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Efficacy of Pharmacotherapy vs Psychotherapy for Insomnia: A Clinical Review

Logan Lovell
loganglovell@gmail.com

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Logan Lovell, PA-S

Evidence-based Medicine SCPE

Gardner-Webb University

Department of PA Medicine

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Abstract

Introduction: Insomnia is a widespread sleep disorder with significant impacts on public health, economics, and vulnerable populations including the elderly and those with chronic health conditions. This review examines current literature comparing pharmacologic and non-pharmacologic treatments for insomnia.

Methods: A comprehensive literature search was conducted via PubMed using the keywords “insomnia,” “cognitive behavioral therapy,” and “pharmacotherapeutics” which was refined using MeSH terms, Boolean operators, and specific parameters (English, free full-text, published between 2019 and 2024). Six articles were selected for an in-depth review of pharmacotherapeutic and psychotherapeutic treatments for insomnia.

Results: The selected articles from the PubMed search were reviewed and analyzed to evaluate their methodologies, study designs, and findings on the efficacy of cognitive behavioral therapy versus pharmacotherapy for insomnia. 1 systematic review/meta-analysis, 1 RCT, 2 cohort studies, and 1 general review. Key findings include the efficacy of cognitive behavioral therapy as the preferred first-line treatment, particularly in reducing insomnia symptoms and improving sleep quality, with the digital form showing comparable effectiveness to traditional face-to-face cognitive behavioral therapy.

Discussion: The findings presented in this review emphasize the importance of prioritizing non-pharmacological approaches in the management of insomnia, while future research should focus on optimization of the digital form of cognitive behavioral therapy and the refinement of pharmacological strategies should they be a necessary supplement.

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INTRODUCTION

Insomnia is the most common sleep disorder in the world and commonly affects vulnerable patient groups including military personnel, veterans, elderly, traumatic brain injury patients, patients living with poor health, low socioeconomic status, alcohol/substance abuse patients, and homeless.[1-3] It is estimated that 10-20% of adults worldwide meet the diagnostic criteria triad for insomnia.[1-3,4] In the US alone, roughly 30-40% of the adult population have reported symptoms of insomnia at some point in the given year and approximately 22% of the population would meet diagnostic criteria.[1-3,8] This number rapidly increased during the COVID-19 pandemic, with a growth rate of roughly 47%, and has been steadily growing since.[1-3] Insomnia is both a public health concern and a substantial economic burden.[1] The incidence of the disorder and the cost of treatment in the US are both drastically increasing with current estimations exceeding $100 billion annually.[1,3]

Insomnia is defined as a disorder characterized by difficulty initiating or maintaining sleep leading to impaired daytime functioning.[1-3] This impairment may include fatigue, daytime sleepiness, difficulty functioning, poor work performance, increased work injuries, increased traffic accidents, social dysfunction, mood disturbances, irritability, and behavioral problems.[1] This sleep impairment also has detrimental effects on the immune system and metabolism.[3] Insomnia often coexists with other medical conditions such as depression, anxiety, cardiovascular disease, cerebrovascular disease, obesity, obstructive sleep apnea, diabetes, gastroesophageal reflux disease, respiratory disorders, chronic kidney disease, and cancer.[1-9] Insomnia is a clinical diagnosis that requires a triad of persistent sleep difficulties, adequate sleep opportunities, and associated daytime dysfunction.[1,3] Insomnia is further classified into acute and chronic based on the timeframe of symptoms with chronic requiring at least three months of symptoms occurring three or more times a week.[1-3] The timeframe is important to distinguish as

duration of symptoms may help determine the most appropriate treatment plans and minimize poor outcomes.[1,2,4]

Treatment can be complex but usually begins with non-pharmacologic options such as sleep hygiene, sleep restriction, stimulus control, relaxation therapy, and cognitive behavioral therapy (CBT).[4-8] Sleep hygiene includes lifestyle modifications such as limiting daytime naps, avoiding late-night dinners, and restricting the use of electronics in the evening.[4-7,9] Sleep restriction is a therapy that aims to reduce sleep time by limiting the number of sleeping hours.[4-7,9] Stimulus control involves the restriction of behaviors like eating, reading, or using digital devices while physically in bed.[4-7,9] Relaxation therapy is the regular practice of breathing exercises, meditation, or yoga to reduce underlying stress and anxiety and improve overall relaxation and mindfulness.[4-7,9] CBT is direct therapy, done several times throughout treatment that involves combinations of the previously mentioned techniques and therapies.[4] CBT may also be managed by a therapist, relieving some of the pressure from the patient.[4,5] These psychotherapeutic treatment components may be used individually, but studies have shown that the more components combined the more successful the treatment.[4] An alternative to this first-line treatment is digital cognitive behavioral therapy (dCBT) which is similar to CBT but is conducted via technology such as phone, tablet, or computer, making it more convenient for the patient while still delivering the core content of the therapy.[4,9] Some of these programs connect the patient to a therapist while others work as a type of planner or guideline the patient can follow on their own.[4,9]

