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REVIEW

Suvorexant for insomnia in older adults: a perspective review

Rajesh R Tampi[1,2], Geetha Manikkara[1,2], Silpa Balachandran[1,2], Piyush Taparia[1,2], Stephanie Hrisko[3], Shilpa Srinivasan[3], Deena J Tampi[4]

[1]Case Western Reserve University School of Medicine, Cleveland, OH 44106, USA; [2]Department of Psychiatry, MetroHealth, 2500 MetroHealth Drive, Cleveland, OH 44109, USA; [3]Department of Neuropsychiatry and Behavioral Sciences, Palmetto Health USC, 15 Medical Park, Suite 141, Columbia, SC 29203, USA; [4]Diamond Healthcare, 701 E. Byrd Street, 15th Floor, Richmond, VA 23219, USA

Abstract

The aim of this review was to identify published randomized control trials (RCTs) that evaluated the efficacy and tolerability of suvorexant for the treatment of insomnia among older adults (≥65 years). A literature search was conducted of PubMed, MEDLINE, EMBASE, PsycINFO and Cochrane collaboration databases for RCTs in any language evaluating suvorexant for the treatment of insomnia in older adults. Additionally, references of full-text articles that were included in this review were searched for further studies. Data from three RCTs of suvorexant were included in this review. All the three studies fulfilled the criteria for being of good quality based on the items listed by the Center for Evidence Based Medicine (CEBM) for the assessment of RCTs. None of the three studies were conducted exclusively among older adults. However, they also included older individuals diagnosed with primary insomnia. These studies included a total of 1298 participants aged ≥65 years in age. Trial durations ranged from 3 months to 1 year. Available data from these studies indicate that suvorexant improves multiple subjective and polysomnographic sleep parameters for sleep onset and maintenance among older individuals with a diagnosis of primary insomnia and is generally well tolerated. Current evidence, although limited, indicates that suvorexant benefits older adults with primary insomnia and is generally well tolerated.

Keywords: aged, elderly, geriatrics, insomnia, orexin receptor antagonists, sleep, sleep initiation and maintenance disorders, suvorexant.

Citation

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Introduction

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), defines insomnia as a disorder where there is dissatisfaction with sleep quantity or quality that results in clinically significant distress or impairment in social, occupational, or other important areas of functioning [1]. Additionally, the DSM-5 states that this disorder should be associated with one or more of the following symptoms: difficulty initiating sleep, difficulty maintaining sleep, or early-morning awakening with the inability to return to sleep. The definition also requires that sleep difficulty occurs at least three nights per week for at least 3 months and occurs despite adequate opportunity for sleep. Furthermore, the sleep disturbance should not be attributable to the physiological effects of a substance or coexisting medical or psychiatric conditions [1].

The International Classification of Sleep Disorders Edition Three (ICSD-3) combined primary insomnia and comorbid insomnia under the diagnosis chronic insomnia [2]. As per the ICSD-3, the criteria for chronic insomnia include the following: (1) A report of sleep initiation or maintenance problems, (2) Adequate opportunity and circumstances to sleep and (3) Daytime consequences. The criteria also state that the sleep problems should occur at least three times per week and last for 3 months.

Studies estimate that the prevalence of insomnia among adults is approximately 30% [3], with greater risk for women and older individuals [4]. The prevalence of insomnia among the elderly is more noted to be approximately 50% [4,5]. The sleep cycle is controlled by two biological mechanisms: the sleep–wake homeostasis and the circadian rhythm [6]. As we age, there is a partial breakdown of these mechanisms that may

be responsible for the high prevalence of insomnia in older individuals. In addition, many comorbid medical conditions may result in or worsen insomnia among older adults including respiratory disorders, cardiovascular disorders, digestive disorders and chronic pain [4,6].

Sleep impairment can have a significant negative impact on an individual's quality of life by causing malaise, chronic fatigue and increased risk of accidents [3]. Additionally, insomnia is associated with increased anxiety, irritability, cognitive decline, greater risk of falls and higher rates of mortality [7]. One study found that sleep deprivation causes the US economy to lose 1.2 million working days annually and US$411 billion in lost productivity [8].

Pharmacological treatments for insomnia can be divided into four categories [9]. These include the following: 1. Medications approved by regulatory agencies and requiring prescriptions (e.g., benzodiazepines, non-benzodiazepine receptor agonists (non-BzRA), melatonin receptor agonists and histamine receptor antagonists); 2. Off-label uses of prescription medications that can enhance sleep (e.g., trazodone, mirtazapine); 3. Over-the-counter sleep aids (e.g., diphenhydramine, doxylamine succinate); 4. All other unregulated compounds taken for insomnia (e.g., valerian) [8]. Although these medications can be effective for the treatment of insomnia, they are noted to have considerable adverse effect profiles. For instance, benzodiazepines are associated with psychomotor retardation, memory impairment, paradoxical disinhibition and high addictive potential, and should be avoided among the elderly because of the risks for falls, fractures, cognitive impairment and delirium [10].

