) -Sleep disturbances (item 10 of MDAS by direct observation during interview or reports from nurses or family) -Adverse events	2 weeks
Avidan et al, 2010	USA, Medicare databases.	Retrospective cohort analysis	n=443359 (trazodone) and n=988 (ramelteon)	>65y new initiators of benzodiazepine, Z-drug, trazodone or ramelteon.	-nursing home admissions -insomnia medication polytherapy	Long-acting BZP (36.4%), short-acting BZP (18.2%), Z-drug (35.3%), **trazodone** (9.9%) or **ramelteon** (0.22%) taken for at least 3 months	Adverse events during the first 30 days of treatment and after 90 days.	3 months
Baskett et al, 2003	New Zealand, outpatient.	Randomized double-blind placebo-controlled crossover trial	n=40	>65y normal and problem sleepers.	-MMSE<26 -GDS >6 -poor sleep hygiene -medical conditions interfering with sleep -use of sedatives	**Melatonin fast release 5mg** and placebo, taken for 4 weeks, separated by a 4 week washout period	-Sleep diaries -LSEQ -Actigraphy (measuring sleep duration, SL, awakenings and SE) -Alertness scale	12 weeks
Fainstein et al, 1997	Argentina, outpatient.	Single center open-label pilot study	n=41	>56y (mean age 74y) insomnia 3 groups (sleep disturbance alone; SD+ depression, SD + AD)	-psychiatric illness other than depression/dementia-organic or neurological disorder -addiction	**Melatonin 3mg**, taken for 21 days	-Sleep quality, NAW and next-day function assessed by interviews and sleep logs -Ability to discontinue BZP -Adverse events	3 weeks
Fan et al, 2017	China, hospitalized patients.	Single center, randomized placebo-controlled trial	n=139	>65y scheduled for hip arthroplasty	-MMSE <23 -sleep disorder -addiction -psychiatric or neurological diseases	**Melatonin 1mg** or placebo during 6 days	-MMSE score -Subjective sleep quality (VAS) -General well-being (VAS) -Postoperative fatigue (fatigue scale) -Pain (VAS) -Adverse events	1 week

Garfinkel et al, 1995	UK, outpatient.	Single center randomized, double-blind, crossover study	n=12	68-93y Long-term insomnia	Dementia (not specified)	**Melatonin 2 mg** for 2 weeks and placebo for 3 weeks with a 1-week washout period in between	-Amount of 6-SMT excreted in urine at night -Wrist actigraphy (SL, SE, TST, WASO) -Adverse events	7 weeks
Garzón et al, 2009	Spain, outpatient.	Single center randomized, double-blind, placebo-controlled crossover trial	n=22	>65y history of sleep disorder	-secondary sleep disorder -dementia -psychiatric or medical disease.	**Melatonin 5mg** and placebo during 8 weeks, separated by a 2-week washout period	-Sleep quality (NHSMI). -Ability to discontinue hypnotic drug treatment. -Behavioral disorders (GDS, GAS).	18 weeks
Glass et al, 2008	Canada, outpatient.	Single center randomized, double-blind, crossover trial	n=19	>70-89y insomnia (DSM IV)	-Mini-mental state examination < 27 -GDS ≥ 10 -anxiety disorder -alcohol or nicotine abuse	**Diphenhydramine 50mg,** temazepam 15mg and placebo (each taken for 14 nights with a minimum of 14 days of washout time)	-Sleep diary: sleep quality, SL, NAW, TST. -Secondary: morning-after psychomotor impairment (DSST, MTT), morning-after memory impairment. -Adverse events	10 weeks
Herring et al, 2017	USA, phase III trials.	Subgroup analyses of 2 (efficacy) and 3 (safety) randomized, double-blind, placebo-controlled, parallel group trials	n= 839 (efficacy dataset) n=1298 (safety dataset)	≥65y primary insomnia (DSM IV), sTST <6.5 hours, sLSO ≥30minutes PSG criteria: LPS > 20 minutes and WASO ≥ 60 minutes.	- use of other hypnotic medication	**Suvorexant 30 mg or 15 mg** or placebo during 3 months	-Sleep diary/questionnaire (sTST, sLSO, sWASO) -Polysomnography (LPS, WASO) -Adverse events -Residual effects (DSST)	3 months
Jaiswal et al, 2018	USA, hospitalized patients	Single center randomized double-blind placebo-controlled clinical trial	n=69	≥65y new admission to internal medicine service (non-intensive care units), expected stay of ≥ 48h.	- confusion at admission	**Melatonin 3 mg** or placebo during hospitalization (maximum 14 nights)	-Delirium (CAM) and relation to sleep parameters. -Actigraphy (nighttime sleep, TST/24h, sleep fragmentation)	Length of hospital stay (with a max. of 14 nights)

							-Subjective sleep quality (RCSQ)	
Krystal et al, 2010	UK, outpatient and sleep laboratory.	Single center randomized double-blind, placebo-controlled trial	n=240	>65y insomnia (DSM IV + PSG criteria)	-sleep medication, -use of alcohol, caffeine, nicotine -intentional napping >2/week -variation in bedtime >2h for 5 of 7 nights	**Doxepin 1mg** or **doxepin 3mg** or placebo during 12 weeks	-Polysomnography (WASO, TST, SE, NAW, LPS) -Patient reports (SL, TST, sleep quality). -CGI, PGI, ISI. -Next-day hangover/residual effects: DSST, SCT, VAS for sleepiness. -Adverse events	12 weeks
Lankford A et al 2012	USA, outpatient.	Single center, randomized double-blind, placebo-controlled trial	n=254	>65y insomnia (DSM IV)	-sleep medication -use of alcohol, caffeine, nicotine -intentional napping >2/week -variation in bedtime >2h for 5 of 7 nights	**Doxepin 6mg** or placebo for 4 weeks	-Patient reports (subjective TST, WASO, SL, sleep quality) -CGI, PGI, ISI -Adverse events	4 weeks
Lemoine et al, 2007	France and Israel, outpatient.	Randomized, double-blind, placebo-controlled trial in 47 GP clinics.	n=170	>55y (mean 68.5y) insomnia (DSM IV) for 1 month.	-OSAS -dementia -psychiatric disorders -medical disorder -psychotropic medication.	**Melatonin PR 2 mg** or placebo during 3 weeks, preceded by a 2 week run-in of placebo and followed by a 2 week run-out of placebo	-Subjective sleep quality (LSEQ) -Morning alertness (BFW) with LSEQ -Adverse events - Withdrawal effects (BWSQ)	7 weeks
Mini et al, 2007	USA, outpatient.	Subset analysis of randomized, double-blind placebo-controlled trial	n=327	≥ 65y primary insomnia (DSM IV), sSL >60min	-significant medical or psychiatric disorder -use of psychotropic medication within 1 week of the placebo lead-in period. -BMI <18 or >34 kg/m^2	**Ramelteon 8 mg** or placebo for 5 weeks, preceded by a run-in of 7 days placebo and followed by a run-out of 7 days placebo	-Mean sSL at week 1, 3 and 5. -Adverse events	5 weeks