Dietary supplements such as melatonin are also frequently used in conjunction with therapeutic options on an as-needed basis.[4,5,8] More complex cases often require pharmacologic agents such as benzodiazepine receptor agonists (BRZAs; triazolam, estazolam, temazepam, flurazepam), nonbenzodiazeipine receptor agonists (nBRZAs; eszopiclone, zaleplone, zolpidem), dual orexin receptor antagonists (DORAs; daridorexant, Lemborexant, suvorexant), histamine receptor antagonist (doxepin),

and melatonin receptor agonists (ramelteon).[4-9] Many cases of insomnia treatment will follow a stepwise approach but may ultimately involve a combination of varying therapies and pharmacotherapeutics.[4-9]

The purpose of this paper is to review the current literature on insomnia, highlight the importance and significance of the disorder, and analyze the comparative efficacies of pharmacotherapeutics, psychotherapies, or combinations of the two for the management and treatment of the condition. Analysis will also be done on the ease of access to both pharmacotherapeutics and psychotherapies, as well as any risks or benefits associated with either option.

METHODS

A search via PubMed using the keywords “insomnia”, “cognitive behavioral therapy”, and “pharmacotherapeutics” was performed. MeSH and Boolean operators were then added to produce a final search of “insomnia” AND “cognitive behavioral therapy” AND “pharmacotherapeutics”, which populated 104 results that were in English, free full-text access, and were from 2019-2024. Further filters were applied to only include articles that were systematic reviews, randomized control trials (RCT), or meta-analyses, resulting in 28 articles. One of these articles was eliminated due to the study focusing solely on the pediatric population. Four articles were eliminated as the primary focus was on alternative therapies making use of herbal supplements. Fifteen articles were eliminated as each one focused on specific pre-existing conditions or comorbidities improvement rates in relation to the treatment of insomnia. One article was eliminated as it was a protocol for a future study which had not been conducted yet. Seven articles remained for review of pharmacotherapeutic and psychotherapeutic efficacies in treatment of insomnia. Of these seven, one was a meta-analysis on insomnia and treatment options, three were RCTs/meta-analyses directly comparing pharmacologic vs non-pharmacologic treatments, one was on pharmacotherapies vs dCBT, and lastly, one focused on the different treatment options for both acute and chronic insomnia.

RESULTS

The articles chosen from the PubMed search were reviewed and analyzed to assess the methodologies, study designs, and results of their respective topics. Each result was also categorized and summarized in varying tables below for reference. See Table 1 for supplemental information on the design of each paper assessed, Table 2 for participant selection, inclusion/exclusion criteria, and Table 3 for ethics, fundings, and conflicts of interest. The order in which the articles are listed is based solely on the order of appearance in this paper and does not reflect the quality, importance, or weight of the studies involved.

Efficacy, Acceptability, and Tolerability of Treatment in Elderly: The systematic review and meta-analysis conducted by Samara et al[4] evaluated the efficacy, acceptability, and tolerability of all available treatments for insomnia in the elderly population (>65 years old) at the time. The stated goal by Samara et al[4] was to assess the efficacy and safety of both the pharmacologic and non-pharmacologic treatment options for insomnia. The two primary outcomes focused on were total sleep time and sleep quality while undergoing one of the treatment options. The study analyzed 53 randomly controlled trials with 6832 participants, who were 75 years old on average, and assessed both pharmacologic and psychotherapeutic treatment efficacies. These articles were found in MEDLINE, Embase, PsycINFO, and WHOICTRP. For the pharmacologic studies, only studies with a minimum of 5 days of drug/supplement treatment were included. Treatment involving psychotherapy had no minimum duration requirement. CBT reduced sleep onset latency compared to benzodiazepines by approximately 7.42 minutes (MD: -7.42, 95% CI: -21.87 to 7.03), however, there were no significant changes in total sleep time compared to other treatment options. Diazepam significantly reduced sleep onset latency compared to placebo with a mean difference (MD) of -24.67 minutes (95% CI: -29.30 to -20.04). Temazepam also reduced sleep onset latency with a MD of -11.40 minutes (95% CI: -16.27 to -6.53), though less pronounced than diazepam.