Suvorexant, a dual orexin receptor antagonist (DORA), was approved by the US Food and Drug Administration (FDA) in 2014 for the treatment of insomnia [11]. Orexin, a neuropeptide secreted by the lateral hypothalamus, is postulated to regulate the sleep–wake cycle [12]. There are two types of orexin: orexin-A and orexin-B. Orexin-A and orexin-B are derived from a common precursor peptide, prepro-orexin. Suvorexant suppresses wakefulness and promotes sleep by selectively blocking the binding of orexin-A and orexin-B neuropeptides to OX1R and OX2R receptors [13]. Animal studies suggest that DORAs may have less impact on motor performance [14] and cognition [15] when compared to benzodiazepines, characteristics that may be beneficial to older adults. Because suvorexant acts on a receptor different from those targeted by traditional sedative hypnotics, it may be used as an alternative for the treatment of insomnia among older adults who do not benefit from these traditional sedative hypnotics or develop adverse effects when treated with them [11].

Two meta-analyses found suvorexant was superior to placebo in improving subjective time to sleep onset, subjective total sleep time and subjective quality of sleep in individuals with primary insomnia. In these studies, suvorexant was fairly well tolerated among participants [16,17]. However, these meta-analyses included both younger and older adults. The aim of this current review is to identify published randomized control trials (RCTs) that evaluated the efficacy and tolerability of suvorexant for the treatment of insomnia among older adults (≥65 years).

Methods

We performed a literature search of PubMed, MEDLINE, EMBASE, PsycINFO and Cochrane collaboration databases on 30 September 2017 using the following key words: Suvorexant and RCT. The search was not restricted by the age of the participants or the language in which the study was published. However, the final analysis only included studies in human subjects published in English-language journals or those with official English translations. Internal full-text references were also searched for additional relevant studies.

All authors reviewed the abstracts and full-text articles from the citations obtained via the database search. The decision of which studies to include or exclude from the final analysis was reached after a review of the full-text articles by all authors. Disagreements between authors were resolved by a consensus.

Four authors (RRT, GM, SH and SS) abstracted the following data from each study: the year of publication of the study, country of origin, total number of participants, mean age of participants, type of setting in which the study was conducted, the comparators and the duration of the trial. Additionally, the authors collected the names of the rating scales used in each study, the primary and secondary outcomes and the tolerability of the medications used in each of the studies.

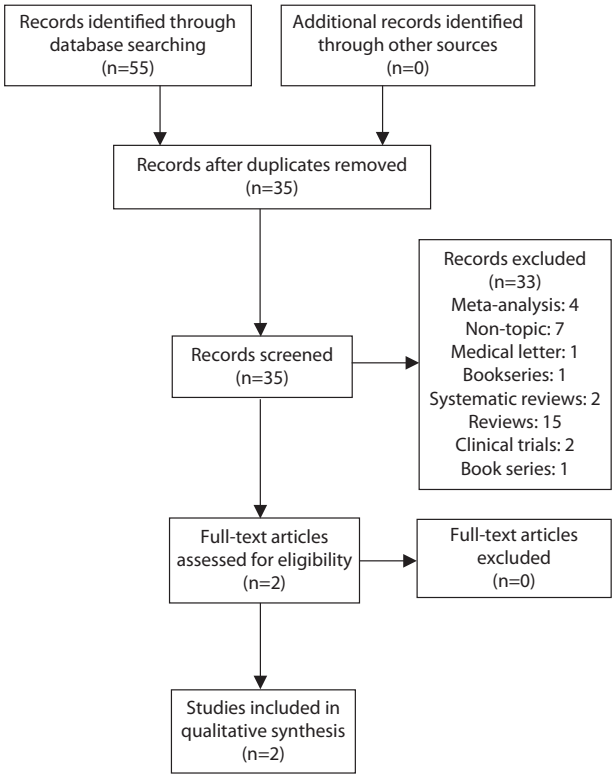
The quality of included studies was assessed by two authors (RRT, GM) using a checklist created based on the criteria developed by the Center for Evidence Based Medicine (CEBM) for the assessment of RCTs [18]. Study quality was rated as 'good' if all six items were met on the checklist, 'fair' if one or two items were absent or 'poor' if ≥3 items on the checklist were absent. All studies were included in the final review irrespective of the quality of the study.

