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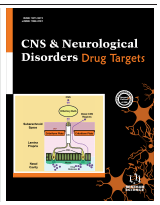
SYSTEMATIC REVIEW ARTICLE



Benzodiazepines and Sleep Architecture: A Systematic Review

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Abstract: ***Background*:** Insomnia, defined as a difficulty in initiating or maintaining sleep, is a relevant medical issue. Benzodiazepines (BZDs) are commonly prescribed to treat insomnia. Two phases characterize human sleep structure: sleep with Non-Rapid Eye Movement (NREM) and sleep with Rapid Eye Movement (REM). Physiological sleep includes NREM and REM phases in a continuous cycle known as "Sleep Architecture."

***Objective*:** This systematic review summarizes the studies that have investigated effects of BZDs on Sleep Architecture.

***Methods*:** The articles selection included human clinical trials (in English, Portuguese, or Spanish) only, specifically focused on BZDs effects on sleep architecture. PubMed, BVS, and Google Scholar databases were searched.

***Results*:** Findings on BZDs effects on sleep architecture confirm an increase in stage 2 of NREM sleep and a decrease in time of stages 3 and 4 of NREM sleep with a reduction in time of REM sleep during the nocturnal sleep.

***Conclusion*:** Variations in NREM and REM sleep may lead to deficits in concentration and working memory and weight gain. The increase in stage 2 of NREM sleep may lead to a subjective improvement of sleep quality with no awakenings. BZDz should be prescribed with zeal and professional judgment. These patients should be closely monitored for possible long-term side effects.

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1. INTRODUCTION

Sleep is a physiological process, a reversible state that leads to a shutdown of perception and responsiveness towards the environment, allowing the occurrence of essential neurobiological processes that lead to maintaining good physical and cognitive health in humans [1,2]. Insomnia, which is characterized by difficulty in initiating or maintaining a physiological sleep, is a relevant clinical issue, affecting not only the elderly population (from 20% to 40%) [3], but also the general population since 30% of adults report problems in sleeping properly [4]. In addition, 30-40% of adults report complaints about sleep quality lifetime, and 10-15% report chronic insomnia [5].

Two different phases characterize human sleep: sleep with Non-Rapid Eye Movement (NREM) and sleep with Rapid Eye Movement (REM). The NREM phase may be divided into four stages. Human physiological sleep includes NREM and REM phases in a continuous cycle known as Sleep Architecture. The first sleep cycle takes an average time of 70-100 minutes. Each following sleep cycle lasts an average time of 90-120 minutes [6]. This complete cycle usually occurs 4-6 times in a "good night's sleep," depending on variables such as age, body temperature, total sleep time, and medication use [7].

In a physiological sleep cycle, stage 1 of NREM sleep takes approximately 5% of a cycle time. It is characterized by the transition from wakefulness to sleep. Sleep is light and includes muscle relaxation, reduction in heart and respiratory rates, and reduction in eye-movement. Also, in this stage, a sharp decrease in the number of cerebral waves oc-

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curs compared to wakefulness states. Stage 2 takes approximately 50% of a cycle time. It precedes deep sleep stages, including a decrease in heart and respiratory rates, and further body muscle relaxation with a concurrent decrease in body temperature and cerebral waves activity. Stages 3 and 4 of NREM sleep take approximately 25% of a cycle time and are characterized by deep sleep. Body muscles are usually in total relaxation with a concurrent decrease in brain activity. However, in these stages, an increase in heart and respiratory rates is registered. REM sleep usually begins 90 minutes after the sleep onset, and it is characterized by an increase in brain activity and eye-movement. REM sleep time progressively decreases with age [7,8].