Reynolds et al, 2006	USA, outpatient.	Single center double-blind placebo-controlled trial	n=27	≥55y (mean age 67.4y in intervention group, 66.5y in placebo group) primary insomnia (DSM-IV)	-coexisting medical or psychiatric disorder -substance abuse	**Paroxetine 10 mg** (and adjusted after 2 weeks up to a maximum dose of 20 mg daily if possible) or placebo for 6 weeks	-Pittsburgh Sleep Diary (sleep quality, daytime alertness and mood) -Polysomnography (SL, WASO, overall SE)	6 weeks
Richardson et al, 2009	USA, outpatient.	Open-label, fixed-dose observational study in 123 sites.	n=248	≥65y primary insomnia (DSM IV) for ≥3 months	-psychotropic drug use -drug or alcohol abuse or addiction -sleep schedule changes -organic or psychiatric disorder -abnormal findings on ECG or laboratory	**Ramelteon 8 mg** for 48 weeks	-Safety assessments (physical examination, clinical chemistry, urinalysis, ECG). -Sleep diaries (subjective SL and TST) -CGI	12 months
Roth et al, 2007	USA, sleep laboratory	Randomized double-blind, placebo-controlled, 3-period crossover study in 17 sleep centers.	n=100	> 65y primary insomnia (DSM IV + PSG criteria).	-psychiatric or medical illness -sedative or CNS medications -use of tobacco products -substantial change in diet or exercise or sleep-wake schedule	**Ramelteon 4 mg**, **ramelteon 8 mg** and placebo (3 treatment phases for 2 consecutive nights; each phase separated by 5- to 12-day washout periods)	-Polysomnography (LPS, TST, SE, NAW, WASO) -Questionnaire (sSL, sTST, sNAW, sWASO) -Residual effects (DSST, memory test, postsleep questionnaire) -Feelings and mood (VAS) -Adverse events	9 weeks
Roth T, Wright KP, et al, 2006	USA, sleep laboratory.	Double-blind, parallel-group, dose-response study in 30 sleep centers.	n=207	65-85y primary insomnia (DSM IV + PSG criteria).	-psychiatric or relevant organic disorder -alcohol, smoking, substance abuse -psychotropic medication -shift work -BMI ≥34 kg/m^2	**Tiagabine 2, 4, 6, or 8 mg** or placebo for 2 nights	-Polysomnography (SL, NAW, WASO, TST) -Postsleep Questionnaire -Assessment of Daily Functioning questionnaire -Residual effects -Adverse events	2 nights
Roth T, Seiden D, et al, 2006	USA, outpatient.	Randomized double-blind, placebo-controlled trial in multiple centers.	n=829	≥65y primary insomnia (DSM IV), sleep latency ≥45 min, TST ≤6.5h/night during 3 nights/week.	-medical or psychiatric disorder -CNS medication use -BMI <18 or >34 kg/m^2	**Ramelteon 4 mg, 8 mg** or placebo during 5 weeks	-Sleep diaries (SL, TST, NAW, ease of falling back to sleep after awakening, sleep quality) -Withdrawal effects (BSWQ) -CGI	6 weeks

Scharf et al, 2008	USA, sleep laboratory.	Randomized, double-blind, placebo-controlled, 4-period crossover, dose-response study in 11 centers.	n=76	≥65y primary insomnia (DSM IV + PSG criteria)	-alcohol, nicotine or substance abuse -variation in bedtime -cognitive or psychiatric disorders -chronic pain, glaucoma, frequent nightly urination -use of sedative or CNS medication	**Doxepin 1 mg, 3 mg, 6 mg** and placebo 4 x 2-day treatment periods with a 5- or 12-day drug-free interval between)	-PSG (WTDS, WASO, SE, TST, LPS, NAW). -Patient-reported measures (LSO, sWASO, sTST, sNAW, sleep quality). -Residual effects (DSST, SCT, VAS sleepiness). -Adverse events	2 days
Taibi et al, 2009	USA, sleep laboratory.	Phase 2 randomized, double-blind, crossover controlled trial	n=16 women	Women, 55-80y (mean age 69.4y) disturbed sleep (PSQI ≥ 5) and no severe insomnia (ISI <22), ≥ 30 min LSO or WASO, daytime sleepiness or fatigue	-major psychiatric or medical illness -MMSe ≤ 26 -sleep medication -alcohol, tobacco or caffeine use -hormone replacement therapy -shift work -BMI <18 or >32 kg/m^2	**Valerian 300 mg** or placebo for 2 weeks	-Self-reported sleep with MSQ and sleep logs (SL, WASO, TST, sleep quality) -Polysomnography (sleep stages, SL, WASO, SE) -Wrist actigraphy at home -Adverse events	2 weeks
Wade et al, 2007	UK, primary care.	Randomized, double-blind, placebo-controlled study	n=354	55-80y (mean age 65.7) primary insomnia (DSM IV)	-psychiatric or medical disorders -MMSe ≤24 -psychoactive medication -alcohol abuse - shift work	**PR melatonin (Circadin 2 mg)** 2-week placebo run-in period, 3-week double blind treatment period	-Questionnaires (LSEQ, PSQI measuring BFW, sleep quality, SL) -Diary (QON, QOD) -CGI -QoL (WHO-5 wellbeing index) -Adverse events	3 weeks
Wade et al, 2010	UK, outpatient.	Randomized, double-blind, parallel group clinical trial	n=281	subgroup 65-80y primary insomnia (DSM IV)	-psychotropic medication -psychiatric or medical disorder -alcohol abuse	**PR melatonin (Circadin 2 mg)** 2-week placebo run-in period, 3 week double-blind treatment period, then PRM patients continued whereas placebo completers were re-randomized 1:1 to PRM or placebo for 26 weeks with 2	-PSQI and sleep diary -QoL (WHO-5wellbeing index) -CGI-I -Adverse events	29 weeks

						weeks of single-blind placebo wash-out		
Walsh JK et al, 2005	USA, sleep laboratory.	Randomized double-blind Latin-square design	n=24	60-80y (mean age 68.2y) healthy older adults without sleep complaints	-medical or psychiatric disorders -psychotropic medications -alcohol or caffeine abuse -irregular sleep schedule	**Tiagabine 2 mg, 4 mg, 8 mg** or placebo. 4 periods of 2 consecutive nights, separated by 5 nights at home without study medication.	-Polysomnography -Postsleep questionnaire -Morning sedation and memory (DSST, Karolinska Sleepiness Scale, Immediate and Delayed Recall Word test) -Adverse events	2 days per treatment

Abbreviations used: BFW: behaviour following wakening, BSWQ: benzodiazepine withdrawal symptom questionnaire, CAM: Confusion Assessment Scale; CGI: Clinical Global Impression; CGI-I: Clinical Global Impression of Improvement, DSST: digit symbol substitution task , GAS: Goldberg Anxiety Scale , GDS: Geriatric Depression Scale, ISI: insomnia severity index., LPS: latency to persistent sleep, LSEQ: Leeds Sleep Evaluation Questionnaire, LSO: latency to sleep onset, MDAS: Memorial Delirium Assessment Scale, MMSE: Mini mental state examination, MSQ: Morning Sleep Questionnaire, MTT: manual tracking task, NAW: number of awakenings, NHSMI: Northside Hospital Sleep Medicine Institute Test, PGI: Patient Global Impression, PR: Prolonged Release, PSQI: Pittsburgh Sleep Quality Index, QOD: quality of day, QoL: quality of life, QON: quality of night, SCT: symbol copying test, SE: sleep efficiency, sSL: subjective Sleep Latency, TST: total sleep time, VAS: visual analogue scale, WASO: wake time after sleep onset

Table 2: Outcomes of the included studies. *Abbreviations are alphabetically listed in Supplementary material 1.*

Study	Subjective sleep parameters (sleep diaries, questionnaires)	Next-day alertness, wellbeing, feelings and mood	Delirium/Cognition	Objective sleep parameters (polysomnography, actigraphy)	Medication discontinuation	Adverse events, withdrawal effects
Melatonin						
Al Aama et al, 2011	No difference in **sleep disturbance** (60.7% placebo vs 63.9% on melatonin, p=0.81)		12% **delirium** on melatonin vs 31% on placebo (p=0.014, CI: 0.11-0.74)			2 patients reported **adverse events** (nightmares, hallucinations) (2/122)
Baskett JJ et al, 2003	-Problem sleepers: no difference in diary **awakenings** of melatonin vs placebo (0.12, 95% CI -0.13 to 0.26), nor in **sleep quality** (0.01, 95% CI -0.29 to 0.31) - Normal sleepers: also no difference.	No difference in **alertness** scale in problem sleepers (0.00, 95% CI -0.28 to 0.16), nor in normal sleepers (0.12, 95% CI -0.04 to 0.26).		- Problem sleepers: no significant effect on any measure of **actigraphy**. - Normal sleepers: less **awakenings** vs placebo (-4.4, 95% CI -7.0 to -1.0), no difference in **SL**, **TST** and **SE**.		
Fainstein I et al, 1997	Melatonin improved **sleep quality** VAS (Fr=65.11, p < 0.0001) and decreased **NAW** (Fr=77.34, p < 0.0001) in subgroup without depression or AD	Melatonin improved **morning alertness** (Fr=60.24, p < 0.0001) and **daytime alertness** (Fr=60.69, p < 0.0001).			8/13 **discontinued benzodiazepine**.	No **adverse events** attributable to melatonin.
Fan Y et al, 2017	Postoperative impairment of **subjective sleep quality** (Fr = 7.95, p < 0.05) in placebo compared with the melatonin group.	Postoperative impairment in **general well-being** (F = 5.791, p < 0.05) and **fatigue** (F = 8.333, p < 0.05) in placebo compared with the melatonin group. No difference in **pain**.	**MMSE score** decreased after surgery on day 1, 3 and 5 postoperative (F=3.595, p < 0.05) in placebo compared to melatonin group. MMSE score in the placebo group recovered by day 7 (F = 0.307, p > 0.05)			No difference in **adverse events** including dizziness, headache, paresthesia and nausea between the 2 groups (p > 0.05)
Garfinkel et al, 1995				- Peak excretion of 6-SMT was delayed.		2 cases of pruritus, 1 during melatonin and 1 during placebo treatment; both resolved spontaneously.