Results

A total of 55 articles were identified from the literature search. After excluding duplicates, 35 articles remained for screening by the authors. Among these, 33 studies were excluded as they dealt with younger patients, did not pertain with the safety and efficacy of suvorexant or were not RCTs (Figure 1). Among the remaining two articles [19,20], one article [20] contained data from two separate RCTs.

None of the three RCTs identified in the literature search evaluated the use of suvorexant for the treatment of insomnia exclusively among individuals aged ≥65 years. However, they did include individuals ≥65 years in age [19,20] (Table 1). All included studies were rated as being of good quality based on the CEBM criteria (Table 2).

Figure 1. Flow diagram.



The study by Michelson et al. was conducted in academic and private investigational centers in the Americas, Australia, Europe and South Africa [19]. The second set of studies by Herring et al. was conducted at multiple investigational sites in the Americas, Europe, Asia and South Africa [20]. All three studies used placebo as a comparator to suvorexant [19,20]. The three studies are described in detail in the next section of the article. Table 3 summarizes the results from these three studies (Table 3).

Michelson et al.

Individuals who were ≥18 years in age and met the DSM-IV-TR criteria for primary insomnia were included in the study [19]. Based on age, this study was stratified into two groups – one group <65 years old and the other group ≥65 years in age. The investigators utilized a randomized, placebo-controlled, parallel-group design. After a 1-week single-blind placebo run-in screening period, participants were randomly assigned to receive either nightly suvorexant or placebo in a 2:1 ratio. The participants who were ≥65 years in age received 30 mg of suvorexant for 1 year. At the end of 1 year, participants were randomized to continued treatment with suvorexant or switched to placebo in a 1:1 ratio for another 2 months. Participants receiving placebo remained on placebo. Although we wanted to investigate the outcomes exclusively among

Table 1. Summary of included studies.

Name of study	Total number of participants	Age (years)	Type of setting	Comparators	Duration
Michelson et al. [19]	781	≥18	Outpatient	Suvorexant *vs* placebo	1 year treatment period
Herring et al. [20]	Trial 1-1021 Trial 2-1009	≥18	Outpatient	Suvorexant *vs* placebo	3 months duration for each study

Table 2. Quality of reviewed studies.

Name of study	Randomization?	Similar groups initially?	Equal treatments?	All participants accounted for?	Analyzed in groups to which they were randomized?	Objective/ 'blind' treatments?	Overall quality of the study
Michelson et al. [19]	Yes	Yes	Yes	Yes	Yes	Yes	Good
Herring et al. [20] Trial 1	Yes	Yes	Yes	Yes	Yes	Yes	Good
Herring et al. [20] Trial 2	Yes	Yes	Yes	Yes	Yes	Yes	Good

Table 3. Summary of results from included studies.