Benzodiazepines (BZDs) are commonly prescribed to treat insomnia and sleep disorders. Approximately 4% of the general population reports the use of these medications [9]. BZDs show a rapid sedative and anxiolytic effect, successfully used in the acute treatment of insomnia as well as anxiety, agitation, or anxiety associated with any type of psychiatric disorder [10]. Their use is associated with potential side effects such as residual daytime sleepiness, ataxia, and dizziness. More severe side effects (*i.e*., marked drowsiness, disinhibition, and respiratory depression) may occur when other sedative substances, including drugs and alcohol, are used concurrently [10]. Long-term BZDs use may lead to drug abuse, tolerance, drug dependency, and abstinence [11]. For instance, BZDs abrupt withdrawal can lead to severe symptoms such as insomnia and/or rebound anxiety, an increase in heart rate and blood pressure, nausea and/or vomiting, sweating, diarrhea, convulsions, and other neurological and psychiatric symptoms [12]. This systematic review aimed to summarize evidence regarding the effect of BZDs treatment on human Sleep Architecture.

2. METHODS

2.1. Search Strategy

This systematic review has been performed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [13]. We included clinical trials on humans (in English, Portuguese, or Spanish) that specifically focused on BZDs effects on sleep architecture. There were no restrictions regarding the population size, gender, publishing dates, settings, patients' age, and birthplaces. Three online databases were searched (last search date: June 2020), PubMed, through index resource Medical Subject Headings (MeSH), using the following search strategy: ("BENZODIAPINE"[Mesh]) and ("SLEEP STAGES" [Mesh];).

Biblioteca Virtual em Saúde (BVS, Health Virtual Library), through the use of the following Health Science Descriptors: (DeCS: initials in Portuguese that stand for "Descritores em Ciência da Saúde"), using the following search strategy: (tw:(fases do sono)) and (tw(benzodiazepinas)); and Scholar Google, using the following search strategy: Benzodiazepine and Sleep Stages.

2.2. Study Selection

We identified 911 studies, and 313 studies were excluded because of duplication. The remaining 598 studies were screened by titles and abstracts, independently by the first and last author. In case of discordance, the penultimate author decided about the inclusion/exclusion. Thirty-five articles were considered to be focused on the topic and selected for full-text reading. During this step, 14 out of the remaining 35 studies were excluded. After all these screening stages, 21 studies were included in the present systematic review, as shown in Fig. (**1**).

2.3. Data Collection Process

Twenty-one included studies were analyzed in detail, and their findings were tabulated. The following variables were collected: author(s), year of publication, sample characteristics, length of the study, number of participants, BDZs used, and changes in patients' sleep architecture.

3. RESULTS

3.1. Publication Years

The 21 included studies have been published in four different decades [14-34]. Seven studies were published in the 1970s, three in the 1980s, seven in the 1990s, and four in the 2000s.

3.2. Sample's Characteristics

A mean of 10.4 individuals involved per study has been found (ranging from 5-28 subjects). Ten studies included men only, ten included males and females, and 1 included women only. 12/21 studies evaluated adults, whereas 6/21 included young adults (18-25 years old). Two articles evaluated elderly patients, and 1 article included adults and elderly.

3.3. Study Length

The duration of the studies also varied, with 19 of them developed in 4 weeks or less (mean = 12.3 nights, range = 3-43). Only in 2 studies, long-term BZDs use was evaluated (*i.e*., 43 days of follow-up).

3.4. Types of BZDs

Thirteen different BZDs, including Alprazolam, Brotizolam, Diazepam, Flunitrazepam, Flurazepam, Fosazepam, Haloxazolam, Lorazepam, Midazolam, Nitrazepam, Temazepam, Triazolam, and Quazepam, were considered in the 21 studies selected. Five studies considered two or more BZDs. Some studies described changes in sleep architecture related to the Z-drugs usage as a comparative group of patients, which were not considered in this review.

3.5. Sleep Architecture Alterations

An increase in NREM sleep stage 2 was reported in 76,2% of the studies, but a decrease in all other NREM sleep stages (42,9%, 30.4%, and 14.3% of the studies reported shorter stages 4, 3, and 1, respectively). Shorter REM sleep

time was also described, particularly a 62-66% decrease in sleep latency and a reduction of night awakenings. Table **1** shows a summary of the studies' findings. Table **2** summarizes changes in sleep architecture due to treatments with BZDs.

Table 1. Main Findings.

