Commonly Prescribed Sleep Medications And Treatment for Insomnia

Shizuka Tomatsu M.D., Shilpa Krishnan D.O., David Puder, M.D.

This PDF is a supplement to the podcast "Psychiatry & Psychotherapy" **Episode 124** found on **iTunes**, **Google Play**, **Stitcher**, **Overcast**, **PlayerFM**, **PodBean**, **TuneIn**, **Podtail**, **Blubrry**, **Podfanatic**

*Both Dr. Tomatsu and Dr. Krishnan are first authors for different sections of this handout.

Dr. Tomatsu, Dr. Krishnan, and Dr. Puder don't have any conflicts of interest to report.

Table of Contents

INSOMNIA: INTRODUCTION

- A fairly common problem; it is likely that almost all individuals suffer from at least transient insomnia.
- Insomnia Criteria: American Academy of Sleep Medicine (AASM Practice Guidelines)
  - Sleep symptoms:
    - difficulty initiating sleep
    - difficulty maintaining sleep
    - waking up earlier than desired
    - resistance to going to bed on an appropriate schedule
    - difficulty sleeping without caregiver intervention
  - Daytime symptoms:
    - fatigue/malaise
    - attention, concentration, or memory impairment
    - Impaired social, family, vocational, or academic performance

        - Mood disturbance or irritability
        - Daytime sleepiness
        - Behavioral problems
        - Reduced motivation/energy/initiative
        - Proneness for errors/accidents
        - Concerns about or dissatisfaction with sleep
    - Short-term insomnia: at least *one* of the sleep symptoms and at least *one* of the daytime symptoms have been experienced for fewer than 3 months
    - Chronic insomnia: at least *one* of the sleep symptoms and at least *one* of the daytime symptoms have been experienced for more than 3 months
        - The *International Classification of Sleep Disorders, Third Edition* also includes frequency of at least 3 times per week for at least 3 months (Sateia, 2014)
- **DSM-V Definition:** The inability to fall asleep or maintain sleep for at least 3x/week for at least 3 months
- Insomnia architecture:
    - Initial insomnia: Difficulty going to sleep
    - Middle insomnia: Difficulty maintaining sleep, waking up in the middle of the night
    - Terminal insomnia: early awakening
- Sleep Architecture:
    - NREM sleep is essential for the following functions: repair and regenerate body tissues, flush out toxic waste
    - REM sleep (atonic, vivid dreams) is essential for memory consolidation and improves depression and anxiety
- No single medication has strong evidence for long-term use in insomnia. The primary purpose of medications in insomnia is as short-term adjunctive therapy while the patient works on CBTi (including sleep hygiene)
- Medications may physically knock you out but may not enhance the quality of sleep. Medications mask the underlying cause of insomnia
    - Clinicians should attempt to identify the underlying cause of insomnia and treat accordingly
- Common problems that impair proper sleep:
    - Screen time prior to bed: phase delays sleep-wake cycle
        - Particular issue with emission of blue light, which has the shortest wavelength and therefore produces the highest energy, is suppression of melatonin production
        - Of note, there is *a lack of high quality evidence* demonstrating that blue light blocking glasses improve insomnia. They likely don't help enough and screens should be turned off 2 hours before bed
    - Maladaptive sleep associations, i.e., watching television

        - Per Dr. Cummings: make sure to dim the light emanating from the screen if watching television before bed
    - Exercise prior to bed
        - Per Dr. Cummings: Exercise, in general, is helpful for insomnia. However, doing so immediately prior to going to sleep at night increases sympathetic activity, promotes energy, and negatively impacts the ability to fall asleep
        - Of note, exercise earlier in the day is helpful for sleep
- Non-pharmaceutical options to promote sleep in the inpatient psychiatric setting:
    - Discontinue nocturnal or early morning vitals measurements if they are not necessary for treatment
    - Schedule HS medications prior to going to bed
    - Work with administration and nursing staff to change lighting and noise levels during the evening and overnight, as appropriate

- **CBTi BRIEF OVERVIEW** (Bootzin, 1972, Morin, 2004, Lichstein, 2001)
    - Gold standard treatment for insomnia
    - Performed primarily by a sleep psychologist or CBTi trained psychiatrist
    - Time intensive treatment requires maintenance of sleep log prior to intervention as well. This can be a barrier for many individuals
    - Main components
        - Sleep restriction/sleep consolidation
        - Stimulus control
        - CBT
        - Sleep habits (rarely effective by itself in treating chronic insomnia)
        - Relaxation Technique

PHARMACOTHERAPY : SEDATIVE-HYPNOTICS

1. **Benzodiazepines/Barbiturates**

- History: (APA Publishing Textbook of Substance Use Disorders)
    - Barbituric acid was synthesized in 1864 by Adolf von Baeyer of Bayer Chemical Company. In 1904, barbital (diethylbarbituric acid) was marketed and began to be used clinically. During the 1st and 2nd world wars, barbiturates were widely used for induction of anesthesia, refractory psychiatric conditions, insomnia, and epilepsy. By the late 1960s, concern grew for overdose potential of barbiturates (namely respiratory depression) and addictive properties.

    - In 1955, chemist Leo Sternbach identified chlordiazepoxide (Librium) which soon became widely marketed and used in a clinical setting. This was soon followed with diazepam (Valium). These medications initially appeared safer, less toxic in overdose and there was apparently less potential for abuse. Widely began to be used, peaking in 1970s for insomnia and anxiety.
    - The first benzodiazepine that was approved/indicated for sleep was Flurazepam in 1970
    - Increase awareness in the 1980s and 1990s for overdose risk potential, especially in combination with other sedatives, and concern for the dangers of using benzodiazepines in the elderly population
- Mechanism of Action: Barbiturates (Scatzberg's Manual of Clinical Psychopharmacology)
    - Increase duration of $GABA_A$ receptors
    - Capable of activating the $GABA_A$ complex even in absence of GABA so they carry increased risk of toxicity in overdose
- Mechanism of Action: Benzodiazepines (Scatzberg's Manual of Clinical Psychopharmacology)
    - Increase frequency of channel opening
    - Benzodiazepines have anxiolytic and sedative-hypnotic properties ***Exception: Quazepam, strictly a hypnotic***
        - Binds to type 1 and type 2 $GABA_A$ receptors, broad subunits both centrally and peripherally that have anxiolytic, hypnotic, and muscle relaxant properties
        - Quazepam: binds only to $GABA_A$ receptors that contain the α_1 subunit responsible for the hypnotic effect, similar to the Z-drugs
- Current medical uses: anxiety disorders, sleep disorders, seizure disorders, muscle spasticity, movement disorders, management of acute intoxication (cocaine, meth) and acute withdrawal (alcohol), catatonia
    - Barbiturates: tx of seizures (phenoba\rbital, primidone), general anesthesia (sodium thiopental), migraine headaches (Butalbital)
- Prevalence of Benzodiazepine use:
    - Using data from the 2015 and 2016 National Survey on Drug Use and Health (Maust, 2019)
        - In the United States, 12.6% of adults reported past-year benzodiazepine use
        - Misuse accounted for nearly 20% of overall use, highest in ages 18-25yo (5.2%) and lowest in the elderly (0.6%)
        - However, use as-prescribed was highest among adults aged 50-64yo. The second highest subgroup that used benzodiazepines as prescribed were ages greater than 65yo
- Class adverse effects:
    - Acute: (Lader, 2014), (The APA Publishing Textbook of Psychopharmacology)
        - Sedation and daytime sleepiness can develop tolerance over time
        - Ataxia

        - Slurred speech, disorientation
        - Memory dysfunction, particularly anterograde amnesia
        - Psychomotor impairment
    - Chronic: evidence of cognitive impairment with long term use
        - A meta-analysis on the effects of benzodiazepine use on cognitive functioning, published in 2017 in *Archives of Clinical Neuropsychology*, demonstrated significant cognitive impairments in the domains listed below. Includes current users as well as those who have recently withdrawn and abstained from use -up to 42 months post-withdrawal. (Crowe, 2017)
            - Working memory
            - Processing speed
            - Divided and sustained attention
            - Visuoconstruction
            - Expressive language (deficit only found in current users, not seen in those who have successfully abstained)
            - Executive function (deficit only found in current users, not seen in those who have successfully abstained)
        - Cognitive deficits in the elderly: Liu, 2020
            - A meta-analysis from 2020, published in *Frontiers in Psychiatry,* looked at benzodiazepine use and abuse in the elderly population
                - Found significant impairment in processing speed (digital symbol test scores), both with long term use and abuse
                - Global cognition, assessed with Mini-Mental State Examination, was found to be significantly impaired only with long term abuse
                    - Studies included in this meta-analysis had large heterogeneity regarding tests for memory (auditory and verbal recall) and executive function (planning/reasoning, inhibitory control). However, most studies did find significant impairments in the above cognitive domains with benzodiazepine use and abuse
        - Association with dementia:
            - A 2018 meta-analysis included six case-control studies, four prospective cohort studies, and one retrospective cohort study. Most studies adjusted for depression, anxiety, and/or insomnia (Lucchetta, 2018).
                - Found that benzodiazepine ever-users were 1.38 times more likely to develop dementia as compared to non-users (OR 1.38, 95% CI 1.07–1.77) and that benzodiazepine users have a 28% higher risk of developing dementia (RR 1.28, 95% CI 1.06–1.55)

    - Large heterogeneity in the studies, lack of consistent adjustment of confounding variables, and inability to differentiate between short-term and long-term use or dose relationship provided significant limitations to this meta-analysis
- A 2020 study done in Denmark attempted to mitigate the above limitations. They analyzed prescription registry data for benzodiazepines and Z-drugs in patients with affective disorders (ICD-10 codes F30-F30.9) from 1969 to 2016, and looked for diagnosis of dementia or prescriptions for dementia medication during the 6 year follow up period. The authors then compared members of the population that remained dementia-free (control) and matched them with subjects who developed dementia (Osler, 2020)
    - Explored rates of dementia with regards to drug type (benzodiazepines, Z-drugs, long or short-acting drugs) and timing of exposure and duration of treatment.
    - They found no association between the use of any benzodiazepines or Z-drugs and subsequent diagnosis of dementia. No association with the timing of exposure, between long and short-acting drugs, and no dose-response effect was observed
- Possible protective effect?
    - The same 2020 Denmark study above demonstrated that continued and new users of benzodiazepines had lower rates of dementia than patients with no lifetime use or patients with former use (Osler, 2020)
        - Adjusted hazard ratio: as compared to control (never users)
            - Continuing use: 0.78 (CI 0.70-0.88)
            - New use: 0.83 (CI 0.76-0.89)
            - Former use: 1.05 (CI 0.96-1.16)
    - The odds of developing dementia were slightly higher among individuals with the lowest rates of benzodiazepine use
        - OR: 1.08 (CI 1.01-1.15)
    - It is well known that benzodiazepines impair cognition, especially in the elderly. However, the use of short-acting benzodiazepines in low doses can reduce stress and, some argue, promote sleep.
    - Affective disorders are associated with the risk of developing dementia later in life; perhaps the calming effect of

benzodiazepines in reducing the pathological effects of stress on the brain is protective and thereby decreases the risk of developing dementia (Salzman, 2020)
    - Dr. Cummings commented that "Taking Benzodiazepines chronically is statistically associated with an increased rate of dementia. It's not clear that the benzodiazepine is causing the dementia. It may well be that people who suffer from chronic anxiety, insomnia, and other issues for which they are taking the benzodiazepine - these people may also have a greater burden of general physical illness which may also be risk factors for dementia".
    - Dr. Cummings further noted that "Benzodiazepines are good, short term rescue medications, either for sleep or for anxiety. They are generally dangerous long term medications because of the increased mortality risk and increased cognitive impairment".
- Tapering Benzodiazepines:
    - Very gradual. If an individual has been taking benzodiazepines chronically, the taper needs to be slow; as long as 6 months to more than 1 year
- Benzodiazepines as drugs of abuse:
    - Using data from the 2015 and 2016 National Survey on Drug Use and Health (Blanco, 2018)
        - 17.1% of benzodiazepine users reported misuse; however, only 1.5% had a diagnosis of benzodiazepine use disorder
        - The same data showed that benzodiazepine use was associated with emergency room visits, suicidal ideation, use of other illicit substances, and mental illness
    - Benzodiazepines have played a major role in opiate overdose and deaths in the United States (Bachhuber, 2016)
    - 2018 data from National Institute on Drug Abuse showed benzodiazepine involvement one third of fatal overdoses (National Institute on Drug Abuse)
    - Risk of respiratory depression when combined with opiates and/or alcohol (Blanco, 2018)
- Benzodiazepines and Mortality:
    - A large retrospective, matched cohort study done in the United Kingdom, spanning the years 1998-2011, studied the association between prescriptions for anxiolytics and hypnotics, including benzodiazepines and Z drugs, with mortality. (Weich, 2014)
        - For the benzodiazepines, the **hazard ratio for mortality averaged 3.68** compared to matched controls, with a significant dose-response pattern observed. This was after adjusting for confounders, including physical comorbidities, psychiatric diagnoses, sleep disorders, and prescriptions for non-study drugs
- Benzodiazepine use is common in patients who complete suicide