Name of study	Outcomes and measures	Outcomes (suvorexant compared to placebo)	Tolerability
Michelson et al. [19]	sTST sTSO sWASO sNAW sQUAL sFRESH CGI-S CGI-I PGI-I PGI-S ISI	1. At month 1 and month 12 sTST: 23.3, 27.5, both $p<0.0001$ sTSO: −10.3, $p=0.0004$; −9.7, $p=0.0055$ sWASO: −9.0, $p=0.0003$; −9.7, $p=0.0048$ sQUAL: 0.2, 0.1, $p<0.0001$ sFRESH: 0.2, $p=0.001$; 0.2, $p<0.0001$ sNAW: 0.1, $p=0.19$; 0.2, $p=0.02$ ISI: −1.4, $p<0.0001$; −0.9, $p=0.04$ CGI-S: −0.3, $p<0.0001$; −0.4, $p=0.0003$ PGI-S: −0.2, $p=0.0026$; −0.3, $p=0.011$ CGI-I: −0.4, −0.5, both $p<0.0001$ PGI-I: −0.5, −0.5, both $p<0.0001$ QIDS-SR: −0.2, $p=0.16$; −0.1, $p=0.51$ 2. Continuing treatment after 1 year ISI, $p=0.05$ sTST 20%, $p=0.03$	There were no deaths noted in the study Suvorexant compared to placebo: Discontinued because of adverse events: 11.7 *vs* 8.5% Proportion of individuals with serious adverse events: 5.2 *vs* 6.6% Somnolence was the adverse event with the highest incidence for discontinuations: 4 *vs* 1% Common adverse events: a. Somnolence: 13.2 *vs* 2.7% b. Fatigue: 6.5 *vs* 1.9% c. Dry mouth: 5 *vs* 1.6%
Herring et al. [20]	sTST WASO sTSO LPS sWASO sQUAL sFRESH ISI CGI-S PGI-S CGI-I PGI-I	1. Suvorexant 40/30 mg A. Trial 1 a. At month 1, month 3 and week 1/night 1 sTST: 19.6, 19.7, 21.4, all $p<0.001$ WASO: −26.2, −22.9, −38.4, all $p<0.001$ sTSO: −7.4, −8.4, 5.7, all $p<0.01$ LPS: −11.2, −9.4, −10.3, all $p<0.001$ b. At week 1 sWASO: −10.5, $p<0.001$ sQUAL: 0.1, $p<0.001$ sFRESH: 0.1, $p<0.01$ c. At month 3 sWASO: −6.9, $p<0.01$ sQUAL: 0.1, $p<0.05$ B. Trial 2 The outcomes in suvorexant 40/30 mg group were generally similar to those in Trial 1 ($p<0.001$) Difference in LPS (−3.6) at month 3 was not significant C. Both trials ISI score ($p<0.001$) was higher in the placebo group when compared to the suvorexant group Suvorexant improved scores on the patient- and physician-rated global outcomes ($p<0.001$ at all time-points) 2. Suvorexant 20/15 mg A. Trial 1 a. At month 1, month 3 and week 1/night 1 sTST: 16.3, $p<0.001$; 10.7, $p<0.05$; 13.6. $p<0.001$ WASO: −26.4, −16.6, −32.5, all $p<0.001$ sTSO: −5.4, −5.2, −5.2 b. At month 3 and night 1 LPS: −8.1 and −9.6	0.8% of individuals with serious AEs on suvorexant 40/30 mg 0.6% individuals with serious AEs on 20/15 mg of suvorexant 2.1% of individuals with serious AEs on placebo Somnolence severe enough to necessitate discontinuation occurred in <2% of the individuals in any treatment group. Excessive daytime sleepiness was higher for suvorexant (0.4–0.8%) compared to placebo (0–0.3%).

Table 3. (*Continued*)

Name of study	Outcomes and measures	Outcomes (suvorexant compared to placebo)	Tolerability
		c. At month 1 LPS: –10.3, $p<0.001$ d. At month 3 Improvements were noted for suvorexant 20/15 mg on the patient- and physician-rated global outcomes at all time-points ($p<0.01$ or $p<0.001$) 2. Trial 2 The outcomes were very similar to those in Trial 1 3. Both trials ISI responders were higher for suvorexant 15 mg when compared to placebo ($p<0.001$).	

CGI-I, Clinician Global Impression of Improvement; CGI-S, Clinician Global Impression Severity; DSCT, Digit Symbol Copying Test; DSST, Digit Symbol Substitution Test; ISI, Insomnia Severity Index; LPS, Latent Persistent Sleep; PGI-S, Patient Global Impression Severity; QIDS-SR, Quick Inventory of Depression Symptomatology-Self Report; SE, Sleep Efficiency; sFRESH, subjective Refreshed Feeling on Waking; sNAW, subjective Number of Awakenings; sQUAL, subjective Quality of Sleep; sTSO, subjective Time to Sleep Onset; sTST, subjective Total Sleep Time; sWASO, subjective Wake After Sleep Onset; WASO, Wake After Sleep Onset.

individuals ≥65 years in age, it was not possible as the results were not stratified by age in this study.

Efficacy was assessed daily throughout the study by electronic morning sleep diaries completed by participants. The subjective measures included subjective total sleep time (sTST), subjective time to sleep onset (sTSO), subjective wake after sleep onset (sWASO), subjective number of awakenings (sNAW), subjective quality of sleep (sQUAL) and subjective refreshed feeling on waking (sFRESH). Clinician Global Impression of Severity (CGI-S), Clinician Global Impression of Improvement (CGI-I), Patient Global Impression of Improvement (PGI-I) and Patient Global Impression of Severity (PGI-S) were completed at week 2 and at months 1, 3, 6, 9, 12, 13 and 14. Phone calls were conducted during each of the intervening months. Participants completed the Insomnia Severity Index (ISI) scale at week 2 and at months 1, 3, 6 and 12.

Safety assessments were conducted by open-ended questioning for adverse events at each clinic visit and during phone calls conducted at the intervening months. The Columbia Suicide Severity Rating Scale (CSSRS), laboratory studies and EKG were also conducted at the clinic visits. The Motor Vehicle Accidents and Violations (MVAV) questionnaire and the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) were also administered.

