The efficacy and safety of trazodone and mirtazapine in treating insomnia in adults: a systematic review

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De werkzaamheid en de veiligheid van trazodon en mirtazapine bij slapeloosheid bij volwassenen: een systematische review

Samenvatting

Context: Ongeveer 1/3 van de volwassen bevolking zou ooit symptomen van slapeloosheid vertonen en bij 6-10% van de bevolking spreken we zelfs van een slaapstoornis met belangrijke gevolgen overdag. Het is dan ook een veelvoorkomende klacht in de huisartsenpraktijk. Slapeloosheid heeft tal van negatieve gevolgen, zowel voor de patiënt zelf, als voor de maatschappij. Adviezen geven over slaaphygiëne en andere niet-medicamenteuze maatregelen zoals cognitieve gedragstherapie vormen de hoeksteen in de behandeling van slapeloosheid, maar vergen tijd en geduld en zijn soms moeilijk toegankelijk. Daarom wordt er vaak naar slaapmedicatie gegrepen. Volgens recente cijfers gebruikt 1/5 van de Belgen benzodiazepines of Z-producten voor verschillende aandoeningen, waaronder ook slapeloosheid. Helaas hebben deze geneesmiddelen veel (gevaarlijke) bijwerkingen en zijn ze bovendien verslavend. Op zoek naar een veiliger en minder verslavend alternatief worden vaak sederende antidepressiva zoals trazodon en mirtazapine geprobeerd, maar dit gebruik is off-label.

Onderzoeksvraag: Het doel van deze systematische review is om de beschikbare literatuur over trazodon en mirtazapine bij slapeloosheid samen te vatten en na te gaan wat het effect op slapeloosheid is en wat de veiligheid van deze sederende antidepressiva is.

Methode: Na het opstellen van inclusie- en exclusiecriteria werden, aan de hand van zorgvuldig gekozen trefwoorden, zoekopdrachten uitgevoerd in PubMed, EMBASE, Web of Science en de Cochrane Library. Op 19 september 2023 werden de resultaten van de zoekopdracht geïmporteerd in EndNote en duplicaten werden verwijderd. Vervolgens screenden twee auteurs onafhankelijk de overgebleven artikelen.

Resultaten: 3132 resultaten werden doorgenomen en 30 RCT's voldeden uiteindelijk aan de inclusiecriteria. Er waren 22 RCT's over trazodon, 4 RCT's over mirtazapine, 3 RCT's over esmirtazapine en 1 RCT ging over zowel trazodon als mirtazapine. Verschillende studies die trazodon onderzochten, toonden aan dat het de totale slaapduur, slaap latentie en de wakkere tijd na het slapengaan kan verbeteren en dat deze meer uitgesproken waren bij primaire insomnie dan bij secundaire insomnie. Bovendien verbeterde het ook de resultaten van subjectieve slaapenquêtes. Zowel bij acute als chronische inname werden gelijkaardige resultaten gevonden voor zowel objectieve als subjectieve uitkomsten. Het ziet ernaar uit dat trazodon positieve effecten heeft bij acute toediening, zelfs wanneer het slechts éénmaal werd toegediend en deze effecten blijven aanwezig wanneer het chronisch wordt gebruikt. De meest gebruikte dosissen waren 50mg en 100mg. Trazodon bleek in de onderzochte studies relatief veilig te zijn. De meest voorkomende bijwerkingen waren slaperigheid 's morgens, duizeligheid, misselijkheid en hoofdpijn. Er werden geen ernstige bijwerkingen gemeld na gebruik van trazodon. Enkele studies die mirtazapine onderzochten, allen bij patiënten met secundaire insomnia, toonden aan dat mirtazapine de totale

slaapduur, slaap latentie, tijd wakker na het slapengaan en subjectieve slaapscores kan verbeteren. De studies gebruikten verschillende dosissen (15-60mg). De veiligheid van deze stof was relatief goed in de onderzochte studies. Er werd één ernstige bijwerking gemeld: één patiënt had last van overmatige sedatie na enkelvoudige inname. Andere vaak voorkomende bijwerkingen waren gewichtstoename, slaperigheid en sinusitis. De effecten en veiligheid van trazodon en mirtazapine leken vergelijkbaar met die van benzodiazepines en Z-producten, maar tolerantie en verslavende eigenschappen werden nog onvoldoende onderzocht.

Conclusie: Zowel trazodon als mirtazapine tonen potentieel om (symptomen van) slapeloosheid te verbeteren, met name bij patiënten met comorbiditeiten of wanneer eerstelijnsbehandeling onvoldoende of niet mogelijk is. Voor trazodon is het beschikbare bewijs uitgebreider: meerdere RCT’s tonen aan dat het, vooral in een acute setting en bij lage doseringen (50–100 mg), doeltreffend kan zijn en het lijkt ook relatief veilig te zijn. Het huidige bewijs blijft echter beperkt en er wordt voorgesteld dat grootschalige en kwalitatieve RCT's worden uitgevoerd om een definitieve uitspraak te doen over de effectiviteit en veiligheid van trazodon en mirtazapine voor de eerstelijnsbehandeling van slapeloosheid. Met name de mogelijke ontwikkeling van tolerantie en het verslavingspotentieel zijn nog onvoldoende onderzocht en er zijn nog te weinig studies die vergelijken met de huidige eerstelijnsbehandeling.

The efficacy and safety of trazodone and mirtazapine in treating insomnia in adults: a systematic review

Abstract

Background: Approximately 1/3 of adults report occasional insomnia symptoms and around 6-10% of adults meet the criteria of insomnia disorder and have symptoms of daytime functional impairment. It is therefore a common complaint at the GP's office. Insomnia has numerous negative consequences, both for the patient and society. Sleep hygiene and other non-drug measures such as cognitive behavioural therapy are the cornerstone in the treatment of insomnia, but take time and patience and professional help is sometimes difficult to obtain. Hence, sleep medication is often resorted to. According to recent figures, 1/5 of Belgians use benzodiazepines or Z-drugs for various conditions, including insomnia. Unfortunately, these drugs have many (dangerous) side effects and are also addictive. In search of safer and less addictive sleeping aids, sedative antidepressants such as trazodone and mirtazapine are often tried, but this use is off-label.

Objectives: The aim of this systematic review is to summarise the available literature on trazodone and mirtazapine in insomnia and to investigate the effect on insomnia and the safety of these sedating antidepressants.

Methods: After establishing inclusion and exclusion criteria, PubMed, EMBASE, Web of Science and Cochrane Library databases were searched. The search queries consisted of carefully chosen keywords that fully cover the research question. The database research was conducted on 19 September 2023. The results were imported into EndNote and duplicate records were removed. Subsequently, all remaining articles were reviewed by two authors.

Results: 3,132 results were screened and finally 30 RCTs were included in this systematic review. There were 22 RCTs concerning trazodone, 4 RCTs concerning mirtazapine, 3 RCTs concerning esmirtazapine and 1 RCT studied both trazodone and mirtazapine. The trials that studied trazodone showed that it can improve the total sleep time (TST), sleep latency (SL) and wake time after sleep onset (WASO) and these improvements were more pronounced in primary insomnia compared to secondary insomnia. Furthermore, it also improved subjective sleep scores. When comparing acute and chronic administration, similar results seem to be found for both objective and subjective outcomes. It appears that trazodone has positive effects in acute administration, even when it was given only once. These effects remain present when the compound is taken chronically. The doses that were most used are 50mg and 100mg. The safety of this compound was relatively good in the examined studies. The most common side effects were sedation, dizziness, nausea and headache. There were no severe side effects reported after using trazodone. The few trials that studied mirtazapine, all in secondary insomniac patients, showed that mirtazapine can improve the TST, SL, WASO and ISI. All studies used different doses (15mg-60mg). The safety of this compound was relatively good in the examined studies There was one severe side effect reported: a patient had excessive sedation after one intake. Other common side effects were weight gain, somnolence

and sinus congestion. The effects and safety of trazodone and mirtazapine seemed similar to those of benzodiazepines and Z-drugs, however, tolerance and addictiveness have not been sufficiently investigated yet.

Conclusion: Both trazodone and mirtazapine show potential to improve (symptoms of) insomnia, especially in patients with comorbidities or when first-line treatment is insufficient or not possible. For trazodone, the available evidence is more extensive: multiple RCTs show that, especially in acute settings and at low doses (50-100 mg), it can be effective and it also appears to be relatively safe. However, the current evidence remains limited and it is suggested that large-scale, qualitative RCTs should be conducted to make a definitive statement on the efficacy and safety of trazodone and mirtazapine for the first-line treatment of insomnia. In particular, the possible development of tolerance and addiction potential have not yet been sufficiently investigated and there are not enough studies comparing with current first-line treatment.

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1. Introduction

1.1. Insomnia: definition, prevalence and pathophysiology

1.1.1. Definition

The term “insomnia” is used and interpreted in different ways. It is often characterised by difficulty falling or staying asleep (1-3) or waking up too early (4). Another characteristic that is used a lot is unrefreshing sleep or poor sleep quality (5).

Sleep problems is a broad term that refers to all kinds of problems with sleeping and can be a symptom of several conditions, but it does not always have to be serious or chronic. Insomnia, on the other hand, usually refers to a specific sleep disorder that meets specific criteria (5, 6).

The most known nomenclature used by clinicians and researchers for the classification of mental disorders, is the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (7). According to the DSM-5, insomnia disorder is a predominant complaint of dissatisfaction with sleep quantity or quality associated with one (or more) nocturnal symptoms, such as difficulty initiating sleep and difficulty maintaining sleep (criterion A) and this sleep disturbance causes significant daytime impairment or distress (criterion B). The sleep difficulties occur at least 3 nights per week (criterion C) and are present for at least 3 months (criterion D). The sleep difficulties occur despite adequate sleep opportunities (criterion E), the insomnia is not better explained by another sleep-wake disorder (criterion F) and is not due to the physiological effects of a substance (criterion G). Finally, the complaint of insomnia is not explained by co-existing mental disorders or medical conditions (criterion H) (7).

1.1.2. Prevalence

Insomnia is the most prevalent type of sleep disturbance and one of the most frequent issues during primary care visits (1, 5, 8). The prevalence depends on the criteria that are used and the population that is studied. Approximately one third of adults report occasional insomnia symptoms (2, 5, 8-10) and around 6-10% of adults meet the criteria of insomnia disorder and have symptoms of daytime functional impairment (4-6, 9, 11). In most of the cases, it is a chronic complaint (1, 9, 11, 12).

The prevalence of insomnia varies globally and depends on factors such as age, gender, ethnicity and socio-economic status (5, 9). Many studies have found a higher prevalence of insomnia among older people. A possible explanation can be the declining health and/or more institutionalisation (5). Regarding gender, there is a higher prevalence in women, especially with the onset of menses, during perimenopause and in the postmenopausal years (5, 9, 13). There is a higher risk for (secondary) insomnia in many medical disorders, such as cardiopulmonary

diseases, musculoskeletal diseases, Parkinson's disease, stroke and incontinence (5, 12) and especially in psychiatric disorders (14). Some studies associate lower education and income with a higher prevalence of insomnia (5). People who work at night suffer more from insomnia too (15).

All these factors do not independently cause insomnia, but can facilitate it in patients who are predisposed to develop insomnia (2).

1.1.3. Pathophysiology

The complete pathophysiology of insomnia is multifactorial and not yet fully understood. To understand insomnia in an individual, it is important to perform a thorough examination of both biomedical symptoms and causes and psychological causes and behaviours (11). Also medical and psychiatric history and medication and drug use and abuse need to be assessed (11). Furthermore, there are many environmental and genetic factors that can impact sleep in an individual (11).

In insomnia, the body is thought to be in a continuous state of hyperarousal (11, 16). This hyperarousal can be exposed as a state of hypervigilance during the day as well as during the night with difficulties initiating and maintaining sleep (16-18).

There are currently 2 models to explain the hyperarousal in insomnia, the cognitive model and the physiological model (2):

The cognitive model's suggestion is that worrying and fretting about life stresses can cause an acute episode of insomnia with difficulties initiating sleep and returning back to sleep after an awakening (19). Once people have sleep problems, instead of worrying about life stresses, they start worrying about the sleep problems and its consequences during the day from not getting enough sleep and so they end up in a vicious circle (2).

The physiological model suggests that hyperarousal is due to (neuro)physiological factors. Physiological arousal is evaluated measuring for example metabolic rate, heart rate variability and neuroendocrine measures (2). In insomnia patients, the heart rates seem to increase and the heart rate variability seems to decrease in all stages of sleep compared to normal sleepers (20). The neuroendocrine system may also play an important role. The levels of 24-hour urinary free cortisol excretion are higher in insomniacs and have been positively correlated with total wake time (21-23). It seems that plasma measures of cortisol and adrenocorticotropic hormone (ACTH) too are higher in insomnia patients which suggests that the hypothalamic-pituitary-adrenal (HPA) axis may play an important role in the pathology of insomnia (21, 23, 24).

1.2. Insomnia: consequences

Although insomnia seems to be a harmless condition, it has a great impact on the quality of life of patients and it has an important economic burden (4). Insomnia leads to impaired work

performance and higher healthcare resource use (e.g. more emergency room visits, more hospitalisations) (4) which results in increased health care costs (11).

Insomnia has been linked to impaired cognitive function, including difficulties with attention, memory, and executive function (25). This may explain why untreated chronic insomnia patients have much more serious accidents and injuries than people without sleep problems and insomniacs who are treated (26).

Recent studies suppose that insomnia can be an independent risk factor for dementia, but more studies are needed to research if insomnia could be an early symptom of dementia, a risk factor, or both (27, 28).

Furthermore, insomnia is associated with major depression (14, 29). Compared to people without sleep difficulties, non-depressed people with insomnia might have double the risk of getting depression (29). Comorbid psychiatric disorders may be a consequence as well as a risk factor (2).

Additionally, chronic insomnia can have an important impact on the immune system with a higher risk of infections (30) and insomnia is even associated with an increased risk of diabetes type 2 (31) and with a higher risk of developing and/or dying from cardiovascular disease (32, 33).

These associations suggest that insomnia is a new potentially modifiable risk factor that could be targeted to prevent other medical disorders.

1.3. Insomnia: diagnosis and measures

The diagnosis of insomnia is primarily based on the clinical interview. According to the DSM-5 (5, 7), the patient must meet several criteria to be diagnosed with insomnia disorder (see above). Various other tools have been used, but often there is a lack of standardisation (5).

Self-reported tools can help to determinate the nature and severity of insomnia, differentiate from other sleep disorders and monitor the treatment (1). Subjective measures are for example clinical interviews, sleep questionnaires and diaries (3). Sleep questionnaires and sleep diaries have a relatively high accuracy and have a very low cost because they can be self-administered and there is no need for a sleep laboratory (unlike for example polysomnography) (34).

Some examples of subjective assessment tools that are used a lot are the Insomnia Severity Index (ISI), the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS) (34). The ISI is a 7-items questionnaire that evaluates 7 dimensions such as severity of sleep onset, sleep maintenance and interference with daytime functioning during the last month (35). Each item receives a score from 0 (= no problem) to 4 (= severe problem) which makes a total score from 0-28. If a person scores 0-7 there is no insomnia, if a person scores 8-14 there is sub-threshold insomnia, 15-21 means moderate insomnia and a score of 22-28 means severe insomnia (35, 36).

The Pittsburgh Sleep Quality Index (PSQI) is similar in use and consists of seven components too (37). The ESS measures the level of sleepiness during the day. The respondents have to rate their chances of dozing off or falling asleep during eight different activities (38). This means that the ESS does not directly measure sleep parameters such as sleep onset and awakenings.

Objective measures are for example actigraphy (39), neuroimaging (40) and polysomnography (PSG) (3, 41, 42). PSG and actigraphy can be useful in some studies, but are not recommended for the routine evaluation of insomnia (3). Both may be useful for differential diagnosis if other sleep disorders are suspected (e.g. periodic limb movement disorder, sleep-related breathing disorder, etc.) or to evaluate treatment-resistant insomnia (3).

In actigraphic analysis, an accelerometer (wristwatch) is used to measure the degree and intensity of body movements (39). This non-invasive method is improving in quality and can easily be done at home (39).

Neuroimaging can also provide objective information about brain activity during the sleep-wake cycle and can provide interesting data on interactions between insomnia and neurological or psychiatric disorders (40).

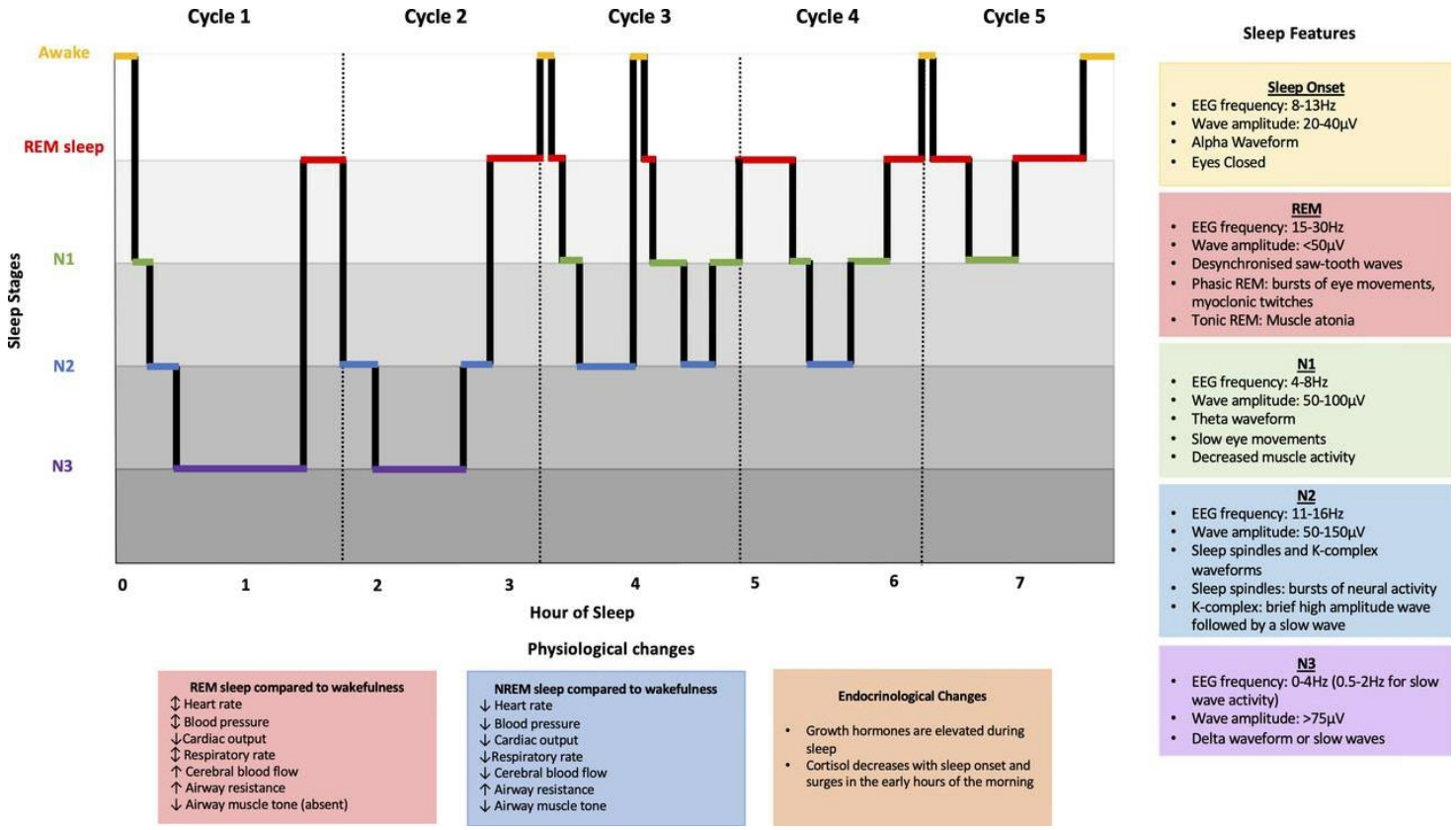
In a PSG, several objective measurements are taken, using an electroencephalogram (EEG), electro-oculogram, electromyogram, electrocardiogram (ECG), and pulse oximetry, as well as airflow and respiratory effort (41). This method is expensive, requires professional assistance and is done most of the time in a sleep clinic or a hospital which is not a normal sleep situation (34). Although PSG is not the first choice and not necessary for the diagnosis of insomnia, it can offer a lot of information.

A meta-analysis of the use of PSG in insomnia showed that insomniac patients have a significant reduction in sleep efficiency, less total sleep time, more nocturnal awakenings and reductions in slow-wave sleep (SWS) and rapid eye movement sleep (REM sleep) (29).

The human sleep consists of 2 types of sleep, rapid eye movement sleep (REM sleep) and non-rapid eye movement sleep (NREM sleep). The NREM sleep is further divided into 3 stages with progressively deeper sleep: N1, N2 and N3 (43).

In total there are 5 sleep stages: wake (stage W), N1 (stage 1), N2 (stage 2), N3 (stage 3) and REM sleep and each stage has different brain wave patterns, muscle tone and eye movements (44). Furthermore, sleep at night normally consists of 4 to 5 sleep cycles on average. Figure 1 shows a sleep hypnogram taken from Bailey et al. (43).

Figure 1



Note. Sleep hypnogram. From "Sleep disturbance in movement disorders: insights, treatments and challenges" by Bailey GA, Hubbard EK, Fasano A, et al., 2021, *Journal of Neurology, Neurosurgery & Psychiatry* 2021;92:723-736.

A typical sleep cycle consists of different sleep stages, usually in the following order: N1, N2, N3, N2, REM sleep (45). Each sleep cycle takes 90-120 minutes (43, 46). About 75% of sleep time is spent in the NREM stages (47). N1 means light sleep, N2 deeper sleep and N3 the deepest sleep or slow wave sleep (SWS) (delta waves) (44). In the beginning of the night there is more NREM sleep than at the end of the night and the exact opposite is true for REM sleep with longer periods as the night progresses (44).

The function of the different sleep stages is not yet well understood, especially for REM sleep (48, 49), however the effects of poor sleep are well documented including reduced memory and cognitive function (50).

NREM sleep consists of N1, N2 and N3 sleep. Numerous studies suggest that K-complexes and sleep spindles that are seen using EEG recording during N2 sleep play an important role in memory consolidation (51, 52). N3 sleep is the deepest and most restorative sleep and the stage during which the body repairs and regrows tissues, bones and muscles are built and the immune system is strengthened (44, 53). Sleepwalking occurs during this stage (53).

Nevertheless REM sleep is supposed to play an important role in multiple functions too such as the replay of activities during the day, modulation of the neural activity, synaptic function, memory processing, developmental functions and psychological functions (49). REM sleep is associated with dreaming (49).

1.4. Insomnia: current treatment

Guidelines for treatment that are frequently used by Belgian clinicians are for example “Aanpak van slaapklachten en insomnie bij volwassenen in de eerste lijn” (54), which was drafted by “Werkgroep Ontwikkeling Richtlijnen Eerste Lijn” (WOREL) and “Domus Medica” and the guideline “Slaapproblemen” (55) of “Nederlands Huisartsen Genootschap” (NHG). A guideline that is frequently used worldwide is the “Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults” (56) of the “American Academy of Sleep Medicine” (AASM).

These guidelines all recommend non-pharmacological interventions as first-line treatment for insomnia disorder in adults. Furthermore, the guidelines advise general practitioners to thoroughly investigate the underlying causes of sleep problems and educate patients about sleep hygiene and behavioural interventions and possibly collaborate with primary care psychologists or refer patients to sleep courses. This approach is designed to reduce the use of sleep medication and address the underlying problems of insomnia. The most prominent non-pharmacological treatment is cognitive behavioural therapy for insomnia (CBT-I) (1, 3, 57). CBT-I is efficacious for improving insomnia symptoms. Even in insomnia with comorbidities, CBT-I can have positive effects, especially in psychiatric conditions (57). CBT-I can be done in-person as well as digitally (eCBT-I) (1). The goal is to change behavioural and psychological factors such as unhelpful beliefs about sleep and excessive worries (1). CBT-I can comprise different treatments such as psychoeducation, sleep hygiene, relaxation therapy, sleep-restriction therapy and stimulus control therapy (3).