- A study done in 2013 pulled data from the National Violent Death Reporting System to compare factors that led to suicide between physician and non-physician victims (Gold, 2013).
  - 27% of all suicides had one or more illicit drug or alcohol levels above 0.8%
  - Compared to non-physicians, physicians were at significantly higher odds of having benzodiazepines or barbiturates, as well as antipsychotics, in their system (measured via toxicology testing).
    - Benzodiazepines: OR 21.0, CI 11.4-38.6, p <0.0005
    - Barbiturates: OR 39.5, CI 15.8-99.0, p <0.0005
  - This study also showed no significant difference in the presence of antidepressants, opiates, amphetamines, or cocaine between physicians and non-physicians

- **FDA-approved indication for insomnia (only 5): Flurazepam, Temazepam, Estazolam, Quazepam, and Triazolam**

A. Flurazepam:
Oxidized in the liver and has a long half-life (40 hours). It also forms a long acting metabolite (desalkylflurazepam) that has a half-life of 100 hours

- Efficacy/Uses:
  - 15 and 30mg doses were studied for sleep onset and maintenance insomnia
  - American Academy of Sleep Medicine makes no recommendations for or against Flurazepam, given numerous inconsistencies in studies and high variability across studies
    - In their meta-analysis, the American Academy of Sleep Medicine found mixed data for sleep latency:
      - Increases in Total Sleep Time with 30mg dosing
      - Moderate improvement in Wake After Sleep Onset at 30mg
      - Increase in sleep quality subjectively reported at both 15 and 30mg doses (ASM, 2017)
  - Limited studies reporting moderate to large effect sizes on subjective measurements of sleep latency, total sleep time, and number of awakenings with 30mg dosing (Nowell, 1997)
    - Effect size 0.43 for sleep latency; 0.60 for Total Sleep Time; 0.99 for Number of Awakenings (Elie 1990)
    - Effect size 0.49 for sleep latency; 1.00 for TST; 0.64 for Number of Awakenings (Scharf, 1990)
    - Effect size 0.40 for sleep latency; 0.97 for Total Sleep Time; 1.00 for Number of Awakenings (Dominguez 1986)

    - Studies ranging from 4 weeks to 12 weeks have been done to study the efficacy of Flurazepam 15 and 30mg and have not demonstrated significant tolerance development over this period of time (Reeves 1977), (Leibowitz, 1979)
- Adverse effects:
    - Dose-dependent relationship
    - Reports of significant daytime somnolence, drowsiness, and fatigue (Dominguez, 1986)
    - Impairments in daytime psychomotor functioning (reaction time, pursuit rotor, tapping speed) with 30mg dosing (Salkind, 1975)
    - Carryover effectiveness of Flurazepam 2-3 days after abrupt discontinuation without rebound insomnia (Kales, 1982)

B. Quazepam: Benzodiazepine hypnotic

Pharmacokinetics is similar to Flurazepam. Uniquely, Quazepam is selective for type 1 $GABA_A$ receptors containing the α_1 subunit, similar to the Z-drugs; therefore, little to no anxiolytic or muscle relaxant properties. However, the long-acting metabolite (desalkylflurazepam) binds selectively to type 1 and type 2 $GABA_A$ receptors

- Efficacy/Uses:
    - Doses: 7.5 to 15mg
    - Academy of Sleep Medicine makes no recommendations for or against Quazepam
        - Subjective reports indicated a small reduction in sleep latency and modest improvement in quality of sleep (ASM, 2017)
    - Data on effect sizes were not published for Quazepam and only a few studies exist that have adequate data and utilize randomization, placebo control, and double-blind assessments
        - Measurement of sleep latency, total sleep time, number of awakenings, and sleep quality using Quazepam 30mg: significantly better (*p-value* 0.05) subjective reports in all categories measured compared to placebo (Aden, 1983)
        - Subjective rating scale measurements of short-term use of 15mg Quazepam. Significant improvements with sleep latency (*p-value* 0.01), total sleep time (*p-value* 0.05), and sleep quality (*p-value* 0.03). (Hernandez, 1983)
- Adverse effects:
    - Daytime drowsiness, fatigue, lethargy, and hypokinesia (Aden, 1983)
    - Carryover effectiveness of Quazepam 2-3 days after abrupt discontinuation without rebound insomnia (Kales, 1982)

C. Temazepam

Conjugated in the liver and with a much shorter half-life of 8 hours, no active metabolites

- Efficacy/Uses:
    - Doses: usually 15mg. Can start at 7.5, highest dose is 30mg

- Academy of Sleep Medicine recommends use for sleep onset and sleep maintenance insomnia
  - From their meta-analysis:
    - Mean reduction in Sleep Latency of 37min greater than placebo (CI 21 - 53min reduction)
    - Total Sleep Time - mean 99min longer compared to placebo (CI 18 to 76min improvement)
    - Small improvement in quality of sleep (ASM, 2017)
- Limited studies have shown moderate to large effect size on subjective reports on sleep latency, total sleep time, number of awakenings, and sleep quality
  - Temazepam 20mg - Effect size 0.80 for Sleep Latency; 0.89 for Total Sleep Time (Cuanang, 1982)
  - Temazepam 30mg - Effect size 0.76 for Sleep Latency; 0.57 for Total Sleep Time; 0.76 for Number of Awakenings; 0.76 for Sleep Quality (Fillingim 1979)
- Studies over the course of 1-3 months have not shown significant development of tolerance with 15 or 30mg dosing; subjective reports of efficacy were maintained over this period of time (Allen, 1987), (Mitler, 1979)

- CBTI vs. Temazepam: A 2006 RCT compared CBTI with combination CBTI + Temazepam, Temazepam alone, and placebo; treatment duration of 8 weeks. Follow-ups were conducted at 3 and 8 months (Wu, 2006).
  - Initially (within the 8 weeks), measurements of sleep latency, sleep efficacy, and total sleep time were significantly better in the Temazepam alone group than in CBTI group
  - At the 3 and 8 month follow-ups, however, sustained improvements in sleep latency, sleep efficacy, and total sleep time were **observed only with the CBTI group**; Temazepam alone group were gradually returning to pretreatment baseline and combination therapy yielded variable results.
    - The combined group yielded the greatest reduction in sleep latency and the highest increase in sleep efficiency immediately after the 8-week treatment duration; however, this was not sustained at the 3 and 8 month follow ups, with sleep latency and sleep efficiency returning to baseline, similar to the temazepam alone group.
  - Psychological tests: using the Pre-Sleep Arousal Scale (PSAS), Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS), and Daytime Dysfunction Questionnaire (Pittsburgh Sleep Quality Index)
    - All three measures for sleep quality improved over time and was significantly better with the CBTI group alone as compared to temazepam and combination therapy
- Adverse effects:

- A 2-week trial done on elderly patients with insomnia demonstrated no increase in overall adverse effects with 15mg dosing though there was one reported fall (Glass, 2008)
- Higher doses (20 and 30mg) were associated with headache, blurred vision, depression, lethargy, vertigo and confusion (Cuanang, 1982) (Heffron, 1979)

D. Triazolam

Oxidized in the liver. Extremely short half-life of 3-6 hours. No active metabolites.

- Efficacy/Uses:
  - Dosing: 0.125, 0.25, 0.5mg
  - Academy of Sleep Medicine recommends for sleep-onset insomnia
    - From their meta-analysis: Mean reduction in Sleep Latency 9 min greater compared to placebo (CI 4 to 22 min reduction).
    - Quality of sleep: moderate improvement compared to placebo (ASM, 2017)
  - Objective measurements of sleep using polysomnography demonstrated short-term improvements in sleep onset and maintenance; however, tolerance developed with loss of effectiveness over the course of 2 weeks, as well as a significant rebound insomnia following discontinuation (Kales, 1976)
  - A study looked at behavioral therapy vs. triazolam treatment for the management of sleep-onset insomnia. Found Triazolam treatment was initially superior to behavioral therapy with greater initial reductions in sleep latency; however, the effect quickly weaned and returned to baseline during follow-up measurements (McCulsky, 1991)
  - No data measuring effect sizes could be found in literature review; however, randomized control trials looking at subjective measurements of sleep reported significant p-values
    - Sleep Latency (*p-value* 0.01), Total Sleep Time (*p-value* 0.05), Sleep Quality (*p-value* 0.002). (Hajak, 1994)
    - *P-value* of 0.01 measured in all categories (Sleep Latency, Total Sleep Time, Number of Awakenings, Sleep Quality). (Cohn, 1984)
  - Studies have shown significant development of tolerance in as little as 2 weeks of administration (Kales, 1978), (McCulsky, 1991). A meta-analysis looking at sleep laboratory studies from 1966 to 1997 found the development of tolerance with intermediate and long-term use of triazolam (Soldatos, 1999)
- Adverse effects: (Institute of Medicine Committee Reports)
  - Increased incidence of nervousness/anxiety with 0.25 and 0.5mg dosing
  - Increased evidence of memory impairment with longer duration of use rather than dose-related effects
  - Impaired coordination: higher risk with 0.25mg and 0.5mg
  - Rebound insomnia has been demonstrated in the first 1-2 nights following withdrawal (Soldatos, 1999), (Gillin, 1989)
- CBTI vs. Triazolam:

- A 1991 RCT compared behavioral therapy (stimulus control/relaxation training) with triazolam; treatment duration of 4 weeks, with follow-up conducted 5 weeks later (McClusky, 1991)
  - Triazolam was initially superior to behavioral therapy in measures of sleep latency (with effects even seen on the first night of administration); however, its effectiveness decreased after discontinuation and gradually returned to pretreatment baseline.
  - Behavioral therapy decreased sleep latency over the course of treatment duration, with sustained effects seen on follow-up.

E. Estazolam

Oxidized in the liver. Similar half-life to Temazepam (approximately 8 hours). No active metabolites.

- Efficacy/Uses:
  - Dosing: 1-2mg
  - Academy of Sleep Medicine makes no recommendations for or against use, given limited data
  - Statistically significant improvement in Sleep Latency with Estazolam 2mg, improvements in sleep duration with 2mg, sleep quality improved with 1 and 2mg (Cohn 1991), (Dominguez, 1986), (Scharf, 1990)
  - Only one study found which reported moderate effect size with Estazolam 2mg in measurements of sleep latency, total sleep time, number of awakenings, and sleep quality (Walsh, 1984)
    - Effect size 0.56 for Sleep Latency; 0.67 for Total Sleep Time; 0.57 for Number of Awakenings; 0.63 for Sleep Quality
  - Limited data looking at long-term efficacy. Sleep laboratory studies over the course of 4 to 6 weeks have found no significant development of tolerance (Pierce, 1990), (Vogel, 1992)
- Adverse effects:
  - Limited data on rebound insomnia, significant only one night after discontinuation (Vogel, 1992)
  - Somnolence, hypokinesia, residual daytime fatigue and sleepiness were reported with Estazolam in a dose-related fashion (Dominguez, 1986), (Scharf, 1990)