Suvorexant was superior to placebo on the following subjective sleep measures at month 1 and month 12: sTST (23.3 and 27.5 minutes more, respectively, both $p<0.0001$), sTSO (–10.3 minutes, $p=0.0004$; –9.7 minutes, $p=0.0055$), sWASO (–9.0 minutes, $p=0.0003$; –9.7 minutes, $p=0.0048$), sQUAL (0.2, $p<0.0001$; 0.1, $p=0.0338$), sFRESH (0.2, $p=0.001$; 0.2, $p=0.0162$). There was not a significant difference in sNAW at month 1 (0.1, $p=0.19$). However, sNAW was improved at month 12 for those taking suvorexant when compared to placebo (0.2; $p=0.02$). Suvorexant was also superior to placebo on ISI (–1.4, $p<0.0001$; –0.9, $p=0.04$), CGI-S (–0.3, $p<0.0001$; –0.4, $p=0.0003$), PGI-S (–0.3, $p=0.0026$; –0.3, $p=0.011$), CGI-I (–0.4, –0.5, both $p<0.0001$) and PGI-I (–0.5, –0.5, both $p<0.0001$) at month 1 and month 12, respectively. There was no effect on mood based on QIDS-SR responses at month 1 (–0.2, $p=0.17$) or month 12 (–0.1, $p=0.52$).

Continuing treatment after 1 year showed better retention of treatment gains than treatment discontinuation (sTST 20%, HR 0.471, 95% CI 0.286–0.776, $p=0.003$). Moreover, there was no consistent pattern suggestive of withdrawal effects or rebound insomnia from suvorexant. There were no deaths noted in the study. Similar proportions of individuals treated with suvorexant or placebo discontinued treatment because of adverse events (11.7 *vs* 8.5%). The proportion of individuals with >1 serious adverse events was similar among the treatment groups (5.2% for the suvorexant treatment group *vs* 6.6% for the placebo treatment group). Somnolence was the adverse event with the highest incidence of discontinuations (4 *vs* 1%). Common adverse events noted in the study were somnolence (13.2 *vs* 2.7%) followed by fatigue (6.5 *vs* 1.9%) and dry mouth (5 *vs* 1.6%). There were no clinically meaningful differences between groups in vital signs or laboratory values.

Herring et al.

The study by Herring et al. included two RCTs of participants who met DSM-IV-TR criteria for primary insomnia [20]. The two studies were of the dose regimens of 40/30 and 20/15 mg; both included non-elderly (18–65 years in age) and elderly (≥65 years in age) subjects. In each trial there was a 2-week, single-blind placebo run-in followed by 3-month, double-blind, placebo-controlled phase, which included three treatment arms. In addition, Trial 1 had the option for a 3-month double-blind extension phase for those individuals who completed the initial treatment phase. In both trials, there was a 1-week double-blind run-out at the end of treatment phase at 3 or 6 months. Although we wanted to investigate the outcomes exclusively among individuals ≥65 years in age, it was not possible as the results were not stratified by age in these two studies.

Once the participants completed the run-in period, they were randomized to 3 months of treatment with suvorexant 40/30 mg, suvorexant 20/15 mg, or placebo. The doses were adjusted for age (<65 years: 40 mg or 20 mg; >65 years: 30 mg or 15 mg). The randomization was performed in a 3:2:3 ratio in Trial 1, and a 1:1:1 ratio (Q-cohort) or a 2:1:2 ratio (PQ-cohort) in Trial 2. After the run-out at the end of treatment, half of those individuals who were initially randomized to suvorexant were again randomized to receive either the same dose of suvorexant (suvorexant to suvorexant) or were switched to placebo (suvorexant to placebo) in a 1:1 ratio. Those individuals who were initially randomized to placebo were continued on placebo (placebo to placebo).

For the suvorexant 40/30 mg group, the primary efficacy end points were change from baseline at months 1 and 3 for subjective (sleep diary) and objective (PS) measures of sleep maintenance (sTST, WASO) and sleep onset (sTSO, LPS) from baseline to months 1 and 3, respectively. The secondary end points were changes in these variables that were assessed at week 1 for the subjective end points (sTST and sTSO) and night 1 for objective end points (WASO and LPS). For the suvorexant 15 mg group, these variables were assessed as secondary end points in Trial 1 and exploratory end points in Trial 2. Additional exploratory end points included the sleep diary end points – WASO, number of awakenings, sQUAL, sFRESH and the rating scale end points – ISI, CGI-S, PGI-S, CGI-I, PGI-I.