Authors	Publication Year	Studied Population	N	Medications Used in the Study	Changes Found	Study Length (Number of Nights)
Uchida *et al*. [14]	1996	Healthy young men	5	Flunitrazepam	↑ stage 2 of NREM sleep and ↓ in stage 4 of NREM sleep	14
Kales *et al*. [15]	1986	Adults with insomnia	6	Lorazepam	↓ stage 3 of NREM sleep, ↓ stage 4 of NREM sleep and ↓ REM sleep	16
Gaillard JM &Tissot R [16]	1975	Adults (4 male and 4 female) with insomnia	8	Flunitrazepam	↑ stage 2 of NREM sleep and ↓ REM sleep	between 7 and 406
Bixler *et al*. [17]	1977	Adults with insomnia complaints	28	Flunitrazepam	↑ stage 2 of NREM sleep, ↓ stage 4 of NREM sleep, ↓ stage 3 of NREM sleep, ↓stage 1 of NREM sleep and ↓ REM sleep	12
Jovanovic UJ [18]	1977	Adults with insomnia	10	Flunitrazepam	↓ REM sleep	10
Aesbach *et al*. [19]	1994	Healthy men	9	Midazolam	↑ stage 2 of NREM sleep and ↓ stage 3 of NREM sleep	9
Zarcone Jr. *et al*. [20]	1994	Adult men with Major Depressive Disorder (MDD)	9	Alprazolam	↓ REM sleep	43
Vgontzas *et al*. [21]	1994	Seniors with sleep apnea or sleep myoclonus	8	Temazepam	↓ REM sleep	14
Feinberg *et al*. [22]	1977	Medical students	4	Flurazepam	↑ stage 2 of NREM sleep and ↓ stage 4 of NREM sleep	8
Grozinger *et al*. [23]	1998	Healthy men (22 to 35 years old)	6	Lorazepam	↑ stage 2 of NREM sleep and ↓ REM sleep	3
Hemmeter etl al. [24]	2000	Healthy seniors (6 male and 6 female)	12	Temazepam	No changes in sleep architecture	15
Uchimura *et al*. [25]	2005	Adults with insomnia (3 male and 11 female)	14	Brotizolam	↑ stage 2 of NREM sleep	9
Roehrs *et al*. [26]	1982	Young men with insomnia	9	Flurazepam	No changes in sleep architecture	14
Calvo JM [27]	1996	Healthy men	11	Alprazolam and Lorazepam	↑ stage 2 of NREM sleep, ↓ stage 4 of NREM sleep and ↓ REM sleep	7
Declerek etl al. [28]	1992	Healthy women	18	Flunitrazepam	↑stage 2 of NREM sleep and ↓ REM sleep	21
Feinberg *et al*. [29]	2000	Healthy male(10) and female(6), from 19 to 26 years old	16	Triazolam and Temazepam	↑ stage 2 of NREM sleep, ↓ stage 4 of NREM sleep, ↓ stage 3 of NREM sleep, ↓ stage 1 of NREM sleep and ↓ REM sleep	5
Freemon etl al. [30]	1977	Healthy men (18 to 20 years old)	10	Quazepam	↑ stage 2 of NREM sleep and ↓ REM sleep	4
Nicholson *et al*. [31]	1976	Healthy men (19 to 43 years old)	6	Diazepam and Fosazepam	↑ stage 2 of NREM sleep, ↓ stage 4 of NREM sleep and ↓ stage 3 of NREM sleep	4
Risberg *et al*. [32]	1977	Healthy men (20 to 25 years old)	8	Fosazepam and Nitrazepam	↑ stage 2 of NREM sleep, ↓ stage 4 of NREM sleep, ↓ stage 3 of NREM sleep and ↓ REM sleep	15
Monti *et al*. [33]	1982	Adult (2males and 4 females) with insomnia (29 to 60 years old)	6	Midazolam	↑ stage 2 of NREM sleep	21
Tan *et al*. [34]	2003	Healthy men (20 to 25 years old)	17	Haloxazolam, Flunitrazepam, Triazolam	↑ stage 2 of NREM sleep, ↓ stage 4 of NREM sleep, ↓ stage 3 of NREM sleep, ↓ stage 1 of NREM sleep and ↓ REM sleep*	3

*= only Flunitrazepam.