				- **SE** improved after melatonin vs placebo (83 vs 75%, p<0.001) - **WASO** was shorter (49 vs 73 min, p<0.001) - **SL** decreased, but not significantly (19 vs 33 min, p=0.088) - **TST** was not affected.		
Garzón C et al, 2009	Melatonin improved **sleep quality** on NHSMI test (1.78 ±0.40), compared with basal (3.72±0.45, p=0.001) and placebo (3.44±0.56; p=0.025)	**GDS** and **GAS** improved after melatonin administration (p=0.043 and p=0.009, resp)			9/14 subjects were able to **discontinue hypnotic drug** during melatonin but not placebo administration.	
Jaiswal SJ et al, 2018	No statistical significance in **subjective sleep quality** on all 5 RCSQ answers.		- No significant difference in **delirium** (22.2% in melatonin and 9.1% in placebo, RR 2.4, 95% CI 0.7-8.4, p=0.16). -Delirious subjects had more sleep fragmentation (sleep bout length 7.0 ± 3.0 vs 9.5 ± 5.3 min, p=0.03)	- No differences in **nighttime sleep** in melatonin vs placebo (539.8 vs 492.3 min, 95% CI -41.9 to 136.8, p=0.29) -No differences in **TST per 24 hours** and **sleep fragmentation**.		
Lemoine P et al, 2007	-PR-melatonin improved **sleep quality** (-22.5 vs -16.5 mm, p = 0.047) on LSEQ. -Improvements in sleep quality and BFW were strongly correlated (Rval = 0.77, p < 0.001).	- PR-melatonin improved **BFW** on LSEQ (-15.7 vs -6.8 mm, p=0.002)				- Amount of **AEs** was the same in both groups (9 in each), most were mild. - No **rebound insomnia** or **withdrawal effects** after treatment discontinuation.
Wade AG et al, 2007	- Improvement on **sleep quality** and **BFW** scales of the LSEQ for PR-melatonin compared to placebo (26% vs 15%, p=0.014).	- **QOD** assessed by sleep diaries did not differ significantly (0.1, 95% CI -0.0-0.2, p=0.21).				No difference in **AEs**: 24% of the PR-melatonin group and 21% of the placebo group reported adverse events.

	- Shortening of **sleep latency** on PSQI (-24.3 min. vs -12.9 min, p=0.028). - No difference in **QON** in diaries (0.2, 95% CI -0.0-0.2, p=0.21) - **CGI** did not differ significantly (-0.2, p=0.14).	- **QoL** (WHO-5 index) improved significantly (0.8, 95% CI 0.1-1.5, p=0.034).				
Wade AG et al, 2010	- PR-melatonin reduced **sSL** after 3 weeks (-15.6 min, 95% CI -25.3 to -6.0, p=0.002) and after 29 weeks (-14.5 min, 95% CI -21.4 to -7.7, p<0.001). - No difference in **TST**, **sleep maintenance** and **sleep quality** in diaries. - **Global PSQI score** was better on short term (-0.64, 95% CI -1.25 to -0.02, p=0.042) and long term (-0.70, 95% CI -1.17 to -0.23, p=0.003). - **CGI-I scores** improved on long term (-0.20, 95% CI -0.38 to -0.02, p = 0.027).	- Significantly more **alertness in the morning** with PR-melatonin vs placebo (-0.10, 95% CI -0.19 to -0.01, p=0.032). - **WHO-5 index** improved not significantly at short and long term.				Most **AEs** were mild with no differences between PR-melatonin and placebo.
Ramelteon						
Avidan et al, 2010						No adverse events after 1 month and 3 month follow-up (0%)
Mini LJ, et al, 2007	Ramelteon 8 mg reduced **sSL** vs. placebo (change from baseline, -23.2 vs -7.5 min, p = 0.002), at week 3 (-33.7 vs -19.8 min, p = 0.005) and at week 5 (-37.4 vs -17.1 min, p < 0.001).					Dizziness (ramelteon: 8.9%; placebo: 7.1%), dysgeusia (ramelteon: 7.0%; placebo: 2.9%), myalgia (ramelteon: 6.4%; placebo 3.5%) and headache (ramelteon: 5.1%; placebo 5.9%).

Richardson GA et al, 2009	- Ramelteon 8 mg improved **sSL** and **TST** by month 1 and during 1 year (no p-values given). - **CGI** improved at 6 months and 1 year (no p-values given).					- No change in **vital signs**, **physical examination**, **laboratory** results and **ECG**. - Statistically significant ($p<0.05$) decreases in **free thyroxine** (in adults) and **free testosterone** (in older men) were detected. - 40.8% reported **AEs**, most mild or moderate. - **Drop-out** 57.7% (144/248)
Roth T et al, 2007	- Ramelteon 4 mg but not 8 mg reduced **sSL** ($p=0.037$ and $p=0.120$, resp.). - No significant differences on other subjective sleep assessments.	- No residual pharmacologic effects via **DSST**, **memory recall tests** (immediate and delayed) and postsleep questionnaire -No significant difference in VAS of **feelings** and **mood**.		Ramelteon 4 and 8 mg reduced **LPS** (28.7 min vs 38.4 min, $p<0.001$; 30.8 min vs 38.4 min, $p=0.005$, resp.), improved **TST** (+9min, $p=0.036$ and +11.6 min, $p=0.007$, resp.) and **sleep efficiency** ($p=0.037$ and $p=0.007$, resp.) compared to placebo.		Overall incidence of **AEs** was slightly higher in the ramelteon 4 mg group (14%) compared with placebo (9%) and ramelteon 8 mg (7%).
Roth T, Seiden D, et al, 2006	- Significant decrease in **SL** with ramelteon 4 mg and 8 mg at week 1(-8.3 min, $p=0.008$ for R4mg and R8mg) and week 5 (-7.2 min, $p=0.028$ for R4mg and -12.9, $p<0.001$ for R8mg). - Increase in **TST** with ramelteon 4 mg and 8 mg at week 1 (+10.7 min, $p=0.004$ for R4mg, +7.2 min, $p=0.055$ for R8mg) and week 3 (+11.7 min, $p=0.007$ for R4 mg and +7.8 min,					- No significant **rebound insomnia** or **withdrawal effects** after treatment dicontinuation. - Incidence of **AEs** was similar in all treatment groups; most AEs were mild or moderate.

	p=0.071 for R8mg), but not at week 5. - No significant effect of ramelteon on **NAW**, **ease of falling back asleep**, **sleep quality**. - CGI did not differ among treatment groups.					
Trazodone						
Avidan AY et al, 2010						- Higher risk of **adverse event** in 3-month period using sedating antidepressant (0.36%, OR 1.56, p<0.05)
Diphenhydramine						
Glass JR et al, 2008	- Diphenhydramine reduced **NAW** vs placebo (mean, 1.7 ± 1.1 vs 2.0 ± 1.2; p < 0.05). - No effect on **sleep quality**, **TST** or **SL**.	No changes in **DSST** or **MTT** scores or **memory assessment** with any treatment.				Same number of **adverse events** (n = 90) between groups.
Suvorexant						
Herring WJ et al, 2017	- Suvorexant 30mg improved **sTST**, **sLSO** and **sWASO** on week 1, month 1 and month 3 (all p < 0.01) [with on month 3 sTST +20.4 min (95% CI:11.0, 29.7), sLSO -9.2 min (-15.0, -3.3) and sWASO -9.4 min (-15.1, -3.7)] - Suvorexant 15mg improved **sTST** and **sWASO** on week 1, month 1 and month 3 (all p < 0.01) [with on month 3 sTST +18.9 min (8.3, 29.5) and sWASO -10.8 min (-17.2, -			- Suvorexant 30 mg improved PSG measured **LPS** at night 1, month 1 and month 3 (p < 0.05) [with on month 3 LPS -7.7 min (95% CI: -14.0, -1.4)] and **WASO** at night 1, month 1 and month 3 (all p < 0.001) [with on month 3 WASO -24.7 min (-32.7, -16.7)] - Suvorexant 15 mg did not improve **LPS** at month 1 and month 3, **WASO** was improved at all time points (p < 0.001) [with on month		- Similar **serious AEs** among treatment groups. - Somnolence was **most common AE** (8.8% for 30 mg, 5.4% for 15 mg, 3.2% for placebo). - No significant difference in **withdrawal** and **residual effects** (6.4% in 30mg suveroxant, 3.5% in 15mg, 5.5% in placebo).