Where non-pharmacological treatments are not sufficient or not available, sleep medications are recommended only for severe short-term insomnia or a flare-up of chronic insomnia with high suffering (54). Drug treatment can be offered in monotherapy or combined with CBT-I within the context of shared decision making (1, 3). It is important to know that sleep medications, unlike CBT-I, do not contribute to behavioural change and therefore do not provide a lasting solution for insomnia (55). Benzodiazepines and benzodiazepine receptor agonists (Z-drugs), are most studied and are effective for the acute treatment of insomnia (less than 4 weeks) (3, 58). Some meta-analyses suggest positive effects of Z-drug eszopiclone up to 6 months in certain cases (59, 60), but overall there is few information about long-term effectiveness (3, 58).

Benzodiazepines act on the gamma amino butyric acid (GABA)-A receptor, thereby enhancing the action of the neurotransmitter GABA. This neurotransmitter has an inhibiting effect on the central

nervous system and is known for its sedating, anxiolytic, myorelaxant and anticonvulsant effects (61). Z-drugs on the other hand are more selective and bind primarily to α1 subunits of the GABA-A receptor which are primarily found in the brain and mediate sedation and amnesia (62, 63). Z-products have rather weak anxiolytic, myorelaxant and anticonvulsant effects (63). Benzodiazepines are classified as very short-acting (e.g. midazolam: T1/2 (half-life time) = 1.4-2.4h), mid-long-acting (e.g. lorazepam: T1/2 = 12-16h) and long-acting (e.g. diazepam: T1/2 = 20-80h). The elimination half-life of Z-drugs is generally short (e.g. zolpidem: T1/2 = 2.5h and zopiclone: T1/2 = 5h) (64).

Usually, benzodiazepines with mid-long duration of action (e.g. lormetazepam) or Z-drugs are preferred for insomnia, but at the lowest possible dose and as short as possible (maximum 1 week) (54). It is recommended to talk about a stopping strategy at the beginning of the treatment (54). Benzodiazepines and Z-drugs have important side effects. The most known side-effects are tolerance and dependence, falling during the night, negative effects on cognitive functioning, hangover effects and rebound insomnia after withdrawal (3). Especially in elder patients the physician should prescribe these medications even more restrictively and at the lowest possible dose, because of the negative risk-benefit ratio (54). Unfortunately, many patients often use these drugs for months or even years. “Domus Medica” reported that in 2022 almost 1/5 of the Belgian population used benzodiazepines or Z-drugs for different indications such as insomnia and anxiety (65). They often use higher doses which makes the chances of tolerance, dependence and withdrawal when stopping much higher. Tolerance depends on the type of benzodiazepine and is dose-dependent but usually occurs after only a few weeks. For long-term daily use (>4 weeks), it is therefore recommended to taper off gradually before stopping (66, 67). The dose reduction depends on the case and the drug that is used and varies between 10-25% every 1-4 weeks (66, 68, 69). Non-pharmacological interventions can help this process (70).

A systematic review and meta-analysis of De Crescenzo et al. (58) published in the Lancet in 2022, compared 30 different medications and reported that for the acute treatment of insomnia, benzodiazepines, eszopiclone, zolpidem, zopiclone, lemborexant, doxylamine and seltorexant were more efficacious than placebo in improving subjective sleep quality and total sleep time (SMD range: 0·36–0·83) (58). Eszopiclone (a Z-drug) and lemborexant (an orexin receptor antagonist) showed the best overall results regarding efficacy, acceptability and tolerability, but the safety data were not always conclusive (58).

Orexin (hypocretin) is a neuropeptide that was identified in 1998 and was initially thought to play a role in stimulating appetite, but it is now known to play an important role in the maintenance of wakefulness (71). Orexin receptor antagonists such as lemborexant and daridorexant are newer agents that seem to have good effects on sleep parameters and have mild adverse effects, but more research is needed and they are still unavailable in some countries (3, 72).

Melatonin and melatonin receptor agonists such as ramelteon have a limited place in the treatment of insomnia. There are many different forms and doses and often it can be easily purchased without a prescription (3). Fast-release melatonin and ramelteon are only recommended for insomnia caused by shifting circadian rhythm (e.g. jetlag) (3). Prolonged-release melatonin has only been approved for insomnia in patients older than 55 years (3). Melatonin seems to be less effective than benzodiazepines and Z-drugs, but more long-term studies are needed (58).

Phytotherapeutics are another class of substances that are widely used (3). A popular herbal medicine is valerian (Valeriana officinalis L.). There are small effects in some (low quality) studies, but two recent meta-analyses showed no significant effects and little is known about side effects and interactions with other medications (73, 74).

The evidence concerning antihistaminergic drugs and antipsychotics (such as quetiapine) is insufficient because there are little or no RCTs about insomnia treatment (3).

Sedating antidepressants at lower doses are frequently used in Europe for secondary, but also for primary insomnia, but this use is off-label because of lacking evidence (3). Examples are tricyclic antidepressants (e.g. amitriptyline, doxepin), trazodone and mirtazapine (3). The aim of this systematic review is to summarise the available literature on trazodone and mirtazapine in insomnia.

1.5. Trazodone and mirtazapine in insomnia

Trazodone and mirtazapine are two sedating antidepressants that are used off-label for the treatment of insomnia (3).

Trazodone is a serotonin antagonist and reuptake inhibitor (SARI) that is primarily used as an antidepressant. It has recently been used more frequently off-label as a sleep aid due to its sedating effects (75, 76). The antidepressant action derives from its ability to increase serotonin levels in the brain, caused by inhibiting reuptake of serotonin. Trazodone has a similar effectiveness in comparison to other antidepressants, but trazodone also contradictorily blocks certain serotonin receptors (5-HT2a receptors) which reduces some side effects of purely elevated serotonin and therefore it has less negative effects on an anxiety, sexual function and sleep compared to the classic serotonin reuptake inhibitors (SSRIs) (75, 77). The antidepressant properties of trazodone are believed to be caused by regulating the serotonin neurotransmission, but the full range of its working mechanism has yet to be discovered (75). Trazodone also has inhibiting properties of histamine receptors, particularly H1 receptors, which promotes drowsiness and facilitates sleep onset, causing trazodone to be used as a sleeping aid (75). Additionally, trazodone's alpha-1 adrenergic blocking activity could further contribute to its sedating effects due to the reduction of arousal and promoting relaxation (75). Within 1 hour of oral intake, maximal plasma concentration can be reached (78). Trazodone has a half-life time of 5 to 9 hours and is

primarily excreted renally after being metabolised by CYP3A4 (78-81). Finally, due to trazodone's different pharmacological actions, it has the potential to be effective both as an antidepressant and as a sleep aid (75).

Mirtazapine is a tetracyclic antidepressant that is in the first place prescribed for the treatment of depression. More recently it is frequently used off-label for insomnia because of its sedative characteristics (82, 83). The antidepressant action stems from its ability to inhibit alpha-2 adrenergic receptors, which leads to an increased release of norepinephrine and serotonin (83). The sedative effects of mirtazapine are attributed to the antagonism of histamine H1 receptors, resulting in drowsiness and promoting sleep onset (82, 83). Mirtazapine does not affect the reuptake of serotonin or other neurotransmitters (83-85). When taken orally, maximal plasma concentrations are reached after 2 hours (83, 86). Mirtazapine has a half-life time of 20 to 40 hours and is primarily excreted renally and faecally after being metabolised by CYP1A2, CYP2D6 and CYP3A4 (83, 86). Overall, the various pharmacological actions of mirtazapine could play a role in treating both depression and insomnia.

1.6. Aim and objectives

Considering the high prevalence and the extensive consequences insomnia has on both the individual patient and society, there is an increasing need for a safe and effective treatment for insomnia. Trazodone and mirtazapine are often used off-label to treat insomnia in clinical practice, because of their sedative (side) effects. Since there is currently a lack of evidence regarding the effectiveness and safety of this off-label use, this review aims to provide an overview of the efficacy and safety of trazodone and mirtazapine in insomnia in adults. Because these drugs are more often used as a seemingly ‘safer’ alternative for other sleeping aids, it is vital that we are sure that the potential risks do not outweigh the possible benefits. The objective of this review is to provide a systematic summary of the existing/available evidence and complement the current guideline for Belgian clinicians.

2. Methods

2.1. Selection criteria

The Population, Intervention/Exposure, Comparison, Outcome, Study type (PICOS/PECOS) acronym was used in the determination of the inclusion and exclusion criteria for this review. A detailed PROSPERO protocol can be found in the appendices (appendix 1).

Types of studies

This review is based on primarily relevant randomised controlled trials (RCTs).
Observational studies, animal studies, in vitro studies, editorials, letters, notes and reviews were excluded.

Types of participants

Studies were included if the interventions were performed on adult humans with insomnia or combined with other co-morbidities. Studies concerning healthy volunteers (without insomnia) will not be taken into consideration. No restriction was made regarding gender, country or ethnicity. Pregnant women were excluded. Studies were patients took other sedative drugs (e.g. benzodiazepines, opioids, marihuana, alcohol…) were excluded, whereas patients taking chronic non sedative drugs were included.

Types of intervention(s) or exposure(s) and comparison

The interventions include patients who will be taking trazodone or mirtazapine, without any limits to dosage, frequency and mode of administration. Studies concerning any duration of intake will be included. Intervention includes the intake of a single drug, as well as the combination of trazodone and/or mirtazapine with any other chronic drug that has no known sedative (side) effect.

Types of outcome measures

Primary outcomes

We will assess the efficacy of trazodone and mirtazapine used as a hypnotic drug. The effects can be patient-reported changes (subjective) in quality of sleep, sleep latency, nocturnal awakenings and duration of sleep using different rating scales. Effects can also be compared objectively by using sleep studies such as polysomnography or EEG.
Further, we will check the safety of using trazodone or mirtazapine for this indication. We define safety as a serious health hazard caused by the intake of trazodone or mirtazapine

(like mortality, falling down at night, toxicity or adverse events that have a permanent impact on the quality of life).

Secondary outcomes

Secondary outcomes are the effects of higher doses on effectiveness and safety, other non-severe side effects such as drowsiness at daytime, the effect of stopping/phasing out the drugs, tolerance. Also the difference in effect between trazodone and mirtazapine on one hand and other hypnotics on the other hand will be examined.

2.2. Search methods

PubMed, EMBASE, Web of Science and Cochrane Library databases were searched. The search queries were comprised of carefully chosen keywords that fully cover the research question. The full search strategies are provided in the appendices (appendix 2-5). Only studies published in English were included. No limitations were applied on the date of publication.

2.3. Data collection

The database research was conducted on 19 September 2023. The results were imported into EndNote and duplicate records were removed. Two authors screened the articles individually based on the titles. Then the abstract of the included studies was examined. Finally, the full text of the residual articles was screened. In the event of disagreement, the opinion of a third person was requested (Ellen Van Leeuwen). A detailed PRISMA flowchart can be found in the appendices (appendix 6).

2.4. Data extraction and risk of bias assessment

Data were extracted using a standard template. The author, year of publication, type of insomnia with or without comorbidity, study design, number of participants, intervention, dosage, comparison, duration of the studies and outcomes relevant to the review question were extracted from each eligible RCT. Summary tables of characteristics, effects and safety can be found in the appendices (appendices 7-12).

Methodological quality of the included randomised controlled trials was assessed using Version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) (87). A summary table of the assessment can be found in appendix 13.

3. Results

3.1. Review selection

The final search in PubMed, Embase, Web of Science and Cochrane Library databases was conducted on the 19th of September 2023. The 3132 results were imported into EndNote and 1480 duplicate records were removed. The selection of the articles was done by two independent reviewers. 1652 titles were screened of which 1042 were excluded. 546 articles were excluded based on the abstract screening. The full text of 64 articles was screened and 34 articles were excluded. Thirty RCTs were included in this systematic review (88-117). Twenty-two studies (88-109) examined trazodone and insomnia, seven studies (110-116) (es)mirtazapine and insomnia and one study (117) examined both trazodone and mirtazapine in insomnia. A PRISMA flow diagram which shows the study selection in detail can be found in appendix 6.

3.2. Trazodone

3.2.1. Characteristics of included studies

Twenty-three RCT's (88-109, 117) examining trazodone in insomnia published between 1994 and 2023 were selected. These studies involved a total of 1045 participants.

Participants had primary insomnia in 13 (89, 93, 95, 96, 98, 100, 102-107, 109) of the 23 studies. In 10 studies (88, 90-92, 94, 97, 99, 101, 108, 117) participants had insomnia with comorbidities, such as Alzheimer's Disease (88, 99), Parkinson's Disease (90) and depression (91, 92, 94, 97, 101, 117). Six trials (91, 94, 97, 98, 100, 101) were crossover RCTs. Ten trials were placebo-controlled (88, 91, 94, 97, 98, 100-102, 107, 108).

The dose of trazodone ranged from 25 to 200 mg, twelve studies (88, 90, 91, 93, 94, 98, 100-102, 107-109) used fixed doses. The most used dosages were 50 and 100 mg. Seven studies reported non fixed (89, 96, 97, 99, 106, 117) or progressive doses (95), whilst 4 studies did not mention the dosage (92, 103-105). The duration of the studies varied from 1 night to 9 months.

Eight studies (89, 90, 92, 93, 96, 97, 107, 117) examined the effect of trazodone on subjective outcomes. The most reported subjective outcomes were the Pittsburgh Sleep Quality Index (PSQI) (90, 92, 94, 97, 102, 108, 117), the Insomnia Severity Index (ISI) (93, 95, 96, 103, 105, 106, 109), the Hamilton Depression Rating Scale (HAM-D) (89, 91, 108, 117) and the Epworth Sleepiness scale (ESS) (90, 92, 108, 109).

Most of the included studies reported objective outcomes as well as subjective outcomes (91, 94, 95, 98-103, 105, 106, 108, 109), 2 studies reported only subjective data (92, 96) and 2 studies reported objective outcomes exclusively (88, 104). Most of the time polysomnography (PSG) was used to obtain objective results (91, 94, 98, 100, 101, 108, 109). Most reported outcomes were total sleep time (TST), sleep latency (SL), sleep efficiency (SE) and slow wave sleep (SWS).

Camargos et al. (88) and Vgontzas et al. (2018) (104) used actigraphy to measure their outcomes. Some studies examined possible daytime impairments, such as cognitive function (88, 100, 101, 108).

Eight studies (92, 95, 96, 103-106, 109) compared trazodone treatment with (cognitive) behavioural therapy or examined the combination of the two.

A summary of the characteristics can be found in appendix 7 and a summary of the efficacy and safety of trazodone can be found in appendices 9 and 11.

3.2.2. Efficacy

Participants had primary insomnia in 13 (89, 93, 95, 96, 98, 100, 102-107, 109) of the 23 studies.

Eraslan et al. (89) compared a dose of 50-100mg of trazodone with 3.75-7.5mg zopiclone for 4 weeks in 50 post-menopausal women. In this RCT there was a significant reduction of the sleep items scores of the Hamilton Depression Rating Scale with both drugs ($p<0.01$). The effect of both drugs was similar ($p=0.79$), but zopiclone was slightly superior.

Janjic et al. (93) compared trazodone 50mg (n=52) and zolpidem 10mg (n=53) in a 2-week RCT in perimenopausal women with insomnia. After 1 week of treatment there was no statistically significant difference in ISI scores between the two groups. After 2 weeks, patients in the trazodone group reported significantly lower ISI scores compared to the zolpidem group.

Li et al. (95) studied patients with chronic primary insomnia and focused on the high- and slow-frequency EEG activity during NREM sleep. They examined delta (0.39-3.91 Hz), theta (4.30-7.81 Hz), alpha (8.20-11.72 Hz), sigma (12.11-14.84 Hz), beta (15.23-35.16 Hz) and gamma (35.55-49.61) relative power during NREM sleep. Some studies indicate that insomnia is a disorder of hyperarousal (16, 18) and some studies found that there is high-frequency EEG activity in insomnia (i.e., beta and gamma power) during NREM sleep (118).

Eleven participants with chronic insomnia received cognitive behavioural therapy for insomnia (CBTI) and 8 patients received trazodone for 9 months. They started with 50mg, but two participants increased to 100mg and three to 75mg.

Trazodone significantly decreased sigma and beta power during NREM sleep after 3 months, but not after 9 months; CBT-I however could not show a significant effect. There was a significant improvement in ISI with trazodone and CBT-I. The association between changes in the ISI and EEG was not significant.

Morin et al. (96) did a multiple-assignment single-blinded randomised trial where insomniac patients received in a first stage either behavioural therapy (BT) (n=104) or zolpidem (n=107) for 6 weeks. Afterwards the non-remitters in the BT group received zolpidem or cognitive therapy (CT) and the non-remitters in the zolpidem group received BT or trazodone. First stage treatment with

BT or zolpidem showed equivalent outcomes. Second stage treatment produced significant increases in responders in the groups that started with BT, but no significant change in the groups that started with zolpidem treatment. The 54 patients who did not remit with zolpidem received BT (n=27) or trazodone (50-150mg) (n=27). Twenty-one patients completed treatment in the BT group and 15 patients completed the treatment in the trazodone group. There was no significant change in response rates for the zolpidem+BT condition (52.9%-47.9%; p=0.59) nor for the zolpidem+trazodone condition (46.4%-55.7%; p=0.44). There was a significant increase in remitters in the zolpidem+BT condition (38.1% to 55.9%; OR 2.06; 95% CI, 1.04-4,11) and a non-significant increase in the zolpidem+trazodone condition (31.4% to 49.4%; OR, 2.13; 95% CI, 0.91-5.00). There were no significant overall differences in cumulative remission rates between groups.

Paterson et al. (98) performed a crossover double-blind randomised placebo-controlled polysomnographic study. Twelve primary insomniac subjects received placebo or trazodone 100mg in a crossover design for one week. Trazodone increased total sleep time by 38 minutes (trazodone: 433±19 min, placebo: 395±15 min, $p<0.05$). SWS increased due to an increase in stage 3 sleep (trazodone: 129±20 min, placebo: 96±10 min, $p<0.05$) and wake after sleep onset (WASO) decreased significantly (trazodone: 57±20 min, placebo: 77±13 min, $p<0.05$). Trazodone also significantly reduced the number of awakenings, but compared to placebo did not alter sleep efficiency, sleep onset or REM sleep. Subjective sleep parameters significantly improved: there was a significant improvement in the experience of ‘getting to sleep’ and ‘quality of sleep’ in the Leeds Sleep Evaluation Questionnaire (LSEQ) and ‘sleep satisfaction’ and ‘sleep quality’ scores obtained in the St Mary’s Hospital Sleep Questionnaire (SMHSQ) increased.

Roth et al. (100) did a randomised double-blind placebo-controlled crossover study with 16 participants with primary insomnia receiving trazodone 50mg or placebo during one week. PSG results showed a significant reduction in total awakenings, sleep in stage 1 and self-reports of difficulty sleeping. On day 7, but not on day 1, there was significantly more SWS with trazodone. There was no significant effect on sleep latency, REM sleep or sleep efficiency. Roth et al. specifically examined daytime impairments of trazodone use. It caused small but significant impairments of short-term memory, verbal learning, arm and muscle endurance and equilibrium. There were no significant main effects on driving errors or speeding.

Shell et al. (102) found a subjective improvement in sleep quality quantified by PSQI, but this was not significant. Thirty-six insomniac participants took trazodone 50mg in a placebo (n=25) controlled RCT. There was a mild improvement in depression, but no significant effect on subjective sleep latency, duration or quality of sleep.

Vgontzas et al. did 2 pilot RCT's (2015 and 2016) (103, 105) in 10 middle-aged men and women with insomnia. Five subjects received trazodone (the given dosage was not reported) and 5 participants CBT-I for 3 months. ISI improved largely either with trazodone or with CBT-I. Trazodone decreased mean arterial pressure (MAP) and morning CRP levels, primarily in insomniacs with PSG-measured short sleep duration (MAP= -4.0mmHg and CRP=-1.1ng/ml), while CBT-I did not (MAP=+0.4mmHg and CRP=+0.3ng/ml) (103). There was a moderate improvement in morning cortisol levels in both groups. In the trazodone group, the evening cortisol levels improved largely (-8.2 ± 10.8 ng/ml), but not in the CBT-I group (+1.7 ± 3.5 ng/ml) (105).
In another pilot trial of 2018, the same research group (104) reported that after 3 months there was no significant effect on TST (measured with actigraphy) or cortisol levels in the overall sample (n=20), but when focusing on those with short sleep duration (<7h), there was a large increase in objective TST with trazodone (+59.85 min) and a small decrease with CBT-I (-6.08 min). Trazodone was associated with a clinically meaningful impact on decreasing cortisol levels (-3.23 ± 4.11 ng/ml) in contrast to CBT-I (-0.51 ± 2.48 ng/ml) and there was a significant correlation between the decrease in cortisol levels and the increase in TST (p=0.036) in those with short sleep duration (104).
Another study of Vgontzas et al. published in 2020 (106) focusing on short sleep duration reported similar results after 3 months. After 6 months TST (measured with actigraphy) was still increased with trazodone compared to CBT-I (+50.35 min vs. -7.56 min; P=0.012) and cortisol levels were decreased (-21.37% vs. -5.79%) (106).

Walsh et al. (107) compared trazodone 50mg (n=90) with zolpidem 10mg (n=91) and placebo (n=97) in a double-blind RCT for 2 weeks in patients with primary insomnia. Self-reported sleep latency was significantly shorter with both drugs after 1 week. Self-reported sleep duration was significantly longer. After 2 weeks, only the zolpidem group maintained a significantly shorter sleep latency. The sleep duration was similar in all groups after 2 weeks.

Zavesicka et al. (109) compared CBT with CBT+100 mg trazodone in an 8-week RCT in chronic primary insomnia patients. Each group counted 10 participants. Both groups reported significant subjective sleep improvements, SL measured with PSG was significantly shorter (p=0.03) and SE significantly increased (p=0.004). Based on subjective parameters and sleep continuity measures (TST, SL, WASO, SE), the combined treatment was not significantly better than CBT alone. However there was a significant increase in duration of SWS in the CBT+trazodone group which was not observed in the CBT group.

In 10 studies (88, 90-92, 94, 97, 99, 101, 108, 117) participants had insomnia with comorbidities, such as Alzheimer's Disease (88, 99), Parkinson's Disease (90) and depression (91, 92, 94, 97, 101, 117).

In the randomised, double-blind and placebo-controlled trial of Camargos et al. (88) 15 Alzheimer patients with insomnia received 50mg of trazodone for 2 weeks and 15 patients received placebo. Trazodone users slept 42.5 minutes more per night and the nighttime sleep percent increased by 8.5% according to actigraphic data. There was no significant effect on the amount of time spent awake after sleep onset or amount of awakenings. Trazodone and placebo did not significantly induce daytime sleepiness or naps and did not show any effects on cognition or functionality.

Hadi et al. (90) examined the effect of trazodone 50mg, melatonin 3mg and clonazepam 1mg in a double-blind RCT for 4 weeks. Each treatment arm contained 31 patients with Parkinson's disease and sleep disorders. Pittsburgh Sleep Quality Index (PSQI) scores decreased significantly in all groups and the changes from baseline were similar among the three treatment groups. As secondary outcomes REM Sleep Behaviour Disorder Screening Questionnaire (RBDSQ) and ESS decreased significantly after 4 weeks in all groups. In the melatonin group there was a significantly higher decrease in RBDSQ score compared to trazodone ($p=0.011$) and clonazepam ($p=0.004$). However, regarding the ESS score, there was a significantly higher decrease in the trazodone group compared to the clonazepam group ($p=0.010$). Between the other groups, there were no significant differences.