Total sleep time was improved in the diazepam group (MD: 49.93 minutes; 95% CI: 9.05 to 90.81) compared to placebo. Melatonin did not show any significant reductions in sleep onset latency (MD: -8.65 minutes; 95% CI: -21.48 to 4.18), and only had limited effects on total sleep time (MD: -5.00 minutes; 95% CI: -40.01 to 30.01). In terms of sleep quality, melatonin had a standardized mean difference (SMD) of -0.71 (95% CI: -1.26 to -0.15), indicating some improvement. Antidepressants and antihistamines were found to be less effective at treating insomnia and more associated with increased side effects. Diphenhydramine was evaluated and showed no significant improvement in sleep onset latency compared to placebo (MD: -2.60 minutes, 95% CI: -7.46 to 2.26), and had a minor effect on sleep quality, with a standardized mean difference (SMD) of -0.12 (95% CI: -0.21 to -0.03), indicating some improvement in subjective sleep quality. Doxepin, a tricyclic antidepressant, significantly reduced sleep onset latency (MD: -16.76 minutes, 95% CI: -26.33 to -7.19) and improved sleep quality with an (SMD: -0.35 (95% CI: -0.54 to -0.74). Doxepin also improved total sleep time (MD: 31.17 minutes, 95% CI: 5.12 to 57.23). The analysis of the treatments recommended for insomnia suggests that CBT is the first-line treatment for chronic insomnia due to its effectiveness in improving both subjective and objective sleep outcomes, while having better safety and fewer adverse effects, particularly when compared to medications like benzodiazepines and Z-drugs. The pharmacological treatments, including benzodiazepines, Z-drugs, and antidepressants, were recommended as short-term solutions, when necessary, particularly in cases where immediate symptom relief was required. However, due to their potential side effects, including dependency and daytime drowsiness, their use is generally limited to short durations.

Daytime Functioning: Morin et al[5] conducted a randomized controlled trial (RCT) to determine which first-line treatment option was most optimal for improving daytime functions among patients with insomnia, as well as which second-line treatment offered the best additional therapeutic effects in patients whose insomnia had persisted through the first-line treatment. The 211 adult participants

enrolled in the study, ranging from Canada to the United States, were randomly assigned either face-to-face CBT or zolpidem as their first-line treatment option. 104 participants were allocated to CBT, while 107 participants were allocated to zolpidem. The patients would be initially treated and seen by a provider monthly over a course of 12 months. Patients who received either CBT or zolpidem yielded significant and equivalent benefits for most of the daytime outcomes including depressive symptoms (Beck Depression Inventory-II mean score change, [−3.5, 95% CI, −4.7 to −2.3] vs [−4.3, 95% CI, −5.7 to −2.9]), fatigue (Multidimensional Fatigue Inventory mean score change, [−4.7, 95% CI, −7.3 to −2.2] vs [−5.2, 95% CI, −7.9 to −2.5]), functional impairments (Work and Social Adjustment Scale mean score change, [−5.0, 95% CI, −6.7 to −3.3] vs [−5.1, 95% CI, −7.2 to −2.9]), and mental health (SF-36 mental health subscale mean score change, [3.5, 95% CI, 1.9-5.1] vs [2.5, 95% CI, 0.4-4.5]), while CBT produced larger improvements for anxiety symptoms relative to zolpidem (State-Trait Anxiety Inventory mean score change, [−4.1, 95% CI, –5.8 to –2.4] vs [−1.2, 95% CI, −3.0 to 0.5]; P = .02; Cohen d = 0.55). Patients who still experienced symptoms of insomnia after their respective first-line treatments were given a second-line treatment option which consisted of either just zolpidem, zolpidem and trazodone, or zolpidem and CBT depending on what their first line treatment was. Second-line therapy produced additional improvements for anxiety, depression, and daytime fatigue. Zolpidem used in posttreatment for fatigue (Multidimensional Fatigue Inventory mean score change: zolpidem plus CBT, [−3.8, 95% CI, −7.1 to −0.4]; zolpidem plus trazodone, [−3.7, 95% CI, −6.3 to −1.1]), functional impairments (Work and Social Adjustment Scale mean score change: zolpidem plus CBT, [−3.7, 95% CI, −6.4 to −1.0]; zolpidem plus trazodone, [−3.3, 95% CI, −5.9 to −0.7]) and mental health (SF-36 mental health subscale mean score change: zolpidem plus CBT, [5.3, 95% CI, 2.7-7.9]; zolpidem plus trazodone, [2.0, 95% CI, 0.1-4.0]). Ultimately, it was concluded that CBT and zolpidem both produced equal improvements for various daytime symptoms of insomnia when only treated with one or the other and adding a second-line treatment offered an additional value for further improvements to daytime functionality of patients.