	4.3)], but no difference in sLSO at month 1 and month 3.			3 WASO -23.4 min (-32.7, -14.2)]		
Doxepin						
Krystal AD et al, 2010	- Doxepin 1 mg and 3 mg improved **LSO, sTST and sleep quality** in weeks 4 and 12 (all p-values < 0.05). - Doxepin 3 mg improved the **CGI** after 2, 4 and 12 weeks, doxepin 1 mg improved the CGI after 12 weeks (all p-values < 0.05). - After 12 weeks: both doxepin groups improved all 5 items of the **PGI** (all p-values < 0.05). - Doxepin 3 mg improved the **ISI score** at N15, N29 and N85 (all p-values < 0.05).	No differences on objective **psychomotor function** (DSST and SCT) or subjective **next-day alertness** (VAS) or drowsiness.	There were no reports of **memory impairment**.	- Doxepin 3 mg improved **WASO**, **TST**, **overall SE** on N1 (all p < 0.0001). Significant effects (p < 0.05) were maintained on N29 and N85. - Doxepin 1 mg improved **WASO** (p < 0.01), **TST** and **overall SE** (p < 0.05), this effect was not maintained on N29, but on N85 WASO and TST reached statistical significance (p < 0.05). - **LPS** was not significantly reduced at any time point		Comparable safety profiles across the 3 treatment groups: 52% **AEs** in the placebo group, 40% in the doxepin 1 mg group and 38% in the doxepin 3 mg group.
Lankford A et al 2012	- Doxepin 6 mg improved **sTST** and **sWASO** at week 1 (both p-values < 0.0001), week 2 and 4 (all p-values < 0.05). - It improved **sleep quality** (weeks 1, 3 and 4 ; p < 0.05). - No significant differences in **LSO**.		No reports of **memory impairment** or **cognitive disorder** in any doxepin-treated patient.			- Comparable safety profiles: 27% **AEs** in placebo vs 31% in doxepin 6 mg group. - **Most common AEs** were somnolence/sedation and dizziness. - **Discontinuation** of 5% in doxepin 6 mg vs 10% in placebo group.

	- **CGI scale scores** improved at week 1 and 2 (but not at week 3 and 4). - 4 of 5 items of the **PGI scale** significantly improved at week 4 ($p < 0.05$). - The **ISI** significantly improved at all 4 weeks ($p < 0.02$).					
Scharf M et al, 2008	- Dose-related improvement in **sWASO**, **sTST** and **sleep quality** for all doxepin doses (all $p < 0.05$) vs placebo. - Significant decrease in **LSO** only for doxepin 6 mg (-11.7 min, p=0.018) - No difference in **sNAW** for any dose	No differences between placebo and doxepin on **psychomotor function** (DSST and SCT) or **next-day sleepiness**.		- Dose-related improvement on **WTDS**, **TST** and overall **SE** for all doxepin doses (all $p<0.0001$) vs placebo. - Improvement of **WASO** only for 3 mg (-6.2 min, p=0.02) and 6 mg (-7.4 min, p=0.0005) - No difference in **NAW** and **LPS** for any dose.		Number of **AEs** were similar across treatment groups. All were mild or moderate.
Paroxetine						
Reynolds CF et al, 2006	- Paroxetine improved **subjective sleep quality** (F=5.42, df=1,25, p=0.03).	- Paroxetine improved **daytime alertness** (F=8.19, df=1,25, p=0.008) and **mood** (F=6.12, df=1,136, p=0.02).		- Paroxetine increased **SL** (F=4.61, df=1,25, p=0.04), decreased **WASO** (F=6.09, df=1,25, p=0.02). - No difference in **SE**.		
Tiagabine						
Roth T, Wright P et al, 2006	- No effects on ratings of sleep (**SL**, **NAW**, **WASO**, **TST**, **sleep depth**, **sleep quality**, **refreshing quality of sleep**) with tiagabine 2, 4 and 6 mg vs placebo. - Tiagabine 8 mg decreased **TST** and **refreshing quality of sleep** ($p<0.05$) compared to placebo.	- No differences in **ability to think clearly**, **level of alertness**, **sense of physical well-being** with tiagabine 2, 4 and 6 mg. - Tiagabine 8 mg decreased the **ability to think clearly** (-6.3 ± 2.9, $p<0.01$), **level of alertness** (-5.6 ± 2.6, $p<0.05$) and **sense of**		- Tiagabine (any dose) did not affect **WASO**, **LPS** and **TST** compared with placebo - Increased **deep sleep** is observed for tiagabine 4 mg (19.9 ± 3.5 min), 6 mg (38.0 ± 5.2 min) and 8 mg (46.9 ± 6.4 min) vs placebo (all $p<0.05$). - Reduction of **NAW** with tiagabine 6 mg (-2.0 ± 1.5)		-Tiagabine 2, 4 and 6 mg have comparable **AEs** compared to placebo. - Tiagabine 8 mg has more AEs: 1 **serious AE** (confusional state), **most common AEs** were dizziness (23% vs 3% with placebo) and nausea (16% vs 0%).

		physical well-being (-6.1 ± 3.2, p<0.05). - Significant decrease on **DSST** with tiagabine 8 mg (-0.2 ± 4.06, -<0.05)		and 8 mg (-0.7 ± 1.8),(all p< 0.05).		
Walsh CK et al, 2005	- Decreased **NAW** with tiagabine 8 mg vs placebo (3.70 ± 3.44 vs 2.65 ± 1.50, p<0.032). - All other self-reported sleep variables for any tiagabine dose did not differ from placebo.	- The **Karolinkska Sleepiness Scale**, the **DSST**, ratings of **alertness** and **concentration** showed no differences for any dose. - No differences in **immediate word recall** for any dose. - The mean **delayed word recall** score was lower in the T 8 mg compared to placebo (8.75 ± 3.79 vs 9.80 ± 3.37, p < 0.036)		- T 2 mg did not differ from placebo. - T 4 mg increased **TST** (407.7 vs 396.0 min, p=0.022), reduced **WASO** (64.9 vs 77.2 min, p=0.019), increased **deep sleep** (59.7 vs 44.5 min, p=0.015) compared to placebo. - T 8 mg: no difference for **WASO** (p=0.073), more **deep sleep** (87.0 vs 44.5 min, p < 0.0001), improved **sleep-continuity index** (1.03 ± 1.27 vs 0.37 ± 0.37, p<0.0002).		**Central nervous system AEs** were higher in the 8-mg condition only: 13 AEs with T8 mg vs 3 in placebo, 2 in T 2 mg and 2 in T 4 mg.
Valerian						
Taibi DM et al, 2009.	No difference of the self-reported **SL**, **WASO**, **SE**, overall **sleep quality** (p-values not reported).			- No differences in **PSG SL**, **WASO** and **SE** between valerian and placebo. - Compared to baseline separately, **PSG WASO** increased significantly after 2 weeks of valerian (+17.7 ± 25.6 min, Z=-2.33, p=0.02) but not after placebo (+6.8±26.4 min, NS) - No differences in **actigraphy-based WASO** and **SE** between valerian and placebo.		Minor **side effects**, no significant difference between valerian (6.8 ± 4.0 symptoms) and placebo (6.4 ± 5.2 symptoms).