Haffmans et al. (91) did a double-blind placebo-controlled study with a crossover design. Seven patients with insomnia induced by a monoamine oxidase inhibitor (MAO-I) received 1 week placebo and 1 week trazodone 50mg or vice versa. The subjective sleep quality scale (SQS) improved in all subjects after the trazodone week and this persisted during the placebo period. In the group that received placebo first, trazodone significantly decreased the number of awakenings ($p=0.021$) and the number of shifts ($p=0.044$). In the group that received trazodone first, the number of shifts and stage 2 sleep decreased significantly, but returned to baseline values during placebo. SWS increased in both groups after trazodone treatment, but this increase was only significant in the group receiving trazodone first ($p=0.02$ vs $p=0.13$).

He et al. (92) did a 4-week RCT and compared cognitive behavioural therapy for insomnia (CBTI) (n=30), trazodone (n=30) and CBTI+trazodone (n=30) in elderly patients with insomnia and depression for 4 weeks. The given dosage was not mentioned. The PSQI and ESS of the three groups were significantly lower than before treatment. The scores were significantly lower in the combined group than in the other groups and the scores were significantly lower in the trazodone group than in the CBTI group. In all groups, sleep latency was significantly shorter after 4 weeks and total sleep time was significantly longer. Sleep latency was significantly shorter in the trazodone than in the CBTI group and the TST was significantly longer. Sleep efficiency was significantly better in the trazodone and the combination group than before treatment.

Ilinoiu et al. (117) conducted a randomised controlled trial (RCT) where 32 older patients with depression (according to the DSM-IV criteria) treated with SSRIs were divided into three groups: one group of 10 patients had to take mirtazapine at a dose of 15-30mg/day, another group of 12 patients was assigned to take trazodone 50-100mg/day and the last group of 10 patients had to take pregabalin at a dosage of 75-150 mg/day. The mean dosage was 22.5mg/day of mirtazapine, 67mg/day of trazodone and 112.5mg/day of pregabalin during the 24-week study. All three treatments improved the HAM-D scores (mirtazapine -19%, trazodone – 17.6% and pregabalin – 16.5%) and PSQI score (mirtazapine -30.2%, trazodone – 38.7% and pregabalin – 31.2%) compared to baseline without significant differences between the groups.

Kaynak et al. (94) did a double-blind placebo-controlled study in twelve female depressed insomnia patients treated with SSRIs. In a crossover design they were given either 100mg trazodone or placebo for 7 days with a 7-day washout period in between. Polysomnographic (PSG) recordings were done during baseline night, during the first night receiving trazodone or placebo and during the last night. Regarding subjective outcomes, at the start of the study the mean score of the PSQI was 15 ± 2.5. After 3 weeks there was a similar and significant improvement in subjective sleep in both groups, even though 1 group had just received placebo for 15 days. The mean score of the PSQI was reduced to 5 ± 1.6 ($p<0.005$).
Regarding objective outcomes, trazodone significantly increased TST, SWS, SEI (sleep efficiency index) and SCI (sleep continuity index) and significantly decreased the percentage of stage 1, number of awakenings and number of stage shifts both after the first night and after the last night. The increase in SWS was more significant in the last treatment night. There was no significant effect on sleep latency, REM sleep, REM latency and duration of the sleep cycle. Placebo had no significant improving effect on PSG sleep parameters.

Nierenberg et al. (97) examined 17 patients with insomnia taking fluoxetine or bupropion for depression. In a double-blind crossover placebo-controlled RCT, the study population received trazodone during approximately one week. In patients taking 50-100mg of trazodone, 67% (95% CI: 43-91%) experienced overall improvement in sleep as compared to 13% (95% CI: 4-30%) in the placebo group. The total PSQI scores, sleep duration and early morning awakenings were significantly improved with trazodone. There was no significant difference in sleep efficiency and there was a trend towards improvement in sleep latency, but it was not significant.

Petrescu et al. (99) compared the effectiveness of trazodone and quetiapine in Alzheimer patients with insomnia in a randomised open label controlled trial. The duration of the study was not found. The first group was treated with trazodone 50-200 mg (n=23) and the second group with quetiapine 50-300 mg (n=20). Mean TST hours were longer in the trazodone group versus the quetiapine group (patients' subjective reports: 7.82 vs 7.22; $p<0.01$) (nursing sleep logs: 8.42 vs

8.01; p=0.04). The sleep efficiency (SE) according to the nursing log report was more or less the same (trazodone 0.89 vs quetiapine 0.85).

Saletu-Zyhlarz et al. (101) did a single-blind crossover placebo-controlled study in 11 insomniac depressive patients and compared the results with 11 healthy controls. Baseline PSG in insomniac patients, compared to healthy controls, showed significantly lower sleep efficiency (SE) (77% vs 92%), longer sleep latency to S1,S2 and S3, a higher number of awakenings and shorter TST and total sleep period (including awakenings) (TSP). Acute treatment with trazodone 100mg, compared to placebo significantly increased SE in insomniac patients (from 77% to 84%), TST, TSP, and SWS, but not sleep latency. There was a subjective improvement in sleep quality, affectivity, numerical memory and somatic complaints. Morning diastolic blood pressure had significantly decreased too after trazodone use.

In a randomised double-blind placebo-controlled pilot study, Wang et al. (108) explored the effect of trazodone 50mg on sleep quality (PSG and PSQI) and cognitive function (MoCA screening) in patients suffering from arteriosclerotic cerebral small vessel disease and insomnia. Twenty patients received trazodone and twenty placebo for 4 weeks. Trazodone treatment resulted in a significantly greater improvement in concentration and recall abilities in comparison to the placebo group ($p<0.05$). The PSG results showed a significant increase in SE and S3 sleep ratio and a significant decrease in wake time after sleep onset (WASO), S1 sleep ratio and arousal index ($p<0.05$). Finally trazodone caused greater improvements than placebo in PSQI, ESS and the Hamilton Anxiety Scale (HAMA) ($p<0.05$). The improved concentration and recall abilities were positively related to the improvement of PSQI, ESS, HAMA, S3 ratio, WASO and SE.

3.2.3. Safety

Information about the safety of trazodone was reported or assessed in 13 of the 23 studies (89-91, 93, 94, 97, 99-102, 107, 108, 117).

None of the reported or observed adverse reactions were rated as severe by the researchers, however in the study of Nierenberg et al. (97) one patient dropped out of the study because of excessive daytime sedation after one night of trazodone 50mg. Most reported side effects were daytime sedation/somnolence in the morning (89, 93, 94, 97, 102, 107), dizziness/vertigo (89-91, 93, 99, 108) headache (93, 107, 108) and gastro-intestinal side effects, like nausea or constipation (91, 93, 99, 108).

Other less reported side effects were orthostatic hypotension (90), dry mouth (91), mild and transient acid indigestion (94), moderate heartburn (91), prolonged erection (no priapism) (97) and loss of appetite (108).

Walsh et al. (107) reported that 5 patients of 100 discontinued the study because of side effects. The most reported adverse events were headache and somnolence with incidence rates of 30% and 23% respectively. In the study of Wang et al. (108) of the 20 participants receiving trazodone 50mg, 1 withdrew due to insomnia deterioration and 1 due to nausea. Other reported side effects were akathisia (psychomotor restlessness, an inability to remain still), loss of appetite, dizziness and headache. These side effects were reported in the placebo group too and there was no significant difference in occurrence of side effects between the two groups. No serious abnormal laboratory results were reported. Camargos et al. (88) too found no difference in frequency of adverse events between the trazodone and placebo group.

Janjic et al. (93) compared trazodone and zolpidem. After 1 week of treatment most reported side effects in the trazodone group were somnolence (25% of patients), dizziness (22%), nausea and hypotension (both 19%). After 2 weeks most reported side effects were headache (19%), nausea (12%) and somnolence (6%). In the zolpidem group the most reported side effects after 1 week were nausea (18%) and irritability (12%) and after 2 weeks the most reported side effect was dizziness (9%).

Petrescu et al. (99) compared trazodone with quetiapine. There were more gastro-intestinal patient-reported side effects in the trazodone group. There was no significant difference in risk of falls.

Ilinoiu et al. (117) reported more residual sleepiness in the morning with trazodone (8/12 participants) compared with pregabalin (5/10 participants) and mirtazapine (3/10 participants). Participants received a mean dose of 67mg/day of trazodone for 24 weeks. Regarding discontinuation of treatment, 3 patients did not finish the study in the pregabalin group and one from each of the other groups did not finish the study due to mild and moderate side effects.

As already mentioned above, Roth et al. (100) specifically examined daytime impairments of trazodone use. It caused small but significant impairments of short-term memory, verbal learning, arm and muscle endurance and equilibrium. There were no significant effects on driving errors or speeding.
However in the study of Camargos et al. (88) trazodone and placebo did not show any effects on cognition or functionality.
Saletu-Zyhlarz et al. (101) reported a mild, but significant improvement in numerical memory. Wang et al. (108) reported a significant greater improvement in concentration and recall abilities in the trazodone group than in the placebo group ($p<0.05$).

3.3. Mirtazapine

3.3.1. Characteristics of included studies

Eight RCT's (110-117) examining (es)mirtazapine in insomnia, published between 1999 and 2020, were selected. These studies involved a total of 1524 participants.

Participants had primary insomnia in 3 (110-112) of the 8 studies. In 5 studies (113-117) participants had insomnia with comorbidities, such as Alzheimer's Disease (114), and depression (113, 115-117). Four trials were placebo-controlled (110-112, 114), 6 trials were double-blinded (110-115).

The dose of mirtazapine ranged from 15mg to 45mg, esmirtazapine maleate (the maleic salt of mirtazapine) was used in 3 studies (110-112) and the dosage ranged from 1.5mg to 4.5mg. Five studies used fixed doses (110-112, 114, 116), 3 studies reported non fixed or progressive doses (113, 115, 117). The duration of the studies varied from 2 weeks to 6 months.

Four studies (110, 111, 113, 117) reported only subjective outcomes, one study only objective outcomes (114) and 3 studies (112, 115, 116) reported both subjective and objective data. The most reported subjective outcomes were the Hamilton Depression Rating Scale (HAM-D) (115-117) and the Pittsburgh Sleep Quality Index (PSQI) (116, 117). One study used the Leeds Sleep Evaluation Questionnaire (LSEQ) (113) and a few studies (110, 111) used self-reported total sleep time (TST), sleep latency (SL), number of awakenings (NA) and wake time after sleep onset (WASO). Most of the time polysomnography was used to obtain objective results (112, 115, 116) and one study used actigraphy to obtain the results (114). Most reported outcomes were total sleep time (TST), sleep latency (SL), sleep efficiency (SE) and the different sleep stages.

A summary of the characteristics can be found in appendix 8 and a summary of the efficacy and safety of mirtazapine can be found in appendices 10 and 12.

3.3.2. Efficacy

In 3 of the 8 studies, participants had primary insomnia (110-112), however these studies examined esmirtazapine (this will be explained and discussed later). There were no trials found that studied mirtazapine itself. In the remaining 5 studies participants had insomnia with comorbidities, such as Alzheimer's Disease (114) and depression (113, 115-117).

Ilinoiu et al. (117) conducted a randomised controlled trial (RCT) where 32 elderly depressed patients (according to the DSM-IV criteria) treated with SSRIs were divided into three groups: one group of 10 patients had to take mirtazapine at a dose of 15-30mg/day, another group of 12 patients was assigned to take trazodone 50-100mg/day and the last group of 10 patients had to take pregabalin at a dosage of 75-150 mg/day. The mean dosage was 22.5mg/day of mirtazapine, 67mg/day of trazodone and 112.5mg/day of pregabalin during the 24 weeks during study. All three

treatments improved the HAM-D scores (mirtazapine -19%, trazodone – 17.6% and pregabalin – 16.5%) and PSQI score (mirtazapine -30.2%, trazodone – 38.7% and pregabalin – 31.2%) compared to baseline without significant differences between the groups.

Leinonen et al. (113) conducted a double-blinded RCT where 240 patients with a major depressive episode (according to the DSM-IV criteria) were divided into two groups: one group of 136 patients had to take mirtazapine at a dose of 15-60 mg/day, the other group of 133 patients was assigned to take citalopram 20-60mg/day, both following a dosing schedule. The mean dosage was 35.9mg/day of mirtazapine and 36,6mg/day of citalopram in the 8-week study. Mirtazapine and citalopram were both effective in improving getting to sleep, awakening following sleep and quality of sleep along the self-rating Leeds Sleep Evaluation Questionnaire-adapted (LSEQ) in comparison to baseline. There was however no significant difference between the two treatments.

Scoralick et al. (114) conducted a double-blinded, placebo-controlled pilot RCT with actigraphy where 24 patients with Alzheimer's Disease, who were 60 years or older and were community-dwelling at night time, had to take either placebo (n = 16) or 15mg of mirtazapine (n = 8) during 14 consecutive nights. The use of mirtazapine showed no significant effects on the different parameters measured: TST, WASO and number of awakenings in comparison to placebo.

Winokur et al. (115) conducted a double-blinded, randomised controlled study with PSG where 22 patients with major depressive disorder were divided into two groups: 9 patients had to take mirtazapine 15mg/day for the initial 3 days of the study, followed by 30mg/day through the end of week 2 and then upscaling to 45 mg/day for the remaining period of the 8-week study; another 13 patients were assigned to take fluoxetine 20mg/day for the first 4 weeks, followed by 40mg/day for the remaining 4 weeks. Patients assigned in the mirtazapine group had significant improvements of both the HAM-D scores (from 25.6 to 7.1 ; $p<0,05$) and the 3-item sleep scores (from 4.8 to 1.3 ; $p<0,05$) in comparison to baseline. There was also a significant improvement in sleep latency (-23 min; $p=0.0015$), total sleep time (+100min; $p = 0.044$), sleep efficiency (+13% ; $p = 0.0004$) and WASO (-42min; $p = 0.0008$) in comparison to baseline. There was no significant change observed in individual sleep stages or REM latency in comparison to baseline.
Patients assigned in the fluoxetine group had significant improvements of both the HAM-D scores (from 26.7 to 12.2 ; $p<0,05$) and the 3-item sleep scores (from 5.2 to 2.9 ; $p<0.05$) in comparison to baseline. There was no significant improvement of sleep latency (+4 min), total sleep time (+8min), sleep efficiency (-2%) or WASO (+10min) in comparison to baseline. There was a significant change observed in individual stage 1 sleep time (+29min) and REM latency ($p = 0.033$) in comparison to baseline.
In comparison to fluoxetine, there was a significant difference in favour of mirtazapine for the following parameters: sleep latency and total sleep time (both $p<0.05$).

Zhang et al. (116) conducted a randomised controlled study with PSG where 51 patients with depressive disorder were divided into two groups: one group had to take paroxetine 75mg/day (n=29) and the second group had to take mirtazapine 30mg/day (n=22) during 6 weeks. The scores of the HAM-D, PSQI and HAM-D sleep factors were reduced significantly in both groups compared to baseline ($p<0.05$). There was, however, no significant difference between the two groups. After the results of the questionnaires were analysed, the PSG of the treatment responders (HAM-D score reduction of >50%) was analysed in depth. The responders of the paroxetine group (n=22) had significantly lower sleep efficiency (-10%), more awakenings (+7), higher stage 1 sleep percentage, higher delta sleep ratio, lower first sleep cycle REM sleep time percentage, higher REM sleep latency, lower REM activity, intensity and density ($p<0.05$). The good responders of the mirtazapine group (n=16) had lower sleep latency (-1min), lower awakenings (-11), higher delta sleep ratio and a spectacularly higher total sleep time (+268min) compared to baseline ($p<0,05$). These results are further analysed in the discussion.

3.3.2.1. Esmirtazapine

Esmirtazapine maleate is the maleic salt of mirtazapine and it has a shorter half-life (10h) (110-112) in comparison to mirtazapine (20-40h) (83, 86). The research group of Ivgy-May et al. (110-112) used this compound to conduct three studies on its effect and safety used for treating primary insomnia. They used this compound because it was thought that esmirtazapine could have fewer sedative properties because of its shorter half-life (110-112).

Their first study (111) was a 2-week, double-blinded, placebo-controlled RCT where 525 patients with primary insomnia were divided into 4 groups: placebo, esmirtazapine 1.5mg daily, esmirtazapine 3.0 mg daily and esmirtazapine 4.5mg daily. The TST increased by 30-40 minutes in all three esmirtazapine groups compared to placebo ($p<0.0001$). The SL decreased by approximately 12 minutes in all three esmirtazapine groups ($p<0.001$). The dose of 4.5mg was associated with a significant reduction in WASO (-19 min; $p<0.01$). The examined outcomes (TST, SL, WASO, number of awakenings, quality of sleep, satisfaction with sleep duration and ISI) were all changed in favour of treatment in comparison to placebo. Although the more objective parameters differed the most for the 4.5mg group, the subjective quality of sleep and satisfaction of sleep were in favour of the 1.5mg group.

The same authors conducted another study (112) with a nearly identical method: the study was a 6-week, double-blinded, placebo-controlled RCT where 413 patients with primary insomnia were divided into 3 groups: placebo, esmirtazapine 3.0 mg daily and esmirtazapine 4.5mg daily. In this study PSG too was used to assess possible effects and outcomes. There was a significant improvement in the WASO in both groups compared to placebo with a decrease of 17-20 minutes ($p<0.0001$) comparable to the previous study. There was also a statistically significant

improvement in SL ($p<0.006$), TST with an increase of 32-45 minutes ($p<0.0001$), the number of awakenings (decrease of 0.3-0.1 times awake) ($p= 0.03$), total time in SWS ($p < 0.05$) and stage 2 sleep ($p<0.0001$). There was no significant difference for stage 1 sleep, total REM time or REM latency compared to placebo. The same conclusion can be drawn in this study as well: the more objective parameters differed the most for the 4.5mg group in comparison to placebo.

Another study was conducted again by the same research group (110). The study was a 6-month, double-blinded, placebo-controlled RCT where 342 patients with primary insomnia took 4.5mg of esmirtazapine daily and 115 patients were assigned to the placebo group. There was an improvement in almost all observed parameters in favour of the esmirtazapine group: the TST improved by 49 minutes ($p<0.0001$) and this improvement was already seen after 1 week of treatment. The SL improved by 5 minutes ($p=0.2145$) and the WASO was improved by 25 minutes. 41% of the treated patients were considered ISI responders versus 18% in the placebo group. The findings of this study surpasses those of the past studies with the same dosage.

3.3.3. Safety

The safety of mirtazapine was reported or assessed in 6 of the 8 studies (110-112, 114, 117). There were a few serious side effects that occurred during the studies.

One patient treated with mirtazapine in the study of Scoralick et al. (114) discontinued the treatment due to excessive sedation after the first dose of mirtazapine.
One patient treated with esmirtazapine in the 6-week during study of Ivgy-May et al. (112) encountered neutropenia, a streptococcal pneumonia and sepsis, was treated with IV antibiotics and recovered. One patient treated with esmirtazapine in the 6-month during study of Ivgy-May et al. (110) had an acute myocardial infarction caused by an acute occlusion of the anterior-descending coronary artery without previously having any symptoms of blood vessel disease.

Apart from these serious adverse effects, there were a number of other adverse effects reported. One of the most common adverse effects was residual somnolence (110-114, 117). When the different studies are compared, it seems that when the given dosage of (es)mirtazapine is higher, the percentage of patients who reported the side effect rises as well. Another striking observation is that this percentage also rises if the duration of the study is longer, although it is claimed that the somnolence is generally resolved after repeated administration. The percentage of patients who reported somnolence in the trials with mirtazapine, seems to be in line with those of esmirtazapine in the highest dosage and the longest study (110-114, 117).

Increased appetite was also a frequently reported side effect (110, 111, 113). Weight gain was reported in 4 studies (110-113). In the 2-week during study of Ivgy-May et al. (111) there was a weight-gain noticeable after 2 weeks of treatment between 0.4kg and 0.8kg. In one subject there

was a weight gain of >7% whilst another subject lost >7% of their body weight (111). After 6 weeks of treatment with esmirtazapine there was a weight-gain of 0.3kg in the 3.0mg group and 0.8kg in the 4.5mg group (112). After 6 months there was a weight gain of 0.9kg compared to placebo in patients who took 4.5mg of esmirtazapine daily (110). When the esmirtazapine studies are compared, it seems that the absolute weight gain on one hand and the percentage of patients who reported this effect on the other hand, is larger in the 6-month during study of Ivgy-May et al. (110) with a longer duration, although they claim that weight gain reached its plateau at 12 weeks. In the study of Leinonen et al. (113) there was also a weight gain reported of +1.9kg on average. Sixteen percent of this population reported weight gain whilst taking mirtazapine.

Other reported side effects for mirtazapine and esmirtazapine in order of frequency were: nasopharyngitis, dizziness, nausea, dry mouth, arthralgia, fatigue upper respiratory tract infection, restless leg syndrome, constipation, hypertension, GGT increase, ALT increase, peripheral edema, sinusitis, abnormal dreams, anxiety, sinus congestion, cough, back pain, insomnia, hypercholesterolemia, diarrhea, increased sweating and gastro-enteritis (110-114).

There were no signs of rebound effect after quitting the treatment and there was no significant difference in residual daytime effects in the trials that studied esmirtazapine (110-112).

3.4. Summary

3.4.1. Trazodone

There were 23 different trials that studied trazodone: participants had primary insomnia in 13 (89, 93, 95, 96, 98, 100, 102-107, 109) of the 23 studies and had secondary insomnia in 10 studies (88, 90-92, 94, 97, 99, 101, 108, 117).

Trazodone improved the TST in primary insomniac patients with 12-60 minutes compared to baseline with a mean of +51 minutes (96, 104, 106, 109). When compared to placebo in primary insomniacs, the gain is less pronounced with +12 and +38 minutes and a mean of +25 minutes (98, 107). The studies that examined the efficacy of trazodone in secondary insomniac patients all compared to placebo and reported an improvement of the TST with 10-45 minutes (88, 94, 101, 108), except for the study of Haffmans et al. (91) where placebo was superior with a difference of 33 minutes, which causes the mean improvement of the TST compared to placebo to be +20 minutes.

Trazodone improved the SL in primary insomniac patients with -12 and -51 minutes compared to baseline with a mean of -31.5 minutes (96, 109). When compared to placebo in primary insomniacs, the gain is less pronounced with -2 and -10 minutes and a mean of -6 minutes (100, 107). The studies that examined the efficacy of trazodone in secondary insomniac patients all

compared to placebo and improved the SL with -3 to -19 minutes (91, 94, 108), which causes the mean improvement of the SL compared to placebo to be -9 minutes.

Trazodone improved the WASO in primary insomniac patients with -12 and -34 minutes compared to baseline with a mean of -23 minutes (96, 109). When compared to placebo in primary insomniacs, the gain is less pronounced with -8 to -21 minutes and a mean of -16 minutes (98, 100, 107). The studies that examined the efficacy of trazodone in secondary insomniac patients all compared to placebo and improved the WASO with -13 to -25 minutes (101, 108), except for the study of Haffmans et al. (91) where placebo was superior with a difference of 15 minutes, which causes the mean improvement of the TST compared to placebo to be -8 minutes.

There is not enough data to compare the effect of trazodone on sleep questionnaires like ISI and PSQI between primary and secondary insomniac patients (ISI numerical results were reported only by studies with primary insomnia and only one study with primary insomnia reported PSQI numerical results, the other results came from studies with secondary insomnia).

When acute and chronic administration are compared (the cut-off at 4 weeks duration was used), similar results seem to be found for both objective and subjective outcomes, although available data to compare specific outcomes was limited. It appears that trazodone has positive effects in acute administration, even when it was given only once (101) and these effects remain present when the compound is taken chronically. But further research is needed to establish this conclusion.