Effects of Trazadone as a Sleep Aid: Vgontzas et al[7] conducted a randomized controlled trial consisting of 15 patients with chronic insomnia. The goal of this study was to assess whether insomnia patients with a known objective short sleep duration phenotype responded better to pharmacological treatment compared to CBT. Of these 15 participants in the study, 8 were randomly selected to undergo CBT while 7 were selected to take trazadone as first line treatment. Patients were examined with 2 weeks of actigraphy, salivary cortisol, and insomnia severity index (ISI) at 3 points of time: pre-treatment, 3-month post-treatment, and 6-month post-treatment. This research concluded that trazadone significantly lengthened total sleep time compared to CBT, both at 3-month post-treatment (51.01 minutes vs –11.73 minutes; P = .051; Cohen's d = 1.383) and at 6-month post-treatment (50.35 minutes vs –7.56 minutes; P = .012; Cohen's d = 1.725), respectively. In addition, trazadone showed a clinically meaningful decrease in salivary cortisol from pre-treatment to 3-month post-treatment (–36.07% vs –11.70%; Cohen's d = 0.793) and from pre-treatment to 6-month post-treatment (–21.37% vs –5.79%; Cohen's d = 0.284) respectively. This result was not seen in the participants who underwent CBT treatment for insomnia. Lastly, there were no significant differences on ISI scores between the participants who were taking trazodone compared to those who underwent CBT.

Efficacy and Safety of Pharmacotherapeutics: A review by Del Rio Verduzco et al[8] was conducted using articles from PubMed and Google Scholar focusing on adverse side effects of all available pharmacotherapeutic options for the treatment of insomnia. This review study sought to compare the recommendations of the 3 major clinical guidelines, provide an overview of pharmacotherapy options, and assess the quality of use and side effects of these pharmacotherapeutics in the treatment of insomnia. In this review, the 3 most recent guidelines published in the United States, as well as 15 case reports and 13 clinical studies reporting on side effects were included. These guidelines were from the 2016 American College of Physicians (ACP), the 2017 American Academy of Sleep Medicine (AASM) and the 2019 Veterans Affairs and Department of Defense (VA/DoD), which all recommended the use of CBT

as first-line treatment and pharmacotherapeutics as a second-line or supplemental therapy should CBT not be readily available. Medication classes that were assessed include benzodiazepines, BZD receptor agonists, dual orexin receptor antagonists, melatonin agonists, antidepressants, antipsychotics, anticonvulsants, and over-the-counter medications. This review found that while cognitive behavioral therapy for insomnia is strongly recommended by all three guidelines (ACP, AASM, VA/DoD), most pharmacotherapy options have weak recommendations due to safety and efficacy concerns. For instance, benzodiazepines, including triazolam and temazepam, are associated with adverse effects like CNS depression, with temazepam showing a 1.3% incidence of delirium, 4.8% for fatigue, and 1.7% for depression. "Z-drugs" like zolpidem have moderate efficacy but carry risks such as complex sleep behaviors. Suvorexant, a dual orexin receptor antagonists (DORA), demonstrated favorable side-effect profiles compared to GABAs, benzodiazepines or hypnotics. Suvorexant had similar results in sleep-aid effect to zolpidem but a lower increase of abuse potential (30.6% vs 58.3%), lower instances of euphoric moods (11.1% vs 19.4%), and lower chance of visual hallucination (2.8% vs 11.1%). The VA/DoD guideline reported a weak recommendation against the use of medications like melatonin and valerian root due to lack of significant clinical evidence. In comparison, suvorexant, a dual orexin receptor antagonist, was associated with a 7% incidence of somnolence and a 4% incidence of headaches. Among newer agents, ramelteon showed a 3% incidence of dizziness and fatigue.