2. Non-benzodiazepine hypnotics: Zolpidem, Zaleplon, Eszopiclone

- History: (The Big Sleep, 2013)
  - Zopiclone was the first non-benzodiazepine, developed in the 1970s in France. The first in the new category, “z-drugs.” It has a similar broad receptor profile to the

benzodiazepines, with muscle relaxing, anticonvulsant, hypnotic and anxiolytic properties.
    - Zolpidem was introduced to the market in 1988 and launched by the French pharmaceutical company Synthélabo. It was brought to the United States as Ambien in 1992. Unique *selectiveness* of Zolpidem's mechanism of action made it more appealing; theoretically, the selectivity was thought to lead to fewer adverse effects as compared to the benzodiazepines.
    - Development of Zaleplon and Eszopiclone followed (Eszopiclone is the active stereoisomer of Zopiclone. Approved by FDA in 2004).
- Mechanism of Action: Act on the benzo α_1 sites on the $GABA_A$ receptor. Lack of activity at α_2 and peripheral benzodiazepine sites, therefore little to no muscle relaxing, anticonvulsant, or anxiolytic effects (Scatzberg's Manual of Clinical Psychopharmacology)
- Current Medical Uses: Used only in the treatment of insomnia
    - Use in Obstructive Sleep Apnea is being studied:
        - Obstructive Sleep Apnea is associated with low respiratory arousal threshold (LAT), meaning low levels of respiratory effort leads to frequent awakening, greater ease of arousal.
            - Prior studies have shown a slight increase in the respiratory arousal threshold with the use of sedative hypnotics, Eszopiclone and Zolpidem specifically (Eckert, 2011).
            - However, a recent large retrospective study did not demonstrate a significant reduction in the low arousal threshold with either Eszopiclone or Zolpidem in individuals with mild to moderate disease; these participants still met the criteria for low arousal threshold, leading to frequent awakenings (Smith, 2017).
        - Per Dr. Cummings: melatonin is a safe option for individuals with OSA as it doesn't directly affect respiration.
- Z drugs dependence, misuse, and abuse:
    - Z drugs have been associated with the following adverse drug effects:
        - Withdrawal effects including insomnia, anxiety, tremor, restlessness, disorientation, and even case reports of tonic-clonic seizures with Zopiclone and Zolpidem (Flynn, 2006), (Aranko, 1991) (Pitchot, 2009), (Russo, 2021)
        - Paradoxical effects of euphoria, excitability, and hyperactivity that may drive misuse and abuse with high doses of Zolpidem (Victorri-Vigneau, 2007)
            - Increased likelihood of dependence with history of psychiatric disorder and previous history of substance abuse. Doses up to 300mg were reported.
        - Risks of misuse and abuse:

- A study published in the *International Journal of Neuropsychopharmacology* in 2019 looked at reports made to the European Medicines Agency database of adverse drug effects in relation to the Z drugs, spanned between 2003 and 2017. This study found that among the Z drugs, Zolpidem had the highest rate of misuse/abuse and rates of the following adverse effects (Schifano, 2019)
    - A total of 23,420 adverse drug reactions related to misuse/abuse/dependence/withdrawal of Zolpidem
    - Intentional overdose involving Zolpidem 16.7%, suicide attempt 13.2%, intentional self injuiry 0.5%
    - Use alongside other recreational illicit drugs including cocaine, alcohol, cannabis, and amphetamines
    - Atypical use including intravenous, nasal, and sublingual modalities
- The same study above (Schifano, 2019) had data for Zaleplon as well. Zaleplon was associated with the following (though much less frequent as compared to Zolpidem):
    - A total of 537 adverse drug reactions related to misuse/abuse/dependence/withdrawal of Zaleplon
    - Intentional overdose involving Zaleplon 51.9%, suicide attempt 13.6%, suicidal ideation 5.21%
    - A few case reports of atypical nasal use modality
- With Eszopiclone, no evidence of misuse or abuse could be found in individuals without an already established history of drug abuse
    - One study, unpublished, shows that Eszopiclone at 6mg and 12mg doses (not dosages approved for insomnia) produce euphoric effects similar to diazepam 20mg (Scharf, 2006)

- Z drugs and Mortality:
    - A large retrospective, matched cohort study done in the United Kingdom, spanning the years 1998-2011, studied the association between prescriptions for anxiolytics and hypnotics, including benzodiazepines and Z drugs, with mortality. (Weich, 2014)
        - For the Z drugs, the hazard ratio for mortality averaged 3.19 compared to matched controls, with a significant dose-response pattern observed. This was after adjusting for confounders including physical comorbidities, psychiatric diagnoses, sleep disorders, and prescriptions for non-study drugs.

A. Zolpidem (Ambien)

Half-life of 2-4 hours. Zolpidem ER has a similar half-life but is absorbed over a longer period of time.

- Efficacy/Uses:

- Dosing: 5 or 10mg
- Academy of Sleep Medicine recommends for sleep onset and sleep maintenance insomnia
  - From their meta-analysis:
    - Sleep Latency mean reduction was 5–12 minutes greater compared to placebo
    - Total Sleep Time mean improvement was 29 minutes longer compared to placebo
    - Wake After Sleep Onset mean reduction was 25 minutes greater compared to placebo
    - Moderate improvement in quality of sleep (ASM, 2017)
- A 2012 prospective 8 month placebo-controlled study, in adults ages 23-70, showed a significant increase in Total Sleep Time compared to baseline and placebo, as well as decreases in Sleep Latency and Wake After Sleep Onset, that was sustained over the course of 8 months. (Randall, 2012)
  - Subjective questionnaires and objective polysomnography measures were correlated
- Using polysomnography, limited studies have shown moderate to large effect size for sleep latency, however variable effect sizes for total sleep time and small effect size for the number of awakenings. Zolpidem 10mg was used for evaluation.
  - Effect size 1.00 for Sleep Latency; 0.81 for Total Sleep Time; 0.38 for Number of Awakenings (Herrmann, 1993)
  - Effect size 0.68 for Sleep Latency; 0.22 for Total Sleep Time (Scharf, 1994)
    - Also studied Zolpidem 15mg, however, found no significant advantage compared to 10mg.
- A 2008 randomized placebo-controlled study, using polysomnography and studying Zolpidem 10mg dosing, demonstrated similar efficacy with regards to sleep latency (significant reduction in latency to persistent sleep measurements); however, reductions in night time awakenings and wake after sleep onset were not statistically significant compared to placebo. (Erman, 2008)

- CBTI vs. Zolpidem:
  - A 2004 RCT compared CBTI alone with combination CBTI + Zolpidem and Zolpidem use alone, along with placebo, in adults with sleep-onset insomnia; treatment phase was 8 weeks. The primary outcome measure was sleep latency, with sleep efficiency and total sleep time measured as secondary outcomes (Jacobs, 2004). Their findings are as follows:
    - With regards to sleep latency and sleep efficiency mid and post treatment:
      - CBTI, alone or in combination with Zolpidem, is more effective than pharmacotherapy alone
      - CBTI was equal to or superior to combination therapy

- CBTI was significantly superior to Zolpidem alone mid and post-treatment
- Effect sizes were only reported for sleep latency:
  - Mid treatment: CBTI effect size 1.17, combined treatment effect size 1.08, Zolpidem alone effect size 0.51
  - Post treatment: CBTI effect size 1.22, combined treatment effect size 1.12, Zolpidem alone effect size -0.1
- No significant differences among all groups on total sleep time, including placebo

- A 2009 RCT compared CBTI alone to the combination CBTI + Zolpidem for acute insomnia treatment (6 weeks duration) and maintenance treatment (6 months duration) in adults with persistent insomnia. Participants in the combined group during the acute phase were subsequently randomized to CBT alone or CBT + Zolpidem in the maintenance phase (Morin, 2011).
  - During the acute phase of treatment:
    - CBTI + Zolpidem showed a modest, but significant increase in Total Sleep Time relative to those treated with CBTI alone
    - Significant reductions in sleep latency and wake after sleep onset for CBTI alone and in combination with Zolpidem, without substantial differences
  - Maintenance treatment:
    - The best outcome, defined as the highest rate of remission measured by the insomnia Severity Index, was achieved in participants who were initially treated by combination therapy (CBTI + Zolpidem) and then maintained by CBTI alone rather than continuing with combination therapy.
    - Those maintained by CBTI alone had significant, sustained increases in Total Sleep Time

- Adverse effects:
  - Rebound insomnia: very little evidence to support this happens. Only one study found in literature review showed possible rebound insomnia day one after discontinuation but didn't extend further (Ware, 1997)
  - Withdrawal:
    - In a 2012 RCT, no evidence of clinically significant withdrawal symptoms were found (Roehrs, 2012)
    - However, numerous case reports have been published demonstrating clinically significant withdrawal from Zolpidem (Victorri-Vigneau, 2007) as well as case reports linking Zolpidem withdrawal to delirium ((Mattoo, 2011) and seizure-like activity (Gilbert, 1997), (Aragona, 2000)

- Global impairments were reported in psychomotor function, attention, memory, cognition. Most prominent in the middle of the night, a few hours after administration. (Kleykamp, 2012)
- Anterograde Amnesia: dose-dependent effect
  - Significant memory and cognitive impairments 6 hours after administration with 20mg dosing (Verster, 2002)
- Psychomotor performance: dizziness, postural instability, ataxia, falls
  - Increased odds of fracture in elderly population associated with Zolpidem use, by at least two-fold: (Kang, 2012), (Wang, 2001)
  - Profound dose-dependent impairments with body balance and standing steadiness, even after a single administration (Mets, 2010)

- Next day performance:
  - Driving:
    - 2016 literature review found an association with Zolpidem use and motor vehicle collisions (Rudisill, 2016)
    - Studies have reported a relationship between early or middle of the night administration of Zolpidem and residual next-day driving impairments in healthy and elderly participants (Leufkens, 2009), (Bocca, 2011), (Otmani, 2008)
  - Complex sleep-related behaviors:
    - Parasomnia behaviors: nightmares/terrors, somnambulism, sleep-driving
      - These neuropsychiatric effects, including hallucinations, were extensively reported in association with Zolpidem in a systematic review of the drug database in Australia from 2001-2008. (Ben-Hamou, 2011)
    - A study in Taiwan published in the *Journal of Clinical Psychiatry* in 2010 reported an incidence of 15.2% of complex sleep-related behaviors associated with Zolpidem use in patients with depressive and anxiety disorders (matched controls). (Hwang, 2010)
      - Somnambulance, sleep-talking, sleep-related eating disorders, hallucinations, and one instance of sleep-driving.
      - Increased risk with doses greater than 10mg of Zolpidem, younger age, and it affected females more than males
    - In Australia, by 2007, the Adverse Drug Reactions Advisory Committee had received 104 reports of hallucinations, 62 of amnesia, and 16 of "unusual or inappropriate behavior" linked to Zolpidem (Olson, 2008)
    - Sleep-eating, sleep-cleaning, and sleep-shopping have been reported (Tsai, 2007)
    - Confusional arousal vs. sleepwalking
      - Perhaps the unusual behaviors described above are related to amnesia and disorientation that is indicative of confusional arousal (a side effect of any sedative) rather than sleepwalking. Sleepwalking is constricted to

what can be done without cortical input, as the cortex is asleep, rather than the complex behaviors described above (Olson, 2008)

- Sleep-Driving:
  - Prior to 2006, 14 post-marketing cases of sleep-driving was reported to the FDA, 13 associated with Zolpidem (Southworth, 2008)
  - Case reports of sleep-driving in association with Zolpidem:
    - *Zolpidem-induced sleep-driving*
    - Zolpidem-induced sleepwalking, sleep related eating disorder, and sleep-driving: fluorine-18-flourodeoxyglucose positron emission tomography analysis, and a literature review of other unexpected clinical effects of zolpidem.

B. Zaleplon (Sonata)

Extremely short half-life of 1-2 hours.

- Efficacy/Uses:
  - Dosing: 5 or 10mg, max 20mg
  - Academy of Sleep Medicine recommends only for sleep-onset insomnia. In their meta-analysis, Sleep Latency mean reduction was 10 minutes greater compared to placebo (ASM, 2017)
  - A double-blind placebo-controlled RCT (published in 2000) assessed the efficacy of Zaleplon 10mg dose using polysomnography over a course of 5 weeks. Found significant reduction in Sleep Latency without effect on Total Sleep Time or the number of awakenings (Walsh, 2000).
  - A Multi-center, double-blind RCT in 2000 that lasted for 2 weeks assessed Zaleplon efficacy in elderly population greater than 65 years old. Subjective sleep latency was significantly reduced at both 5 and 10mg doses and subjective sleep quality was significantly improved with the 10mg dose (Hedner, 2000)
  - A 2014 meta-analysis of polysomnographic randomized placebo-controlled trials calculated effect size using data from the above study (Winkler, 2014). Found small effect sizes for sleep latency and total sleep time.
    - Effect size 0.35 for Sleep Latency; 0.12 for Total Sleep Time (Walsh, 2000)
  - No evidence of tolerance development/decrease in efficacy in studies from 4 weeks up to 12 months (Heesch, 2014), (Fry, 2000)
- Adverse effects:
  - No evidence of rebound insomnia in literature review (Fry, 2000), (Dooley, 2000), (Israel, 2002)
  - Headache, dizziness, and somnolence are the most reported symptoms; however, there is no significant difference from placebo (Walsh, 2000).
  - No impairments found with driving ability, psychomotor performance, or memory 4 hours and 6 hours after administration of 10mg or 20mg doses (Verster, 2002)

    - One case of sleep-driving associated with zaleplon use that was reported to the FDA prior to 2006 (Southworth, 2008)
- Next day performance:
    - No studies were found that demonstrated significant impairments in next-day performance specifically

C. Eszopiclone (Lunesta)

Half-life of 4-5 hours.