Trazodone was studied in comparison to placebo 10 times (88, 91, 94, 97, 98, 100-102, 107, 108) and furthermore in comparison to zopiclone (89), melatonin and clonazepam (90), CBT-I (92, 95, 96, 103-106, 109), mirtazapine and pregabalin (117), zolpidem (93, 107) and quetiapine (99).

The ten studies that compared trazodone with placebo produced comparable results.
Overall it was seen that trazodone improved the total sleep time in all studies, but the difference in total sleep time compared to placebo showed great variations between the studies (between +12.2 and +45 minutes per night) (88, 91, 94, 98, 101, 107, 108). The studies that used a greater dosage of trazodone had the best results. The sleep latency improved only mildly and also showed big variations (-1.7 to -19 minutes; total SL after treatment was 14 to 54 minutes) (91, 94, 100, 107-109), whilst the wake time after sleep onset improved the most for the highest dose of trazodone with on average -22.5 minutes (98, 101). The highest doses of trazodone showed an increase in the slow wave sleep (98, 101). This suggests that trazodone can improve falling asleep and facilitates sleeping longer through the night and helps patients to fall asleep again faster after waking up during the night. These improvements can already be noticed within the first week(s)

of treatment. Only a few studies examined the effect of trazodone in comparison to placebo on sleep questionnaires and showed on average positive results (94, 97, 98, 102, 108).

A few other interesting conclusions could be drawn from the remaining studies, who compared trazodone to other drugs.
In comparison to CBT-I, trazodone had a superior effect on the PSQI (92) and was superior in improving the self-reported SL and TST (92, 104, 106). The add-on of trazodone to CBT did additionally improve the TST, SL, WASO or SE, but not significantly (109).
In comparison to clonazepam, trazodone had a similar effect on the PSQI but was significantly superior in improving the ESS (90).
In comparison to zolpidem, trazodone had a similar effect on the ISI (93) but was significantly inferior in improving the self-reported SL (107). A combination of the two drugs had no significant additional benefits (96).
In comparison to zopiclone, trazodone had a similar effect on the HAM-D 3-item sleep score (89).
In comparison to quetiapine, trazodone had a better effect on the TST and sleep efficiency (99).
In comparison to mirtazapine, trazodone had a similar, but slightly better effect on the PSQI and was similar, but slightly inferior in improving the HAM-D (117).
In comparison to pregabalin, trazodone had a similar, but slightly superior effect on the PSQI and HAM-D (117).
In comparison to melatonin, trazodone had a similar effect on the PSQI but was significantly inferior in improving the ESS (90).

The safety of this compound was relatively good in the examined studies. Only 13 of the studies (89-91, 93, 94, 97, 99-102, 107, 108, 117) concerning trazodone documented numerous side effects sometimes with the reported percentages. The most common side effects were sedation, dizziness, nausea and headache. Cognitive functions were also analysed in some of the included studies and conflicting results were reported. As already mentioned above, Roth et al. (100) specifically examined daytime impairments of trazodone use. It caused small but significant impairments of short-term memory, verbal learning, arm and muscle endurance and equilibrium. There were no significant effects on driving errors or speeding found in the examined studies. Trazodone and placebo did not show any effects on cognition or functionality in the study of Camargos et al. (88). Saletu-Zyhlarz et al. (101) reported a mild, but significant improvement in numerical memory. Wang et al. (108) reported a significant greater improvement in concentration and recall abilities in the trazodone group than in the placebo group ($p<0.05$).

This systematic review shows that trazodone can improve sleep in patients with insomnia and can be used as add-on therapy if needed. The total sleep time improved in all (but one) studies and the difference in total sleep time compared to placebo showed similar results between the studies (on average 22.5 minutes per night). The sleep latency improved only mildly (minus 6 to 9

minutes), as well as the wake time after sleep onset, which improved with on average minus 11 minutes. This suggests that trazodone can improve falling asleep but significantly facilitates sleeping longer through the night and helps patients fall asleep again faster after waking up during the night. These improvements can already be noticed within the first week(s) of treatment. The few studies comparing trazodone with the current standard of care (CBT and benzodiazepines/Z-drugs) show that the compound has similar results in improving a numerous of subjective and objective sleep parameters. Overall trazodone was well tolerated: no severe adverse effects were reported, the most common side effects were sedation, dizziness, nausea and headache.

3.4.2. Mirtazapine

There were 5 different trials that studied mirtazapine: all participants had secondary insomnia (113-117). The 3 trials studying esmirtazapine (110-112) were all performed in patients with primary insomnia, these results are discussed later.

Mirtazapine improved the TST in secondary insomniac patients with +100 and +268 minutes compared to baseline with a mean of +184 minutes (115, 116). When compared to placebo in secondary insomniacs, the gain is less pronounced with +22 minutes (114).

Mirtazapine improved the SL in secondary insomniac patients with -1 and - 23 minutes compared to baseline with a mean of -12 minutes (115, 116). There was no comparison to placebo.
Mirtazapine improved the WASO in secondary insomniac patients with -32 and -42 minutes compared to baseline with a mean of -37 minutes (115, 116). When compared to placebo in secondary insomniacs, the gain is less pronounced with -6 minutes (114).

There is not enough data to compare the effect of mirtazapine on sleep questionnaires like HAM-D 3-item sleep score (numerical results were reported by only 2 studies comparing to baseline with a mean of -2.7 (115, 116)) and PSQI (one study reported a numerical result (116) and one a percentage (117)).

When acute and chronic administration are compared (the cut-off at 4 weeks duration was used), it seems that the longer mirtazapine is taken, the better the effect, although this conclusion is based on only 3 studies (1 acute (114) and 2 chronic (115, 116)), thus available data to compare specific outcomes was limited. It appears that mirtazapine has limited effects in acute administration, but further research is needed to establish these conclusions.

In the 5 different trials that studied mirtazapine: mirtazapine was studied in comparison to placebo once (114) and in comparison to fluoxetine (115), paroxetine (116), citalopram (113) and trazodone and pregabalin (117).

There is one trial where mirtazapine was compared to placebo (114). In this study of Scoralick et al. 24 patients with Alzheimer's Disease, who were community-dwelling at nighttime, had to take either placebo or 15mg of mirtazapine during 14 consecutive nights. The use of mirtazapine showed no significant effects on the different parameters measured: TST (+22 min), WASO (-6min) and number of awakenings (did not differ) in comparison to placebo.
In comparison to fluoxetine 40mg/day, there was a significant difference in favour of mirtazapine 45mg/day for the following parameters: sleep latency (-23 min; p=0.0015), total sleep time (+100min; p = 0.044). There was no significant change observed in individual sleep stages or REM latency in comparison to baseline for patients who took mirtazapine in this trial. Mirtazapine and fluoxetine significantly improved the HAM-D and 3-item sleep scores in comparison to baseline (115).
Mirtazapine (30mg/day) was also compared to paroxetine 75mg/day (116). The scores of the HAM-D, PSQI and the 3-item sleep score were reduced significantly in both groups compared to baseline ($p<0.05$). There was, however, no significant difference between the two groups. Mirtazapine was superior in improving the total sleep time, the number of awakenings and the wake time after sleep onset in comparison to paroxetine.
Mirtazapine at a mean dose of 35.9mg/day was finally also compared to citalopram at a mean dose of 36.6mg/day (113). Mirtazapine and citalopram both improved getting to sleep, awakening following sleep and quality of sleep along the self-rating Leeds Sleep Evaluation Questionnaire-adapted (LSEQ), but could not reach statistical significance.
When compared to trazodone and pregabalin, mirtazapine had a similar, but a slightly less pronounced effect on the PSQI and was similar, but slightly superior in improving the HAM-D (117).

The safety of this compound was relatively good based on the 3 studies that examined safety and adverse effects (113, 114, 117). There was one severe side effect reported: in the study of Scoralick et al. (114) there was one patient who ended the study early because of excessive sedation after one intake. Only one of the studies (113) concerning mirtazapine documented numerous side effects with the reported percentages. Other common side effects were weight gain (15.3% of the patients had weight gain with a mean gain of 1.9kg after 8 weeks), somnolence (reported by 16% of the patients) and sinus congestion (reported by 14.6% of the patients).

The three studies concerning the use of esmirtazapine in primary insomnia (110-112), show that the compound could improve a number of objective sleep parameters. Overall was the highest dosage of esmirtazapine (4.5mg/day) associated with the largest improvement in objective sleep parameters. The total sleep time improved by on average between 45 and 49 minutes per night. The sleep latency improved only mildly (minus 5-12 minutes; total SL was 40-46 minutes), whilst the wake time after sleep onset improved largely for the highest dose of 4.5mg of esmirtazapine

with on average 20 minutes. When comparing acute (111) and chronic use (110, 112), it seems that the effect is already observed at the beginning of the treatment and remains stable when used for longer periods of time. This suggests that esmirtazapine can improve falling asleep but significantly facilitates sleeping longer through the night and helps patients fall asleep again faster after waking up during the night. These improvements can already be noticed within the first week(s) of treatment.

The safety of esmirtazapine was relatively good, although there were 2 severe (rare) side effects reported: neutropenia which led to sepsis and an acute occlusion of the anterior-descending coronary artery without previously having any symptoms of blood vessel disease which led to an acute myocardial infarction (110, 112). Apart from these events, other common side effects were weight gain (in the study period of 6 months, 9% of the patients had an increase of 7% or more of their weight) and somnolence.

This systematic review shows that mirtazapine could improve sleep in patients with primary or secondary insomnia. The five studies concerning mirtazapine show that the compound could improve a numerous of subjective and objective sleep parameters, but further research is needed. Overall it was seen that a higher dosage of mirtazapine was associated with a more distinct improvement in sleep parameters. The total sleep time improved in all studies, but the difference in total sleep time compared to baseline showed great variations between the studies (on average between 22 and 268 minutes per night). The sleep latency improved only mildly and again showed big variations (minus 1 to 25 minutes; total SL after treatment was 11 to 12 minutes), whilst the wake time after sleep onset improved largely for the highest dose of 45mg of mirtazapine with on average 23 minutes. The study of Scoralick et al. (114) showed a slight but non-significant improvement of all sleep parameters. There were no studies comparing mirtazapine with the current standard of care (CBT and benzodiazepines/Z-drugs). Overall mirtazapine was well tolerated: one patient experienced excessive sedation, the most common side effects were sedation, weight gain and sinus congestion. This suggests that mirtazapine can improve falling asleep but significantly facilitates sleeping longer through the night and helps patients fall asleep again faster after waking up during the night. These improvements can already be noticed within the first week(s) of treatment.

4. Discussion

4.1. Trazodone

4.1.1. Major findings

After systematic research, careful selection and extensive examination of published papers concerning the effectiveness and safety of trazodone used in insomnia, 23 articles were included in this systematic review. In 13 different trials participants had primary insomnia (89, 93, 95, 96, 98, 100, 102-107, 109) and in 10 studies participants had secondary insomnia (88, 90-92, 94, 97, 99, 101, 108, 117).

Trazodone improved the TST in primary insomniac patients compared to baseline with a mean of +51 minutes (96, 104, 106, 109). The effect compared to placebo was similar in primary insomniac patients and secondary insomniac patients with a mean of +25 and +20 minutes respectively (88, 91, 94, 98, 101, 107, 108).
When excluding the results in favour of placebo of the study of Haffmans et al. (91) a mean of +32.5 minutes is reached in patients with secondary insomnia.

Trazodone improved the SL in patients with primary insomnia compared to baseline with a mean of -31.5 minutes (96, 109). When compared to placebo in primary insomniacs, the gain is less pronounced with a mean of -6 minutes (100, 107). The studies that examined the efficiency of trazodone in secondary insomniac patients all compared to placebo and improved the SL with a mean improvement of -9 minutes (91, 94, 108).

Trazodone improved the WASO in primary insomniac patients with a mean of -23 minutes (96, 109). When compared to placebo in primary insomniacs, the gain is less pronounced with a mean of -16 minutes (98, 100, 107). The effect compared to placebo was superior in primary insomniac patients versus in secondary insomniac patients (with a mean of -8 minutes respectively (91, 101, 108)). When excluding the results in favour of placebo of the study of Haffmans et al. (91) a mean of -19 minutes is reached in patients with secondary insomnia, making the results more similar.

When acute and chronic administration are compared, similar results seem to be found for both objective and subjective outcomes, although data available to compare specific outcomes was limited. It appears that trazodone has positive effects in acute administration, even when it was given only once (101) and these effects remain present when the compound is taken chronically.

Our findings show that there does not seem to be a big difference in the effect on sleep parameters in primary versus secondary insomnia. There also does not appear to be a big difference in acute versus chronic administration. However, further research is needed to establish these conclusions:

first of all, the number of studies that could be compared is rather small and furthermore, the average values mentioned above are not based on the amount of participants in total, but on the amount of reported studies in total.

Most studies used subjective questionnaires. Eight studies (89, 90, 92, 93, 96, 97, 107, 117) reported only subjective outcomes, 2 studies only objective outcomes (88, 104) and 13 studies (91, 94, 95, 98-103, 105, 106, 108, 109) reported both subjective and objective data.

The subjective results are often more pronounced than, for example, measurements with PSG. In the study of Kaynak et al. (94) it was observed that placebo had a significant effect on the outcomes obtained from questionnaires. It can be envisioned that the increased attention given to patients with sleep problems during a study, can lead to an improvement in the outcomes, even without medication (Hawthorne-effect).
In contrast, there were the objective outcomes, such as PSG data, which seem to be highly wanted and more reliable than subjective outcomes. However the subjective outcome is also of great importance for general/clinical practice. Therefore, it is important to compare both subjective and objective outcomes.

Trazodone seems to be relatively safe. Information about the safety of trazodone was reported or assessed in 13 of the 23 studies (89-91, 93, 94, 97, 99-102, 107, 108, 117). None of the reported or observed adverse reactions were rated as severe by the researchers, however in the study of Nierenberg et al. (97) one patient dropped out of the study because of excessive daytime sedation after one night of trazodone 50mg.
Another commonly reported side effect is morning somnolence, however, when the quality of life is seen to improve, these side effects may not be as important to patients as thought by clinicians. Moreover, one study showed that placebo also produces side effects and there was no significant difference observed between the placebo group and the trazodone group (108).
The side effects seem to diminish over time (93) and the side effects mentioned in the RCTs may also be dose-related. Often 1 dose is imposed (often 50mg or 100mg or even more) and this may already be too high for many participants, especially for older patients. Slowly increasing in dosage may be a better option. In clinical practice, it is possible to start with 25mg or 50mg of trazodone, and depending on how well the treatment is tolerated, the dosage can be increased if necessary.

Although no serious side effects were reported, some other studies report examples of rare but (potentially) serious side effects, including prolonged QT interval (with risk of ventricular tachycardia) (119), priapism (120) and serotonin syndrome (75).
Long QT is a serious side effect that is mentioned in the package leaflet and in numerous studies (119), however it was not mentioned in one of the examined studies.

Another well-known, but rare side effect is priapism (120). It seems to be dose dependent, because in the study of Nierenberg et al. (97) one patient reported a prolonged erection, but this disappeared after lowering the dose from 50mg to 25mg. Some sources report clitoral priapism with trazodone (121). An increase in libido is another reported side effect (122).
Furthermore a possible dangerous side effect is serotonin syndrome, especially when trazodone is combined with other serotonergic drugs, such as triptans, tricyclic antidepressants, or fentanyl (75).

Regarding daytime impairments and cognitive functions, the included studies reported contrasting results.
Roth et al. (100) reported small but significant impairments of short-time memory, verbal learning, arm and muscle endurance and equilibrium after 1 week administration of trazodone 50mg. Another study with a longer study duration of 2 weeks using the same dose reported no effects on cognition or functionality (88). In another study of 1 day, there was a mild, but significant improvement in numerical memory (101) and in the 4-week study of Wang et al. (108) there was a significant greater improvement in concentration and recall abilities in the trazodone (50mg) group than in the placebo group ($p<0.05$). The improved concentration and recall abilities were positively related to the improvement of PSQI, ESS, HAMA, S3 ratio, WASO and SE.
A possible explanation of cognitive impairment is the sedative effect of trazodone. As the patient becomes accustomed to the medication or the correct dosage is found, it is possible that these effects will diminish or that trazodone may even improve cognitive functions. As mentioned above, trazodone improved sleep continuity and the ratio of SWS, which is considered to be crucial for memory consolidation (123). It looks like SWS is not only important for cognitive functions, but also for physiological functions, such as maintenance of normal glucose homeostasis, which may influence the risk of type 2 diabetes (124). Vgontzas et al. (106) reported a significant association between lengthening of TST and reduction of cortisol levels. Even though causality could not be verified, a downregulation of the stress system could be present.

4.1.2. Limitations of the included studies

A meticulous analysis of the included studies was performed to assess the quality of the included trials. Each of the included trials had its own strengths and limitations. The most important limitations are summarised below. The limitations in detail per trial studying trazodone can be found in appendix 14. A risk of bias assessment was performed for both trazodone and mirtazapine. For more details see heading 4.4. Risk of bias assessment.

Our findings show that there does not seem to be a big difference in the effect on sleep parameters in primary versus secondary insomnia. However, further research is needed to establish these conclusions. First of all the number of studies that could be compared is rather small because of

the heterogeneity of the results. Secondly, some studies reported numerical differences, whilst others expressed the results in percentages, which also caused comparison to be inconvenient. Thirdly, the (average) values mentioned above are not based on the number of participants in total, but on the amount of reported studies in total.

Only 10 of the 23 RCTs compared trazodone with placebo (88, 91, 94, 97, 98, 100-102, 107, 108), despite this being an important part of testing the effect and safety of a treatment. The simple act of taking ‘a pill’ can already cause improvements in subjective and objective outcomes and can even cause side effects without having active treatment. Furthermore, trazodone was only compared to the current medicinal treatment (benzodiazepines and Z-drugs) for insomnia in four studies (89, 90, 93, 107) and it was mostly not superior to the examined benzodiazepines and Z-drugs.

There were 10 RCTs with less than 20 participants (91, 94, 95, 97, 98, 100, 101, 103, 105, 106) and there were only 7 RCTs with a total of 50 or more participants (control group inclusive) (89, 90, 92, 93, 96, 102, 107). The two biggest intervention groups that received trazodone counted 90 and 50 participants (93, 107). To be able to draw conclusions that can be used in clinical practice, it is important to have a broad and large study population. In a smaller study population, it is possible that some groups have been selected on certain factors, maybe unwillingly or unknown and rare side effects may be harder to detect.
Furthermore, in some studies several participants did not finish the study. In the RCT of Roth et al. (100) of the 63 patients who were initially randomised, 47 patients did not finish the study for various reasons and their results were not included in the final analysis. In the RCT of Morin et al. (96) it was noticeable that a large number of participants in different treatment groups (not only the trazodone group) did not finish the study, however, it was not mentioned why. Eraslan et al. (89) mentioned that 7 patients did not finish the study due to side effects, which were not further discussed.

Only 13 studies (89-91, 93, 94, 97, 99-102, 107, 108, 117) examined the safety of trazodone for its indication of treating primary insomnia. Together 355 participants were examined and questioned to intercept possible side effects. This is insufficient to confidently discover all rare and very rare side effects. Finally, none of the studies examined dependency and withdrawal effects of trazodone treatment, which is a very important factor to be able to confidently prescribe the drug for this indication, especially when compared to benzodiazepines which are known for their addictive properties.

The authors of the included studies used different doses of trazodone, which makes it difficult to compare the effects. The dose of trazodone ranged from 25 to 200 mg; twelve studies used fixed doses (88, 90, 91, 93, 94, 98, 100-102, 107-109). The most used dosages were 50 and 100 mg.

Six studies reported non-fixed (89, 96, 97, 99, 117) or progressive doses (95), whilst 5 studies did not mention the dosage (92, 103-106).
In most studies different doses are used in different patients. In the results, the different dosages are fused together in one outcome. It would be much more interesting if studies compared different doses, but we have not found a study like that. It was not clear why they used different doses. The dose could be increased in patients who had insufficient effect or in contrast it might have been the intention to give everyone a higher dose, but some patients experienced too many side effects. Therefore, the results need to be interpreted with caution. The best results were in general seen with a dosage of 100mg trazodone (94, 98, 101, 109), but the studies with a higher dosage, also showed more side effects.

In this review, trials where participants took other sedatives were excluded. Four trials, however, tested the efficacy of trazodone in treating insomnia in depressed patients who were being treated with antidepressant drugs such as bupropion (97), MAO-I (91) and SSRIs (94, 117) which can cause sleep disturbances. Although this purpose also needs to be examined, it can give a distorted picture of our results. Furthermore, the combination with trazodone should be strictly monitored because of the higher risk of serotonin syndrome.

There were big differences in treatment duration seen in the examined studies.
Ten studies examined acute trazodone intake (1 day: Saletu-Zyhlarz et al. (101); 1 week: Haffmans et al. (91), Kaynak et al. (94), Nierenberg et al. (97), Paterson et al. (98), Roth et al. (100); 2 weeks: Camargos et al. (88), Janjic et al. (93), Shell et al. (102), Walsh et al. (107)).
Twelve studies examined chronic trazodone intake (4 weeks: Eraslan et al. (89), Hadi et al. (90), He et al. (92), Wang et al. (108); 6 weeks: Morin et al. (96); 2 months: Zavesicka et al. (109); 3 months: 3 trials of Vgontzas et al. (103-105); 24 weeks: Ilinoiu et al. (117); 6 months: Vgontzas et al. (106); 9 months: Li et al. (95)).
One study did not mention the study duration (Petrescu et al. (99)).
In the study of Saletu-Zyhlarz et al. (101), where one-time intake of trazodone was examined, there were significant improvements seen in sleep efficiency, TST and number of awakenings. This is an interesting finding for clinical practice since improvement could already be noticed in a short period of time. However this conclusion is only based on one trial. Nevertheless, similar results were reported in the remaining trials mentioned above with acute administration, thus supporting the previous hypothesis.
When comparing the studies mentioned above that examined chronic intake of trazodone, it becomes clear that more trials are needed that measure objective outcomes. Only three studies (96, 108, 109) provided sufficient objective data to compare and two of them (96, 109) used trazodone as add-on therapy. When looking at the subjective outcomes, trazodone can hardly be called superior in comparison to other treatments such as zopiclone, clonazepam, pregabalin,

CBT and mirtazapine (89, 90, 92, 103, 105, 117). When comparing the results with CBT, it has to be nuanced that each study and furthermore each instructor have different methods of practicing CBT. Sometimes it comprises sleep restriction which can cause a false underestimation of the TST for example.

An important remark of 9 studies (88, 92, 93, 98, 99, 103-105, 117) was the fact that only their abstract was available, with merely a few reported results. It was not possible to analyse the study protocol or further patient characteristics. Furthermore, only significant improvements were reported in 4 studies (88, 92, 98, 99). This means the results need to be interpreted with caution which makes it hard to compare these trials with others.
Of three studies of Vgontzas et al. (103-105) only the abstract was available, which contained little information about the study protocol. The fourth study of Vgontzas et al. (106) was an open-label study with a small population where the CBT group had to use sleep restriction as part of the treatment, but one of the outcomes was TST, which will be obviously in favour of trazodone when compared. Also, although it is difficult to verify, it is possible that these four studies each involve (approximately) the same patients, so we have to be careful when drawing conclusions.

When reading the various study protocols, some concerns arose. When a patient consults a clinician because of sleep problems, sleep hygienic measurements will inevitably be addressed and if needed corrected. In the various study protocols, there was often no mention of these kinds of influencing factors. To have a good night's sleep it is important to know what the activities were during daytime. Is the patient sedentary or did he exercise during the day and at which time? Were there other confounding variables like the amount of screentime and blue light in the evening and before bedtime, caffeine use, timing of the last meal of the day, sugar intake etc. There was not one single study that tried to ensure those factors were similar between patients during the study or that created an identical environment. This is of great importance to estimate the Hawthorne effect and the actual therapeutic effect of trazodone.
Of all analysed trials examining trazodone, we found that half of the trials had a publication date older than 2015. There were only 5 studies that were published five or less years ago. During the selection process of articles for this review, it was apparent that there are still a few trials ongoing for the moment that could be interesting to further strengthen the conclusions drawn in this review.