Table 2. Sleep architecture variations induced by BZDs.

Sleep Architecture Alteration	BZDs
Increased time of NREM sleep stage 2	Flunitrazepam, Diazepam, Lorazepam, Flurazepam, Nitrazepam, Midazolam, Alprazolam, Temazepam, Fosazepam, Triazolam, Brotizolam, Quazepam and Haloxazolam
Decreased time of NREM sleep stage 4	Flunitrazepam, Diazepam, Lorazepam, Flurazepam, Nitrazepam, Alprazolam, Tenazepam, Fosazepam, Triazolam and Haloxazolam
Decreased time of NREM sleep stage 3	Flunitrazepam, Diazepam, Lorazepam, Nitrazepam, Midazolam, Fosazepam, Triazolam and Haloxazolam
Decreased time of REM sleep	Flunitrazepam, Diazepam, Lorazepam, Nitrazepam, Alprazolam, Temazepam, Fosazepam, Triazolam and Quazepam
Decreased latency of sleep and reduction in the number of night awakenings	Flunitrazepam, Diazepam, Lorazepam, Nitrazepam, Midazolam, Alprazolam, Tenazepam, Fosazepam, Triazolam, Brotizolam, Quazepam and Haloxazolam
Decreased time of NREM sleep stage 1	Flunitrazepam, Flurazepam and Temazepam

BZDs: benzodiazepines.

4. DISCUSSION

This systematic review shows data involving heterogeneous samples and methodologies, reporting on different types of BZDs. The generalizability of findings is limited. Regarding the NREM sleep, our review shows that prolonged use of benzodiazepines leads to an increase of time spent in stages 2 and a decrease of time in stages 1, 3, and 4. Some studies considered stages 3 and 4 as one stage characterized by a slow-wave sleep (SWS) [35, 36].

Data regarding the effects of BZD on NREM sleep stage 1, which represents a transition between wakefulness and sleep taking 5 to 15 minutes per cycle, are not conclusive [8]. Although some studies support the idea that BZDs lead to a decrease in NREM stage 1 [17, 29, 34], some other authors that were not included in our review support the opposite idea (*i.e*., BZDs use leads to an increase in total time spent in stage 1 during the NREM sleep) [37].

Stage 2 of NREM sleep is characterized by a reduction in heart and respiratory rates and increased muscle relaxation, compared to stage 1. There are also sleep spindles and K complexes in this stage, suppressing cortical arousal in response to stimuli and aiding sleep-based memory consolidation [8]. According to our review, BZDs increase time in this stage in human sleep [14, 16, 17, 19, 22, 23, 25, 27, 28, 29, 30-34]. In addition, the prolonged use of BZDs may lead to cognitive impairment, a reduction in the capability of executing motor sequence learning tasks, a lesser relaxation in body muscles, and an increase in the number of sleepwalking events. All these symptoms are mostly related to an increased time spent in stage 2 of NREM sleep [38]. Song *et al*. [38] also found in their research that males who spent more time in this stage were more likely to take BZDs, and had higher rates of angina, hypertension, and myocardial infarction compared to those that spent less time there.

Our review also adds evidence to NREM sleep stage operating structures' importance, especially in stage 2, to induce a restful sleep feeling when waking up [39]. The average brain metabolism and brain blood flow are reduced in stage 2 compared to wakefulness [40,41]. NREM stage 2 presents a relevant number of micro-awakenings and is related to the restorative quality of sleep. If it is not interrupted, sleep will be deep and of good perceived quality. If it is interrupted, sleep will be fragmented, leading to poor sleep quality [39]. Precocious sleep interruption is a risk factor for cognitive and metabolic brain negative outcomes. At the core of all neurological and psychiatric diseases is an abnormality in one or more neurotransmitter systems [42, 43]. This increased risk can be explained, considering that sleep disruption and the circadian rhythm impair all aspects of neural and neuroendocrine function, like the stress axis.