Per Dr. Cummings: For individuals with terminal insomnia, of all the Z-drugs, Eszopiclone has been shown to have the most benefit given its longer half-life.

- Efficacy/Uses:
    - Dosing: 1-3mg
    - Academy of Sleep Medicine recommends for sleep onset and sleep maintenance insomnia
        - From their meta-analysis:
            - Sleep Latency mean reduction was 14 min greater compared to placebo.
            - Total Sleep Time mean improvement was 28–57 min longer compared to placebo
            - Wake After Sleep Onset mean reduction was 10–14 min greater compared to placebo
            - Moderate-to-Large improvement in quality of sleep (ASM, 2017)
    - Significant reductions in subjective reports of Sleep Latency, Wake After Sleep Onset, and Number of Awakenings along with a significant increase in subjective reports of Total Sleep Time over a course of 6 months in adults with chronic insomnia (Krystal, 2003)
    - Polysomnography measurements over 2 nights demonstrated decreases in Sleep Latency with all doses (1-3mg). Nighttime awakenings and Wake After Sleep Onset improved with only 2.5 and 3mg doses (Erman, 2008)
    - 2014 meta-analysis of polysomnographic randomized placebo-controlled trials found two studies that assessed Eszopiclone and had adequate data to calculate effect size (Winkler, 2014). At 2mg dosing, the effect size was moderate for total sleep time but small for measures of sleep latency and variable (small-moderate) for sleep efficiency. At 3mg dosing, the effect size was moderate for all three categories: total sleep time, sleep latency, and sleep efficiency. This suggests a clinical advantage with higher Eszopiclone dosing.
        - (McCall, 2006) Eszopiclone 2mg: effect size 0.52 for Total Sleep Time, 0.40 for Sleep Latency, 0.51 for Sleep Efficiency
        - (Zammit, 2004)

        - Eszopiclone 2mg: effect size 0.23 for Sleep Latency, 0.32 for Sleep Efficiency
        - Eszopiclone 3mg: effect size 0.61 for Sleep Latency, 0.54 for Sleep Efficiency
    - Insomnia in conjunction with depression:
        - 2 large multi-center trials have demonstrated that 1-3mg of Eszopiclone can help improve symptoms of insomnia (sleep onset and maintenance) in individuals diagnosed with depressive disorders (Fava, 2006), (Joffe, 2010)
    - No evidence of rebound insomnia or development of tolerance in studies ranging from 3 to 12 months (Heesch, 2014), (Ancoli-Israel, 2010), (Roth, 2005), (Walsh, 2007)
    - Bipolar disorder:
        - It is well known that insomnia in these individuals can precipitate manic episodes. Per Dr. Cummings: Eszopiclone can be used for individuals with bipolar disorder and insomnia.
            - During acute mania, sometimes Eszopiclone has been used in doses up to 8mg.
- Adverse effects:
    - In both non-elderly patients (2-3mg of Eszopiclone) and elderly patients (1-2mg of Eszopiclone), only dry mouth and unpleasant taste were found to be statistically significant compared to placebo (Zammit, 2004), (Scharf, 2005)
        - Adverse effects of headache, dizziness, residual somnolence, dyspepsia were reported by both groups; however, incidence was not significantly different from placebo
- Next day performance:
    - No studies were found that demonstrated significant impairments in next-day performance specifically.

3. <u>Non-benzodiazepine hypnotics: Orexin Receptor Antagonists</u>

- History: 1998 gene encoding hypothalamic orexin neuropeptides, OX-1 and OX-2 were described. There are 50,000-80,000 orexin neurons originating in the lateral hypothalamus (Winrow, 2014, Janto, 2018).
- Mechanism of Action: Competitive antagonist of OX1 and 2 receptors. Prevents Orexin A and B from binding. Blocks orexin-mediated wake signaling, allowing maintenance of sleep.

A. Almorexant

GlaxoSmithKline and Actelion abandoned the project in 2011 due to undisclosed reasons relating to its safety profile despite concluding Phase III clinical trial, RESTORA 1 (Press release, 2011).

Commonly Prescribed Sleep Medications And Treatment for Insomnia

Shizuka Tomatsu M.D., Shilpa Krishnan D.O., David Puder, M.D.

B. Suvorexant (Belsomra)

2014 (Merck), Suvorexant became the first FDA approved therapeutic agent for the treatment of insomnia. Two trials were conducted consisting of two weeks of placebo for everybody followed by a 3m double-blinded placebo-controlled 3 arm phase (Suvorexant 40/30, Suvorexant 20/15, or placebo). Trial 1: ratio of 3:2:3, Trial 2: ratio of 1:1:1 in Q cohort, 2:1:2 in PQ cohort (Herring, 2016).

- Efficacy/Uses:
    - Recommended for sleep maintenance insomnia.
    - 10 mg starting dose, 20 mg max dose.
        - If using another CNS depressant drug or moderate CYP3A inhibitors, half the dosing range (5-10 mg).
        - Take 30 min before bed, with or without a meal. Don't take with alcohol (Belsomra info packet)
    - Clinically significant reduction in wake after sleep onset (16-28m) for both 10 and 20 mg doses.
        - **EFFECT SIZE (difference in the least square mean): Suvorexant 20/15 vs. Placebo**
            - Trial 1: Night 1 -32.5 min; Month 1 -26.4 min; Month 3 -16.6 min
            - Trial 2: Night 1 -37.0 min; Month 1 -24.1 min; Month 3 -31.1 min
    - Clinically significant reduction in sleep onset at 20 mg dose, suggesting higher doses may help with sleep onset (Herring, 2016).
        - **EFFECT SIZE (difference in the least square mean): Suvorexant 20/15 vs. Placebo**
            - Trial 1: Night 1 -9.6 min; Month 1 -10.3 min; Month 3 -8.1 min
            - Trial 2: Night 1 -12.4 min; Month 1 -7.8 min; Month 3 -0.3 min (crosses 0 CI for months 1 and 3).
- Adverse effects/potential for abuse
    - Twice the rate of somnolence compared with placebo, but overall placebo had more discontinuation rate due to adverse events (Herring, 2016).
    - No plasma concentration difference in moderate hepatic or renal dysfunction (Bennett, 2014)
    - Contraindicated if on a strong CYP3A inhibitor
    - Addiction liability is lower than Zolpidem (Schoedel, 2016)
- Next day performance
    - No data on subjective sleep quality or next day performance (limitation of trial) (AASM, 2017)

C. Lembroexant (Dayvigo)

Commonly Prescribed Sleep Medications And Treatment for Insomnia

Shizuka Tomatsu M.D., Shilpa Krishnan D.O., David Puder, M.D.

In June 2016, Eisai pharmaceuticals initiated a pair of phase III clinical trials in the US, France, Germany, Italy, Japan, Poland, Spain, and the UK. Three years later, in December 2019, at the completion of these industry-sponsored trials (SUNRISE I and II), Lemborexant was approved for use in the US by the FDA.

- SUNRISE I (Rosenburg, 2019)
- SUNRISE II (Yardley, 2020)

- Efficacy/Uses:
  - FDA approval: Recommended for sleep onset and sleep maintenance insomnia
  - 2.5mg – 10mg efficacious while minimizing next-morning residual sleepiness.
  - Statistically significant improvements in sleep onset compared to placebo.
    - **EFFECT SIZE (difference in raw mean change from baseline)**
      - Lemborexant 5mg: Night 1&2 was -10.1 min; Night 29&30 was -11.6 min.
      - Lemborexant 10mg: Night 1&2 was -13 min; Night 29&30 was -13.6 min.
  - Statistically significant improvements in wake after sleep onset compared to placebo.
    - **EFFECT SIZE (difference in raw mean change from baseline)**
      - Lemborexant 5mg: Night 1&2 was -34.9 min; Night 29&30 was -25.3 min.
      - Lemborexant 10mg: Night 1&2 was -44.5 min; Night 29&30 was -27.8 min
- Adverse effects/potential for abuse
  - Headache and somnolence (SUNRISE I)
  - Somnolence, nasopharyngitis, and headache (SUNRISE II)
  - Similar to suvorexant, limited abuse potential. Doses up to 7 times the recommended dose only caused an increase in somnolence (Murphy, 2017, Ardeljan, 2021)
  - No dependence or withdrawal symptoms were noted (Murphy, 2017, Ardeljan, 2021)
- Next day performance
  - Statistically significant improvements in insomnia Severity Index (ISI) compared to placebo (Yardley, 2020).
    - **EFFECT SIZE (difference in raw mean change from baseline score)**
      - Lemborexant 5mg: Month 1 was -1.0; Month 3 was -1.5; Month 6 was -1.7.
      - Lemborexant 10mg: Month 1 was -1.1; Month 3 was -1.5; Month 6 was -1.4.
  - Statistically significant improvements in Fatigue Severity Scale (FSS) compared to placebo (Yardley, 2020).
    - **EFFECT SIZE (difference in raw mean change from baseline score)**
      - Lemborexant 5mg: Month 1 was -2.7; Month 3 was -3.4; Month 6 was -3.8.

- Lemborexant 10mg: Month 1 was -2.5; Month 3 was -3.6; Month 6 was -2.6.

D. Daridorexant

Phase III, 04/2020 (Press Release, 2020)

- Efficacy/Uses:
  - Not yet FDA approved: Maybe early 2022?
  - Requesting recommendation for sleep onset and sleep maintenance insomnia
- Adverse effects/potential for abuse
  - Nasopharyngitis, headache, somnolence, and fatigue
- Next day performance
  - No next day somnolence, no final data.

4. Non-benzodiazepine hypnotics: Melatonin Receptor Agonists

- History: Researchers investigated the modulation of the core structure of melatonin to develop a better agonist. Things that were more potent and better pharmacokinetic and had a longer half-life by changing the structure of melatonin. (Zammit, 2007)
- Mechanism of action: Acts on MT1 and MT2 receptors to promote sleep and exert an effect on circadian rhythms.

A. Ramelteon (Rozarem)

- Efficacy/Uses:
  - Recommended for sleep-onset insomnia
  - Reduced sleep onset over 5 weeks with no clinically significant changes to sleep architecture (Zammit, 2007)
  - Sleep onset latency @ 1 week: Placebo (47.9 min), Ramelteon 8mg (32.2 min), Ramelteon 16mg (28.9 min)
    - Effect size via raw mean difference: 15.7 min Placebo vs. Ramelteon 8mg
    - Effect size via raw mean difference: 19 min Placebo vs. Ramelteon 16mg
  - No improvement in quality of sleep (Zammit, 2007)
  - Take 8mg 30 minutes before bedtime
- Adverse effects/potential for abuse
  - No next morning drowsiness (Zammit, 2007)
  - No rebound insomnia, no withdrawal due to no affinity to CNS receptors associated with sedation (Zammit, 2007)
- Next day performance
  - Limited data.
- Cummings: good for sleep-onset

B. Agomelatine (Valdoxan, Melitor, Thymanax)
Approved in Europe and Australia but was discontinued in the US due to the negative outcome of phase III clinical trials (Parkinson Disease and MDD) and side effects included severe liver toxicity. (Zajecka, 2010, Clinical Trial, 2019, Press Release, 2019).

C. Tasimelteon (Hetlioz) Not used for insomnia
FDA approved for non-24 hour sleep wake disorder (Lockley, 2015).

5. Non-benzodiazepine hypnotics: Heterocyclics

- Mechanism of action: Low dose doxepin blocks H1 receptors to treat insomnia. Has a binding affinity 100 times more towards H1 receptors than any other receptors, which then inhibits the arousal pathway and produces the hypnotic action. Increases concentration of serotonin and norepinephrine at higher doses.

A. Doxepin (Silenor)

- Efficacy/Uses
  - FDA approved for short and long-term insomnia
  - AASM recommended for sleep maintenance insomnia
  - 3-6mg for insomnia
    - Lower doses (less than 25mg) produce anti-anxiety and sedative effects
    - Higher doses (greater than 25mg) produce anti-depressant effects
  - Sleep onset latency is not clinically significant from placebo (Katwala, 2013)
  - Total sleep time 26-32 minutes longer compared to placebo (Katwala, 2013)
  - Statistically significant improvements in wake after sleep onset compared to placebo (Krystal, 2010)
  - Dr. Puder and Dr. Tomatsu's recommended first-line medication for many patients due to the lower side effect profile at the 3-6mg dosage
    - **EFFECT SIZE (difference in raw mean from baseline)**
      - Doxepin 1mg Night 1 was -17.1 min; Night 29 was -8.2 min; Night 85 was -12.2 min.
      - Doxepin 3mg: Night 1 was -34.4 min; Night 29 was -20.3 min; Night 85 was -33.5 min.
  - Statistically significant improvements in WASO compared to placebo (Krystal, 2011)
    - **EFFECT SIZE (difference in raw mean from baseline)**
      - Doxepin 3mg: Night 1 was -25.4 min; Night 15 was -15.8 min; Night 29 was -13.3 min.