4.1.3. Future perspectives

Based on the data available to date, it seems that trazodone has positive effects on various objective and subjective sleep parameters such as TST, SL, NA, WASO, HAM-D and ISI. These findings need to be interpreted with caution and are not ready yet to be applied in clinical practice. More research is required to evaluate the effectiveness of trazodone used for treating insomnia. We suggest that future research contains a double-blinded, placebo-controlled RCT, with a larger

study population with both the use of PSG and subjective outcome measures to examine sleep parameters. There is also a need for trials that have a longer study duration to assess the effect and safety of chronic use, to detect other drug interactions and to assess dependency and withdrawal. Furthermore, we propose that trazodone is also compared to the current treatment for insomnia: CBT, benzodiazepines and Z-drugs. A recent cohort study of Bronskill et al. (125) showed that the amount of serious fall incidents reported in a nursing home after trazodone use was similar to those reported after using benzodiazepines, both drugs gave a 6% chance of hospitalisation within the first 90 days of starting treatment.

It is important to note that numerous studies about trazodone and insomnia are still being conducted and that there might be studies that have been published recently but that are not included in this review.

Today we notice that various nutritional supplements (melatonin, passionflower, valerian) claiming to tackle insomnia, are gaining popularity. The companies making these supplements also claim that they have none to very little side effects. Although it is beyond the scope of this review, it would be interesting to examine how they compare to the current standard of care and to trazodone.

4.2. Mirtazapine

4.2.1. Major findings

After systematic research, careful selection and extensive examination of published papers concerning the effectiveness and safety of mirtazapine used in insomnia, eight articles were retained to include in this systematic review. There were 5 different trials that studied mirtazapine: all participants had secondary insomnia (113-117). The 3 trials studying esmirtazapine (110-112) were all performed in patients with primary insomnia, these results are discussed later.

Mirtazapine improved the TST in secondary insomniac patients with a mean of +184 minutes (115, 116). This was a startling conclusion that can be explained by the fact that the baseline measurement of TST in the mirtazapine group (186 minutes) was significantly lower than that of the paroxetine group (454 minutes) in the study of Zhang et al. (116). Especially when looking at the values of the different sleep stages in the mirtazapine group, a serious mistake is suspected. The gap between the two groups is even more pronounced since paroxetine has activating properties. When the study of Zang et al. (116) is excluded, only that of Winokur et al. (115) remains with a reported improvement of the TST compared to baseline of +100 minutes. This result could be explained by the fact that the results are based on the PSG of one single night, which can also lead to a more uncertain outcome. Only one study compared mirtazapine to

placebo in secondary insomniac patients and the gain in TST was less pronounced with +22 minutes (114).

Mirtazapine improved the SL in secondary insomniac patients compared to baseline with a mean of -12 minutes (115, 116). There was no comparison to placebo.

Mirtazapine improved the WASO in secondary insomniac patients compared to baseline with a mean of -37 minutes (115, 116). When compared to placebo in secondary insomniacs, the gain is less pronounced with -6 minutes (114).

There is not enough data to compare the effect of mirtazapine on sleep questionnaires like HAM-D 3-item sleep score (numerical results were reported by only 2 studies comparing to baseline with a mean of -2.7 (115, 116)) and PSQI (one study reported a numerical result (116) and one a percentage (117)).

When acute and chronic administration are compared (cut-off at 4 weeks was used), it seems that the longer mirtazapine is taken, the better the effect, although this conclusion is based on 3 studies only (1 acute: Scoralick et al. (114) and 2 chronic: Winokur et al. (115) and Zhang et al. (116)), hence available data to compare specific outcomes were limited. It appears that mirtazapine has limited effects in acute administration, but further research is needed to establish these conclusions.

Our findings show that it is nearly impossible to draw useful conclusions about the effectiveness of mirtazapine in primary insomnia compared to secondary insomnia. More extensive research is also required to compare the difference in acute versus chronic administration. Thus further research is needed to establish these conclusions, seeing as the amount of studies that could be compared is rather small and the average values mentioned above are not based on the amount of participants in total, but on the amount of reported studies in total.

Our findings show that mirtazapine could improve sleep in non-elderly patients with primary insomnia. The five studies concerning mirtazapine suggest that the compound could improve numerous subjective and objective sleep parameters. Overall, mirtazapine was associated with a distinct improvement in the total sleep time, the sleep latency improved only mildly and the wake time after sleep improved largely.

The safety of this compound was relatively good based on the 3 studies that examined safety and adverse effects (113, 114, 117). A single severe side effect was reported: in the study of Scoralick et al. (114) a patient ended the study early because of excessive sedation after one intake. Only one of the studies (Leinonen et al. (113)) documented numerous side effects with the reported percentages. Other common side effects were weight gain (15.3% of the patients had weight gain

with a mean gain of 1.9kg after 8 weeks), somnolence (reported by 16% of the patients) and sinus congestion (reported by 14.6% of the patients). Adverse effects are a common reason for patients to end an intervention prematurely. As discussed below in heading 4.3 Risk of bias assessment, domain 3 examines the risk of bias caused by missing outcome data (87). Ilinoiu et al. (117) and Zhang et al. (116) scored a high risk of bias in this domain, and reported few to no adverse effects. Which means possible (serious) adverse effects can be missed. A total of 185 participants were examined and most of the time questioned to intercept possible side effects. This is insufficient to confidently discover all rare and very rare side effects.

One research group (110-112) examined esmirtazapine and showed that the compound could improve numerous objective sleep parameters. Overall, the highest dosage of esmirtazapine (4.5mg/day) was associated with the largest improvement in objective sleep parameters. The total sleep time, the sleep latency and the wake time after sleep onset improved largely. This suggests that esmirtazapine can improve falling asleep but significantly facilitates sleeping longer through the night and helps patients fall asleep again faster after waking up during the night. These improvements can already be noticed within the first week(s) of treatment. The safety of this compound was generally good, although there were 2 severe side effects reported. Other common side effects were weight gain and somnolence. A commonly reported side effect is morning somnolence, however, if it is seen that the quality of life improves, these side effects may not be as important to patients as we clinicians think.

Most studies used subjective questionnaires. Four studies (110, 111, 113, 117) reported only subjective outcomes, 1 study only objective outcomes (114) and 3 studies (112, 115, 116) reported both subjective and objective data.

The subjective results are often more pronounced than, for example, measurements with PSG. It can be envisioned that the increased attention given to patients with sleep problems during a study can lead to an improvement in the outcomes, even without medication (Hawthorne-effect).
In contrast, there were the objective outcomes, such as PSG data, which seem to be highly wanted and more reliable than subjective outcomes. However the subjective outcome is also of great importance for general/clinical practice. Therefore, it is important to compare both subjective and objective outcomes.

The severity of the side effects seem to diminish over time (110, 112) and the side effects mentioned in the RCTs may also be dose-related. Often 1 dose is imposed (between 15mg and 60mg or even more), which may already be too high for many participants, especially for geriatric patients. Slowly increasing in dosage may be a better option. In clinical practice, it is possible to start with 20mg or even 15mg and depending on how well the treatment is tolerated, the dosage can be increased if necessary.

This systematic review shows that mirtazapine could improve sleep in patients with insomnia or could be used as add-on therapy if needed. When compared to the current standard of care (CBT and benzodiazepines/Z-drugs), mirtazapine has similar results in improving numerous subjective and objective sleep parameters.

4.2.2. Limitations of the included studies

A meticulous analysis of the included studies was performed to assess the quality of the included trials. Each included trial had its own strengths and limitations. The most important limitations are summarised below. The limitations in detail per trial studying (es)mirtazapine can be found in appendix 15. A risk of bias assessment was performed for both trazodone and mirtazapine. For more details see heading 4.4. Risk of bias assessment.

There was no comparison of mirtazapine with the current recommended treatment for insomnia. This makes it impossible to say whether mirtazapine is superior or inferior to the use of CBT, benzodiazepines or Z-drugs. Furthermore, there was only one trial where mirtazapine was compared to placebo (114), which makes it difficult to claim it has true treatment effects on insomnia symptoms. Since there were few qualitative studies found within the scope of this review, there is still a lot of uncertainty left concerning the correct use of mirtazapine. This is evident in the large range of dosages that are used concerning mirtazapine and when to use it. Because of experience with clinical practice, it was generally administered 30 minutes before bedtime, but there is no experimental or scientific evidence that these dosages or this timeframe are the most optimal way of using this medicine.

Only one RCT that studied mirtazapine had a total of over 50 participants (113). The 3 studies concerning esmirtazapine involved a larger population (110-112). To be able to draw conclusions that can be used in clinical practice, it is important to have a broad and large study population. In a smaller study population, it is possible that some groups have been selected on certain factors, maybe unwillingly or unknown.

There were 3 studies that examined safety and adverse effects. Only one of the studies (Leinonen et al. (113)) concerning mirtazapine documented numerous side effects with the reported percentages. Ilinoiu et al. (117) and Zhang et al. (116) reported few to no adverse effects. Which means possible (serious) adverse effects can be missed. A total of 185 participants were examined and most of the time questioned to intercept possible side effects. This is insufficient to confidently discover all rare and very rare side effects.

The authors of the included studies used different doses of mirtazapine, which makes it difficult to compare the effects. The dose of trazodone ranged from 15 to 60 mg; three studies (114-116) used fixed doses. Two studies reported non-fixed (113, 117). In the studies of Ivgy-May et al. (110-

112) 3 fixed doses of esmirtazapine were used: 4.5mg was most frequently used, followed by 3.0mg and 1.5mg respectively. In most studies that used different doses in different patients, it was not clear why. The dose could be increased in patients who had insufficient effect or in contrast it might have been the intention to give everyone a higher dose, but some patients experienced too many side effects. Therefore the results need to be interpreted with caution. The best results were in general seen with a higher dosage, but the studies with a higher dosage, also showed more side effects.

Furthermore, in 4 trials (113, 115-117) participants either received already SSRIs or mirtazapine was compared to SSRIs such as citalopram, fluoxetine and paroxetine which can cause agitation, insomnia and sedation. Although this purpose also needs to be examined, it can give a distorted picture to our results. A final important side note of the study of Zhang et al. (116) that compared mirtazapine and paroxetine was the fact that the baseline results of the mirtazapine group were spectacularly worse than those of the paroxetine group. There was a big difference in total sleep time at baseline (186 minutes for mirtazapine and 408 minutes for paroxetine) which suggests that there may have been an error in the reporting of the numbers or the randomisation. This causes the results found in favour of mirtazapine to be interpreted with great caution.

There were big differences in treatment duration seen in the examined studies. There was one study that examined acute mirtazapine intake (2 weeks: Scoralick et al. (114)) and 4 studies that examined chronic trazodone intake (6 weeks: Leinonen et al. (113) and Zhang et al. (116); 2 months: Winokur et al. (115); 24 weeks: Ilinoiu et al. (117)).
When acute and chronic administration are compared, it seems that the longer mirtazapine is taken, the better the effect, although this conclusion is based mainly on only 3 studies (1 acute and 2 chronic), thus available data to compare specific outcomes was limited. It appears that mirtazapine has limited effects in acute administration, but further research is needed to establish these conclusions.

An important remark of the study of Ilinoiu et al. (117) was the fact that only the abstract of the study was available with only few reported results. It was not possible to analyse the study protocol or further patient characteristics. This means the results need to be interpreted with caution which makes it hard to compare these trials with others.

The research group of Ivgy-May et al. conducted three studies (110-112) concerning esmirtazapine. The studies were double-blinded, placebo-controlled, RCT’s with a large population, but only focused on non-elderly patients, therefore the conclusions drawn above are less applicable for a geriatric population or for patients with comorbid insomnia. Only one study was conducted over a longer period of time (6 months) (110), so there is little data to predict the effect and side effects of esmirtazapine in chronic use. This study had a dropout rate of 40% due

to either inefficiency or side effects. If this compound would be used in the future, more research is definitely needed.
Another important acknowledgement is the conflicts of interest of the authors: N. Ivgy-May and F. Ruwe are current or former Merck & co. (a pharmaceutical company) and they owned or own stock/stock options of that company. The studies were also funded by Merck & co. Esmirtazapine is no longer available because it was discontinued in 2010 by Merck & co. for strategic reasons.

4.2.3. Future perspectives

When looking at the results found and available to date, it seems that mirtazapine has positive effects on various objective and subjective sleep parameters such as TST, SL, NA, WASO, HAM-D and ISI. However these findings are to be interpreted with caution and are not yet ready to be applied in clinical practice. More research needs to be done to assess its effectiveness used for treating insomnia. We suggest that future research contains a double-blinded, placebo-controlled RCT, with a larger study population with the use of PSG to examine sleep parameters. Furthermore, we suggest that mirtazapine is also compared to the current treatment for insomnia: CBT, benzodiazepines and Z-drugs.

Upon finalising this thesis, it stood out that numerous studies are still being conducted or were finished recently. For example a very recent RCT of Nguyen et al. (126) was coincidentally discovered examining mirtazapine for chronic insomnia in older adults. A low dosage of 7.5mg of mirtazapine was used for 28 days, compared to placebo. A significant difference was found in favour of mirtazapine (-5) for the change in ISI score compared to placebo (-2.9) and there was non-significant improvement in the PSQI score, WASO, TST or SE compared to placebo. There were no severe adverse effects reported, but 20% of the patients in the mirtazapine group (n = 30) discontinued treatment because of side effects: daytime sedation (n = 2; 33%), confusion (n = 2; 33%), hot flush (n = 1; 17%) and blurred vision (n = 1; 17%). A weight gain with an average of +0.65kg was observed compared to placebo. These safety-related results are remarkable since the dosage was relatively low, but in line with the outcomes observed in this review. When assessing this trial critically, a few remarks can be made: there was a small population used, it was not compared to the current standard of care, it has a rather short study duration and there is a large percentage of missing valuables. These findings make it necessary to further explore this topic.

4.3. Risk of bias assessment

The quality of the methodology of included studies was judged using the RoB 2 tool (87). This tool is a questionnaire that assesses the risk of bias in randomised controlled trials. It is recommended to use this when creating a Cochrane (Systematic) Review. The tool verifies five different domains

in the methodology of trials that could be prone to bias: 1. the randomisation process, 2. deviations from the intended interventions, 3. missing outcome data, 4. measurement of the outcome and 5. selection of the reported result. For each individual outcome (e.g. TST), a separate risk of bias assessment has to be made. In this review, a few crossover studies were also included: for these studies, the RoB 2 for crossover trials was used with an additional domain: risk of bias arriving from period and carryover effects. The RoB 2 tool was used to assess the following outcomes: TST, SL, WASO, NA, ISI and PSQI.

The two authors independently screened and scored each trial for possible bias using the free RoB 2 tool. Afterwards, differences were discussed until a consensus was reached. The template for completing the assessment and the full guidance document provided by Sterne et al. (87) were used to create and complete an excel file specifically for this review. An overview of the used excel can be found in appendix 13.

Nineteen studies examined the TST: 8 studies had an overall low risk of bias (91, 94, 107, 110-112, 114, 115), 5 studies had some concerns overall (88, 98, 101, 108, 109) and 6 studies had an overall high risk of bias (92, 96, 99, 104, 106, 116).
Thirteen studies examined the SL: 8 studies had an overall low risk of bias (91, 94, 100, 107, 110-112, 115), 2 studies had some concerns overall (108, 109) and 3 studies had an overall high risk of bias (92, 96, 116).
Fifteen studies examined the WASO: 9 studies had an overall low risk of bias (91, 94, 100, 107, 110-112, 114, 115), 4 studies had some concerns overall (98, 101, 108, 109) and 2 studies had an overall high risk of bias (96, 116).
Eleven studies examined the NA: 8 studies had an overall low risk of bias (91, 94, 100, 107, 110-112, 114), 2 studies had some concerns overall (98, 101) and 1 study had an overall high risk of bias (116).
Ten studies examined the ISI: 3 studies had an overall low risk of bias (110-112), 3 studies had some concerns overall (93, 95, 109) and 4 studies had an overall high risk of bias (92, 103, 105, 106).
Seven studies examined the PSQI: 3 studies had an overall low risk of bias (90, 94, 102), 2 studies had some concerns overall (108, 117) and 2 studies had an overall high risk of bias (97, 116).

Examining the outcomes mentioned above, it stands out that studies with low risk of bias in the methodology are scarce. Overall it was observed that domain 2 (deviations from the intended interventions) was most susceptible to bias, followed by domain 4 (measurement of the outcome) and domain 3 (missing outcome data) respectively. This means that the reported outcomes should be interpreted with caution and that more studies of high methodological quality are needed to draw conclusions used for future guidelines.

4.4. Limitations of this review

This literature review was conducted in a systematic manner, however several limitations should be taken into account. Both methodological and practical limitations are reflected upon and discussed below.

Firstly, the search method used will be discussed. PubMed, EMBASE, Web of Science and Cochrane Library databases were searched for articles that matched the query (to be found in appendix 2-5). The search strategy was limited to these four databases, which means that other possible interesting trials could be missed in this manner. The final database research was conducted on 19 September 2023, consequently more recent trials were not analysed in this literature review. Grey literature was not searched for and articles in other languages than English and Dutch were excluded.

Secondly, when drawing conclusions, publication bias needs to be accounted for: most of the time, mainly studies with positive or significant results will be published because of funding etc. Furthermore, the articles found were analysed by two independent authors for meeting inclusion criteria and when in doubt, a discussion took place between the two to resolve the issue. Therefore, the selection can be biased by personal selection and interpretation of the articles found. The inclusion and exclusion criteria were rather strict, because of restricted means, which could lead to losing studies that could fit the scope of this review in a broader context. Due to restricted financial means we were not able to buy full text articles that met our inclusion criteria. Some results are based on abstracts that were available, thus affecting the overall quality of the outcomes. Because of time span limitations, it was not possible to contact authors to ask for further results or full- text papers. These factors explain why this systematic review is rather narrative and why it was not possible to do a meta-analysis. The heterogeneity of the results found is also not beneficial for producing a meta-analysis. A PROSPERO protocol of this review was made, but not published, which could have been beneficial for the overall transparency and reproducibility of this subject.
It is important to note that by using medicinal treatment to improve insomnia symptoms, the underlying cause of insomnia has not been addressed. Therefore it is recommended to practice some form of CBT or sleep hygienic measures.

5. Conclusion

This systematic literature review aimed to assess the efficacy and safety of trazodone and mirtazapine in insomnia in adults. Both drugs are often used off-label as a ‘safer alternative’ for benzodiazepines and Z-drugs but is this claim justifiable?

When the results are compared, it seems that both trazodone and mirtazapine can provide an improvement for patients with insomnia. Our findings show that there does not seem to be a big difference in the effect of trazodone on sleep parameters in primary versus secondary insomnia and in acute versus chronic administration. Our findings show that it is nearly impossible to draw useful conclusions about the effectiveness of mirtazapine in primary insomnia compared to secondary insomnia because of the lack of usable data and more extensive research is also needed to compare the difference in acute versus chronic administration. Overall both subjective and objective measures, however, show positive results compared to baseline mainly in the short term.

Overall, it was seen that trazodone improved the total sleep time in all 10 studies compared to placebo and the studies that used a greater dosage of trazodone had the best results. The sleep latency improved only mildly, whilst the wake time after sleep onset improved the most for the highest dose of trazodone with on average -22.5 minutes. The highest doses of trazodone (100mg) showed an improvement in the slow wave sleep. This suggests that trazodone can improve falling asleep and facilitates sleeping longer through the night and helps patients to fall asleep again faster after waking up during the night. These improvements can already be noticed within the first week(s) of treatment. In comparison to CBT, benzodiazepines and Z-drugs, trazodone had a similar effect on the subjective and objective outcomes. The safety of trazodone was generally good in the examined studies, only one patient experienced sudden excessive sedation after the first intake (based on 13 studies that observed safety). The most common side effects were sedation, dizziness, nausea and headache. It caused small but significant impairments of short-term memory, verbal learning, arm and muscle endurance and equilibrium. However, some studies reported positive effects on cognitive functions. Therefore, it can be concluded that the effect on cognitive functions is inconclusive. There were no significant effects on driving errors or speeding in the examined trials.

In general, we found that mirtazapine improved the total sleep time in all 5 studies, but the difference in total sleep time compared to baseline showed great variations between the studies. The sleep latency improved only mildly and showed also big variations, whilst the wake time after sleep onset improved largely for the highest dose of 45mg of mirtazapine. This suggests that mirtazapine can improve falling asleep but significantly facilitates sleeping longer through the night and helps patients falling asleep again faster after waking up during the night. These

improvements can already be noticed within the first week(s) of treatment. The safety of this compound was generally good in the limited number of studies. There was one severe side effect reported: one patient ended the study early because of excessive sedation after one intake. Other common side effects were weight gain (15.3% of the patients had weight gain with a mean gain of 1.9kg after 8 weeks), somnolence (reported by 16% of the patients) and sinus congestion (reported by 14.6% of the patients). There was unfortunately no comparison to CBT, benzodiazepines or Z-drugs.

There are some important limitations that should be considered when interpreting the results. The examined studies consisted mostly of small to moderate study populations, making it likely that rare and very rare side effects may not have been observed. The heterogeneity of the results makes it hard to compare different studies with each other. Furthermore, there were not enough studies examining chronic use, which definitely needs further research.

Because of these limitations, conclusions that can be applied in clinical practice are restricted. Trazodone and mirtazapine can be used as treatment for insomnia, but mainly if the first choice of treatment fails or is insufficient. The possible (severe) side effects and interactions should be considered in each individual.

To be able to finalise a clear statement about the effectiveness and safety of trazodone and mirtazapine for treating insomnia, more research is definitely needed. It is suggested that large-scale and qualitative RCT's are conducted that evaluate chronic intake and the safety of the products. It is recommended to use uniform measuring methods so results can be easily compared in the future.

In conclusion, both trazodone and mirtazapine show potential to improve (symptoms of) insomnia, especially in patients with comorbidities or when first-line treatment is insufficient or not possible. For trazodone, the available evidence is more extensive: multiple RCTs show that, especially in acute settings and at low doses (50-100 mg), it can be effective and it also appears to be relatively safe. However, the current evidence remains limited and it is suggested that large-scale, qualitative RCTs should be conducted to make a definitive statement on the efficacy and safety of trazodone and mirtazapine for the first-line treatment of insomnia. In particular, the possible development of tolerance and addiction potential have not yet been sufficiently investigated and there are not enough studies comparing with current first-line treatment.

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Appendices

Appendix 1: PROSPERO protocol

1) Review title:
The efficacy and safety of Trazodone and Mirtazapine in treating insomnia in adults: a systematic review.

2) Original language title:
The efficacy and safety of Trazodone and Mirtazapine in treating insomnia in adults: a systematic review.

3) Anticipated or actual start date:
27/01/2023

4) Anticipated completion date:
01/05/2025

5) Stage of review at time of this submission:
This review has not yet started : No

Review stage	**Started**	**Completed**
Preliminary searches	Yes	Yes
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

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11) Funding sources/sponsors:
Ghent University

12) Conflicts of interest:
None

13) Collaborators:
None

14) Review question:
The efficacy and safety of Trazodone and Mirtazapine in treating insomnia in adults: a systematic review.

15) Searches:
Databases that will be consulted are: MEDLINE via PubMed interface, EMBASE via Embase interface, Web of Science and Cochrane Library.
The search strategy will be constructed using thesaurus (e.g. MeSH in PubMed) and free-text terms concerning the concepts 'trazodone', 'mirtazapine' and 'insomnia'. These concepts are combined using Boolean operators and database specific syntax.
We will not include grey literature or any articles written in a language other than English. The search will be performed in English. There will be no restrictions applied for publication date. The search is planned for September 2023.