In Trial 1, suvorexant 40/30 mg was superior to placebo in improving sleep maintenance as measured by sTST (19.6, 19.7, 21.4, all $p<0.001$) and WASO (–26.3, –22.9, –38.4, all $p<0.001$) at month 1, month 3 and week 1/night 1. Suvorexant was also found to be superior to placebo in improving sleep onset as measured by sTSO (–7.4, –8.4, –5.7, all $p<0.01$) and LPS (–11.2, –9.4, –10.3, all $p<0.001$) at month 1, month 3 and week 1/night 1. Furthermore, suvorexant was found to improve sWASO (–10.5, $p<0.001$), sQUAL (0.1, $p<0.001$) and sFRESH at week 1 (0.1, $p<0.01$). The investigators found that the benefits obtained from suvorexant were maintained at month 3 for both sWASO (–6.9, $p<0.01$) and sQUAL (0.1, $p<0.05$). Suvorexant also significantly improved scores on the patient-rated and physician-rated global outcomes at all the time points ($p<0.001$).

The investigators noted that the outcomes in the suvorexant 40/30 mg group in Trial 2 were generally similar to those in Trial 1. However, the difference in LPS (–3.6) at month 3 was not significant. The percentage of 'responders', prospectively defined as a ≥6-point improvement from baseline in the ISI score ($p<0.001$), was higher in the placebo group in both trials.

In Trial 1, suvorexant 20/15 mg was more effective than placebo in improving sleep maintenance measured by sTST (16.3, $p<0.001$; 10.7, $p<0.05$; 13.6. $p<0.001$) and WASO (–26.4, –16.6, –32.5, all $p<0.001$) at months 1 and 3 and week 1/night 1, respectively. In addition, suvorexant 20/15 mg was superior to placebo in improving sleep onset measured by LPS at month 1 (–10.3, $p<0.001$), but it did not significantly differ from placebo on the sTSO (–5.4, –5.2, –5.6) at any time point or on the LPS (–8.1 and –9.6) at month 3 and night 1. However, the differences between groups favored suvorexant compared to placebo. Suvorexant 15 mg also provided improvements at all time-points ($p<0.01$ or $p<0.001$) on the patient-rated and physician-rated global outcomes. In Trial 2, the results from the suvorexant 20/15 mg group were very similar to those in Trial 1. Additionally, in both trials, the percentage of ISI responders in both trials was higher in the suvorexant 20/15 mg group when compared to the placebo group ($p<0.001$).

The investigators found that the effects of suvorexant on sleep parameters observed earlier in the study were maintained throughout the 3-month period. They also found that the effects of suvorexant were more pronounced for sleep maintenance outcomes (sTST and WASO) when compared to sleep onset outcomes (sTSO and LPS). Additionally, suvorexant 40/30 mg appeared to be modestly more effective than suvorexant 20/15 mg for most sleep measures and at all the time points.

During the 3-month period, the individuals who were treated with suvorexant or placebo were found to have similar incidences of adverse effects (AEs) and discontinuation rates owing to AEs. In the suvorexant 40/30 mg group, there were 0.8% of individuals with serious AEs, when compared to 0.6% individuals with serious AEs on 20/15 mg of suvorexant and 2.1% of individuals with serious AEs in the placebo group. Next day somnolence was more common in the suvorexant group; however, somnolence that was severe enough to necessitate discontinuation occurred in <2% of the individuals in any of the treatment groups. The proportion of individuals reporting excessive daytime sleepiness was low among all groups. However, the proportion was higher among the suvorexant groups (0.4–0.8%) when compared to placebo groups (0–0.3%).

The investigators did not discover any clinically relevant changes in laboratory, vital sign, or electrocardiogram measures during the study period. They found that the mean changes from baseline in weight and proportions of patients with ≥7% increase or decrease in weight were similar between treatment groups in each trial. Rebound insomnia was slightly more common

among individuals who switched from suvorexant to placebo in both trials. In Trial 2, the investigators found that there were more individuals meeting the prespecified withdrawal criteria on the first night among the group that switched from suvorexant 40/30 mg to placebo when compared to the individuals who continued on suvorexant 40/30 mg. However, they did not meet the withdrawal criteria on the remaining nights.

Discussion

Our review of the literature did not identify any RCTs that evaluated the efficiency and tolerability of suvorexant for insomnia exclusively among individuals who were ≥65 years in age. However, the three RCTs included in this review that appraised the efficacy and tolerability of suvorexant for insomnia also included individuals ≥65 years in age. All three studies fulfilled the criteria for being of good quality based on the items listed by the CEBM for the assessment of RCTs. A major drawback for all three trials was that the investigators did not stratify the outcomes (efficacy and adverse effects) for individuals ≤65 years in age when compared to ≥65 years in age. Despite this limitation, available data from these RCTs indicate that suvorexant improves both subjective and PS sleep parameters for sleep onset and maintenance among older individuals with primary insomnia and is generally well tolerated.