        - Doxepin 6mg: Night 1 was -30.5 min; Night 15 was -18.8 min; Night 29 was -19.8 min.
- Adverse effects/potential for abuse
    - No physical dependence, withdrawal (Katwala, 2013)
    - Headache, somnolence/sedation, and nausea (Krystal, 2011)
    - When doxepin is greater than or equal to 25mg non-selective and are anticholinergic, anti-adrenergic, and potentiate cardiac conduction abnormalities (Katwala, 2013)
- Next day performance
    - Next day severe somnolence and grogginess (Katwala, 2013)
    - No statistical difference in Digit symbol substitution test (DSST), Symbol copying test (SCT), Subjective alertness and drowsiness (Krystal, 2010)

6. Off-Label / Over the counter

A. Diphenhydramine

- History
    - Not FDA-approved for insomnia. However, it was included by the FDA as a safe and effective nighttime sleep aid as part of the FDA's Final Drug Monograph for OTC use
    - AASM recommends AGAINST using diphenhydramine for the treatment of chronic sleep onset or sleep maintenance insomnia
    - Two RCTs – significant risk of imprecision and publication bias
- Mechanism of action
    - First generation H1 antagonist with non-specific anticholinergic and sedative effects
- Efficacy/Uses
    - **Do not use,** but typically 25-50 mg over the counter
    - Sleep onset latency reduction of 8 min, total sleep time 12 min, No improvement in sleep quality. All were below the threshold of clinical significance thresholds
    - Not clinically significant difference in the number of awakenings with diphenhydramine vs placebo (Glass, 2008)
- Adverse effects/potential for abuse
    - No rebound effects (Morin, 2005)
- Next day performance
    - No difference in morning-after DSST or MTT from placebo
    - Sleep diaries, morning-after psychomotor impairment, morning-after memory impairment: Temazepam worse than Diphenhydramine (Glass, 2008)
    - Diphenhydramine > Placebo for awakenings 1.7 vs. 2.0 (Glass, 2008)
    - Diphenhydramine better sleep efficiency (total sleep time/total time in bed) and total sleep time **but by day 28 no different from placebo** (Morin, 2005)

Commonly Prescribed Sleep Medications And Treatment for Insomnia

Shizuka Tomatsu M.D., Shilpa Krishnan D.O., David Puder, M.D.

B. Valerian

- History
    - Not FDA-approved for the treatment of insomnia
    - Not recommended by the AASM
    - Only one study evaluating valerian for chronic insomnia
- Mechanism of action: Binds to the beta subunit of GABA-A receptor (allosterically modulates the receptor)
- Efficacy/Uses (Morin, 2005) **Not blinded study**
    - Typically 2 mg (no more than 3 mg)
    - Valerian better sleep onset latency compared to placebo (not stat sig) (Morin, 2005)
    - Subjectively rated that quality of life and insomnia improved at the end of 28 days (Morin, 2005)
    - Per Dr. Cummings: It is a sedative but due to the lack of control and variation depending on the product, efficacy is unknown
- Adverse effects/potential for abuse (Morin, 2005)
    - No adverse events compared to placebo group, even at high doses
    - Overall safe with no rebound insomnia (Morin, 2005)
- Next day performance
    - Limited data

C. Melatonin

- Biological Melatonin: pineal gland, action on the sleep/wake cycle
    - Can cross placenta, synchronize fetal biological clock
    - Synthesis affected by ambient light
    - Complex interplay between physiological need and environmental cues
- Mechanism of Action
    - Melatonin is a tryptophan derivative that binds to MT1A receptors
- Efficacy/Uses
    - Not FDA-approved for the treatment of insomnia
    - Not recommended by the AASM
    - First line recommendation by the AAFP
    - Multiple RCTs but no meta-analyses were conducted for melatonin in insomnia, except for sleep quality which was clinically insignificant
    - Not recommended, but studies looked at 2mg nightly
    - **Effect size:** Sleep onset was -8.9min for melatonin compared with placebo (Luthringer, 2009).
    - Total sleep time increased by 2 min for melatonin compared to placebo. Wake after sleep onset was 8.5 min better for placebo compared to melatonin. The confidence interval crossed for all data (Luthringer, 2009).

    - Per Dr. Cummings: Recommends for patients with OSA due to low side effect profile.
- Adverse effects/potential for abuse
    - No harms reported
- Next day performance
    - Limited data

D. L-tryptophan

- Mechanism of action: Tryptophan is hydroxylated to 5-HTP and decarboxylated to 5-HT and melatonin. Increasing blood levels of tryptophan directly increases serotonin and melatonin levels (Hajak, 1991)
- Efficacy/Uses
    - Not FDA-approved for the treatment of insomnia
    - Not recommended by the AASM
    - Limited data
    - Modest decline in TST, decrease in WASO, increase in sleep quality. None met thresholds for clinical significance (Hudson, 2005)
- Adverse effects/potential for abuse
    - Limited and subjective data
- Next day performance
    - Limited and subjective data

E. L-theanine

- History
    - Discovered in 1949 in tea, isolated in 1950 in Kyoto, Japan
    - Marketed as a "natural alternative to prescription sleep aids"
- Mechanism of Action: AMPA receptor antagonist and NMDA receptor agonist. Blocks the reuptake of glutamine and glutamate
- Efficacy/Uses
    - May show some benefit in mice and rat models (Kim, 2018)
- Adverse effects/potential for abuse
    - Found in tea such as green tea→ has caffeine which would potentially counteract effect
- Next day performance
    - Limited data

F. Trazodone

- History: Due to concerns with tolerance and dependency with benzos, physicians increasingly began prescribing sedating antidepressants "off-label," especially trazodone, despite the absence of efficacy. A survey of office-based physician prescribing practices from 1987-1996 revealed a

50% decline in benzo hypnotic prescriptions coinciding with a 150% increase in trazodone prescriptions (Roehrs, 2004).

- Mechanism of action
    - Serotonin (5HT2) antagonist and reuptake inhibitor (SARI)
    - Has effects on serotonin, noradrenaline, dopamine, acetylcholine, and histamine
- Efficacy/Uses
    - Not FDA-approved for insomnia. Used off-label
    - AASM recommends physicians DO NOT use this medication, as the potential harms outweigh any perceived benefits
    - Do not use, but typically 50 mg – 100 mg qHS
    - Only one study-- compared with placebo, at week 1, a modest reduction in sleep onset latency (10.2 min), a modest increase in total sleep time (21.8 min), and a small reduction in wake after sleep onset (7.7 min). By week 2, effects were not sustained. Subjective sleep quality and the number of awakenings were slightly improved. However, every single one of these measures fell below the clinical significance threshold (Walsh, 1998)
    - Per Dr. Cummings: Has not found it very helpful. Don't give it to bipolar patients because it can induce mania/hypomania. It also has alpha antagonist properties that may be dangerous for older adults.
- Adverse effects/potential for abuse
    - Significantly more side effects than the placebo group, with the primary side effects being headache (30% vs 19%) and somnolence (23% vs 8%) (Walsh, 1998)
    - Not habit forming (Jaffer, 2017)
    - Side effects: withdrawal--anxiety, agitation, insomnia (Jaffer, 2017)
- Next day performance
    - Not clinically significant short term memory performance, recall, attention, balance, and muscle endurance (Roth, 2012)

G. Mirtazapine

- Mechanism of action: Noradrenergic and specific serotonergic antagonist. Blocks a2, 5-HT2, and 5-HT3 receptors. Also has histamine 1 antagonism.
- Efficacy/Uses
    - Not FDA-approved for the treatment of insomnia
    - Not recommended by the AASM15 mg once daily (up to 45 mg/day)
    - Statistically significant improvement in sleep onset latency compared to SSRIs/SNRIs in MDD
        - **EFFECT SIZE (difference in raw mean from baseline)**
            - Mirtazapine 15mg-45mg overall had -10.1 minutes compared to SSRIs/SNRIs (Wang, 2013)
- Adverse effects/potential for abuse

    - Contraindicated in those using MAOi
    - Withdrawal causes insomnia
    - Overdose can lead to QT prolongation and torsades
    - Major side effects: discontinuation syndromes, somnolence, appetite increase
        - Per Dr. Cummings: less likely with lower doses; can stop at 7.5mg without issues
- Next day performance
    - Limited data

H. Hydroxyzine

- Mechanism of action: potent and selective H1-receptor inverse agonist
- Efficacy/Uses
    - Not FDA-approved for the treatment of insomnia
    - Not listed on the AASM guidelines
    - See diphenhydramine for general antihistamine efficacy in insomnia
    - Per Dr. Cummings: His personal favorite because it does not have alpha antagonist or anticholinergic properties that trazodone or diphenhydramine may have, respectively.
    - Often dosed at 25-50mg qHS.

Table 1 Summary of clinical practice recommendations based on American Academy of Sleep Medicine (AASM)

			Outcomes by Intervention			
Treatment	**Drug Class**	**AASM Recommendation (compared with no treatment)**	**TST**	**SL**	**WASO**	**QOS**
Temazepam	Benzodiazepine	Sleep onset and sleep maintenance insomnia	+	+	+	+
Triazolam	Benzodiazepine	Sleep onset insomnia		+		+
Eszopiclone	Benzodiazepine receptor agonist	Sleep onset and sleep maintenance insomnia	+	+	+	+
Zaleplon	Benzodiazepine receptor agonist	Sleep onset insomnia	+	+		+
Zolpidem	Benzodiazepine receptor agonist	Sleep onset and sleep maintenance insomnia	+	+	+	+
Suvorexant	Orexin receptor agonist	Sleep maintenance insomnia	+	+	+	+
Ramelteon	Melatonin agonist	Sleep onset insomnia		+		+
Doxepin	Heterocyclic	Sleep maintenance insomnia	+	+	+	+
Trazodone	Heterocyclic	DO NOT use for insomnia	+	+	+	+
Melatonin	Over the counter	DO NOT use for insomnia		+		+
Diphenhydramine	Over the counter	DO NOT use for insomnia	+	+	+	+
Tryptophan	Over the counter	DO NOT use for insomnia		+	+	+
Valerian	Over the counter	DO NOT use for insomnia		+		+

Adapted from American Academy of Sleep Medicine (AASM) Clinical Pracite Guideline 2017. TST=total sleep time, SL=sleep latency, WASO=wake after sleep onset, QOS=quality of sleep.

Acknowledgments:

This article was supported by "Mental Health Education & Research".

Commonly Prescribed Sleep Medications And Treatment for Insomnia

Shizuka Tomatsu M.D., Shilpa Krishnan D.O., David Puder, M.D.