16) URL to search strategy:
None

17) Condition or domain being studied:
Use of Trazodone or Mirtazapine in Insomnia.
Trazodone and Mirtazapine are intended to be used for the treatment of depression. However, because of their sedative effect, they are used off-label for the treatment of insomnia. The effectiveness and safety of this off-label use is not yet in depth established, explaining why this is the scope of this review.

18) Participants/population:
Inclusion : adults, including people with comorbidities in addition to insomnia.
Exclusion : adolescents and children (under 18 years of age), animal studies, pregnant women, if results cannot be assessed separately, tissue models, in vitro experiments.

19) Intervention(s), exposure(s):
The interventions include trazodone and mirtazapine, without any limits to dosage, frequency and mode of administration. Studies concerning any duration of intake will be included. Intervention includes the intake of a single drug, as well as the combination of trazodone and/or mirtazapine with any other chronic drug that has no known sedative (side) effect.

20) Comparator(s)/control:
Placebo, another sedative drug or therapy.
Studies without a control group will be excluded.

21) Types of study to be included:
Only RCTs published in English will be included.

22) Primary outcomes:
We will assess the effectiveness of Trazodone and Mirtazapine used as a hypnotic drug. The effects can be patient-reported changes (subjective) in quality of sleep, sleep latency, nocturnal awakenings and duration of sleep using different rating scales. Effects can also be compared objectively by using sleep studies such as polysomnography or EEG.
Further, we will check the safety of using Trazodone or Mirtazapine for this indication. We define safety as a serious health hazard caused by the intake of trazodone or mirtazapine (like mortality, falling down at night, toxicity or adverse events that have a permanent impact on the quality of life).

23) Secondary outcomes:
Secondary outcomes are the effects of higher doses on effectiveness and safety, other side-effects that do not have a big impact on the quality of life, drowsiness at daytime, the effect of stopping/phasing out the drugs, tolerance.
Also the difference in effect between Trazodone and Mirtazapine on one hand and other hypnotics on the other hand will be examined.

24) Data extraction:
The results of the search strategy will be merged using EndNote (Clarivate Analytics, Philadelphia, US of America) and deduplication will be performed. Titles and/or abstracts will be screened using EndNote (Clarivate Analytics, Philadelphia, US of America), by two authors independently. Full text documents will be retrieved, multiple reports of the same study will be linked together and will be examined in detail by two authors independently. Disagreements in both steps will be resolved via discussion, and if needed, with a third reviewer.
The study selection will be reported in PRISMA flowchart. A pilot tested, review-specific excel form will be utilized for extracting data for both the assessment of study quality and data synthesis. Data from multiple reports of the same study will be extracted and combined where applicable. Two reviewers will independently extract the data using this form. Both reviewers will be supported by a methodologist and trained for use of the form. Discrepancies will be resolved by discussion, with a third reviewer, when necessary.
The data extracted will include information regarding:
Report information, study details, participant selection, study group specifics, population, intervention (for each group), technique of assessment of insomnia, outcome, additional results, risk of bias.

25) Risk of bias (quality) assessment:
The quality of the methodology of included studies will be judged using the RoB 2 tool (87). This tool is a questionnaire that assesses the risk of bias in randomised controlled trials and it is recommended to use this when creating a Cochrane (Systematic) Review. The tool verifies five different domains in the methodology of trials that could be prone to bias: 1. the randomisation process, 2. deviations from the intended interventions, 3. missing outcome data, 4. measurement of the outcome and 5. selection of the reported result. Any disagreements between the reviewers over the risk of bias will be resolved by discussion. If necessary, a third reviewer can be consulted. Each study will be judged for each potential bias as having low, high, or unclear risk, which will be provided in the ‘Risk of bias’ table.

26) Strategy for data synthesis:
A narrative synthesis of the findings from the included studies will be provided. Results will be divided based on health outcomes/endpoints.

27) Analysis of subgroups or subsets:
The results will be analyzed in two subgroups: Trazodone and Mirtazapine

28) Type and method of review:
A Systematic review

29) Language:
English

30) Country:
Belgium

31) Other registration details:
None

32) Reference and/or URL for published protocol:
We do not make this file publicly available until the review is complete.

33) Dissemination plans:
This systematic review will result in a paper used to obtain graduation in “Master of Medicine in Science in de huisartsengeneeskunde” of the University of Ghent. Additionally it could be submitted to a leading journal in this field, aiming at an open-access publication.

34) Keywords:
Antidepressant, Trazodone, Mirtazapine, insomnia, systematic review, effect, safety

35) Details of any existing review of the same topic by the same authors:
None

36) Current review status:
Data analysis

37) Any additional information:
This review will be used to formulate useful advices concerning the effects and safety of trazodone and mirtazapine in treating insomnia. These advices are widely used by different practitioners in Belgium and are part of the commentated medical repertory (gecommentarieerd geneesmiddelenrepertorium) provided by the Belgian Central for pharmacotherapeutic information (BCFI – www.bcfi.be).

38) Details of final report/publication(s):
None

Appendix 2: PubMed search strategy

("trazodone"[Title/Abstract] OR "trazodon"[Title/Abstract] OR "desyrel"[Title/Abstract] OR "molipaxin"[Title/Abstract] OR "trittico"[Title/Abstract] OR "tombran"[Title/Abstract] OR "trazodil"[Title/Abstract] OR "trazonil"[Title/Abstract] OR ("mirtazapine"[Title/Abstract] OR "remeron"[Title/Abstract] OR "avanza"[Title/Abstract] OR "zispin"[Title/Abstract])) AND ("insomnia"[Title/Abstract] OR "insomnie"[Title/Abstract] OR "insomni*"[Title/Abstract] OR "dyssomni*"[Title/Abstract] OR "sleep*"[Title/Abstract] OR "sleep disorder"[Title/Abstract] OR "sleep disturbance"[Title/Abstract] OR "sleep problem"[Title/Abstract] OR "difficulty sleeping"[Title/Abstract] OR "sleep deprivation"[Title/Abstract] OR "sleep impairment"[Title/Abstract])

Note : No results were found for “Nestrolan” and “Remergon”, so these were not included in the search strategy.

Appendix 3: EMBASE search strategy

('trazodone':ti,ab OR 'trazodon':ti,ab OR 'desyrel':ti,ab OR 'molipaxin':ti,ab OR 'trittico':ti,ab OR 'tombran':ti,ab OR 'trazodil':ti,ab OR 'trazonil':ti,ab OR 'mirtazapine':ti,ab OR 'remeron':ti,ab OR 'avanza':ti,ab OR 'zispin':ti,ab) AND ('insomnia':ti,ab OR 'insomnie':ti,ab OR 'insomni*':ti,ab OR 'dyssomni*':ti,ab OR 'sleep*':ti,ab OR 'sleep disorder':ti,ab OR 'sleep disturbance':ti,ab OR 'sleep problem':ti,ab OR 'difficulty sleeping':ti,ab OR 'sleep deprivation':ti,ab OR 'sleep impairment':ti,ab)

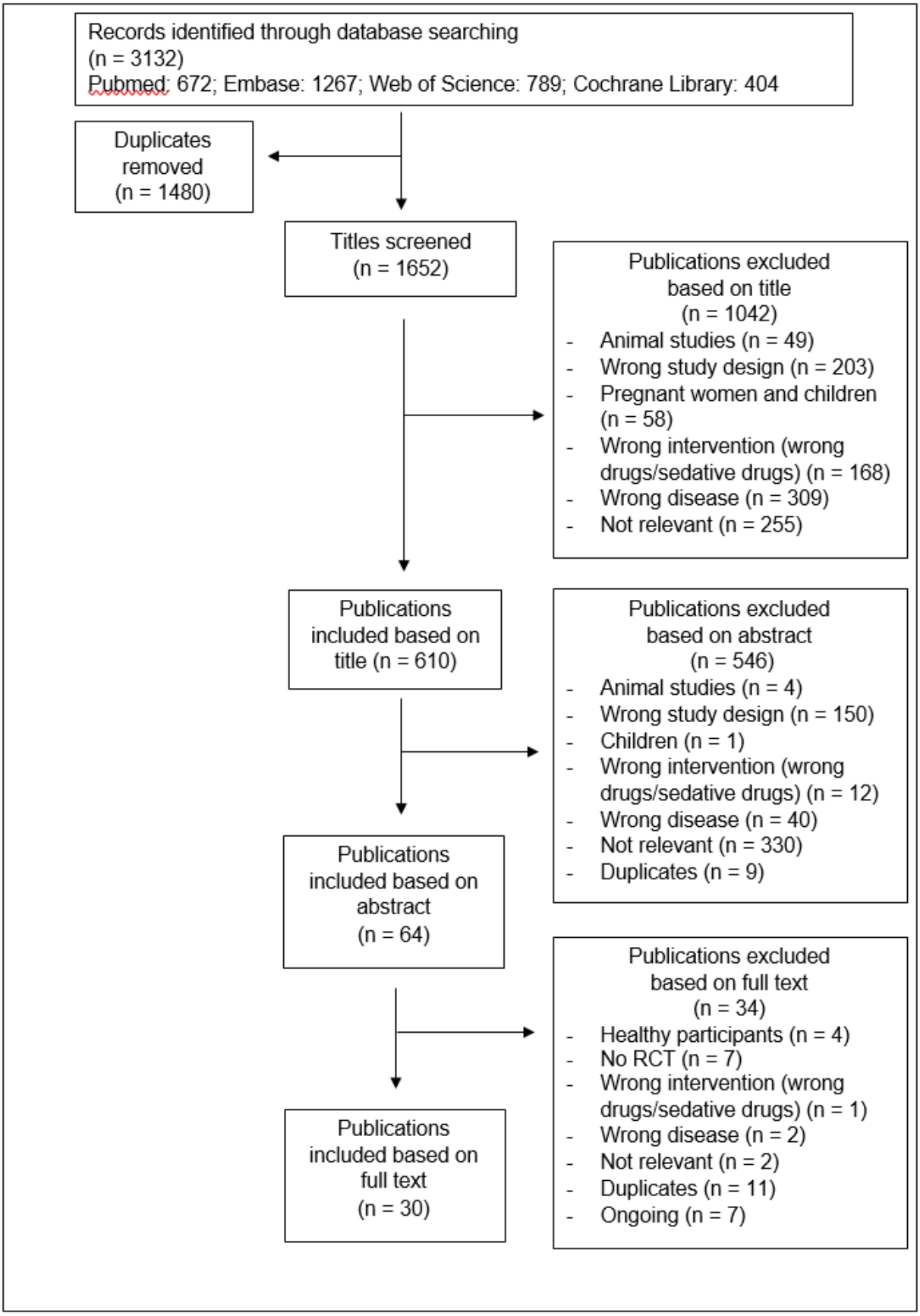
Appendix 4: Web of Science search strategy

TS=(("trazodone" OR "trazodon" OR "desyrel" OR "molipaxin" OR "trittico" OR "tombran" OR "trazodil" OR "trazonil" OR ("mirtazapine" OR "remeron" OR "avanza" OR "zispin")) AND ("insomnia" OR "insomnie" OR "insomni*" OR "dyssomni*" OR "sleep*" OR "sleep disorder" OR "sleep disturbance" OR "sleep problem" OR "difficulty sleeping" OR "sleep deprivation" OR "sleep impairment"))

Appendix 5: Cochrane Library search strategy

(("trazodone"):ti,ab,kw OR ("trazodon"):ti,ab,kw OR ("desyrel"):ti,ab,kw OR ("molipaxin"):ti,ab,kw OR ("trittico"):ti,ab,kw OR ("tombran"):ti,ab,kw OR ("trazodil"):ti,ab,kw OR ("trazonil"):ti,ab,kw OR ("mirtazapine"):ti,ab,kw OR ("remeron"):ti,ab,kw OR ("avanza"):ti,ab,kw OR ("zispin"):ti,ab,kw) AND (("insomnia"):ti,ab,kw OR ("insomnie"):ti,ab,kw OR ("insomni*"):ti,ab,kw OR ("dyssomni*"):ti,ab,kw OR ("sleep*"):ti,ab,kw OR ("sleep disorder"):ti,ab,kw OR ("sleep disturbance"):ti,ab,kw OR ("sleep problem"):ti,ab,kw OR ("difficulty sleeping"):ti,ab,kw OR ("sleep deprivation"):ti,ab,kw OR ("sleep impairment"):ti,ab,kw)

Appendix 6: PRISMA flowchart



Appendix 7: Characteristics trazodone

	Study (Year)	Diagnosis	Study design	Sample size (experimental/control)	Dosage	Control	Duration	Outcomes
1	Camargos (2014)	Insomnia and Alzheimer	Randomized double-blind placebo controlled trial	(15/15)	50mg	Placebo	2 weeks	Objective: actigraphic data
2	Eraslan (2014)	Insomnia (in postmenopausal women)	Randomized open trial	(28/22)	50-100mg	Zopiclone 3,75-7,5mg	4 weeks	Subjective: HAM-D
3	Hadi (2022)	Insomnia and Parkinson's disease	Randomized double-blind trial	(31/31/31)	50mg	Melatonin 3mg and clonazepam 1mg	4 weeks	Subjective: PSQI, RBDSQ, ESS
4	Haffmans (1999)	Insomnia in depressed patients receiving a MAO-I	Randomized double-blind cross-over placebo controlled trial	7, cross-over	50mg	Placebo	1 week	Subjective: HAM-D Objective: PSG
5	He (2023)	Insomnia in elderly depressed patients	Randomized controlled trial	(30/30/30)	Unknown	CBTI and CBTI+trazodone	4 weeks	Subjective: PSQI, ESS, TST, SL, SE
6	Ilinoiu (2015)	Insomnia in old age depressed patients receiving SSRIs	Randomized controlled trial	(12/10/10)	50-100mg	Pregabaline 75-150mg, mirtazapine 15-30mg	24 weeks	Subjective: PSQI, CGI, QOLS, HAM-D
7	Janjic (2010)	Insomnia in perimenopausal women	Randomized controlled trial	(52/53)	50mg	Zolpidem 10mg	2 weeks	Subjective: ISI
8	Kaynak (2004)	Insomnia in depressed patients receiving SSRIs	Randomized double-blind cross-over placebo controlled trial	12, cross-over	100mg	Placebo	1 week	Subjective: PSQI Objective: PSG
9	Li (2021)	Chronic insomnia	Randomized controlled trial	(8/11)	50-100mg	CBTI	9 months	Subjective: ISI Objective: EEG
10	Morin (2020)	Chronic insomnia	Multiple-assignment single-blinded randomized trial	(27/27)	50-150mg	BT	6 weeks	Subjective: ISI
11	Nierenberg (1994)	Insomnia in depressed patients receiving fluoxetine or bupropion	Randomized double-blind cross-over placebo controlled trial	17, cross-over	50-100mg	Placebo	6,5 days	Subjective: PSQI, TST, SL, SE

12	Paterson (2009)	Primary insomnia	Randomized double-blind cross-over placebo controlled trial	12, cross-over	100mg	Placebo	1 week	Subjective: LSEQ, SMHSQ Objective: PSG
13	Petrescu (2019)	Insomnia and Alzheimer	Randomized open-label controlled trial	(23/20)	50-200mg	Quetiapine 50-300mg	Unknown	Subjective: patient reports Objective: nursing sleep logs
14	Roth (2011)	Primary insomnia	Randomized double-blind cross-over placebo controlled trial	16, cross-over	50mg	Placebo	1 week	Subjective: self-reported sleep, VAS Objective: PSG, equilibrium, memory, verbal learning, driving, muscle endurance
15	Saletu-Zyhlarz (2002)	Insomnia and depression	Randomized single-blind cross-over placebo controlled trial	11, cross-over	100mg	Placebo	1 day	Subjective: SSA, somatic complaints Objective: PSG, numerical memory, concentration…
16	Shell (2012)	Insomnia more than 6 weeks	Randomized double-blind placebo controlled trial	(36/25)	50mg	Placebo	2 weeks	Subjective: PSQI, LSEQ
17	Vgontzas (2016)	Insomnia	Randomized controlled pilot trial	(5/5)	Unknown	CBTI	3 months	Subjective: ISI Objective: MAP, CRP
18	Vgontzas (2018)	Insomnia with short sleep duration	Randomized controlled pilot trial	(10/10)	Unknown	CBTI	3 months	Objective: TST (actigraphy), cortisol levels
19	Vgontzas (2015)	Insomnia	Randomized controlled pilot trial	(5/5)	Unknown	CBTI	3 months	Subjective: ISI Objective: cortisol levels
20	Vgontzas (2020)	Insomnia with short sleep duration	Randomized open-label controlled pilot trial	(7/8)	50-100mg	CBTI	6 months	Subjective: ISI Objective: TST (actigraphy), cortisol levels
21	Walsh (1998)	Primary insomnia	Randomized double-blind placebo controlled trial	(90/97/91)	50mg	Placebo, zolpidem 10mg	2 weeks	Subjective: TST, SL
22	Wang (2020)	Chronic insomnia and arteriosclerotic cerebral small vessel disease	Randomized double-blind placebo-controlled pilot trial	(20/20)	50mg	Placebo	4 weeks	Subjective: PSQI, ESS, HAM-D and HAMA Objective: PSG, cognitive function
23	Zavesicka (2008)	Primary insomnia	Randomized controlled trial	(10/10)	100mg + CBTI	CBTI	2 months	Subjective: ISI, ESS Objective: PSG

Appendix 8: Characteristics (es)mirtazapine

	Study (Year)	Diagnosis	Study design	Sample size (experimental/control)	Dosage	Control	Duration	Outcomes
1	Ilinoiu (2015)	Insomnia in old age depressed patients receiving SSRIs	Randomized controlled trial	(10/12/10)	15-30mg	Trazodone 50-100mg, pregabaline 75-150mg	24 weeks	Subjective: PSQI, CGI, QOLS, HAM-D
2	Ivgy-May (2015)	primary insomnia in non-elderly patients	Randomized controlled trial, double-blinded	(137/125/128/135)	esmirtazapine 1.5mg/3.0mg/4.5mg	Placebo	2 weeks	Subjective: patient reported TST, SL, WASO, NA, quality of sleep, satisfaction of sleep, ISI score, IGR-C score
3	Ivgy-May (2015)	primary insomnia in non-elderly patients	Randomized controlled trial, double-blinded	(139/138/136)	esmirtazapine 3.0mg/4.5mg	Placebo	6 weeks	Objective: PSG examined TST, SL, WASO, NA, different stages Subjective: patient reported TST, SL, WASO, NA, quality of sleep, satisfaction of sleep, ISI score, IGR-C score
4	Ivgy-May (2020)	primary insomnia in non-elderly patients	Randomized controlled trial, double-blinded	(342/115)	esmirtazapine 4.5mg	Placebo	6 months	Subjective: patient reported TST, SL, WASO, NA, quality of sleep, satisfaction of sleep, ISI score, IGR-C score
5	Leinonen (1999)	Insomnia in major depressed patients receiving SSRIs	Randomized controlled trial, double-blinded	(136/133)	35.9mg (mean)	citalopram 36,6mg (mean)	8 weeks	Subjective: LSEQ
6	Scoralick (2017)	Sleep disorders in patients with Alzheimer's disease	Randomized controlled trial, double-blinded	(8/16)	15mg	Placebo	2 weeks	Objective: actigraphy examined TST, WASO and NA
7	Winokur (2003)	Insomnia in major depressed patients receiving SSRIs	Randomized controlled trial, double-blinded	(9/13)	45mg	fluoxetine 40mg	8 weeks	Objective: PSG examined TST, SL, WASO, SE, different stages Subjective: HAM-D, 3-item sleep score
8	Zhang (2018)	Insomnia in non-elderly depressed patients receiving SSRIs	Randomized controlled trial	(22/29)	30mg	paroxetine 75mg	6 weeks	Objective: PSG examined TST, SL, NA, WASO, SE, different stages Subjective: HAM-D, 3-item sleep score, PSQI

Appendix 9: Effects trazodone

ACUTE = YELLOW, CHRONIC = BLUE, UNKNOWN = WHITE	Camargos et al.	Eraslan et al.		Hadi et al.		
PRIMARY = LIGHT BLUE, SECONDARY = WHITE	SECONDARY	PRIMARY		SECONDARY		
PLACEBO = ORANGE	data in comparison to placebo	data in comparison to baseline		data in comparison to baseline		
	Traz. 50	Traz 50mg	zopiclone10mg	Traz 50mg	melat. 3mg	clonaz. 1mg
TST (min) after treatment	/	/	/	/	/	/
difference in TST (min)	(+)42,5	/	/	/	/	/
SL (min) after treatment	/	/	/	/	/	/
difference in SL (min)	/	/	/	/	/	/
WASO (min) after treatment	/	/	/	/	/	/
difference in WASO (min)	/	/	/	/	/	/
number of awakenings after treatment	/	/	/	/	/	/
difference in number of awakenings	/	/	/	/	/	/
Quality of sleep after treatment	/	/	/	/	/	/
difference in Quality of sleep	/	/	/	/	/	/
satisfaction with sleep duration after treatment	/	/	/	/	/	/
difference in satisfaction with sleep duration	/	/	/	/	/	/
ISI after treatment	/	/	/	/	/	/
difference in ISI	/	/	/	/	/	/
percentage of ISI responders after treatment	/	/	/	/	/	/
Total time in stage 1 sleep (min) after treatment	/	/	/	/	/	/
Total time in stage 2 sleep (min) after treatment	/	/	/	/	/	/
Total time in SWS (min) after treatment	/	/	/	/	/	/
Total REM time (min) after treatment	/	/	/	/	/	/
REM latency after treatment	/	/	/	/	/	/
HAM-D totaal after treatment	/	/	/	/	/	/
difference in HAMD-D	/	/	/	/	/	/
HAM-D 3-item sleep scores after treatment	/	1,46	1	/	/	/
difference in HAM-D 3-item sleep scores	/	-3,21	-4,27	/	/	/
sleep efficiency (total sleep time/time in bed) (%) after treatment	/	/	/	/	/	/
difference in sleep efficiency (%)	/	/	/	/	/	/
PSQI totaal after treatment	/	/	/	5,8	5,3	6
difference in PSQI	/	/	/	-5,6	-4,8	-5,7
RBDSQ totaal after treatment	/	/	/	3,5	1,3	0,3
difference in RBDSQ	/	/	/	-5,7	-7,5	-5,6
ESS totaal after treatment	/	/	/	4,9	5,9	6,2
difference in ESS	/	/	/	-3	-2,2	-1
Yale-New Haven Hospital Depressive Invetory 3-item sleep scores after treatment	/	/	/	/	/	/
difference in Yale-New Haven Hospital Depressive Invetory 3-item sleep scores	/	/	/	/	/	/
Leeds Sleep Evaluation Questionnaire after treatment	/	/	/	/	/	/
difference in Leeds Sleep Evaluation Questionnaire	/	/	/	/	/	/