Abbreviations used: AE: adverse event, BFW: behaviour following wakening, CGI: Clinical Global Impression, DSST: digit symbol substitution task , GAS: Goldberg Anxiety Scale , GDS: Geriatric Depression Scale, ISI: insomnia severity index., LPS: latency to persistent sleep, LSEQ: Leeds Sleep Evaluation Questionnaire, LSO: latency to sleep onset, MMSE: Mini mental state examination, MTT: manual tracking task, NAW: number of awakenings, NHSMI: Northside Hospital Sleep Medicine Institute Test, PGI: Patient Global Impression, PSQI: Pittsburgh Sleep Quality Index, QOD: quality of day, QoL: quality of life, RCSQ: Richards Campbell Sleep Questionnaire, SCT: symbol copying test, SE: sleep efficiency, sSL: subjective Sleep Latency, TST: total sleep time, VAS: visual analogue scale, WASO: wake time after sleep onset

REFERENCES

1. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M (2008) Clinical guideline for the evaluation and management of chronic insomnia in adults. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 4 (5):487-504
2. Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG (1995) Sleep complaints among elderly persons: an epidemiologic study of three communities. Sleep 18 (6):425-432
3. Foley DJ, Monjan A, Simonsick EM, Wallace RB, Blazer DG (1999) Incidence and remission of insomnia among elderly adults: an epidemiologic study of 6,800 persons over three years. Sleep 22 Suppl 2:S366-372
4. Maggi S, Langlois JA, Minicuci N, Grigoletto F, Pavan M, Foley DJ, Enzi G (1998) Sleep complaints in community-dwelling older persons: prevalence, associated factors, and reported causes. Journal of the American Geriatrics Society 46 (2):161-168
5. Association AP (2013) Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub,
6. Ancoli-Israel S, Cooke JR (2005) Prevalence and comorbidity of insomnia and effect on functioning in elderly populations. Journal of the American Geriatrics Society 53 (7 Suppl):S264-271. doi:10.1111/j.1532-5415.2005.53392.x
7. Roth T, Ancoli-Israel S (1999) Daytime consequences and correlates of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. II. Sleep 22 Suppl 2:S354-358
8. Haimov I, Hanuka E, Horowitz Y (2008) Chronic insomnia and cognitive functioning among older adults. Behavioral sleep medicine 6 (1):32-54. doi:10.1080/15402000701796080
9. Brassington GS, King AC, Bliwise DL (2000) Sleep problems as a risk factor for falls in a sample of community-dwelling adults aged 64-99 years. Journal of the American Geriatrics Society 48 (10):1234-1240
10. Stone KL, Ensrud KE, Ancoli-Israel S (2008) Sleep, insomnia and falls in elderly patients. Sleep Medicine 9 (SUPPL. 1):S18-S22. doi:10.1016/S1389-9457(08)70012-1
11. Avidan AY, Fries BE, James ML, Szafara KL, Wright GT, Chervin RD (2005) Insomnia and hypnotic use, recorded in the minimum data set, as predictors of falls and hip fractures in Michigan nursing homes. Journal of the American Geriatrics Society 53 (6):955-962. doi:10.1111/j.1532-5415.2005.53304.x
12. Shi L, Chen SJ, Ma MY, Bao YP, Han Y, Wang YM, Shi J, Vitiello MV, Lu L (2018) Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis. Sleep medicine reviews 40:4-16. doi:10.1016/j.smrv.2017.06.010
13. Schroeck JL, Ford J, Conway EL, Kurtzhalts KE, Gee ME, Vollmer KA, Mergenhagen KA (2016) Review of Safety and Efficacy of Sleep Medicines in Older Adults. Clinical therapeutics 38 (11):2340-2372. doi:10.1016/j.clinthera.2016.09.010
14. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV (2004) Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 27 (7):1255-1273
15. Abad VC, Guilleminault C (2018) Insomnia in Elderly Patients: Recommendations for Pharmacological Management. Drugs & aging 35 (9):791-817. doi:10.1007/s40266-018-0569-8
16. Brewster GS, Riegel B, Gehrman PR (2018) Insomnia in the Older Adult. Sleep Medicine Clinics 13 (1):13-19. doi:10.1016/j.jsmc.2017.09.002
17. Albrecht JS, Wickwire EM, Vadlamani A, Scharf SM, Tom SE (2019) Trends in Insomnia Diagnosis and Treatment Among Medicare Beneficiaries, 2006-2013. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 27 (3):301-309. doi:10.1016/j.jagp.2018.10.017
18. Barker MJ, Greenwood KM, Jackson M, Crowe SF (2004) Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. Archives of clinical

neuropsychology : the official journal of the National Academy of Neuropsychologists 19 (3):437-454. doi:10.1016/s0887-6177(03)00096-9
19. Zhong G, Wang Y, Zhang Y, Zhao Y (2015) Association between Benzodiazepine Use and Dementia: A Meta-Analysis. PloS one 10 (5):e0127836. doi:10.1371/journal.pone.0127836
20. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD (2016) Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. Annals of internal medicine 165 (2):125-133. doi:10.7326/m15-2175
21. Chen PL, Lee WJ, Sun WZ, Oyang YJ, Fuh JL (2012) Risk of dementia in patients with insomnia and long-term use of hypnotics: a population-based retrospective cohort study. PloS one 7 (11):e49113. doi:10.1371/journal.pone.0049113
22. Kang DY, Park S, Rhee CW, Kim YJ, Choi NK, Lee J, Park BJ (2012) Zolpidem use and risk of fracture in elderly insomnia patients. Journal of preventive medicine and public health = Yebang Uihakhoe chi 45 (4):219-226. doi:10.3961/jpmph.2012.45.4.219
23. Lai MM, Lin CC, Lin CC, Liu CS, Li TC, Kao CH (2014) Long-term use of zolpidem increases the risk of major injury: a population-based cohort study. Mayo Clinic proceedings 89 (5):589-594. doi:10.1016/j.mayocp.2014.01.021
24. Chung S, Sinha SR, Shah A, Stern JM, Cheng H, Jung J, Grinnell T, Blum D (2019) Long-term safety and efficacy following conversion to eslicarbazepine acetate monotherapy in adults with focal seizures. Epilepsy Research 153:59-65. doi:10.1016/j.eplepsyres.2019.03.018
25. Vijay A, Becker JE, Ross JS (2018) Patterns and predictors of off-label prescription of psychiatric drugs. PloS one 13 (7):e0198363. doi:10.1371/journal.pone.0198363
26. Atkin T, Comai S, Gobbi G (2018) Drugs for Insomnia beyond Benzodiazepines: Pharmacology, Clinical Applications, and Discovery. Pharmacological reviews 70 (2):197-245. doi:10.1124/pr.117.014381
27. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J (2003) Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ journal of surgery 73 (9):712-716
28. Al-Aama T, Brymer C, Gutmanis I, Woolmore-Goodwin SM, Esbaugh J, Dasgupta M (2011) Melatonin decreases delirium in elderly patients: A randomized, placebo-controlled trial. International Journal of Geriatric Psychiatry 26 (7):687-694. doi:10.1002/gps.2582
29. Baskett JJ, Broad JB, Wood PC, Duncan JR, Pledger MJ, English J, Arendt J (2003) Does melatonin improve sleep in older people? A randomised crossover trial. Age and ageing 32 (2):164-170
30. Fainstein I, Bonetto AJ, Brusco LI, Cardinali DP (1997) Effects of melatonin in elderly patients with sleep disturbance: A pilot study. Current Therapeutic Research - Clinical and Experimental 58 (12):990-1000. doi:10.1016/S0011-393X(97)80066-5
31. Fan Y, Yuan L, Ji M, Yang J, Gao D (2017) The effect of melatonin on early postoperative cognitive decline in elderly patients undergoing hip arthroplasty: A randomized controlled trial. Journal of clinical anesthesia 39:77-81. doi:10.1016/j.jclinane.2017.03.023
32. Garfinkel D, Laudon M, Nof D, Zisapel N (1995) Improvement of sleep quality in elderly people by controlled-release melatonin. Lancet (London, England) 346 (8974):541-544
33. Garzon C, Guerrero JM, Aramburu O, Guzman T (2009) Effect of melatonin administration on sleep, behavioral disorders and hypnotic drug discontinuation in the elderly: a randomized, double-blind, placebo-controlled study. Aging Clin Exp Res 21 (1):38-42
34. Jaiswal SJ, McCarthy TJ, Wineinger NE, Kang DY, Song J, Garcia S, van Niekerk CJ, Lu CY, Loeks M, Owens RL (2018) Melatonin and Sleep in Preventing Hospitalized Delirium: A Randomized Clinical Trial. The American journal of medicine 131 (9):1110-1117.e1114. doi:10.1016/j.amjmed.2018.04.009
35. Lemoine P, Nir T, Laudon M, Zisapel N (2007) Prolonged-release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 years and older and has no withdrawal effects. J Sleep Res 16 (4):372-380. doi:10.1111/j.1365-2869.2007.00613.x
36. Wade AG, Ford I, Crawford G, McMahon AD, Nir T, Laudon M, Zisapel N (2007) Efficacy of prolonged release melatonin in insomnia patients aged 55-80 years: quality of sleep and next-day