References

1. Spielman AJ YC, Glovinsky PB. (2011). Sleep Restriction Therapy. In Behavioral Treatments for Sleep Disorders. Oxford, UK: Elsevier.
2. Morin CM EC. (2004). Insomnia: A clinical guide to assessment and treatment. New York: Springer.
3. Lichstein KL, Riedel BW, Wilson NM, Lester KW, Aguillard RN. (2001). Relaxation and sleep compression for late-life insomnia: a placebo-controlled trial. J Consult Clin Psychol; 69(2):227-39.
4. American Academy of Sleep Medicine. (2021, September 7). *American Academy of Sleep Medicine Guidelines | AASM*. American Academy of Sleep Medicine – Association for Sleep Clinicians and Researchers. https://aasm.org/clinical-resources/practice-standards/practice-guidelines/
5. Sateia, M. J., Buysse, D. J., Krystal, A. D., Neubauer, D. N., & Heald, J. L. (2017). Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, *13*(2), 307–349. https://doi.org/10.5664/jcsm.6470
6. Edinger, J. D., Buysse, D. J., Deriy, L., Germain, A., Lewin, D. S., Ong, J. C., & Morgenthaler, T. I. (2015). Quality measures for the care of patients with insomnia. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, *11*(3), 311–334. https://doi.org/10.5664/jcsm.4552
7. Brady, K. T., Levin, F. R., Galanter, M., Kleber, H. D., Jones, J. L., VandenBerg, A., & Malcolm, R. (2021). *The American Psychiatric Association Publishing Textbook of Substance Use Disorder Treatment* (6th ed.) [E-book]. Van Haren Publishing.
8. Schatzberg, A. F., & DeBattista, C. (2019). *Schatzberg's Manual of Clinical Psychopharmacology* (Ninth ed.) [E-book]. Amer Psychiatric Pub Inc.
9. *Benzodiazepine harm: how can it be reduced?* (2014, February 1). PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4014015/
10. Sheehan, D. V. (2017). The American Psychiatric Association Publishing Textbook of Psychiatry. In *Chapter 22. Benzodiazepines* (5th ed.). American Psychiatric Association Publishing. https://doi.org/10.1176/appi.books.9781615371624.as22
11. Maust, D. T., Lin, L. A., & Blow, F. C. (2019b). Benzodiazepine Use and Misuse Among Adults in the United States. *Psychiatric Services*, *70*(2), 97–106. https://doi.org/10.1176/appi.ps.201800321
12. Lader, M. (2014). Benzodiazepine harm: how can it be reduced? *British Journal of Clinical Pharmacology*, *77*(2), 295–301. https://doi.org/10.1111/j.1365-2125.2012.04418.x
13. Crowe, S. F., & Stranks, E. K. (2017). The Residual Medium and Long-term Cognitive Effects of Benzodiazepine Use: An Updated Meta-analysis. *Archives of Clinical Neuropsychology*, *33*(7), 901–911. https://doi.org/10.1093/arclin/acx120

14. Liu, L., Jia, L., Jian, P., Zhou, Y., Zhou, J., Wu, F., & Tang, Y. (2020). The Effects of Benzodiazepine Use and Abuse on Cognition in the Elders: A Systematic Review and Meta-Analysis of Comparative Studies. *Frontiers in Psychiatry*, *11*. https://doi.org/10.3389/fpsyt.2020.00755
15. Lucchetta, R. C., da Mata, B. P. M., & Mastroianni, P. D. C. (2018). Association between Development of Dementia and Use of Benzodiazepines: A Systematic Review and Meta-Analysis. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *38*(10), 1010–1020. https://doi.org/10.1002/phar.2170
16. Osler, M., & Jørgensen, M. B. (2020). Associations of Benzodiazepines, Z-Drugs, and Other Anxiolytics With Subsequent Dementia in Patients With Affective Disorders: A Nationwide Cohort and Nested Case-Control Study. *American Journal of Psychiatry*, *177*(6), 497–505. https://doi.org/10.1176/appi.ajp.2019.19030315
17. Salzman, C. (2020). Do Benzodiazepines Cause Alzheimer's Disease? *American Journal of Psychiatry*, *177*(6), 476–478. https://doi.org/10.1176/appi.ajp.2020.20040375
18. Blanco, C., Han, B., Jones, C. M., Johnson, K., & Compton, W. M. (2018). Prevalence and Correlates of Benzodiazepine Use, Misuse, and Use Disorders Among Adults in the United States. *The Journal of Clinical Psychiatry*, *79*(6). https://doi.org/10.4088/jcp.18m12174
19. Weich, S., Pearce, H. L., Croft, P., Singh, S., Crome, I., Bashford, J., & Frisher, M. (2014). Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study. *BMJ*, *348*(mar19 5), g1996. https://doi.org/10.1136/bmj.g1996
20. Bachhuber, M. A., Hennessy, S., Cunningham, C. O., & Starrels, J. L. (2016). Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996–2013. *American Journal of Public Health*, *106*(4), 686–688. https://doi.org/10.2105/ajph.2016.303061
21. *Benzodiazepines and Opioids*. (2021, February 3). National Institute on Drug Abuse. https://www.drugabuse.gov/drug-topics/opioids/benzodiazepines-opioids
22. Gold, K. J., Sen, A., & Schwenk, T. L. (2013). Details on suicide among US physicians: data from the National Violent Death Reporting System. *General Hospital Psychiatry*, *35*(1), 45–49. https://doi.org/10.1016/j.genhosppsych.2012.08.005
23. Nowell, P. D., Mazumdar, S., Buysse, D. J., Dew, M. A., Reynolds, C. F., 3rd, & Kupfer, D. J. (1997). Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. *JAMA*, *278*(24), 2170–2177.
24. Elie, R., Lavoie, G., Bourgouin, J., & Le Morvan, P. (1990). Zopiclone versus flurazepam in insomnia: prolonged administration and withdrawal. *International clinical psychopharmacology*, *5*(4), 279–286. https://doi.org/10.1097/00004850-199010000-00005
25. Scharf, M. B., Roth, P. B., Dominguez, R. A., & Ware, J. C. (1990). Estazolam and flurazepam: a multicenter, placebo-controlled comparative study in outpatients with insomnia. *Journal of clinical pharmacology*, *30*(5), 461–467. https://doi.org/10.1002/j.1552-4604.1990.tb03486.x
26. Dominguez, R. A., Goldstein, B. J., Jacobson, A. F., & Steinbook, R. M. (1986). Comparative efficacy of estazolam, flurazepam, and placebo in outpatients with insomnia. *The Journal of clinical psychiatry*, *47*(7), 362–365.
27. Reeves R. L. (1977). Comparison of triazolam, flurazepam, and placebo as hypnotics in geriatric patients with insomnia. *Journal of clinical pharmacology*, *17*(5-6), 319–323. https://doi.org/10.1002/j.1552-4604.1977.tb04611.x

28. Leibowitz, M., & Sunshine, A. (1978). Long-term hypnotic efficacy and safety of triazolam and flurazepam. *Journal of clinical pharmacology*, *18*(5-6), 302–309. https://doi.org/10.1002/j.1552-4604.1978.tb02450.x
29. Salkind, M. R., & Silverstone, T. (1975). A clinical and psychometric evaluation of flurazepam. *British journal of clinical pharmacology*, *2*(3), 223–226. https://doi.org/10.1111/j.1365-2125.1975.tb01579.x
30. Kales, A., Bixler, E. O., Soldatos, C. R., Vela-Bueno, A., Jacoby, J., & Kales, J. D. (1982). Quazepam and flurazepam: long-term use and extended withdrawal. *Clinical pharmacology and therapeutics*, *32*(6), 781–788. https://doi.org/10.1038/clpt.1982.236
31. Aden, G. C., & Thatcher, C. (1983). Quazepam in the short-term treatment of insomnia in outpatients. *The Journal of clinical psychiatry*, *44*(12), 454–456.
32. Hernández Lara, R., Del Rosal, P. L., & Ponce, M. C. (1983). Short-term study of quazepam 15 milligrams in the treatment of insomnia. *The Journal of international medical research*, *11*(3), 162–166. https://doi.org/10.1177/030006058301100306
33. Cuanang, J. R., & Limos, L. (1982). Treatment of insomnia with temazepam: double-blind, placebo-controlled evaluation. *Clinical therapeutics*, *4*(5), 402–412.
34. Fillingim J. M. (1979). Double-blind evaluation of the efficacy and safety of temazepam in outpatients with insomnia. *British journal of clinical pharmacology*, *8*(1), 73S–77S. https://doi.org/10.1111/j.1365-2125.1979.tb00461.x
35. Allen, R. P., Mendels, J., Nevins, D. B., Chernik, D. A., & Hoddes, E. (1987). Efficacy without tolerance or rebound insomnia for midazolam and temazepam after use for one to three months. *Journal of clinical pharmacology*, *27*(10), 768–775. https://doi.org/10.1002/j.1552-4604.1987.tb02994.x
36. Mitler, M. M., Carskadon, M. A., Phillips, R. L., Sterling, W. R., Zarcone, V. P., Jr, Spiegel, R., Guilleminault, C., & Dement, W. C. (1979). Hypnotic efficacy of temazepam: a long-term sleep laboratory evaluation. *British journal of clinical pharmacology*, *8*(1), 63S–68S. https://doi.org/10.1111/j.1365-2125.1979.tb00459.x
37. Wu, R., Bao, J., Zhang, C., Deng, J., & Long, C. (2006). Comparison of Sleep Condition and Sleep-Related Psychological Activity after Cognitive-Behavior and Pharmacological Therapy for Chronic Insomnia. *Psychotherapy and Psychosomatics*, *75*(4), 220–228. https://doi.org/10.1159/000092892
38. Nicassio, P. M., Mendlowitz, D. R., Fussell, J. J., & Petras, L. (1985). The phenomenology of the pre-sleep state: The development of the pre-sleep arousal scale. *Behaviour Research and Therapy*, *23*(3), 263–271. https://doi.org/10.1016/0005-7967(85)90004-x
39. Morin, C. M., Vallières, A., & Ivers, H. (2007). Dysfunctional Beliefs and Attitudes about Sleep (DBAS): Validation of a Brief Version (DBAS-16). *Sleep*, *30*(11), 1547–1554. https://doi.org/10.1093/sleep/30.11.1547
40. Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193–213. https://doi.org/10.1016/0165-1781(89)90047-4

41. Glass, J. R., Sproule, B. A., Herrmann, N., & Busto, U. E. (2008). Effects of 2-week treatment with temazepam and diphenhydramine in elderly insomniacs: a randomized, placebo-controlled trial. *Journal of clinical psychopharmacology*, *28*(2), 182–188. https://doi.org/10.1097/JCP.0b013e31816a9e4f
42. Heffron, W. A., & Roth, P. (1979). Double-blind evaluation of the safety and hypnotic efficacy of temazepam in insomniac outpatients. *British journal of clinical pharmacology*, *8*(1), 69S–72S. https://doi.org/10.1111/j.1365-2125.1979.tb00460.x
43. Kales, A., Kales, J. D., Bixler, E. O., Scharf, M. B., & Russek, E. (1976). Hypnotic efficacy of triazolam: sleep laboratory evaluation of intermediate-term effectiveness. *Journal of clinical pharmacology*, *16*(8-9), 399–406. https://doi.org/10.1002/j.1552-4604.1976.tb02414.x
44. McClusky, H. Y., Milby, J. B., Switzer, P. K., Williams, V., & Wooten, V. (1991). Efficacy of behavioral versus triazolam treatment in persistent sleep-onset insomnia. *The American journal of psychiatry*, *148*(1), 121–126. https://doi.org/10.1176/ajp.148.1.121
45. Hajak, G., Clarenbach, P., Fischer, W., Haase, W., & Rüther, E. (1994). Zopiclone improves sleep quality and daytime well-being in insomniac patients: comparison with triazolam, flunitrazepam and placebo. *International clinical psychopharmacology*, *9*(4), 251–261.
46. Cohn J. B. (1984). Double-blind crossover comparison of triazolam and lorazepam in the posthypnotic state. *The Journal of clinical psychiatry*, *45*(3), 104–107.
47. Kales, A., Scharf, M. B., & Kales, J. D. (1978). Rebound insomnia: a new clinical syndrome. *Science (New York, N.Y.)*, *201*(4360), 1039–1041. https://doi.org/10.1126/science.684426
48. Soldatos, C. R., Dikeos, D. G., & Whitehead, A. (1999). Tolerance and rebound insomnia with rapidly eliminated hypnotics: a meta-analysis of sleep laboratory studies. *International clinical psychopharmacology*, *14*(5), 287–303.
49. Institute of Medicine (US) Committee on Halcion: An Assessment of Data Adequacy and Confidence. (1997). *Halcion: An Independent Assessment of Safety and Efficacy Data*. National Academies Press (US).
50. Gillin, J. C., Spinweber, C. L., & Johnson, L. C. (1989). Rebound insomnia: a critical review. *Journal of clinical psychopharmacology*, *9*(3), 161–172.
51. Cohn, J. B., Wilcox, C. S., Bremner, J., & Ettinger, M. (1991). Hypnotic efficacy of estazolam compared with flurazepam in outpatients with insomnia. *Journal of clinical pharmacology*, *31*(8), 747–750. https://doi.org/10.1002/j.1552-4604.1991.tb03771.x
52. Walsh, J. K. (1984). A multi-center clinical investigation of estazolam: Short-term efficacy. *Current Therapeutic Research*, 866–874. https://psycnet.apa.org/record/1985-26213-001
53. Pierce, M. W., & Shu, V. S. (1990). Efficacy of estazolam: *The American Journal of Medicine*, *88*(3), S6–S11. https://doi.org/10.1016/0002-9343(90)90279-m
54. Vogel, G. W., & Morris, D. (1992). The effects of estazolam on sleep, performance, and memory: a long-term sleep laboratory study of elderly insomniacs. *Journal of clinical pharmacology*, *32*(7), 647–651. https://doi.org/10.1002/j.1552-4604.1992.tb05776.x
55. Parker, I. (2013, December 2). *The Big Sleep*. The New Yorker. https://www.newyorker.com/magazine/2013/12/09/the-big-sleep-2