The strength of this review includes the collection and evaluation of data from five large databases in an organized manner. The limitations of this review include the use of data exclusively from published RCTs, limiting the search to English language publications and the lack of strict adherence to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [21]. Furthermore, we did not utilize statistical methods to evaluate for the heterogeneity between the included studies or to assess the efficacy or tolerability of the treatments.

The RCTs included in this review had good methodology, large number of participants and included individuals from multiple sites across different countries/continents. Multiple subjective and PS sleep parameters were used as outcome measures and adverse events were carefully assessed.

In a recent review that evaluated the safety and efficacy of benzodiazepines, non-BzRAs, suvorexant, ramelteon, doxepin, trazodone and off-label drugs such as other antidepressants, antihistamines, antipsychotics, gabapentin, pramipexole, tiagabine, valerian and melatonin for insomnia among older adults (age criteria not defined) concluded that, although data on suvorexant are limited, this drug appears to improve sleep maintenance and has mild adverse effects, including somnolence and residual daytime sedation [22]. The use of benzodiazepines, particularly long term, is discouraged in the geriatric population. Non-BzRAs have improved safety profiles when compared to benzodiazepines. However, their side effects including cognitive impairment, serious injury and fractures limit their use. Sedating low-dose antidepressants should only be used for insomnia in individuals with comorbid depression. Antipsychotic agents, pramipexole and tiagabine have not been well studied in older adults, and all have considerable adverse effects. Gabapentin may be useful among individuals with restless leg syndrome or chronic neuropathic pain and insomnia. Diphenhydramine should be avoided in the elderly given its significant adverse effect profile. Valerian and melatonin are unregulated products that have a small impact on sleep latency but can produce residual sedation. Ramelteon had minimal adverse effects and is effective for sleep-onset latency and increased total sleep time making it an option for treating insomnia in the elderly.

The evidence from this review is consistent with the conclusions of the two previous meta-analyses that evaluated the efficacy and tolerability of suvorexant for primary insomnia [16,17]. However, all the studies included only individuals with primary insomnia and limited clinical comorbidities. Hence, it is unclear from these studies whether the efficacy and tolerability of suvorexant will be similar for individuals with other sleep disorders or comorbidities. Even so, available data indicates that suvorexant improves multiple subjective and PS sleep parameters among both younger and older adults and is well tolerated.

Conclusion

Suvorexant is a dual orexin receptor antagonist (DORA) that was approved by the FDA in 2014 for the treatment of insomnia. Available evidence from three RCTs indicates that suvorexant benefits older adults with the diagnosis of primary insomnia and is well tolerated. Based on available evidence, suvorexant could be safely used for the treatment of insomnia among older adults. However, data from multiple large RCTs with good methodology specifically examining older adults with insomnia are still essential for definitive conclusions regarding the safety and efficacy of suvorexant in this population.

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Correspondence: Rajesh R Tampi, Case Western Reserve University School of Medicine, Cleveland, OH 44106, USA; Department of Psychiatry, MetroHealth, 2500 MetroHealth Drive, Cleveland, OH, 44109, USA. rajesh.tampi@gmail.com