alertness outcomes. Current medical research and opinion 23 (10):2597-2605. doi:10.1185/030079907x233098
37. Wade AG, Ford I, Crawford G, McConnachie A, Nir T, Laudon M, Zisapel N (2010) Nightly treatment of primary insomnia with prolonged release melatonin for 6 months: a randomized placebo controlled trial on age and endogenous melatonin as predictors of efficacy and safety. BMC medicine 8:51. doi:10.1186/1741-7015-8-51
38. Roth T, Seiden D, Sainati S, Wang-Weigand S, Zhang J, Zee P (2006) Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia. Sleep Med 7 (4):312-318. doi:10.1016/j.sleep.2006.01.003
39. Mini LJ, Wang-Weigand S, Zhang J (2007) Self-reported efficacy and tolerability of ramelteon 8 mg in older adults experiencing severe sleep-onset difficulty. The American journal of geriatric pharmacotherapy 5 (3):177-184. doi:10.1016/j.amjopharm.2007.09.004
40. Richardson GS, Zammit G, Wang-Weigand S, Zhang J (2009) Safety and subjective sleep effects of ramelteon administration in adults and older adults with chronic primary insomnia: a 1-year, open-label study. J Clin Psychiatry 70 (4):467-476
41. Roth T, Seiden D, Wang-Weigand S, Zhang J (2007) A 2-night, 3-period, crossover study of ramelteon's efficacy and safety in older adults with chronic insomnia. Current medical research and opinion 23 (5):1005-1014. doi:10.1185/030079907x178874
42. Avidan AY, Palmer LA, Doan JF, Baran RW (2010) Insomnia medication use and the probability of an accidental event in an older adult population. Drug, Healthcare and Patient Safety 2 (1):225-232. doi:10.2147/DHPS.S14955
43. Lankford A, Rogowski R, Essink B, Ludington E, Heith Durrence H, Roth T (2012) Efficacy and safety of doxepin 6 mg in a four-week outpatient trial of elderly adults with chronic primary insomnia. Sleep Med 13 (2):133-138. doi:10.1016/j.sleep.2011.09.006
44. Krystal AD, Durrence HH, Scharf M, Jochelson P, Rogowski R, Ludington E, Roth T (2010) Efficacy and safety of doxepin 1 mg and 3 mg in a 12-week sleep laboratory and outpatient trial of elderly subjects with chronic primary insomnia. Sleep 33 (11):1553-1561. doi:10.1093/sleep/33.11.1553
45. Scharf M, Rogowski R, Hull S, Cohn M, Mayleben D, Feldman N, Ereshefsky L, Lankford A, Roth T (2008) Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in elderly patients with primary insomnia: a randomized, double-blind, placebo-controlled crossover study. The Journal of clinical psychiatry 69 (10):1557-1564
46. Reynolds ICF, Buysse DJ, Miller MD, Pollock BG, Hall M, Mazumdar S (2006) Paroxetine treatment of primary insomnia in older adults. American Journal of Geriatric Psychiatry 14 (9):803-807. doi:10.1097/01.JGP.0000218327.21111.de
47. Walsh JK, Randazzo AC, Frankowski S, Shannon K, Schweitzer PK, Roth T (2005) Dose-response effects of tiagabine on the sleep of older adults. Sleep 28 (6):673-676. doi:10.1093/sleep/28.6.673
48. Roth T, Wright Jr KP, Walsh J (2006) Effect of tiagabine on sleep in elderly subjects with primary insomnia: A randomized, double-blind, placebo-controlled study. Sleep 29 (3):335-341. doi:10.1093/sleep/29.3.335
49. Glass JR, Sproule BA, Herrmann N, Busto UE (2008) Effects of 2-week treatment with temazepam and diphenhydramine in elderly insomniacs: A randomized, placebo-controlled trial. Journal of Clinical Psychopharmacology 28 (2):182-188. doi:10.1097/JCP.0b013e31816a9e4f
50. Herring WJ, Connor KM, Snyder E, Snavely DB, Zhang Y, Hutzelmann J, Matzura-Wolfe D, Benca RM, Krystal AD, Walsh JK, Lines C, Roth T, Michelson D (2017) Suvorexant in Elderly Patients with Insomnia: Pooled Analyses of Data from Phase III Randomized Controlled Clinical Trials. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 25 (7):791-802. doi:10.1016/j.jagp.2017.03.004
51. Taibi DM, Vitiello MV, Barsness S, Elmer GW, Anderson GD, Landis CA (2009) A randomized clinical trial of valerian fails to improve self-reported, polysomnographic, and actigraphic sleep in older women with insomnia. Sleep Med 10 (3):319-328. doi:10.1016/j.sleep.2008.02.001
52. McCleery J, Cohen DA, Sharpley AL (2016) Pharmacotherapies for sleep disturbances in dementia. The Cochrane database of systematic reviews 11:Cd009178. doi:10.1002/14651858.CD009178.pub3

53. Kishi T, Matsunaga S, Iwata N (2015) Suvorexant for Primary Insomnia: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials. PloS one 10 (8):e0136910. doi:10.1371/journal.pone.0136910
54. European Medicine Agency (2008) Meeting highlights from the Committee for Medicinal Products for Human Use,27-30 May 2008. https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use27-30-may-2008. Accessed September 1st 2019
55. Jaffer KY, Chang T, Vanle B, Dang J, Steiner AJ, Loera N, Abdelmesseh M, Danovitch I, Ishak WW (2017) Trazodone for Insomnia: A Systematic Review. Innovations in clinical neuroscience 14 (7-8):24-34
56. Camargos EF, Louzada LL, Quintas JL, Naves JOS, Louzada FM, Nóbrega OT (2014) Trazodone improves sleep parameters in Alzheimer disease patients: A randomized, double-blind, and placebo-controlled study. American Journal of Geriatric Psychiatry 22 (12):1565-1574. doi:10.1016/j.jagp.2013.12.174
57. Fernandez-San-Martin MI, Masa-Font R, Palacios-Soler L, Sancho-Gomez P, Calbo-Caldentey C, Flores-Mateo G (2010) Effectiveness of Valerian on insomnia: a meta-analysis of randomized placebo-controlled trials. Sleep Med 11 (6):505-511. doi:10.1016/j.sleep.2009.12.009
58. Taibi DM, Landis CA, Petry H, Vitiello MV (2007) A systematic review of valerian as a sleep aid: safe but not effective. Sleep medicine reviews 11 (3):209-230. doi:10.1016/j.smrv.2007.03.002
59. Bent S, Padula A, Moore D, Patterson M, Mehling W (2006) Valerian for sleep: a systematic review and meta-analysis. The American journal of medicine 119 (12):1005-1012. doi:10.1016/j.amjmed.2006.02.026
60. Reynolds AC, Adams RJ (2019) Treatment of sleep disturbance in older adults. Journal of Pharmacy Practice and Research 49 (3):296-304. doi:10.1002/jppr.1565