56. Eckert, D., Owens, R., Kehlmann, G., Wellman, A., Rahangdale, S., Yim-Yeh, S., White, D., & Malhotra, A. (2011). Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold. *Clinical Science*, *120*(12), 505–514. https://doi.org/10.1042/cs20100588
57. Smith, P. R., Sheikh, K. L., Costan-Toth, C., Forsthoefel, D., Bridges, E., Andrada, T. F., & Holley, A. B. (2017). Eszopiclone and Zolpidem Do Not Affect the Prevalence of the Low Arousal Threshold Phenotype. *Journal of Clinical Sleep Medicine*, *13*(01), 115–119. https://doi.org/10.5664/jcsm.6402
58. Flynn, A. (2006, June 1). *DEPENDENCE ON ZOPICLONE*. Wiley Online Library. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1360-0443.2006.01448.x?sid=nlm%3Apubmed
59. Aranko, K. (1991). *Misuse of zopiclone and convulsions during withdrawal*. PubMed. https://pubmed.ncbi.nlm.nih.gov/1754610/
60. Pitchot, W. (2009). *[Zolpidem dependence and withdrawal seizure]*. PubMed. https://pubmed.ncbi.nlm.nih.gov/19777922/
61. Russo, A. D., Hodgman, M., & Calleo, V. (2020). Seizures secondary to zolpidem withdrawal. *Clinical Toxicology*, *59*(2), 174–175. https://doi.org/10.1080/15563650.2020.1778718
62. Schifano, F., Chiappini, S., Corkery, J. M., & Guirguis, A. (2019). An Insight into Z-Drug Abuse and Dependence: An Examination of Reports to the European Medicines Agency Database of Suspected Adverse Drug Reactions. *International Journal of Neuropsychopharmacology*, *22*(4), 270–277. https://doi.org/10.1093/ijnp/pyz007
63. Randall, S., Roehrs, T. A., & Roth, T. (2012). Efficacy of eight months of nightly zolpidem: a prospective placebo-controlled study. *Sleep*, *35*(11), 1551–1557. https://doi.org/10.5665/sleep.2208
64. Herrmann, W. M., Kubicki, S. T., Boden, S., Eich, F. X., Attali, P., & Coquelin, J. P. (1993). Pilot controlled double-blind study of the hypnotic effects of zolpidem in patients with chronic 'learned' insomnia: psychometric and polysomnographic evaluation. *The Journal of international medical research*, *21*(6), 306–322. https://doi.org/10.1177/030006059302100602
65. Scharf, M. B., Roth, T., Vogel, G. W., & Walsh, J. K. (1994). A multicenter, placebo-controlled study evaluating zolpidem in the treatment of chronic insomnia. *The Journal of clinical psychiatry*, *55*(5), 192–199.
66. Erman, M. K., Zammit, G., Rubens, R., Schaefer, K., Wessel, T., Amato, D., Caron, J., & Walsh, J. K. (2008). A polysomnographic placebo-controlled evaluation of the efficacy and safety of eszopiclone relative to placebo and zolpidem in the treatment of primary insomnia. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, *4*(3), 229–234.
67. Jacobs, G. D., Pace-Schott, E. F., Stickgold, R., & Otto, M. W. (2004). Cognitive Behavior Therapy and Pharmacotherapy for Insomnia. *Archives of Internal Medicine*, *164*(17), 1888. https://doi.org/10.1001/archinte.164.17.1888
68. Morin, C. M., Vallières, A., Guay, B., Ivers, H., Savard, J., Mérette, C., Bastien, C., & Baillargeon, L. (2009). Cognitive Behavioral Therapy, Singly and Combined With Medication, for Persistent Insomnia. *JAMA*, *301*(19), 2005. https://doi.org/10.1001/jama.2009.682

69. Ware, J. C., Walsh, J. K., Scharf, M. B., Roehrs, T., Roth, T., & Vogel, G. W. (1997). Minimal rebound insomnia after treatment with 10-mg zolpidem. *Clinical neuropharmacology*, *20*(2), 116–125. https://doi.org/10.1097/00002826-199704000-00002
70. Roehrs, T. A., Randall, S., Harris, E., Maan, R., & Roth, T. (2012). Twelve months of nightly zolpidem does not lead to rebound insomnia or withdrawal symptoms: a prospective placebo-controlled study. *Journal of psychopharmacology (Oxford, England)*, *26*(8), 1088–1095. https://doi.org/10.1177/0269881111424455
71. Victorri-Vigneau, C., Dailly, E., Veyrac, G., & Jolliet, P. (2007). Evidence of zolpidem abuse and dependence: results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. *British journal of clinical pharmacology*, *64*(2), 198–209. https://doi.org/10.1111/j.1365-2125.2007.02861.x
72. Mattoo, S. K., Gaur, N., & Das, P. P. (2011). Zolpidem withdrawal delirium. *Indian journal of pharmacology*, *43*(6), 729–730. https://doi.org/10.4103/0253-7613.89838
73. Gilbert, D. L., & Staats, P. S. (1997). Seizure after withdrawal from supratherapeutic doses of zolpidem tartrate, a selective omega I benzodiazepine receptor agonist. *Journal of pain and symptom management*, *14*(2), 118–120. https://doi-org.ahecproxy.ncahec.net/10.1016/s0885-3924(97)00017-1
74. Aragona M. (2000). Abuse, dependence, and epileptic seizures after zolpidem withdrawal: review and case report. *Clinical neuropharmacology*, *23*(5), 281–283. https://doi-org.ahecproxy.ncahec.net/10.1097/00002826-200009000-00008
75. Kleykamp, B. A., Griffiths, R. R., McCann, U. D., Smith, M. T., & Mintzer, M. Z. (2012). Acute effects of zolpidem extended-release on cognitive performance and sleep in healthy males after repeated nightly use. *Experimental and clinical psychopharmacology*, *20*(1), 28–39. https://doi-org.ahecproxy.ncahec.net/10.1037/a0025237
76. Verster, J. C., Volkerts, E. R., Schreuder, A. H., Eijken, E. J., van Heuckelum, J. H., Veldhuijzen, D. S., Verbaten, M. N., Paty, I., Darwish, M., Danjou, P., & Patat, A. (2002). Residual effects of middle-of-the-night administration of zaleplon and zolpidem on driving ability, memory functions, and psychomotor performance. *Journal of clinical psychopharmacology*, *22*(6), 576–583. https://doi.org/10.1097/00004714-200212000-00007
77. Kang, D. Y., Park, S., Rhee, C. W., Kim, Y. J., Choi, N. K., Lee, J., & Park, B. J. (2012). Zolpidem use and risk of fracture in elderly insomnia patients. *Journal of preventive medicine and public health = Yebang Uihakhoe chi*, *45*(4), 219–226. https://doi.org/10.3961/jpmph.2012.45.4.219
78. Wang, P. S., Bohn, R. L., Glynn, R. J., Mogun, H., & Avorn, J. (2001). Zolpidem use and hip fractures in older people. *Journal of the American Geriatrics Society*, *49*(12), 1685–1690. https://doi.org/10.1111/j.1532-5415.2001.49280.x
79. Mets, M. A., Volkerts, E. R., Olivier, B., & Verster, J. C. (2010). Effect of hypnotic drugs on body balance and standing steadiness. *Sleep medicine reviews*, *14*(4), 259–267. https://doi.org/10.1016/j.smrv.2009.10.008

80. Rudisill, T. M., Zhu, M., Kelley, G. A., Pilkerton, C., & Rudisill, B. R. (2016). Medication use and the risk of motor vehicle collisions among licensed drivers: A systematic review. *Accident; analysis and prevention*, *96*, 255–270. https://doi.org/10.1016/j.aap.2016.08.001
81. LEUFKENS, T. R. M., LUND, J. S., & VERMEEREN, A. (2009). Highway driving performance and cognitive functioning the morning after bedtime and middle-of-the-night use of gaboxadol, zopiclone and zolpidem. *Journal of Sleep Research*, *18*(4), 387–396. https://doi.org/10.1111/j.1365-2869.2009.00746.x
82. Bocca, M. L., Marie, S., Lelong-Boulouard, V., Bertran, F., Couque, C., Desfemmes, T., Berthelon, C., Amato, J. N., Moessinger, M., Paillet-Loilier, M., Coquerel, A., & Denise, P. (2010). Zolpidem and zopiclone impair similarly monotonous driving performance after a single nighttime intake in aged subjects. *Psychopharmacology*, *214*(3), 699–706. https://doi.org/10.1007/s00213-010-2075-5
83. Otmani, S., Demazières, A., Staner, C., Jacob, N., Nir, T., Zisapel, N., & Staner, L. (2008). Effects of prolonged-release melatonin, zolpidem, and their combination on psychomotor functions, memory recall, and driving skills in healthy middle aged and elderly volunteers. *Human Psychopharmacology: Clinical and Experimental*, *23*(8), 693–705. https://doi.org/10.1002/hup.980
84. Ben-Hamou, M., Marshall, N. S., Grunstein, R. R., Saini, B., & Fois, R. A. (2011). Spontaneous adverse event reports associated with zolpidem in Australia 2001-2008. *Journal of sleep research*, *20*(4), 559–568. https://doi.org/10.1111/j.1365-2869.2011.00919.x
85. Hwang, T. J., Ni, H. C., Chen, H. C., Lin, Y. T., & Liao, S. C. (2010). Risk Predictors for Hypnosedative-Related Complex Sleep Behaviors. *The Journal of Clinical Psychiatry*, *71*(10), 1331–1335. https://doi.org/10.4088/jcp.09m05083bro
86. Olson, L. G. (2008). *Hypnotic hazards: adverse effects of zolpidem and other z-drugs*. NPS MedicineWise.https://www.nps.org.au/australian-prescriber/articles/hypnotic-hazards-adverse-effects-of-zolpidem-and-other-z-drugs#r1
87. Tsai, M. J., Tsai, Y. H., & Huang, Y. B. (2007). Compulsive activity and anterograde amnesia after zolpidem use. *Clinical Toxicology*, *45*(2), 179–181. https://doi.org/10.1080/15563650600956741
88. Southworth, M. R., Kortepeter, C., & Hughes, A. (2008). Nonbenzodiazepine hypnotic use and cases of "sleep driving". *Annals of internal medicine*, *148*(6), 486–487. https://doi.org/10.7326/0003-4819-148-6-200803180-00026
89. Doane, J. A., & Dalpiaz, A. S. (2008). Zolpidem-induced sleep-driving. *The American journal of medicine*, *121*(11), e5. https://doi.org/10.1016/j.amjmed.2008.04.035
90. Hoque, R., & Chesson, A. L., Jr (2009). Zolpidem-induced sleepwalking, sleep related eating disorder, and sleep-driving: fluorine-18-flourodeoxyglucose positron emission tomography analysis, and a literature review of other unexpected clinical effects of zolpidem. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, *5*(5), 471–476.
91. Walsh, J. K., Vogel, G. W., Scharf, M., Erman, M., William Erwin C, Schweitzer, P. K., Mangano, R. M., & Roth, T. (2000). A five week, polysomnographic assessment of zaleplon 10 mg for the

treatment of primary insomnia. *Sleep medicine*, *1*(1), 41–49. https://doi.org/10.1016/s1389-9457(99)00006-4