Haffmans et al.		He et al.		Ilinoiu et al. 2015			Janjic et al.		Kaynak et al.	Li et al.	
SECONDARY		SECONDARY		SECONDARY			PRIMARY		SECONDARY	PRIMARY	
data in comparison to baseline after 1w				data in comparison to baseline					data in comparison to placebo	data in comparison to baseline (EEG)	
Traz 50mg	Placebo	Traz 50mg	CBT	mirt. 22,5mg mean	traz. 67mg mean	pregab. 112,5mg mean	Traz 50mg	zolpidem 10mg	Traz 100mg	CBT-I	Traz 50-100
364	407	significantly superior	significantly inferior	/	/	/	/	/	428	/	/
-5	(+)38	significantly superior	significantly inferior	/	/	/	/	/	(+)45	/	/
34	50	significantly superior	significantly inferior	/	/	/	/	/	14	/	/
-3	(+)5	significantly superior	significantly inferior	/	/	/	/	/	-19	/	/
58	48	/	/	/	/	/	/	/	/	/	/
-7	-22	/	/	/	/	/	/	/	/	/	/
2	5	/	/	/	/	/	/	/	12	/	/
-2	-2	/	/	/	/	/	/	/	-18	/	/
8	3	/	/	/	/	/	/	/	/	/	/
(+)5	0	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/
/	/	no significant difference	no significant difference	/	/	/	/	/	/	4,82	4,75
/	/	no significant difference	no significant difference	/	/	/	significantly superior	significantly inferior	/	-11,36	-12
/	/	/	/	/	/	/	/	/	/	/	/
3,70%	8%	/	/	/	/	/	/	/	3%	/	/
38%	46%	/	/	/	/	/	/	/	50%	/	/
28%	24%	/	/	/	/	/	/	/	31%	/	/
12%	12%	/	/	/	/	/	/	/	16%	/	/
203	258	/	/	/	/	/	/	/	230 min	/	/
/	/	/	/	/	/	/	/	/	11,5	/	/
/	/	/	/	-19%	-17,60%	-16,50%	/	/	-0,7 no sign. diff.	/	/
3,6	6,2	/	/	/	/	/	/	/	/	/	/
-0,4	(+)2	/	/	/	/	/	/	/	/	/	/
/	/	significantly superior	significantly inferior	/	/	/	/	/	89	/	/
/	/	significantly superior	significantly inferior	/	/	/	/	/	10	/	/
/	/	/	/	/	/	/	/	/	5	/	/
/	/	/	/	-30,20%	-38,70%	-31,20%	/	/	-0,34 no sign. diff.	/	/
/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/

Morin et al.		Nierenberg et al.	Paterson et al.	Petrescu et al.		Roth et al.	Saletu et al.	Shell et al.
PRIMARY		SECONDARY	PRIMARY	SECONDARY		PRIMARY	SECONDARY	PRIMARY
data in comparison to baseline		data in comparison to placebo	data in comparison to placebo	data in comparison to baseline		data in comparison to placebo	data in comparison to placebo	data in comparison to placebo
Zolpidem + BT	Zolpidem + traz 50-150	Traz 100mg	Traz 100mg	Quetiap. 50-300mg	Traz 50-200mg	Traz. 50	Traz. 100	Traz 50mg
390,4	431,5	/	433	480,6	505,2	/	375	/
(+)1,9	(+)38,6	/	(+)38	/	/	/	(+)33	/
22,3	17,6	/	/	/	/	26,2	/	/
-8,4	-11,5	/	/	/	/	-1,7	/	/
31,2	32	/	57	/	/	52,9	33	/
-10,5	-11,9	/	-20	/	/	-21,4	-25	/
/	/	/	/	/	/	12,7	4	/
/	/	/	significantly superior	/	/	-7,3	-7	/
/	/	/	/	/	/	/	14	/
/	/	/	/	/	/	/	-2,5	/
/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/
/	/	/	no significant difference	/	/	17,9	33	/
/	/	/	no significant difference	/	/	223,1	167	/
/	/	/	129	/	/	90,4	115	/
/	/	/	no significant difference	/	/	78	72	/
/	/	/	/	/	/	93	68	/
/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/
83,2	84,5	/	/	85	89	85,3	84	/
(+)5,9	(+)6,6	/	no significant difference	/	/	(+)3,6	(+)7	/
/	/	5,9	/	/	/	/	/	1,98
/	/	-4,4	/	/	/	/	/	(+)1,03
/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/
/	/	1,4	/	/	/	/	/	/
/	/	-2,5	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/
/	/	/	significantly superior	/	/	/	/	/

Vgontzas et al. 1		Vgontzas et al. 2		Vgontzas et al. 3		Vgontzas et al. 4		Walsh et al.		Wang et al.	Zavesicka et al.	
PRIMARY		PRIMARY		PRIMARY		PRIMARY		PRIMARY		SECONDARY	PRIMARY	
data in comparison to baseline		data in comparison to baseline		data in comparison to baseline		data in comparison to baseline		data in comparison to placebo		data in comparison to placebo	data in comparison to baseline	
CBT-I	Traz	CBT-I	Traz	CBT-I	Traz	CBT-I	Traz 50-100	zolp. 10mg	traz. 50mg	Traz. 50	CBT	CBT + traz 100
/	/	/	/	/	/	386,63	431,66	378,7	366,4	392,48	359,1	361,9
/	/	(+)6,08	(+)59,85	/	/	-11,73	(+)51,01	(+)18,7	(+)12,2	(+)10,29	(+)35,6	(+)56,3
/	/	/	/	/	/	/	/	48,1	54,5	29,41	12,4	14,1
/	/	/	/	/	/	/	/	-16,6	-10,2	-4,93	-23,8	-51,3
/	/	/	/	/	/	/	/	39,5	42,1	42,42	75	74,8
/	/	/	/	/	/	/	/	-10,3	-7,7	-12,97	-22,3	-33,8
/	/	/	/	/	/	/	/	1,5	1,4	/	/	/
/	/	/	/	/	/	/	/	-0,3	-0,4	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	4,63	5,29	/	/	/	10,1	11
-13,2	-12,8	/	/	-13,2	-12,8	-10,75	-12,29	/	/	/	-6,2	-5,4
/	/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	9,44%	38,5	28,5
/	/	/	/	/	/	/	/	/	/	59,72%	197,4	148,2
/	/	/	/	/	/	/	/	/	/	15,37%	40,2	120,3
/	/	/	/	/	/	/	/	/	/	15%	83	65
/	/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	6,65	/	/
/	/	/	/	/	/	/	/	/	/	-1,2	/	/
/	/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	85,32	90,83	/	/	81,67	80,9	80,8
/	/	/	/	/	/	/	/	/	/	-6,76	(+)10,2	(+)15,6
/	/	/	/	/	/	/	/	/	/	7,33	/	/
/	/	/	/	/	/	/	/	/	/	-3,39	/	/
/	/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	4,12	9,2	8,1
/	/	/	/	/	/	/	/	/	/	-2,38	-1,7	-3,3
/	/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/	/
/	/	/	/	/	/	/	/	/	/	/	/	/

Appendix 10: Effects (es)mirtazapine

ACUTE = YELLOW, CHRONIC = BLUE, UNKNOWN = WHITE	Ilinoiu et al. 2015			Ivgy-May et al. 2015, 2 week			Ivgy-May et al. 2015, 6 week		Ivgy-May et al. 2020	Leinonen et al. 1999		Scoralick et al. 2017	Winokur et al. 2003		Zhang et al. 2018	
PRIMARY = LIGHT BLUE, SECONDARY = WHITE	SECONDARY			PRIMARY			PRIMARY		PRIMARY	SECONDARY		SECONDARY	SECONDARY		SECONDARY	
PLACEBO = ORANGE	data in comparison to baseline			data in comparison to placebo			data in comparison to placebo		data in comparison to placebo	data in comparison to baseline		data in comparison to placebo	data in comparison to baseline		data in comparison to baseline	
	mirt. 22,5mg mean	traz. 67mg mean	pregab. 112,5mg mean	esmirt. 1,5mg	esmirt. 3,0mg	esmirt. 4,5mg	esmirt. 3,0mg	esmirt. 4,5mg	esmirt. 4,5mg	mirt. 15-60mg	cit. 20-60mg	mirt. 15mg	mirt. 45mg	fluox. 40mg	mirt. 30mg	parox. 75mg
TST (min) after treatment	/	/	/	393	390	409	406	419	373	/	/	414	428	325	454	188
difference in TST (min)	/	/	/	(+)33	(+)30	(+)49	(+)32	(+)45	(+)48	/	/	(+)22	(+)100	(+)8	(+)268	-220
SL (min) after treatment	/	/	/	41	40	41	41	45	45,7	/	/	/	11	43	12	12
difference in SL (min)	/	/	/	-11	-12	-11	-10	-6	-5	/	/	/	-23	(+)4	-1	-7
WASO (min) after treatment	/	/	/	56	57	42	57	54	43	/	/	160	39	70	10	46
difference in WASO (min)	/	/	/	-5	-4	-19	-17	-20	-25	/	/	-6	-42	(+)10	-32	(+)27
number of awakenings after treatment	/	/	/	1,2	1,3	1,2	1,6	1,8	1,3	/	/	30	/	/	6	19
difference in number of awakenings	/	/	/	-0,4	-0,4	-0,4	-0,3	-0,1	-0,5	/	/	0	/	/	-11	(+)7
Quality of sleep after treatment	/	/	/	56 (out of 100)	54 (out of 100)	53 (out of 100)	54 (out of 100)	58 (out of 100)	57 (out of 100)	/	/	/	/	/	/	/
difference in Quality of sleep	/	/	/	+8 (out of 100)	+6 (out of 100)	+5 (out of 100)	+3 (out of 100)	+5 (out of 100)	+12 (out of 100)	/	/	/	/	/	/	/
satisfaction with sleep duration after treatment	/	/	/	55 (out of 100)	52 (out of 100)	52 (out of 100)	53 (out of 100)	55 (out of 100)	57 (out of 100)	/	/	/	/	/	/	/
difference in satisfaction with sleep duration	/	/	/	+9 (out of 100)	+6 (out of 100)	+6 (out of 100)	+4 (out of 100)	+6 (out of 100)	+12 (out of 100)	/	/	/	/	/	/	/
ISI after treatment	/	/	/	12	11	11	12	11	11	/	/	/	/	/	/	/
difference in ISI	/	/	/	-3	-4	-3	-3	-4	-3	/	/	/	/	/	/	/
percentage of ISI responders after treatment	/	/	/	41 (placebo = 20)	47 (placebo = 20)	52 (placebo = 20)	/	/	41 (18 in the placebo group)	/	/	/	/	/	/	/
Total time in stage 1 sleep (min) after treatment	/	/	/	/	/	/	/	/	/	/	/	/	111	68	18	61
Total time in stage 2 sleep (min) after treatment	/	/	/	/	/	/	/	/	/	/	/	/	203	180	110	108
Total time in SWS (min) after treatment	/	/	/	/	/	/	/	/	/	/	/	/	43	19	51	19
Total REM time (min) after treatment	/	/	/	/	/	/	/	/	/	/	/	/	72	60	71	40
REM latency after treatment	/	/	/	/	/	/	(+) 30min cf. placebo	(+) 40min cf. placebo	/	/	/	/	141	202	82	171
HAM-D totaal after treatment	/	/	/	/	/	/	/	/	/	/	/	/	7,1	12,2	10,16	8,5
difference in HAMD-D	-19%	-17,60%	-16,50%	/	/	/	/	/	/	/	/	/	-18,5	-14,5	-18,1	-18,65
HAM-D 3-item sleep scores after treatment	/	/	/	/	/	/	/	/	/	/	/	/	1,3	2,9	1,97	2,55
difference in HAM-D 3-item sleep scores	/	/	/	/	/	/	/	/	/	/	/	/	-3,5	-2,3	-1,91	-1,4
sleep efficiency (total sleep time/time in bed) (%) after treatment	/	/	/	/	/	/	/	/	/	/	/	/	92	82	81	79
difference in sleep efficiency (%)	/	/	/	/	/	/	/	/	/	/	/	/	(+)13	-2	-6	-10
PSQI totaal after treatment	/	/	/	/	/	/	/	/	/	/	/	/	/	/	5,77	7,6
difference in PSQI	-30,20%	-38,70%	-31,20%	/	/	/	/	/	/	/	/	/	/	/	-6,49	-4,25

Appendix 11: Safety trazodone

	Eraslan et al.	Hadi et al.	Haffmans et al.	Ilinoiu et al.	Janjic et al.	Kaynak et al.	Nierenberg et al.	Petrescu et al.	Roth et al.	Saletu et al.	Shell et al.	Walsh et al.	Wang et al.
prolonged erection							1 patient						
dizziness	yes	3%	yes		22% after 1w			yes				yes	18.80%
sedation	yes			75%	25% after 1w 6% after 2w	34%	1 patient				18%	23%	
bitter sweet taste	yes												
hypersomnia	yes												
orthostatic hypotention		3%			19% after 1w								
constipation			yes					yes					
nausea			yes		19% after 1w 12%after 2w							yes	12.50%
dry mouth			yes										
palpitations			yes										
heartburn			yes			17%							
thingling feeling in the chin			yes										
headache					19% after 2w							30%	6.20%
short term memory worsening									yes				
verbal learning worsening									yes				
body sway worsening									yes				
arm muscle endurance worsening									yes				
morning and evening well-being deteriorated										yes			
morning drive deteriorated										yes			
mood worsening										yes			
insomnia worsening													12.50%
akathisia													12.50%
loss of appetite													25%

Appendix 12: Safety (es)mirtazapine

	Ilinoiu et al.	Ivgy-May et al. 2015, 2 week (esmirt.)	Ivgy-May et al. 2015, 6 week (esmirt.)	Ivgy-May et al. 2020 (esmirt.)	Leinonen et al.	Scoralick et al.	Winokur et al.	Zhang et al.
somnolence	30%	7 - 9%	11.5-13%	14.90%	16%	yes	/	/
weight gain	/	mean 0.51-0.88kg	0.7-2.2% mean 0.51-1kg	17% mean 1.5kg	15.3% mean 1.9kg	/	/	/
headache	/	1.5-4.7%	3.6-5.1%	8.80%	9.50%	/	/	/
nasopharyngitis	/	0.8-1.5%	0-2.9%	10.20%	5.10%	/	/	/
upper respiratory tract infection	/	0.8-2.3%	/	3.80%	/	/	/	/
increased appetite	/	1.5-3.1%	/	9.90%	8.80%	/	/	/
dizziness	/	0.8-2.4%	2.9-3.6%	7.90%	8.80%	/	/	/
peripheral edema	/	0.7-2.3%	/	2.60%	/	/	/	/
GGT increase	/	0.7-2.4%	/	2.30%	/	/	/	/
ALT increase	/	0-2.4%	/	/	/	/	/	/
sinusitis	/	/	0-2.2%	/	/	/	/	/
abnormal dreams	/	/	0-2.2%	/	/	/	/	/
anxiety	/	/	0-2.2%	/	/	yes	/	/
sinus congestion	/	/	0.7-2.2%		14.60%	/	/	/
dry mouth	/	/	2.2-3.6%	5.80%	/	/	/	/
nausea	/	/	1.4-2.2%	7.90%	10.20%	/	/	/
fatigue	/	/	/	5.30%	12.40%	/	/	/
arthralgia	/	/	/	3.00%	/	/	/	/
cough	/	/	/	2.30%	/	/	/	/
restless leg syndrome	/	/	/	2.90%	/	/	/	/
back pain	/	/	/	2.00%	/	/	/	/
constipation	/	/	/	2.90%	/	/	/	/
hypertention	/	/	/	2.60%	/	/	/	/
insomnia	/	/	/	1.80%	/	/	/	/
hypercholesterolemia	/	/	/	2.00%	/	/	/	/
gastro-enteritis	/	/	/	1.50%	/	/	/	/
diarrhea	/	/	/	/	2.90%	/	/	/
increased swetting	/	/	/	/	2.20%	/	/	/

Appendix 13: RoB 2 risk of bias assessment

Summary

								OUTCOMES										
Study	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain S	Overall	TST	SL	WASO	NA	ISI	HAMD	HAMD3	PSQI	RBDSQ	ESS	
Camargos (2014)	2	3	3	1	2		2	1										TST
Eraslan (2014)	1	3	3	3	2		3							1				HAMD 3
Hadi (2022)	1	2	3	1	1		1								1	1	1	PSQI RBDSQ ESS
Haffmans (1999)	1	1	1	1	1	1	1	1	1	1	1							TST SL WASO NA
He (2023)	2	2	3	3	2		3	1	1			1						TST SL ISI
Ilinoiu (2015)	1	2	3	3	2		2						1		1			HAMD PSQI
Janjic (2010)	2	2	3	3	2		2					1						ISI
Kaynak (2004)	1	1	1	1	1	1	1	1	1	1	1			1	1			TST SL WASO NA HAMD3 PSQI
Li (2021)	2	2	3	1	1		2					1						ISI
Morin (2020)	1	3	3	3	1		3	1	1	1								TST SL WASO
Nierenberg (1994)	1	3	3	3	1	3	3								1			PSQI
Paterson (2009)	1	1	1	1	1	1	2	1		1	1							TST WASO NA
Petrescu (2019)	1	3	3	3	3		3	1										TST
Roth (2011)	1	1	1	1	1	1	1		1	1	1							SL WASO NA
Saletu-Zyhlarz (2002)	1	2	1	2	1	2	2	1		1	1							TST WASO NA
Shell (2012)	1	1	1	1	1		1								1			PSQI
Vgontzas (2016)	2	3	1	3	1		3					1						ISI
Vgontzas (2018)	2	3	1	3	1		3	1										TST
Vgontzas (2015)	2	3	1	3	1		3					1						ISI
Vgontzas (2020)	2	3	1	3	1		3	1				1						TST ISI
Walsh (1998)	1	1	1	1	1		1	1	1	1	1							TST SL WASO NA
Wang (2020)	1	2	2	1	1		2	1	1	1					1		1	TST SL WASO PSQI ESS
Zavesicka (2008)	1	2	1	2	1		2	1	1	1		1					1	TST SL WASO ISI ESS
Ivgy-May (2015)	1	1	1	1	1		1	1	1	1	1	1						TST SL WASO NA ISI
Ivgy-May (2015)	1	1	1	1	1		1	1	1	1	1	1						TST SL WASO NA ISI
Ivgy-May (2020)	1	1	1	1	1		1	1	1	1	1	1						TST SL WASO NA ISI
Leinonen(1999)	1	1	1	1	1		1											/
Scoralick(2017)	1	1	1	1	1		1	1		1	1							TST WASO NA
Winokur(2003)	1	1	1	1	1		1	1	1	1			1	1				TST SL WASO HAMD HAMD3
Zhang(2018)	3	3	3	3	1		3	1	1	1	1		1	1	1			TST SL WASO NA HAMD HAMD3 PSQI
	40	58	53	56	37	9	58	19	13	15	11	10	3	4	7	1	3	

Index	Low Risk	Some Concerns	High Risk
Score	1	2	3

Per outcome

TST	Overall
Camargos (2014)	2
Haffmans (1999)	1
He (2023)	3
Kaynak (2004)	1
Morin (2020)	3
Paterson (2009)	2
Petrescu (2019)	3
Saletu-Zyhlarz (2002)	2
Vgontzas (2018)	3
Vgontzas (2020)	3
Walsh (1998)	1
Wang (2020)	2
Zavesicka (2008)	2
Ivgy-May (2015)	1
Ivgy-May (2015)	1
Ivgy-May (2020)	1
Scoralick(2017)	1
Winokur(2003)	1
Zhang(2018)	3

SL	Overall
Haffmans (1999)	1
He (2023)	3
Kaynak (2004)	1
Morin (2020)	3
Roth (2011)	1
Walsh (1998)	1
Wang (2020)	2
Zavesicka (2008)	2
Ivgy-May (2015)	1
Ivgy-May (2015)	1
Ivgy-May (2020)	1
Winokur(2003)	1
Zhang(2018)	3

WASO	Overall
Haffmans (1999)	1
Kaynak (2004)	1
Morin (2020)	3
Paterson (2009)	2
Roth (2011)	1
Saletu-Zyhlarz (2002)	2
Walsh (1998)	1
Wang (2020)	2
Zavesicka (2008)	2
Ivgy-May (2015)	1
Ivgy-May (2015)	1
Ivgy-May (2020)	1
Scoralick(2017)	1
Winokur(2003)	1
Zhang(2018)	3

NA	Overall
Haffmans (1999)	1
Kaynak (2004)	1
Paterson (2009)	2
Roth (2011)	1
Saletu-Zyhlarz (2002)	2
Walsh (1998)	1
Ivgy-May (2015)	1
Ivgy-May (2015)	1
Ivgy-May (2020)	1
Scoralick(2017)	1
Zhang(2018)	3

ISI	Overall
He (2023)	3
Janjic (2010)	2
Li (2021)	2
Vgontzas (2016)	3
Vgontzas (2015)	3
Vgontzas (2020)	3
Zavesicka (2008)	2
Ivgy-May (2015)	1
Ivgy-May (2015)	1
Ivgy-May (2020)	1

PSQI	Overall
Hadi (2022)	1
Ilinoiu (2015)	2
Kaynak (2004)	1
Nierenberg (1994)	3
Shell (2012)	1
Wang (2020)	2
Zhang(2018)	3

RoB 2 in detail

Question	Response Options	Camargos	Eraslan	Hadi	Haffmans	He	Ilinoiu	Janjic	Kaynak	Li	Morin	Nierenberg	Paterson	Petrescu
		Abstract	Full Text	Full Text	Full Text	Abstract	Abstract	Abstract	Full Text	Full Text	Full Text	Full Text	Abstract	Abstract
Domain 1: Risk of bias arising from the randomization process														
1.1 Was the allocation sequence random?	Y / PY / PN / N / NI	Y	Y	Y	Y	PY	Y	PY	Y	Y	Y	Y	Y	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y / PY / PN / N / NI	NI	PY	Y	Y	NI	PY	NI	Y	NI	Y	Y	Y	PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Y / PY / PN / N / NI	NI	PN	N	NI	NI	NI	NI	PN	N	PN	PN	NI	NI
Risk-of-bias judgement	Low / High / Some concerns	Some concerns	Low Risk	Low Risk	Low Risk	Some concerns	Low Risk	Some concerns	Low Risk	Some concerns	Low Risk	Low Risk	Low Risk	Low Risk
Optional: What is the predicted direction of bias arising from the randomization process?	NA / Favours experimental /Favours comparator / Towards null /Away from null / Unpredictable	Unpredictable	Favours comparator	NA	NA	Favours experimental	NA	Favours experimental	NA	Favours experimental	NA	NA	NA	NA
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)														
2.1. Were participants aware of their assigned intervention during the trial?	Y / PY / PN / N / NI	N	Y	N	N	Y	NI	NI	N	Y	N	N	N	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y / PY / PN / N / NI	N	Y	N	N	Y	NI	NI	N	Y	Y	Y	N	Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	NA / Y / PY / PN / N / NI	NA	NI	NA	NA	NI	NI	NI	NA	NI	PY	PY	NA	PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA / Y / PY / PN / N / NI	NA	NA	NA	NA	NA	NA	NA	NA	NA	PY	PY	NA	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between	NA / Y / PY / PN / N / NI	NA	NA	NA	NA	NA	NI	NI	NA	NA	PN	PN	NA	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y / PY / PN / N / NI	NI	N	N	Y	NI	NI	NI	Y	Y	NI	N	PY	NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA / Y / PY / PN / N / NI	NI	PY	NI	NA	NI	NI	NI	NA	NA	PY	PY	PN	NI
Risk-of-bias judgement	Low / High / Some concerns	High Risk	High Risk	High Risk	Low Risk	Some concerns	Some concerns	Some concerns	Low Risk	Some concerns	High Risk	High Risk	Low Risk	High Risk
Optional: What is the predicted direction of bias due to deviations from intended interventions?	NA / Favours experimental /Favours comparator / Towards null /Away from null / Unpredictable	Unpredictable	Unpredictable	Unpredictable	NA	Favours experimental	Unpredictable	Unpredictable	NA	Favours experimental	Favours experimental	Favours experimental	NA	Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)														
2.1. Were participants aware of their assigned intervention during the trial?	Y / PY / PN / N / NI	N	Y	N	N	Y	NI	NI	N	Y	N	N	N	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y / PY / PN / N / NI	N	Y	N	N	Y	NI	NI	N	Y	Y	Y	N	Y
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NA / Y / PY / PN / N / NI	NA	NI	NA	NA	NI	NI	NI	NA	NI	NI	PN	NA	NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	NA / Y / PY / PN / N / NI	NI	NI	N	N	NI	NI	NI	N	NI	NI	PY	NI	PY
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	NA / Y / PY / PN / N / NI	NI	PY	N	N	NI	NI	NI	N	NI	NI	PY	NI	NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA / Y / PY / PN / N / NI	NI	N	NA	NA	NI	NI	NI	NA	N	N	N	NI	NI
Risk-of-bias judgement	Low / High / Some concerns	High Risk	High Risk	Low Risk	Low Risk	High Risk	High Risk	High Risk	Low Risk	High Risk	High Risk	High Risk	High Risk	High Risk
Optional: What is the predicted direction of bias due to deviations from intended interventions?	NA / Favours experimental /Favours comparator / Towards null /Away from null / Unpredictable	Unpredictable	Unpredictable	NA	NA	Favours experimental	Unpredictable	Unpredictable	NA	Favours experimental	Favours experimental	Favours experimental	NA	Unpredictable
Domain 3: Missing outcome data														
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y / PY / PN / N / NI	NI	N	N	Y	NI	NI	NI	Y	N	N	N	PY	NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA / Y / PY / PN / N	N	N	N	NA	N	N	N	NA	N	N	N	NA	N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA / Y / PY / PN / N / NI	NI	Y	NI	NA	NI	NI	NI	NA	NI	NI	NI	NA	NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA / Y / PY / PN / N / NI	NI	Y	NI	NA	NI	NI	NI	NA	PY	PY	PY	NA	NI
Risk-of-bias judgement	Low / High / Some concerns	High Risk	High Risk	High Risk	Low Risk	High Risk	High Risk	High Risk	Low Risk	High Risk	High Risk	High Risk	Low Risk	High Risk
Optional: What is the predicted direction of bias due to deviations from intended interventions?	NA / Favours experimental /Favours comparator / Towards null /Away from null / Unpredictable	Unpredictable	Unpredictable	Unpredictable	NA	Favours experimental	Unpredictable	Unpredictable	NA	Favours experimental	Favours experimental	Favours experimental	NA	Unpredictable