SUPPLEMENTARY MATERIAL

Supplementary material 1: Search string

A. Search string Pubmed

("aged"[MeSH] OR aged[tiab] OR "geriatrics"[MeSH] OR geriatrics[tiab] OR geriatric[tiab] OR gerontology[tiab] OR "nursing homes"[MeSH] OR nursing homes[tiab] OR "geriatric nursing"[MeSH] OR "homes for the aged"[MeSH] OR old age[tiab] OR older people[tiab] OR older person[tiab] OR older population[tiab] OR older patient[tiab] OR older adult[tiab] OR elderly[tiab] OR "health services for the aged"[MeSH]) **AND** ("Antipsychotic Agents"[MeSH] OR antipsychotic agents[tiab] OR antipsychotic drugs[tiab] OR antipsychotics[tiab] OR neuroleptics[tiab] OR neuroleptic drugs[tiab] OR neuroleptic agents[tiab] OR "Quetiapine Fumarate"[MeSH] OR quetiapine[tiab] OR seroquel[tiab] OR olanzapine[tiab] OR zyprexa[tiab] OR "risperidone"[MeSH] OR risperidone[tiab] OR risperdal[tiab] OR "haloperidol"[MeSH] OR haloperidol[tiab] OR haldol[tiab] OR "Histamine Antagonists"[MeSH] OR histamine antagonists[tiab] OR antihistaminic drugs[tiab] OR antihistaminic agents[tiab] OR antihistamines[tiab] OR "Antidepressive Agents"[MeSH] OR antidepressive agents[tiab] OR antidepressive drugs[tiab] OR antidepressants[tiab] OR antidepressant drugs[tiab] OR antidepressant agents[tiab] OR "trazodone"[MeSH] OR trazodone[tiab] OR mirtazapine[tiab] OR "mianserin"[MeSH] OR mianserin[tiab] OR "Melatonin"[MeSH] OR Melatonin[tiab] OR "Valerian"[MeSH] OR Valerian[tiab] OR "Anticonvulsants"[MeSH] OR anticonvulsants[tiab] OR anticonvulsive agents[tiab] OR anticonvulsive drugs[tiab] OR anticonvulsant drugs[tiab] OR anticonvulsant agents[tiab] OR antiepileptics[tiab] OR antiepileptic agents[tiab] OR antiepileptic drugs[tiab]) **AND** ("Sleep"[Mesh] OR Sleep[Title/Abstract] OR insomnia[Title/Abstract] OR "Sleep Wake Disorders"[Mesh] OR dream[Title/Abstract] OR Somnolence[Title/Abstract] OR Wake[Title/Abstract] OR Drowsiness[Title/Abstract] OR Hypersomnia[Title/Abstract]) **AND** ("Patient Harm"[Mesh] OR Harm[Title/Abstract] OR Safety[Title/Abstract] OR "Patient Safety"[Mesh] OR "Treatment Outcome"[Mesh] OR Treatment Outcome[Title/Abstract] OR Treatment Effectiveness[Title/Abstract] OR Treatment Efficacy[Title/Abstract] OR Clinical Efficacy[Title/Abstract] OR Clinical Outcome[Title/Abstract] OR "Hospitalization"[Mesh] OR Hospitalization[Title/Abstract] OR Patient Admission[Title/Abstract] OR Patient Discharge[Title/Abstract] OR Readmission[Title/Abstract] OR Length of Stay[Title/Abstract] OR Hospital Stay[Title/Abstract] OR "Geriatric Psychiatry"[Mesh] OR Geriatric Psychiatry[Title/Abstract] OR Psychogeriatric[Title/Abstract] OR Gerontopsychiatry[Title/Abstract] OR Delirium[Title/Abstract] OR "Confusion"[Mesh] OR Confusion[Title/Abstract] OR Disorientation[Title/Abstract] OR Confusional state[Title/Abstract] OR Agitation[Title/Abstract] OR Encephalopathy[Title/Abstract] OR "Neurocognitive Disorders"[Mesh] OR Neurocognitive Disorders[Title/Abstract] OR Psychoses[Title/Abstract] OR Mental disorder[Title/Abstract] OR Amnesia[Title/Abstract] OR Dementia[Title/Abstract] OR Alzheimer[Title/Abstract] OR Cognitive[Title/Abstract] OR Cognition[Title/Abstract] OR "Accidental Falls"[Mesh] OR Falls[Title/Abstract] OR Falling[Title/Abstract] OR "Benzodiazepines/therapeutic use"[Mesh] OR Benzodiazepine use[Title/Abstract] OR "Fractures, Bone"[Mesh] OR Fracture[Title/Abstract] OR Broken Bones[Title/Abstract]) **AND** (Dutch[lang] OR English[lang] OR French[lang]) NOT (Case Reports[ptyp] OR Editorial[ptyp])

B. Search string Embase

('aged'/exp OR 'aged':ab,ti OR 'geriatrics'/exp OR 'geriatrics':ab,ti OR 'geriatric':ab,ti OR 'elderly care'/exp OR 'elderly':ab,ti OR 'nursing home'/exp OR 'nursing home':ab,ti OR 'old age home':ab,ti OR 'geriatric patient'/exp OR 'gerontology'/exp OR 'gerontology':ab,ti OR 'old age':ab,ti OR 'older people':ab,ti OR 'older person':ab,ti OR 'older population':ab,ti OR 'older patient':ab,ti OR 'older adult':ab,ti) **AND** ('neuroleptic agent'/exp OR 'neuroleptic agents':ab,ti OR 'neuroleptic drugs':ab,ti OR 'neuroleptics':ab,ti OR 'antipsychotic agents':ab,ti OR 'antipsychotic drugs':ab,ti OR 'antipsychotics':ab,ti OR 'quetiapine':ab,ti OR 'seroquel':ab,ti OR 'olanzapine':ab,ti OR 'zyprexa':ab,ti OR 'risperidone':ab,ti OR 'risperdal':ab,ti OR 'haloperidol':ab,ti OR 'haldol':ab,ti OR 'antihistaminic agent'/exp OR 'histamine antagonists':ab,ti OR 'antihistaminic drugs':ab,ti OR 'antihistaminic agents':ab,ti OR 'antihistamines':ab,ti OR 'antidepressant agent'/exp OR 'antidepressant agents':ab,ti OR 'antidepressant drugs':ab,ti OR 'antidepressive agents':ab,ti OR 'antidepressive drugs':ab,ti OR 'trazodone':ab,ti OR 'mirtazapine':ab,ti OR 'mianserin':ab,ti OR 'melatonin'/exp OR 'melatonin':ab,ti OR 'valerian'/exp OR 'valerian':ab,ti OR 'anticonvulsive agent'/exp OR 'anticonvulsive agents':ab,ti OR 'anticonvulsants':ab,ti OR 'anticonvulsive drugs':ab,ti OR 'anticonvulsant agents':ab,ti OR 'anticonvulsant drugs':ab,ti OR 'antiepileptics':ab,ti OR 'antiepileptic agents':ab,ti OR 'antiepileptic drugs':ab,ti) **AND** ('sleep'/exp OR 'sleep':ti,ab OR 'insomnia':ti,ab OR 'sleep disorder'/exp OR 'dream':ti,ab OR 'somnolence':ti,ab OR 'wake':ti,ab OR 'drowsiness':ti,ab OR 'hypersomnia':ti,ab) **AND** ('patient harm'/exp OR 'harm':ti,ab OR 'safety':ti,ab OR 'patient safety'/exp OR 'treatment outcome'/exp OR 'treatment outcome':ti,ab OR 'treatment effectiveness':ti,ab OR 'treatment efficacy':ti,ab OR 'clinical efficacy':ti,ab OR 'clinical outcome':ti,ab OR 'hospitalization'/exp OR 'hospitalization':ti,ab OR 'patient admission':ti,ab OR 'patient discharge':ti,ab OR 'readmission':ti,ab OR 'length of stay':ti,ab OR 'hospital stay':ti,ab OR 'gerontopsychiatry'/exp OR 'gerontopsychiatry':ti,ab OR 'geriatric psychiatry':ti,ab OR 'psychogeriatric':ti,ab OR 'delirium'/exp OR 'delirium':ti,ab OR 'confusion'/exp OR 'confusion':ti,ab OR 'disorientation':ti,ab OR 'confusional state':ti,ab OR 'agitation':ti,ab OR 'encephalopathy':ti,ab OR 'disorders of higher cerebral function'/exp OR 'neurocognitive disorders':ti,ab OR 'psychoses':ti,ab OR 'mental disorder':ti,ab OR 'amnesia':ti,ab OR 'dementia':ti,ab OR 'alzheimer':ti,ab OR 'cognitive':ti,ab OR 'cognition':ti,ab OR 'falling'/exp OR 'falling':ti,ab OR 'accidental falls':ti,ab OR 'falls':ti,ab OR 'benzodiazepine use':ti,ab OR 'fracture'/exp OR 'fracture':ti,ab OR 'broken bones':ti,ab) **AND** ('english':la OR 'dutch':la OR 'french':la) **NOT** ('case report'/exp OR 'case report'/de) **NOT** ('editorial':it)