Digital CBT vs Medication: A cohort study conducted by Lu et al[8] consisting of 4052 patients with insomnia was analyzed to systematically examine the effectiveness, engagement, durability, and adaptability of treatment options for patients with insomnia in a clinical setting. The study was conducted using longitudinal data collected via a mobile app called Good Sleep 365, and assessed patients undergoing dCBT, patients on medication, and patients both undergoing dCBT and medication for insomnia. These assessments were compared at 1-month post-treatment, 3-month post-treatment, and 6-month post-treatment intervals. The Pittsburgh Sleep Quality Index (PSQI) score was used to

assess the primary outcomes and effectiveness of treatments. A total of 4052 patients (mean [SD] age, 44.29 [12.01] years; 3028 [74.7%] female participants) were selected for dCBT-I (n = 418), medication (n = 862), and their combination (n = 2772). Compared with the change in PSQI score at 6 months for participants receiving medication alone (from a mean [SD] of 12.85 [3.49] to 8.92 [4.03]), both dCBT-I (from a mean [SD] of 13.51 [3.03] to 7.15 [3.25]; Cohen *d*, −0.50; 95% CI, −0.62 to −0.38; *P* < .001; SMD = 0.484) and combination therapy (from a mean [SD] of 12.92 [3.49] to 6.98 [3.43]; Cohen *d*, 0.50; 95% CI, 0.42 to 0.58; *P* < .001; SMD = 0.518) were associated with significant reductions; dCBT-I had a comparable effect as combination therapy (Cohen *d*, 0.05; 95% CI, −0.05 to 0.15; *P* = .66; SMD = 0.05), but showed unstable durability. Patients on dCBT only improved steadily and rapidly during the first 3 months, but results fluctuated from 3 months to 6 months. Results also showed that patients who were on dCBT or a combination of dCBT and medication had better response rates than patients who were solely on a medication treatment.

DISCUSSION

The present analysis of multiple studies on insomnia treatments provides valuable insights into the effectiveness and safety of both pharmacological and non-pharmacological interventions, highlighting significant trends and considerations for clinical practice.[1-9] Evidence reviewed suggests that non-pharmacological options of dCBT or face-to-face CBT, or a combination of dCBT/CBT with supplemental pharmacologic agents, were more effective than sole treatment with pharmacologic agents.[4-9] CBT had the least amount of side effects when compared to pharmacological counterparts for treating insomnia.[4-9] Online cognitive behavioral therapy was also found to be easier, more convenient, cheaper, and more preferred than other options available for patients.[4-7,9] Coexisting anxiety or depression improved when patients were enrolled in either form of CBT suggesting online CBT should be considered first-line treatment for patients suffering from insomnia.[4-7]

Pharmacological Interventions Benefits and Risks: While pharmacological treatments remain a common approach to managing insomnia, the studies reviewed highlight the limitations and risks associated with these treatments.[1-9] The meta-analysis by Samara et al.,[4] which focused on the insomnia treatment in the elderly population, which demonstrated that while certain medications can improve sleep quality and duration, they are often accompanied by significant adverse effects, especially in elderly patients. These pharmacological options, especially benzodiazepine and non-benzodiazepine hypnotics, had higher risks of adverse side effects such as cognitive impairment and falls associated. These adverse effects highlight the significance of CBT as the superior treatment option.

The review conducted by Del Rio Verduzco et al[8] further emphasizes the importance of cautious use of pharmacotherapeutics, recommending short-term use of the lowest effective dose of Z-drugs or doxepin only if CBT is not readily available. The potential for side effects and the lack of long-term safety data in many of the studies reviewed reinforces the necessity of prioritizing non-pharmacological approaches first.[1-9]

Digital CBT, A Viable Option: The increasing accessibility and efficacy of dCBT were highlighted by the cohort study by Lu et al.[9] In which they demonstrated that dCBT is equally as effective in alleviating insomnia symptoms, with the added benefits of convenience, accessibility, and cost effectiveness. Lu et al.[9] also found that dCBT was particularly beneficial for patients with coexisting anxiety or depression, suggesting that digital interventions could be a valuable tool that should be further researched. An interesting note from the study demonstrated fluctuations in the effectiveness of dCBT over time, indicating that while dCBT is a promising alternative, ongoing engagement and supplemental support may be necessary to maintain long-term benefits of therapy.