Domain 4: Risk of bias in measurement of the outcome														
4.1 Was the method of measuring the outcome inappropriate?	Y / PY / PN / N / NI	N	N	N	N	N	PN	N	N	N	N	N	N	Y
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Y / PY / PN / N / NI	PN	PY	N	PN	Y	NI	NI	PN	PN	PN	PN	PN	PY
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	NA / Y / PY / PN / N / NI	N	Y	N	N	Y	NI	NI	N	N	Y	Y	N	Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA / Y / PY / PN / N / NI	NA	Y	NA	NA	Y	Y	Y	NA	NA	PY	PY	NA	PY
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA / Y / PY / PN / N / NI	NA	Y	NA	NA	PY	NI	NI	NA	NA	PY	PY	NA	PY
Risk-of-bias judgement	Low / High / Some concerns	Low Risk	High Risk	Low Risk	Low Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk	High Risk	High Risk	Low Risk	High Risk
Optional: What is the predicted direction of bias in measurement of the outcome?	NA / Favours experimental /Favours comparator / Towards null /Away from null / Unpredictable	NA	Unpredictable	NA	NA	Favours experimental	Unpredictable	Unpredictable	NA	NA	Favours experimental	Favours experimental	NA	Unpredictable
Domain 5: Risk of bias in selection of the reported result														
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y / PY / PN / N / NI	NI	NI	Y	Y	NI	NI	NI	Y	Y	Y	Y	Y	NI
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y / PY / PN / N / NI	NI	PN	PN	N	NI	NI	NI	N	N	N	N	N	PY
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	Y / PY / PN / N / NI	NI	PN	PN	N	NI	NI	NI	N	N	N	N	N	NI
Risk-of-bias judgement	Low / High / Some concerns	Some concerns	Some concerns	Low Risk	Low Risk	Some concerns	Some concerns	Some concerns	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk
Optional: What is the predicted direction of bias due to selection of the reported result?	NA / Favours experimental /Favours comparator / Towards null /Away from null / Unpredictable	Unpredictable	Unpredictable	NA	NA	Favours experimental	Unpredictable	Unpredictable	NA	NA	NA	NA	NA	Unpredictable

Domain S (only for cross-over studies): Risk of bias arising from period and carryover effects														
S.1 Was the number of participants allocated to each of the two sequences equal or nearly equal?	Y / PY / PN / N / NI				Y				Y			N	NI	
S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?	NA / Y / PY / PN / N / NI				NA				NA			N	Y	
S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?	Y / PY / PN / N / NI				PY				PY			NI	Y	
Risk-of-bias judgement	Low / High / Some concerns				Low Risk				Low Risk			High Risk	Low Risk	
Optional: What is the predicted direction of bias arising from period and carryover effects?	NA / Favours experimental /Favours comparator / Towards null /Away from null / Unpredictable				NA				NA			Favours experimental	NA	
Overall risk of bias														
Risk-of-bias judgement	Low / High / Some concerns	Some concerns	High Risk	Low Risk	Low Risk	High Risk	Some concerns	Some concerns	Low Risk	Some concerns	High Risk	High Risk	Some concerns	High Risk
Optional: What is the overall predicted direction of bias for this outcome?	NA / Favours experimental /Favours comparator / Towards null /Away from null / Unpredictable	Unpredictable	Unpredictable	NA	NA	Favours experimental	Unpredictable	Unpredictable	NA	Favours experimental	Favours experimental	Favours experimental	Unpredictable	Unpredictable

Roth	Saletu	Shell	Vgontzas 1	Vgontzas 2	Vgontzas 3	Vgontzas 4	Walsh	Wang	Zavesika	Ivgy-May 1	Ivgy-May 2	Ivgy-May 3	Leinonen	Scoralick	Winokur	Zhang
Full Text	Full Text	Full Text	Abstract	Abstract	Abstract	Full Text	Full Text	Full Text	Full Text	Full Text	Full Text	Full Text	Full Text	Full Text	Full Text	Full Text
Domain 1: Risk of bias arising from the randomization process																
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
PY	PY	PY	NI	NI	NI	Y	Y	Y	Y	Y	Y	Y	PY	Y	Y	NI
N	NI	NI	NI	NI	NI	NI	N	N	N	N	N	N	N	N	N	Y voor TST, SL en AT
Low Risk	Low Risk	Low Risk	Some concerns	Some concerns	Some concerns	Some concerns	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk
NA	NA	NA	Unpredictable	Unpredictable	Unpredictable	Unpredictable	NA	NA	NA	NA	NA	NA	NA	NA	NA	Favours experimental
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)																
N	N	N	NI	NI	NI	Y	N	N	N	N	N	N	N	N	N	NI
N	Y	N	NI	NI	NI	Y	N	N	NI	N	N	N	N	N	N	NI
NA	PN	NA	NI	NI	NI	PY	NA	NA	N	NA	NA	NA	NA	NA	NA	NI
NA	NA	NA	NA	NA	NA	PY	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NI	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Y	Y	Y	NI	NI	NI	Y	Y	NI	Y	Y	Y	Y	Y	Y	Y	NI
NA	NA	NA	NI	NI	NI	NA	NA	PN	NA	NA	NA	NA	NA	NA	NA	N
Low Risk	Low Risk	Low Risk	High Risk	High Risk	High Risk	High Risk	Low Risk	Some concerns	Some concerns	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk
NA	NA	NA	Unpredictable	Unpredictable	Unpredictable	Favours experimental	NA	Unpredictable	Unpredictable	NA	NA	NA	NA	NA	NA	Favours experimental

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)																
N	N	N	NI	NI	NI	Y	N	N	NI	N	N	N	N	N	N	NI
N	Y	N	NI	NI	NI	Y	N	N	NI	N	N	N	N	N	N	NI
NA	NI	NA	NI	NI	NI	NI	NA	NA	PN	NA	NA	NA	NA	NA	NA	NI
N	PN	PN	NI	NI	NI	PY	PN	PN	PN	PN	PN	PN	PN	PN	PN	NI
N	PN	PN	NI	NI	NI	PY	PN	PN	PN	PN	PN	PN	PN	PN	PN	NI
NA	NI	NA	NI	NI	NI	NI	NA	NA	NA	NA	NA	NA	NA	NA	NA	NI
Low Risk	Some concerns	Low Risk	High Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk
NA	Unpredictable	NA	Unpredictable	Unpredictable	Unpredictable	Favours experimental	NA	NA	NA	NA	NA	NA	NA	NA	NA	Favours experimental
Domain 3: Missing outcome																
Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N
PY	PY	Y	Y	Y	Y	Y	Y	NI	Y	Y	Y	Y	Y	Y	Y	N
NA	NA	NA	NA	NA	NA	NA	NA	NI	NA	NA	NA	NA	NA	NA	NA	PY
NA	NA	NA	NA	NA	NA	NA	NA	PN	NA	NA	NA	NA	NA	NA	NA	PY
Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Some concerns	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk
NA	NA	NA	NA	NA	NA	NA	NA	Favours experimental	NA	NA	NA	NA	NA	NA	NA	Favours experimental

Domain 4: Risk of bias in measurement of the outcome																
N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PN	PN	PN	PN	PN	PN	PN	N	N	N	N	N	N	PN	PN	PN	NI
N	Y	N	NI	NI	NI	NI	N	N	NI	N	N	N	N	N	N	NI
NA	PY	NA	PY	PY	PY	PY	NA	NA	PY	NA	NA	NA	NA	NA	NA	PY
NA	PN	NA	NI	NI	NI	NI	NA	NA	PN	NA	NA	NA	NA	NA	NA	PY
Low Risk	Some concerns	Low Risk	High Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk	Some concerns	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk
NA	Favours experimental	NA	Unpredictable	Unpredictable	Unpredictable	Unpredictable	NA	NA	Favours experimental	NA	NA	NA	NA	NA	NA	Favours experimental
Domain 5: Risk of bias in selection of the reported result																
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Domain S (only for cross-over studies): Risk of bias arising from period and carryover effects																
Y	NI															
NA	NI															
Y	Y															
Low Risk	Some concerns															
NA	Unpredictable															
Overall risk of bias																
Low Risk	Some concerns	Low Risk	High Risk	High Risk	High Risk	High Risk	Low Risk	Some concerns	Some concerns	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Risk
NA	Favours experimental	NA	Unpredictable	Unpredictable	Unpredictable	Favours experimental	NA	Favours experimental	Favours experimental	NA	NA	NA	NA	NA	NA	Favours experimental

Appendix 14: Limitations per trial (trazodone)

The study of Camargos et al. (88) was a randomised double-blind placebo-controlled trial. The size of the population was rather small with 30 patients who were randomised. A final important remark of this study was the fact that only the abstract of the study was available with only few reported results. It was not possible to analyse the study protocol or further patient characteristics. Furthermore only significant improvements were reported. This means the results need to be interpreted with caution and makes it hard to compare this trial with others.

The study of Eraslan et al. (89) was a randomised open-label controlled trial. The size of the population was mediate with 57 female patients who were randomised with a mean age of 51 years. The only sleep parameter that was observed was the HAM-D score, which means that the results are subjective. Patients were given different doses of trazodone (50mg to 100mg) and zopiclone (3,75 to 7,5mg). It was not clear how the dose was determined for a particular patient. In the results, the different dosages are fused together in one outcome. It would be much more interesting if studies compared different doses, but we have not found a study like that. An important remark of this study was the fact that 7 patients did not finish the study due to side effects, which were not further discussed.

The study of Hadi et al. (90) was a randomised double-blind controlled trial. The size of the population was moderate with 93 patients who were randomised with a mean age of 66 years. The only sleep parameter that was observed was the PSQI score, the RBDSQ score and the ESS score, which means that the results are subjective. An important remark of this study was the fact that patients with subjective sleep complaints were included, no distinction was made between types of sleep problems or their severity.

The study of Haffmans et al. (91) was a randomised double-blind crossover placebo-controlled trial with use of PSG. The size of the population was small with 7 patients who were randomised. PSG was performed at baseline, at day 9 and at day 16 with the crossover in between, so only based on one night. An important remark of this study was the fact that patients were included based on sleep complaints caused by brofaromine intake, which is a MAO-A-inhibitor that can cause sleep disturbances. This combination should be strictly monitored because of the higher risk of serotonin syndrome. Only four of the seven participants wished to continue trazodone after the study.

The study of He et al. (92) was a randomised controlled trial. The size of the population was good with 90 patients who were randomised. An important remark of this study was the fact that only the abstract of the study was available with only few reported results. It was not possible to analyse the study protocol or patient characteristics. Furthermore only significant improvements were reported. This means the results need to be interpreted with caution and makes it hard to compare this trial with the others.

The study of Ilinoiu et al. (117) was a randomised controlled trial where trazodone was compared to mirtazapine, pregabalin and baseline values. Unfortunately, there was no comparison to placebo. The size of the population was rather small with 32 patients who were randomised with a mean age of 67 years old. The only sleep parameters that were observed were the PSQI and the HAM-D score, which means that the results are subjective. A final important side note of this study was the fact that only the abstract of the study was available with only few knowable results. This means the results need to be interpreted with caution and makes it hard to compare this trial with the others. Another important fact is that the study population received already SSRIs which can influence the results.

The study of Janjic et al. (93) was a randomised controlled trial. The size of the population was large with 105 patients who were randomised. An important remark of this study was the fact that only the abstract of the study was available with only few reported results. It was not possible to analyse the study protocol or patient characteristics. This means the results need to be interpreted with caution and makes it hard to compare this trial with the others.

The study of Kaynak et al. (94) was a randomised double-blind crossover placebo-controlled trial with use of PSG. They studied insomnia in depressed patients receiving SSRIs. The size of the population was small with 12 female patients who were randomised with a mean age of 42 years. There was a significant improvement in the PSQI seen after 15 days of placebo in one of the groups, which suggests a large placebo and Hawthorne effect. However the results of the PSG measurements could not produce similar outcomes for the placebo group. A final important limitation of this study was the fact that the results are based on the PSG of one single night, which can also lead to a more uncertain outcome.

The study of Li et al. (95) was an open-label randomised controlled trial with use of EEG. The size of the population was small with 19 patients who were randomised with an age range between 30 and 60 years. The study started with a dosage of 50mg a day but 3 patients increased the dosage to 75mg daily and 2 others to 100mg daily. The EEG measurement was during 3 consecutive nights at the beginning of the study and after 3 months of treatment. It was the only study included that used EEG to obtain objective outcomes, which makes it hard to compare the results to other studies. Trazodone was compared to CBT, which means that the study was open-label. There was no placebo group which makes it not possible to estimate the true effect of trazodone.

The study of Morin et al. (96) was a single-blinded randomised controlled trial. The size of the population was moderate with 54 patients who were randomised with a mean age of 46 years. It was noticeable that a large number of participants did not finish the study, however it was not mentioned why. The study design was different to the others: first zolpidem was given and the non-remitters were given trazodone or CBT as add-on therapy. However the other part of the study where CBT was given first followed by zolpidem as an add-on, produced the most ISI-remitters. However the effect of CBT + trazodone was not checked in this study and thus cannot be compared to CBT +

zolpidem. The only sleep parameter that was observed was the ISI, which means that the results are rather subjective and vague compared to those using PSG for example.

The study of Nierenberg et al. (97) was a randomised double-blind crossover placebo-controlled trial. The size of the population was small with 15 patients who were randomised, with a mean age of 41,9 years. Thirteen of the 15 patients doubled the dosage of trazodone to 100mg daily. The only sleep parameter that was observed was the ISI, which means that the results are rather subjective and vague compared to those using PSG for example. An important remark of this study was the fact that patients were included based on sleep complaints caused or aggravated by bupropion or fluoxetine intake. The combination with trazodone should be strictly monitored because of the higher risk of serotonin syndrome. Only four of the seven participants wished to continue trazodone after the study.

The study of Paterson et al. (98) was a randomised double-blind crossover placebo-controlled trial with use of PSG. The size of the population was small with 12 patients who were randomised. An important remark of this study was the fact that only the abstract of the study was available with only few reported results. It was not possible to analyse the study protocol or patient characteristics. Furthermore only significant improvements were reported. This means the results need to be interpreted with caution and makes it hard to compare this trial with the others.

The study of Petrescu et al. (99) was a randomised open-label controlled trial with use of PSG. The size of the population was moderate with 43 patients, with a mean age of 77,4 years and diagnosed with Alzheimer's disease, who were randomised. The results were based on patients and nurses' sleep logs and it was apparent that the baseline and post-treatment results were more positive in the nurses' logs compared to the patients sleep logs. An important remark of this study was the fact that only the abstract of the study was available with only few reported results. It was not possible to analyse the study protocol or patient characteristics. Furthermore only significant improvements were reported. This means the results need to be interpreted with caution and makes it hard to compare this trial with the others.

The study of Roth et al. (100) was a randomised double-blind crossover placebo-controlled trial with use of PSG. The size of the population was small with 16 patients who were randomised with a mean age of 44 years. This study also tested the safety of trazodone with an extensive test battery (e.g. various visual analog scales, dynamic posturography to test equilibrium, verbal learning, short-term memory, simulated driving…).Of the 63 patients who were initially randomised, 47 patients did not finish the study because of various reasons and their results were not included in the final analysis.

The study of Saletu-Zyhlarz et al. (101) was a randomised single-blind crossover placebo-controlled trial with use of PSG. The size of the population was small with 11 patients who were randomised

with a mean age of 53 years. The study was very short with one adaptation night, one placebo night and one trazodone night, which makes it hard to suggest effects and safety used chronically.

The study of Shell et al. (102) was a randomised double-blind controlled trial with use of PSG. The size of the population was moderate with 71 patients who were randomised. The study was conducted in 12 independent sites around the US, making it more plausible that different methods of measurement occurred. This study also tested the effect of a medical food (Sentra PM) which was the main focus of the publication. Because of the relative lack of results for trazodone specifically, it is difficult to interpret the results of trazodone for the scope of our study.

The research group of Vgontzas et al. produced four randomised controlled pilot trials (103-106) comparing trazodone to CBT with a nearly identical study protocol. The study population was rather small with between 10 to 20 patients included. Only the abstract was available of 3 studies of Vgontzas et al. (103-105) which contained little information about the study protocol. The fourth study of Vgontzas et al. (106) was an open-label study with a small population where the CBT group had to use sleep restriction as part of the treatment, but one of the outcomes was TST, which will be obviously in favour of trazodone when compared. Further, although it is difficult to verify, it is possible that these four studies each involve (approximately) the same patients, so we have to be careful when drawing conclusions.

The study of Walsh et al. (107) was a randomised double-blind placebo-controlled trial. The size of the population was large with 100 patients who were randomised in the trazodone group, of which 7 discontinued treatment and were excluded for analysis. This study had only subjective outcomes. The study was conducted in 10 different hospitals, meaning the results could vary between examination sites. People in the placebo group reported side effects as well, but significantly less than those in the trazodone group.

The study of Wang et al. (108) was a randomised double-blind placebo-controlled 4 weeks-during pilot trial with use of PSG. The size of the population was moderate with 40 patients who were randomised. The study was based on patients with cerebral small vessel disease, which causes a large portion of the general population to be excluded. One patient in the trazodone group ended the study prematurely because of deterioration of the insomnia, these results were not included in the reported outcomes.

The study of Zavensicka et al. (109) was a randomised controlled trial with use of PSG where the add-on effect to CBT was examined during 2 months. There was no comparison with placebo and the study was single-blinded. The size of the population was small with 20 patients who were randomised.

Appendix 15: Limitations per trial ((es)mirtazapine)

The study of Ilinoiu et al. (117) was a randomised controlled trial where mirtazapine was compared to trazodone, pregabalin and baseline values. Unfortunately there was no comparison to placebo. The size of the population was rather small with 32 patients who were randomised with a mean age of 67 years old. The only sleep parameters that were observed were the PSQI and the HAM-D score, which means that the results are subjective. A final important side note of this study was the fact that only the abstract of the study was available with only few knowable results. This means the results need to be interpreted with caution and makes it hard to compare this trial with the others. Another important fact is that the study population received already SSRIs which can influence the results.

The study of Leinonen et al. (113) was a double-blinded, randomised controlled trial where mirtazapine was compared to citalopram and baseline values. Unfortunately there was no comparison to placebo. Furthermore citalopram can cause agitation, insomnia and sedation as important side effects, so it could be possible that the significant effects of mirtazapine are possible because the results of citalopram are equal or sometimes even worse than the measures at baseline. The size of the population was good with 240 patients between 20 and 64 years old who were randomised. The only sleep parameter that was observed was the LSEQ, which means that the results are rather subjective and vague compared to those using PSG for example. A final important side note of this study was the fact that the study was conducted in numerous different clinics across Finland, Denmark, Norway and Sweden. Since the experiment was performed with supervision in different clinics, with different PSG devices and by different data collectors, it could be the case that the protocol was not always strictly followed.

The study of Scoralick et al. (114) was a double-blinded, placebo-controlled, pilot RCT where mirtazapine was compared to placebo. Eighty-seven percent of the placebo group are ‘historical’ controls, with data obtained from a previous trial in the same hospital with the same methodology. Unlike the previous studies, in-home actigraphic measurement was used to report sleep parameters, there was no use of PSG, although it is proven that results obtained from actigraphy lean close to those obtained with PSG (39). Finally the study population was quite small with 24 patients in total and very specific. Therefore it is difficult to draw conclusions from this study that can be applicable for clinical practice.

The study of Winokur et al. (115) was a double-blinded, randomised controlled trial where mirtazapine was compared to fluoxetine and baseline values. Unfortunately, there was no comparison to placebo, which leads to the possibility that the results that are reported, might not be as significant in real life because of the placebo effect. Furthermore fluoxetine can have sedation, agitation and insomnia as important side effects, so it could be possible that the significant effects of mirtazapine are possible because the results of fluoxetine are equal or sometimes even worse than the measures at baseline. The population was also very small with only 19 patients (18-75-year-old)

who were randomised. Therefore it is difficult to draw conclusions from this study that can be applicable for clinical practice. A final important limitation of this study was the fact that the results are based on the PSG of one single night, which can also lead to a more uncertain outcome.

The study of Zhang et al. (116) was a randomised controlled study where mirtazapine was compared to paroxetine and baseline values. Unfortunately, there was again no comparison to placebo. Furthermore paroxetine can cause agitation, insomnia and sedation as important side effects, so it could be possible that the significant effects of mirtazapine are possible because the results of fluoxetine are equal or sometimes even worse than the measures at baseline. The population was also small with only 38 patients who were randomised between 20 and 45 years old. Therefore it is difficult to draw conclusions from this study that can be applicable for clinical practice. A final important side note of this study was the fact that the baseline results of the mirtazapine group were spectacularly worse than those of the paroxetine group. There was a big difference in total sleep time at baseline (186 minutes for mirtazapine and 408 minutes for paroxetine) which suggests that there may have been an error in the reporting of the numbers or the randomisation. This causes the results found in favour of mirtazapine to be interpreted with great caution.

The research group of Ivgy-May et al. conducted three studies (110-112) concerning esmirtazapine and its effect and safety used for treating primary insomnia. The studies were double blinded, placebo-controlled, RCT's with a large population, but was only focused on non-elderly patients, therefore the conclusions drawn above are less applicable for a geriatric population or for patients with comorbid insomnia. It is also possible that an increased time spent in bed contributes to a higher total sleep time. The patients had to complete a sleep diary and different questionnaires to assess the majority of the effects and adverse effects. The lack of objective sleep monitoring has to be taken into account. One of the studies (112) did use polysomnography on a large population (419 patients) that was performed in 43 outpatient research clinics spread across the USA and Canada. One of the sites in the study had to be excluded because an audit raised concerns about the eligibility of patients. Since the experiment was performed with supervision in different clinics, with different PSG devices and by different data collectors, it could be the case that the protocol was not always strictly followed, as was probably the case in the one excluded site. The other studies were also divided over numerous clinics in the USA and Canada. There was only one study that was conducted over a longer period of time (6 months) (110), so there is little data to predict the effect and side effects of esmirtazapine in chronic use. This study had a dropout rate of 40% due to either inefficiency or side effects. If this compound would be used in the future, more research is definitely needed.
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