C. Search string Cochrane

#1 'aged':ab,ti or 'geriatrics':ab,ti or 'geriatric':ab,ti OR'elderly':ab,ti or 'nursing home':ab,ti or 'old age home':ab,ti or 'gerontology':ab,ti or ‘old age’:ab,ti or ‘older people’:ab,ti or ‘older person’:ab,ti or ‘older population’:ab,ti or ‘older patient’:ab,ti or ‘older adult’:ab,ti 134594
#2 MeSH descriptor: [Aged] explode all trees 1248
#3 MeSH descriptor: [Geriatrics] explode all trees 198
#4 MeSH descriptor: [Nursing Homes] explode all trees 1266
#5 MeSH descriptor: [Homes for the Aged] explode all trees 588
#6 MeSH descriptor: [Health Services for the Aged] explode all trees 441
#7 #1 or #3 or #4 or #5 or #6 or #2 135549
#8 ‘neuroleptic agents’:ab,ti or ‘neuroleptic drugs’:ab,ti or ‘neuroleptics’:ab,ti or ‘antipsychotic agents’:ab,ti or ‘antipsychotic drugs’:ab,ti or ‘antipsychotics’:ab,ti or ‘quetiapine’:ab,ti or ‘seroquel’:ab,ti or ‘olanzapine’:ab,ti or ‘zyprexa’:ab,ti or ‘risperidone’:ab,ti or ‘risperdal’:ab,ti or ‘haloperidol’:ab,ti or ‘haldol’:ab,ti or ‘antihistaminic agents’:ab,ti or ‘histamine antagonists’:ab,ti or ‘antihistaminic drugs’:ab,ti or ‘antihistaminic agents’:ab,ti or ‘antihistamines’:ab,ti or ‘antidepressant agents’:ab,ti or ‘antidepressant drugs’:ab,ti or ‘antidepressive agents’:ab,ti or ‘antidepressive drugs’:ab,ti or ‘trazodone’:ab,ti or ‘mirtazapine’:ab,ti or ‘mianserin’:ab,ti or ‘melatonin’:ab,ti or ‘valerian’:ab,ti or ‘anticonvulsive agents’:ab,ti or ‘anticonvulsants’:ab,ti or ‘anticonvulsive drugs’:ab,ti or ‘anticonvulsant agents’:ab,ti or ‘anticonvulsant drugs’:ab,ti or ‘antiepileptics’:ab,ti or ‘antiepileptic agents’:ab,ti or ‘antiepileptic drugs’:ab,ti 21317
#9 MeSH descriptor: [Antipsychotic Agents] explode all trees 4415
#10 MeSH descriptor: [Quetiapine Fumarate] explode all trees 626
#11 MeSH descriptor: [Risperidone] explode all trees 1288
#12 MeSH descriptor: [Haloperidol] explode all trees 1346
#13 MeSH descriptor: [Histamine Antagonists] explode all trees 2747
#14 MeSH descriptor: [Nootropic Agents] explode all trees 556
#15 MeSH descriptor: [Mianserin] explode all trees 445
#16 MeSH descriptor: [Melatonin] explode all trees 1089
#17 MeSH descriptor: [Valerian] explode all trees 56
#18 MeSH descriptor: [Anticonvulsants] explode all trees 2321
#19 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 27002
#20 "Sleep":ti,ab or "insomnia":ti,ab or "dream":ti,ab or "Somnolence":ti,ab or "Wake":ti,ab or "Drowsiness":ti,ab or "Hypersomnia":ti,ab 36003
#21 MeSH descriptor: [Sleep] explode all trees 5348
#22 MeSH descriptor: [Sleep Wake Disorders] explode all trees 7153
#23 #20 or #21 or #22 37609
#24 "Harm":ti,ab or "Safety":ti,ab or "Treatment Outcome":ti,ab or "Treatment Effectiveness":ti,ab or "Treatment Efficacy":ti,ab or "Clinical Efficacy":ti,ab or "Clinical Outcome":ti,ab or "Hospitalization":ti,ab or "Patient Admission":ti,ab or "Patient Discharge":ti,ab or "Readmission":ti,ab or "Length of Stay":ti,ab or "Hospital Stay":ti,ab or "Gerontopsychiatry":ti,ab or "Geriatric Psychiatry":ti,ab or "Psychogeriatric":ti,ab or "Delirium":ti,ab or "Confusion":ti,ab or "Disorientation":ti,ab or "Confusional state":ti,ab or "Agitation":ti,ab or "Encephalopathy":ti,ab or "Neurocognitive Disorders":ti,ab or "Psychoses":ti,ab or "Mental disorder":ti,ab or "Amnesia":ti,ab or "Dementia":ti,ab or "Alzheimer":ti,ab or "Cognitive":ti,ab or "Cognition":ti,ab or "Falling":ti,ab or "Accidental Falls":ti,ab or "Falls":ti,ab or "Benzodiazepine use":ti,ab or "Fracture":ti,ab or "Broken Bones":ti,ab 340161
#25 MeSH descriptor: [Patient Safety] explode all trees 518
#26 MeSH descriptor: [Treatment Outcome] explode all trees 130766
#27 MeSH descriptor: [Hospitalization] explode all trees 13131
#28 MeSH descriptor: [Geriatric Psychiatry] explode all trees 39

#29	MeSH descriptor: [Confusion] explode all trees	707
#30	MeSH descriptor: [Neurocognitive Disorders] explode all trees	9754
#31	MeSH descriptor: [Accidental Falls] explode all trees	1353
#32	MeSH descriptor: [Fractures, Bone] explode all trees	5447
#33	#24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32	434137
#34	#7 and #19 and #23 and #33	442

Supplementary material 2: MINORS quality assessment

Twelve items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported but adequate). NA = non applicable.

	Clearly stated aim	Inclusion of consecutive patients	Prospective data collection	Endpoints appropriate to study aim	Unbiased qssessment of study endpoint	Follow-up period appropriate to study aim	<5% loss to follow-up	Prospective calculation of study size	Adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analysis	Total
Al Aama 2011	2	2	2	2	2	2	1	0	2	2	2	2	21/24
Avidan 2010	1	2	0	2	0	2	2	0	0	0	1	2	12/24
Baskett 2003	2	1	2	2	2	2	1	2	2	2	2	2	22/24
Fainstein 1997	1	1	2	1	0	2	0	0	NA	NA	NA	NA	7/16
Fan 2017	2	2	2	2	0	2	2	0	2	2	2	1	19/24
Garfinkel 1995	2	2	2	2	2	2	0	0	2	2	0	0	16/24
Garzón 2009	2	1	2	2	2	2	2	0	2	2	2	2	21/24
Glass 2008	2	1	2	2	2	2	1	1	2	2	2	1	20/24
Herring 2017	1	2	2	2	2	2	1	0	2	2	2	2	20/24
Jaiswal 2018	2	2	2	2	2	2	1	2	2	2	2	2	23/24
Krystal 2010	2	2	2	2	2	2	1	0	2	2	2	1	20/24
Lankford 2012	2	2	2	2	2	2	1	2	2	2	2	1	22/24
Lemoine 2007	2	2	2	2	2	2	2	0	2	2	2	1	21/24
Mini 2007	2	2	2	2	2	2	0	0	2	2	2	1	19/24
Reynolds 2006	2	2	2	2	2	2	1	0	2	2	0	1	18/24
Richardson 2009	2	2	2	2	1	2	1	0	NA	NA	NA	NA	12/16
Roth 2007	2	2	2	2	2	1	2	0	2	2	2	1	20/24
Roth, Wright 2006	2	2	2	2	2	1	2	0	2	2	2	1	20/24
Roth, Seiden 2006	2	2	2	2	2	2	1	0	2	2	2	1	20/24
Scharf 2008	2	2	2	2	2	1	2	0	2	2	2	1	20/24
Taibi 2009	2	2	2	2	2	2	2	0	2	2	1	1	20/24
Wade 2007	2	2	2	2	2	2	1	2	2	2	2	2	23/24
Wade 2010	2	2	2	2	2	2	1	2	2	2	2	2	23/24
Walsh 2005	2	2	2	2	2	1	1	0	2	2	2	1	19/24