The randomized controlled trial by Morin et al.[5] provides additional insights into the comparative effectiveness of CBT and zolpidem, a commonly prescribed hypnotic. While both treatments produced

equivalent benefits for several daytime symptom outcomes, CBT showed superior results for anxiety or depression symptoms, further supporting its use as a primary treatment modality. Moreover, the addition of a second-line therapy, particularly when combining zolpidem with CBT, offered further improvements, suggesting a potential role for combination therapy in cases where insomnia persists despite initial treatment.

Clinical Practice Implications: The collective findings from these studies advocate for a treatment approach that prioritizes CBT, both in traditional and digital forms, as the cornerstone of management of insomnia.[1-9] The consistent evidence supporting the effectiveness of CBT across differing populations of patients and settings, along with the favorable safety profile, makes it the preferred first-line treatment.[1-9] Pharmacological options should be reserved for cases where CBT is ineffective or inaccessible, and even then, should be used for the shortest duration of time possible and with caution.[1-9] The variability in the effectiveness of dCBT suggests that while a promising alternative, dCBT may require ongoing monitoring and support to ensure sustained benefits. This highlights the need for flexible, patient-centered approaches that consider individual preferences, comorbidities, finances, and access to resources.

Future Directions: Future research should focus on optimizing the delivery and long-term effectiveness of dCBT, exploring strategies to enhance engagement and sustain improvements over time. Additionally, further studies are needed to refine the role of pharmacological interventions, particularly when in combination with CBT, to determine the most effective and safest strategies for managing acute and chronic insomnia across diverse populations. Future studies that do decide to pursue the use of non-pharmacological and pharmacological therapies should consider research on the differing doses of pharmacological agents as well as medical compliance from the patient for both pharmacological agents as well as CBT. As demonstrated by Lu et al.,[9] efficacies of dCBT were less effective after the 3-month mark, suggesting that lack of compliance with the therapy may be the cause. Additionally, future studies

should make use of varying types of digital or in-person CBT. Perhaps focusing on varying lengths of CBT, frequency of CBT, types of CBT offered, and patient feedback on their preferences for these variables. Lastly, the amount of randomly controlled trials for insomnia patients is lacking. More trials, with more patients, longer durations, and more combinations of interventions would be warranted.

In conclusion, the studies reviewed in this paper strongly support the use of CBT as the mainstay first-line treatment option for acute and chronic insomnia, with dCBT emerging as a viable and effective alternative.[1-9] Pharmacotherapy remains a secondary option, best utilized in conjunction with CBT or when options such as CBT are not readily available.[1-9] This approach to treatment aligns with the overarching goal of improving patient outcomes while minimizing the risk of adverse side effects.[1-9]

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Table 1: Study Design

Author	Study Type	Quantity of Studies Assessed or Participants Involved	Method(s) of Measurement	Study Treatment Methods Analyzed
Samara, et al.	Systematic Review, Network Meta-Analysis	53 studies; Systematic Review 48 studies; Network Meta-Analysis	PSQI and actigraphy or diary-assessed SOL>30 minutes for >=3 nights a week ISI.	CBT, Food supplements (melatonin, magnesium, zinc), Pharmacologic agents.
Morin, et al.	RCT	211 Participants: 132 women 79 men	Daytime symptoms of insomnia, mood disturbances, fatigue, functional impairments of insomnia, and scores on the SF-36 physical and mental health components	CBT, Zolpidem, Trazodone
Rios, et al.	Cohort Study, Review	64 studies; Systematic reviews 33 studies; Meta-Analysis	SOL, TST, WASO, Sleep Quality, Sleep Satisfaction, Sleep-efficiency, ISI, Fatigue Severity, Health-related QOL, Morning sedation, Accidental Injury, Addiction or Dependence or Diversion	CBT, Benzodiazepines, Non-benzodiazepines, Anti-depressants, Anti-psychotics, Anti-convulsants
Vgontzas, et al.	RCT	15 participants: 13 women 2 men	Actigraphy, Polysomnography, Salivary cortisol, ISI (measure at 3 different points: pre-treatment, 3- month post-treatment, and 6- month post-treatment)	Trazodone, CBT
Del Rio Verduzco, et al.	Review	15 case reports 13 clinical studies	Side effects of pharmacologic agents and CBT used in the treatment of Insomnia. Efficacy of these same agents on treatment of insomnia.	CBT, Benzodiazepines, BZD receptor agonists, dual orexin receptor antagonists, melatonin agonists, antidepressants, antipsychotics, anticonvulsants, and