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References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th Edition. Arlington, VA, USA. 2013.
2. Sateja MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014;146(5):1387–94. https://dx.doi.org/10.1378/chest.14-0970
3. Roth T. Insomnia: definition, prevalence, etiology, and consequences. J Clin Sleep Med. 2007;3(Suppl 5):S7–S10.
4. Kamel NS, Gammack JK. Insomnia in the elderly: cause, approach, and treatment. Am J Med. 2006;119(6):463–9. https://dx.doi.org/10.1016/j.amjmed.2005.10.051
5. Rodriguez JC, Dzierzewski JM, Alessi CA. Sleep problems in the elderly. Med Clin North Am. 2015;99(2):431–9. https://dx.doi.org/10.1016/j.mcna.2014.11.013
6. Schmidt C, Peigneux P, Cajochen C. Age-Related changes in sleep and circadian rhythms: impact on cognitive performance and underlying neuroanatomical networks. Front Neurol. 2012;3:118. https://dx.doi.org/10.3389/fneur.2012.00118
7. Cochen V, Arbus C, Soto ME, Villars H, Tiberge M, Montemayor T, Hein C, Veccherini MF, Onen SH, Ghorayeb I, Verny M, Fitten LJ, Savage J, Dauvilliers Y, Vellas B. Sleep disorders and their impacts on healthy, dependent, and frail older adults. J Nutr Health Aging. 2009;13(4):322–9.
8. Hafner M, Stepanek M, Taylor J, Troxel WM, van Stolk C. Why sleep matters-the economic costs of insufficient sleep: a cross-country comparative analysis. Rand Health Q. 2017;6(4):11.
9. Neubauer D. New and emerging pharmacotherapeutic approaches for insomnia. Int Rev Psychiatry. 2014;26(2):214–24. https://dx.doi.org/10.3109/09540261.2014.888990
10. Airagnes G, Pelissolo A, Lavallée M, Flament M, Limosin F. Benzodiazepine misuse in the elderly: risk factors, consequences, and management. Curr Psychiatry Rep. 2016;18(10):89. https://dx.doi.org/10.1007/s11920-016-0727-9
11. Lee-Iannotti JK, Parish JM. Suvorexant: a promising, novel treatment for insomnia. Neuropsychiatr Dis Treat. 2016;12:491–5. https://dx.doi.org/10.2147/NDT.S31495
12. Krystal AD, Benca RM, Kilduff TS. Understanding the sleep-wake cycle: sleep, insomnia, and the orexin system. J Clin Psychiatry. 2013;74(Suppl 1):3–20. https://doi.org/10.4088/JCP.13011su1c
13. Dubey AK, Handu SS, Mediratta PK. Suvorexant: the first orexin receptor antagonist to treat insomnia. J Pharmacol Pharmacother. 2015;6(2):118–21. https://doi.org/10.4103/0976-500X.155496
14. Ramirez AD, Gotter AL, Fox SV, Tannenbaum PL, Yao L, Tye SJ, McDonald T, Brunner J, Garson SL, Reiss DR, Kuduk SD, Coleman PJ, Uslaner JM, Hodgson R, Browne SE, Renger JJ, Winrow CJ. Dual orexin receptor antagonists show distinct effects on locomotor performance, ethanol interaction and sleep architecture relative to gamma-aminobutyric acid-A receptor modulators. Front Neurosci. 2013;7:254. https://doi.org/10.3389/fnins.2013.00254
15. Uslaner JM, Tye SJ, Eddins DM, Wang X, Fox SV, Savitz AT, Binns J, Cannon CE, Garson SL, Yao L, Hodgson R, Stevens J, Bowlby MR, Tannenbaum PL, Brunner J, Mcdonald TP, Gotter AL, Kuduk SD, Coleman PJ, Winrow CJ, Renger JJ. Orexin receptor antagonists differ from standard sleep drugs by promoting sleep at doses that do not disrupt cognition. Sci Transl Med. 2013;5(179):179ra44. https://doi.org/10.1126/scitranslmed.3005213

16. Kishi T, Matsunaga S, Iwata N. Suvorexant for primary insomnia: a systematic review and meta-analysis of randomized placebo-controlled trials. PLoS One. 2015;10(8):e0136910. https://dx.doi.org/10.1371/journal.pone.0136910
17. Kuriyama A, Tabata H. Suvorexant for the treatment of primary insomnia: a systematic review and meta-analysis. Sleep Med Rev. 2017;35:1–7. https://dx.doi.org/10.1016/j.smrv.2016.09.004
18. Critical Appraisal Tools, 2017. Available at http://www.cebm.net/critical-appraisal/ [Last accessed: 31 October 2017].
19. Michelson D, Snyder E, Paradis E, Chengan-Liu M, Snavely DB, Hutzelmann J, Walsh JK, Krystal AD, Benca RM, Cohn M, Lines C, Roth T, Herring WJ. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2014;13(5):461–71. https://dx.doi.org/10.1016/S1474-4422(14)70053-5
20. Herring WJ, Connor KM, Ivgy-May N, Snyder E, Liu K, Snavely DB, Krystal AD, Walsh JK, Benca RM, Rosenberg R, Sangal RB, Budd K, Hutzelmann J, Leibensperger H, Froman S, Lines C, Roth T, Michelson D. Suvorexant in individuals with insomnia: results from two 3-month randomized controlled clinical trials. Biol Psychiatry. 2016;79(2):136–48. https://dx.doi.org/10.1016/j.biopsych.2014.10.003
21. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;349:g7647. https://dx.doi.org/10.1136/bmj.g7647
22. Schroeck JL, Ford J, Conway EL, Kurtzhalts KE, Gee ME, Vollmer KA, Mergenhagen KA. Review of safety and efficacy of sleep medicines in older adults. Clin Ther. 2016;38(11):2340–72. https://dx.doi.org/10.1016/j.clinthera.2016.09.010