92. Winkler, A., Auer, C., Doering, B. K., & Rief, W. (2014). Drug Treatment of Primary Insomnia: A Meta-Analysis of Polysomnographic Randomized Controlled Trials. *CNS Drugs*, *28*(9), 799–816. https://doi.org/10.1007/s40263-014-0198-7
93. Hedner, J., Yaeche, R., Emilien, G., Farr, I., & Salinas, E. (2000). Zaleplon shortens subjective sleep latency and improves subjective sleep quality in elderly patients with insomnia. The Zaleplon Clinical Investigator Study Group. *International journal of geriatric psychiatry*, *15*(8), 704–712. https://doi.org/10.1002/1099-1166(200008)15:8<704::aid-gps183>3.0.co;2-s
94. Heesch, C. B. (2014). The long-term use of sedative hypnotics in chronic insomnia. *Mental Health Clinician*, *4*(2), 78–81. https://doi.org/10.9740/mhc.n190097
95. Fry, J., Scharf, M., Mangano, R., & Fujimori, M. (2000). Zaleplon improves sleep without producing rebound effects in outpatients with insomnia. Zaleplon Clinical Study Group. *International clinical psychopharmacology*, *15*(3), 141–152. https://doi.org/10.1097/00004850-200015030-00003
96. Dooley, M., & Plosker, G. L. (2000). Zaleplon: a review of its use in the treatment of insomnia. *Drugs*, *60*(2), 413–445. https://doi.org/10.2165/00003495-200060020-00014
97. Israel, A. G., & Kramer, J. A. (2002). Safety of Zaleplon in the Treatment of Insomnia. *Annals of Pharmacotherapy*, *36*(5), 852–859. https://doi.org/10.1345/aph.1a086
98. Krystal, A. D., Walsh, J. K., Laska, E., Caron, J., Amato, D. A., Wessel, T. C., & Roth, T. (2003). Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep*, *26*(7), 793–799. https://doi.org/10.1093/sleep/26.7.793
99. Vaughn McCall, W., Erman, M., Krystal, A. D., Rosenberg, R., Scharf, M., Zammit, G. K., & Wessel, T. (2006). A polysomnography study of eszopiclone in elderly patients with insomnia. *Current Medical Research and Opinion*, *22*(9), 1633–1642. https://doi.org/10.1185/030079906x112741
100. Zammit, G. K., McNabb, L. J., Caron, J., Amato, D. A., & Roth, T. (2004). Efficacy and safety of eszopiclone across 6-weeks of treatment for primary insomnia. *Current medical research and opinion*, *20*(12), 1979–1991. https://doi.org/10.1185/174234304x15174
101. Fava, M., McCall, W. V., Krystal, A., Wessel, T., Rubens, R., Caron, J., Amato, D., & Roth, T. (2006). Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. *Biological psychiatry*, *59*(11), 1052–1060. https://doi.org/10.1016/j.biopsych.2006.01.016
102. Joffe, H., Petrillo, L., Viguera, A., Koukopoulos, A., Silver-Heilman, K., Farrell, A., Yu, G., Silver, M., & Cohen, L. S. (2010). Eszopiclone improves insomnia and depressive and anxious symptoms in perimenopausal and postmenopausal women with hot flashes: a randomized, double-blinded, placebo-controlled crossover trial. *American journal of obstetrics and gynecology*, *202*(2), 171.e1–171.e11. https://doi.org/10.1016/j.ajog.2009.10.868
103. Ancoli-Israel, S., Krystal, A. D., McCall, W. V., Schaefer, K., Wilson, A., Claus, R., Rubens, R., & Roth, T. (2010). A 12-week, randomized, double-blind, placebo-controlled study evaluating the

effect of eszopiclone 2 mg on sleep/wake function in older adults with primary and comorbid insomnia. *Sleep*, *33*(2), 225–234. https://doi.org/10.1093/sleep/33.2.225

104. Roth, T., Walsh, J., Krystal, A., Wessel, T., & Roehrs, T. (2005). An evaluation of the efficacy and safety of eszopiclone over 12 months in patients with chronic primary insomnia. *Sleep Medicine*, *6*(6), 487–495. https://doi.org/10.1016/j.sleep.2005.06.004
105. Walsh, J. K., Krystal, A. D., Amato, D. A., Rubens, R., Caron, J., Wessel, T. C., Schaefer, K., Roach, J., Wallenstein, G., & Roth, T. (2007). Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations. *Sleep*, *30*(8), 959–968. https://doi.org/10.1093/sleep/30.8.959
106. Scharf, M., Erman, M., Rosenberg, R., Seiden, D., McCall, W. V., Amato, D., & Wessel, T. C. (2005). A 2-Week Efficacy and Safety Study of Eszopiclone in Elderly Patients with Primary Insomnia. *Sleep*, *28*(6), 720–727. https://doi.org/10.1093/sleep/28.6.720
107. Scharf, M. (2006). *Eszopiclone for the treatment of insomnia*. PubMed. https://pubmed.ncbi.nlm.nih.gov/16448328/
108. Janto, K., Prichard, J. R., & Pusalavidyasagar, S. (2018). An Update on Dual Orexin Receptor Antagonists and Their Potential Role in Insomnia Therapeutics. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, *14*(8), 1399–1408. https://doi.org/10.5664/jcsm.7282
109. *GSK and Actelion discontinue clinical development of almorexant*. (2011). GSK and Actelion Discontinue Clinical Development of Almorexant. https://web.archive.org/web/20110704194943/http://www.gsk.com/media/pressreleases/2011/2011_pressrelease_10019.htm
110. Schoedel, K. A., Sun, H., Sellers, E. M., Faulknor, J., Levy-Cooperman, N., Li, X., Kennedy, W. P., Cha, J. H., Lewis, N. M., Liu, W., Bondiskey, P., McCrea, J. B., Panebianco, D. L., Troyer, M. D., & Wagner, J. A. (2016). Assessment of the Abuse Potential of the Orexin Receptor Antagonist, Suvorexant, Compared With Zolpidem in a Randomized Crossover Study. *Journal of clinical psychopharmacology*, *36*(4), 314–323. https://doi.org/10.1097/JCP.0000000000000516
111. *Suvorexant in the Management Comorbid Sleep Disorder and Alcohol Dependence - Full Text View - ClinicalTrials.gov*. (2019). Suvorexant in the Management Comorbid Sleep Disorder and Alcohol Dependence. https://clinicaltrials.gov/ct2/show/NCT03897062
112. Herring, W. J., Connor, K. M., Ivgy-May, N., Snyder, E., Liu, K., Snavely, D. B., Krystal, A. D., Walsh, J. K., Benca, R. M., Rosenberg, R., Sangal, R. B., Budd, K., Hutzelmann, J., Leibensperger, H., Froman, S., Lines, C., Roth, T., & Michelson, D. (2016). Suvorexant in Patients With Insomnia: Results From Two 3-Month Randomized Controlled Clinical Trials. *Biological psychiatry*, *79*(2), 136–148. https://doi.org/10.1016/j.biopsych.2014.10.003
113. Herring, W. J., Snyder, E., Budd, K., Hutzelmann, J., Snavely, D., Liu, K., Lines, C., Roth, T., & Michelson, D. (2012). Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. *Neurology*, *79*(23), 2265–2274. https://doi.org/10.1212/WNL.0b013e31827688ee
114. Chabi, A., Zhang, Y., Jackson, S., Cady, R., Lines, C., Herring, W. J., Connor, K. M., & Michelson, D. (2015). Randomized controlled trial of the orexin receptor antagonist filorexant for migraine prophylaxis. *Cephalalgia : an international journal of headache*, *35*(5), 379–388. https://doi.org/10.1177/0333102414544979

115. Connor, K. M., Ceesay, P., Hutzelmann, J., Snavely, D., Krystal, A. D., Trivedi, M. H., Thase, M., Lines, C., Herring, W. J., & Michelson, D. (2017). Phase II Proof-of-Concept Trial of the Orexin Receptor Antagonist Filorexant (MK-6096) in Patients with Major Depressive Disorder. *The international journal of neuropsychopharmacology*, *20*(8), 613–618. https://doi.org/10.1093/ijnp/pyx033
116. Rosenberg R, Murphy P, Zammit G, et al. Comparison of Lemborexant With Placebo and Zolpidem Tartrate Extended Release for the Treatment of Older Adults With Insomnia Disorder: A Phase 3 Randomized Clinical Trial. *JAMA Netw Open.* 2019;2(12):e1918254. doi:10.1001/jamanetworkopen.2019.18254.
117. Kärppä, M., Yardley, J., Pinner, K., Filippov, G., Zammit, G., Moline, M., Perdomo, C., Inoue, Y., Ishikawa, K., & Kubota, N. (2020). Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2. *Sleep*, *43*(9), zsaa123. https://doi.org/10.1093/sleep/zsaa123
118. Murphy, P., Moline, M., Mayleben, D., Rosenberg, R., Zammit, G., Pinner, K., Dhadda, S., Hong, Q., Giorgi, L., & Satlin, A. (2017). Lemborexant, A Dual Orexin Receptor Antagonist (DORA) for the Treatment of Insomnia Disorder: Results From a Bayesian, Adaptive, Randomized, Double-Blind, Placebo-Controlled Study. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, *13*(11), 1289–1299. https://doi.org/10.5664/jcsm.6800
119. Ardeljan, A. D., & Hurezeanu, R. (2021). Lemborexant. In *StatPearls*. StatPearls Publishing.
120. Bigica, A. (2020, September 1). *Insomnia Treatment Daridorexant Builds Momentum With Confirmatory Phase 3 Results*. Neurology Live. https://www.neurologylive.com/view/insomnia-treatment-daridorexant-confirmatory-phase-3-trial-results
121. Zammit, G., Erman, M., Wang-Weigand, S., Sainati, S., Zhang, J., & Roth, T. (2007). Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, *3*(5), 495–504.
122. Zammit G. K. (2007). Ramelteon: a novel hypnotic indicated for the treatment of insomnia. *Psychiatry (Edgmont (Pa. : Township))*, *4*(9), 36–42.
123. *The Efficacy and Safety of Agomelatine in the Patients With Parkinson's Disease - Full Text View - ClinicalTrials.gov*. (2019). The Efficacy and Safety of Agomelatine in the Patients With Parkinson's Disease. https://clinicaltrials.gov/ct2/show/NCT03977441
124. Lockley, S. W., Dressman, M. A., Licamele, L., Xiao, C., Fisher, D. M., Flynn-Evans, E. E., Hull, J. T., Torres, R., Lavedan, C., & Polymeropoulos, M. H. (2015). Tasimelteon for non-24-hour sleep-wake disorder in totally blind people (SET and RESET): two multicentre, randomised, double-masked, placebo-controlled phase 3 trials. *Lancet (London, England)*, *386*(10005), 1754–1764. https://doi.org/10.1016/S0140-6736(15)60031-9
125. Katwala, J., Kumar, A. K., Sejpal, J. J., Terrence, M., & Mishra, M. (2013). Therapeutic rationale for low dose doxepin in insomnia patients. *Asian Pacific Journal of Tropical Disease*, *3*(4), 331–336. https://doi.org/10.1016/S2222-1808(13)60080-8
126. Roehrs, T., & Roth, T. (2004). 'Hypnotic' prescription patterns in a large managed-care population. *Sleep medicine*, *5*(5), 463–466. https://doi.org/10.1016/j.sleep.2004.03.007

127. Jaffer, K. Y., Chang, T., Vanle, B., Dang, J., Steiner, A. J., Loera, N., Abdelmesseh, M., Danovitch, I., & Ishak, W. W. (2017). Trazodone for Insomnia: A Systematic Review. *Innovations in clinical neuroscience*, *14*(7-8), 24–34.
128. Roth, A. J., McCall, W. V., & Liguori, A. (2011). Cognitive, psychomotor and polysomnographic effects of trazodone in primary insomniacs. *Journal of sleep research*, *20*(4), 552–558. https://doi.org/10.1111/j.1365-2869.2011.00928.x
129. Morin, C. M., Koetter, U., Bastien, C., Ware, J. C., & Wooten, V. (2005). Valerian-hops combination and diphenhydramine for treating insomnia: a randomized placebo-controlled clinical trial. *Sleep*, *28*(11), 1465–1471. https://doi.org/10.1093/sleep/28.11.1465
130. Lemoine, P., Nir, T., Laudon, M., & Zisapel, N. (2007). Prolonged-release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 years and older and has no withdrawal effects. *Journal of sleep research*, *16*(4), 372–380. https://doi.org/10.1111/j.1365-2869.2007.00613.x
131. Luthringer, R., Muzet, M., Zisapel, N., & Staner, L. (2009). The effect of prolonged-release melatonin on sleep measures and psychomotor performance in elderly patients with insomnia. *International clinical psychopharmacology*, *24*(5), 239–249. https://doi.org/10.1097/YIC.0b013e32832e9b08
132. Wade, A. G., Ford, I., Crawford, G., McMahon, A. D., Nir, T., Laudon, M., & Zisapel, N. (2007). Efficacy of prolonged release melatonin in insomnia patients aged 55-80 years: quality of sleep and next-day alertness outcomes. *Current medical research and opinion*, *23*(10), 2597–2605. https://doi.org/10.1185/030079907X233098
133. Hudson, C., Hudson, S. P., Hecht, T., & MacKenzie, J. (2005). Protein source tryptophan versus pharmaceutical grade tryptophan as an efficacious treatment for chronic insomnia. *Nutritional neuroscience*, *8*(2), 121–127. https://doi.org/10.1080/10284150500069561
134. Hudson C, Hudson SP, Hecht T, MacKenzie J. Protein source tryptophan versus pharmaceutical grade tryptophan as an efficacious treatment for chronic insomnia. Nutr Neurosci. 2005 Apr;8(2):121-7. doi: 10.1080/10284150500069561. PMID: 16053244.
135. Wang, D., Li, Z., Li, L. and Hao, W. (2014), Mirtazapine's effect on sleep in depression. Asia-Pacific Psychiatry, 6: 152-160. https://doi-org.laneproxy.stanford.edu/10.1111/appy.12060