				over-the-counter medications
Lu, et al.	Cohort Study, Review	4052 patients with insomnia. 3082 women 970 men	PSQI, PHQ-9, GAD-7, PHQ-15, ESS Scores	dCBT, CBT, "medication therapy"

Abbreviations:

Randomized Controlled Trial (RCT)
Grading of Recommendations Assessment, Development, and Evaluation (GRADE)
Pittsburgh Sleep Quality Index (PSQI)
Cognitive Behavioral Therapy (CBT)
Digital Cognitive Behavioral Therapy (dCBT)
Sleep Onset Latency (SOL)
Total Sleep Time (TST)
Sleep Efficiency (SE)
Wakefulness After Sleep Onset (WASO)
Time in Bed (TIB)
Number of Awakenings (NOA)
Insomnia Severity Index (ISI)
International Classification of Sleep Disorders (ICSD)
Internet-based online CBT(ICBT)
36-item Short-Form Health Survey(SF-36)
Consolidated Standards of Reporting Trials (CONSORT)
Research Diagnostic Criteria (RDC)

Table 2: Participant Selection

Author(s)	Recruitment	Inclusion	Exclusion
Samara, et al.	Comprehensive Systematic Review and Network Meta-Analysis of 53 and 48 studies respectively.	- Patients involved must have insomnia diagnosis or sleep-disorder. - Patients must be older than 65 years. - Trials analyzed required high quality and reliability in their own reviews.	- Fixed effects instead of random effects models. - Open-label and single blind studies - Studies that did not use operationalized criteria to diagnose insomnia - Studies that presented only completers analyses - Studies with high risks of bias in blinding, missing outcome data, selective reporting, or other biases. - Secondary insomnia diagnoses or patients with severe somatic or psychiatric conditions
Morin, et al.	211 participants recruited from the community via media advertisements and physician referrals.	- Complaint of persistent (>1 month) difficulties initiating or maintain sleep despite adequate opportunity for sleep. - A SOL or WASO >30 minutes 3 or more nights per week during 2 weeks of sleep diary monitoring. - An ISI score>10 indicating at least “mild” insomnia - A score of ≥ 2 on either the interference or distress item of the screening ISI, indicating the insomnia causes significant distress or impairment in social, occupational, or other areas of functioning.	- an untreated psychiatric disorder (e.g., major depression) as these conditions have specific treatments and it would be inappropriate not to offer those treatments; - a lifetime diagnosis of any psychotic or bipolar disorder as sleep restriction and medications for insomnia may precipitate mania and hallucinations; - an imminent risk for suicide; - alcohol or drug abuse within the past year, since BzRAs are cross-tolerant with alcohol; - terminal or progressive physical illness (e.g., cancer, COPD), or neurological degenerative disease (e.g., dementia); - current use of medications known to cause insomnia (e.g., steroids); - sleep apnea (apnea/hypopnea index > 15), restless legs syndrome, periodic limb movement during sleep (PLMS with arousal > 15 per hour), or a circadian rhythm sleep disorder (e.g., advanced sleep phase syndrome); - habitual bedtimes later than 2:00 AM or rising times later than 10:00 AM; - consuming > 2 alcoholic beverages per day on a regular basis. -
Rios, et al.	Review of 64 studies for systematic review, 31 for Meta-Analysis	- Adult patients 18 years or older	- Not a systemic review - Patients did not have insomnia - Ineligible interventions

		- Diagnosis of acute <3 months or chronic >3 months insomnia disorder according to DSM diagnostic criteria, ICSD, or RDC for insomnia. - Interventions are prescription or non-prescription used to treat insomnia approved for use or under current review for approval in Canada. - Non-pharmacologics included CBT, Sleep restriction, meditation, or a combination. If using a pharmacologic, must have a placebo running as well.	- No relevant outcomes - Companion report/duplicate - Overlapped with another review - Not available/not found.
Vgontzas, et al.	RCT of 15 participants with known short sleep duration phenotype insomnia: 13 women, 2 men recruited in Hershey, Pennsylvania, USA.	- Chronic insomnia with duration of more than 1 year. - Objective Short sleep duration (<6 hours) - BMI <39 - Ages 30-60 years - Men and Women	- Major Mental illness - Substance abuse/dependence - Sleep apnea - Periodic limb movement disorders - Shift work or circadian disorders - Diabetes - Chronic renal failure - Hepatic insufficiency - Chronic heart failure - Current use of hypnotics or sleep inducing sedative antidepressants
Del Rio Verduzco, et al.	Analysis of varying pharmacologic agents, side effects, and efficacies of treatment for insomnia.	- None Listed	- None Listed
Lu, et al.	Cohort study of 4052 patients. 418 receiving dCBT, 862 being put on medications to treat insomnia, and 2772 being given a combination of dCBT and medication for treatment.	- Aged 18-80 years - Must have diagnosis of insomnia with PSQI score of greater than 5 at baseline. - ESS score of 10 or less at baseline.	- No severe psychiatric disorders such as restless leg syndrome, sleep apnea, epilepsy, or bipolar disorder. - Patients with incomplete demographic or treatment information.

Table 3: Ethics, Funding, and COI's

Author	Ethical Approval	Funding	Conflict(s) of interest
Samara, et al.	N/A	German Federal Ministry of Education and Research	See attached footnote 2.
Morin, et al.	Local ethics committees of both sites (Denver Colorado USA, and Quebec City, Quebec, Canada) and all participants provided written informed consent. CONSORT guidelines	Jack Edinger, PhD	See attached footnote 3.
Rios, et al.	N/A	Canadian Institutes of Health Research through Drug Safety and Effectiveness Network.	See attached footnote 4.
Vgontzas, et al.	Not provided.	Milton S. Hershey Medical Center	Not listed.
Del Rio Verduzco, et al.	N/A	Not listed.	None
Lu, et al.	College of Biomedical Engineering and Instrument Science, Zhejiang University	Not listed.	Conflict of Interest Disclosures: Ms Wang reported being the project manager and data coordinator of Hangzhou slan-health. No other disclosures were reported.

Footnote 1: Declaration of Interest for Samara et al. Study

"In the last 3 years MH has received speaker's honoraria from Janssen. GS was invited to participate in two scientific meetings about the use of real world evidence by Merck (2019) and Biogen (2018). In the last 3 years SL has received honoraria as a consultant or for lectures for LB Pharma, Otsuka, Lundbeck, Boehringer Ingelheim, LTS Lohmann, Janssen, Johnson&Johnson, TEVA, MSD, Sandoz, SanofiAventis, Angelini, Sunovion, Recordati and Geodon Richter. MTS, VC, JST and MW have no conflicts of interest."

Footnote 2: Conflict of Interest Statement for Morin, et al.

“Conflict of Interest Disclosures: Dr Morin reported receiving grants and personal fees from Eisai and Idorsia; grants from Lallemand Health; and royalties from Mapi Research Trust outside the submitted work. Dr Krystal reported receiving grants from Janssen Pharmaceuticals, Axsome Pharmaceutics, Attune, Harmony, Neurocrine Biosciences, Reveal Biosensors, The Ray and Dagmar Dolby Family Fund, and the National Institutes of Health; personal fees from Axsome Therapeutics, Big Health, Eisai, Evecxia, Harmony Biosciences, Idorsia, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Millenium Pharmaceuticals, Merck, Neurocrine Biosciences, Neurawell, Pernix, Otsuka Pharmaceuticals, Sage, and Takeda; and stock options from Big Health and Neurawell outside the submitted work. No other disclosures were reported.”

Footnote 3: Conflict of Interest Statement for Rios, et al.

“Dr. Charles Morin is on the advisory board for Phillips, Merck, and Cereve; holds speaking honorariums from Merck, Eisai, and Abbott; provided expert testimony for Cereve; and receives book royalties from Elsevier and Sogides. Dr. Judith Leech has part ownership of two private sleep labs, Somnocor in Gatineau, Quebec, and West Ottawa Sleep Centre in Ottawa, Ontario. All other authors have no known conflicts of interest to declare. Dr. Tricco is an Associate Editor for BMC Systematic Reviews but will not be involved with any decisions related to this paper.”