The increased NREM stage 2 is associated with a subjective improvement in sleep quality (reducing micro-awakenings), although possibly related to an increased risk of cardiovascular issues, as demonstrated by a cohort of women aged over 50 years where exposure to hypnotic benzodiazepines was associated with increased cardiovascular mortality [38, 44]. In addition, some other evidence is not conclusive regarding the associated risk of dementia [44-47]. Gage *et al*., in 2015, conducted a review where nine of the ten studies concluded an increased risk of dementia in benzodiazepine users. However, the robustness of their results appears variable across studies due to methodological differences. In the most reliable ones, the risk of dementia was found increased in benzodiazepine users by a factor of 1.24-2.30 [45]. More recently, in 2020, Olsler and Jørgensen conducted a cohort and nested case-control study of 235,465 patients from the Danish National Patient Registry. Their large cohort study did not reveal associations between BZDs use and subsequent dementia [47].

The decrease in NREM sleep time in stages 3 and 4 is usually associated with lesser “rest” for the brain, which leads to a lack of concentration [38]. Individuals with SWS deprivations can also present hallucinations and distorted perceptions [38]. It has been argued that the decrease in SWS time leads to a more significant release of free radicals in the human brain [48]. Also, the physiological reduction of cerebral metabolism and cerebral blood flow does not occur properly, affecting the physiological clearance of free radicals [48]. Data from cognitively normal older adults without sleep disorders or hypnotic medication show that shorter SWS is an intermediary factor for impaired hippocampus-dependent memory consolidation and amyloid-beta pathology [49]. This is significantly associated with the risk of Alzheimer disease with impaired cognitive and behavioral performances [50]. Some other authors suggest that a contin-

uous decrease in SWS time throughout life is observed independently of BZDs use [51]. In addition, some studies from our review show that the use of BZDs reduces SWS time in both younger and older people [15,17,19,22,27,31,32,34].

The decrease of REM sleep was observed in 13 studies included in the present review. Chronic use of BZDs has been associated with reduced REM sleep, reversible after BZDs withdrawal [52]. In addition, REM sleep seems to show anti-obesity properties, acting as an appetite suppressor [53]. Food preferences and dislikes development seem to be linked to REM sleep [53]. Schechter *et al*. reported that REM sleep duration was inversely correlated with hunger and carbohydrate intake [54]. Similarly, Gonnissen *et al*. correlated reduced REM sleep with declines in subjective "fullness" and increased desire for snacking [55]. At the same time, REM sleep disruption can be related to some disorders, such as narcolepsy or anorexia nervosa, which is a complex disorder that is marked by a loss of REM sleep in the second half of the night, being replaced by wakefulness and, sometimes, by physical activity (locomotion) [53].

One other discussed impact of REM sleep would be on the affective evaluation and consolidation of emotional memories. It has been studied over the past decades, resulting in a theory called "sleep to forget and sleep to remember" [56]; this theory proposes that REM sleep promotes the consolidation of emotional events as memories ("sleep to remember"), while attenuates memory potential to increase emotional reactions associated with that specific memory [57]. According to Wiesner *et al*. [57], REM sleep contributes to the consolidation of declarative memories providing emotional facilitation [57].

Long- and short-acting BZD hypnotics were included in our review, with half-lives ranging from 1.5 to 123 hours. Short-acting BZDs (1,5-4 hours) were associated with a reduction in REM sleep and SWS [58]. They seem to affect the mechanism that onsets REM sleep and not the one which maintains it. Consequently, a REM sleep rebound may occur during the later part of the night, when the plasma concentration decreases due to its small half-life [59]. In the present review, SWS reduction was observed in all studies using short-acting BZDs [19,29,31-34], but REM sleep reduction was observed only in one [32]. All of the studies that used short-acting BZDs also reported an increased NREM sleep 2 stage [19,29,31-34], which is not usually associated with them. Lynna *et al*. [60] associated short-acting BZDs with lower night sleep quality and more extended day-time napping than long-acting BZDs. Unfortunately, the present review did not find this type of data.

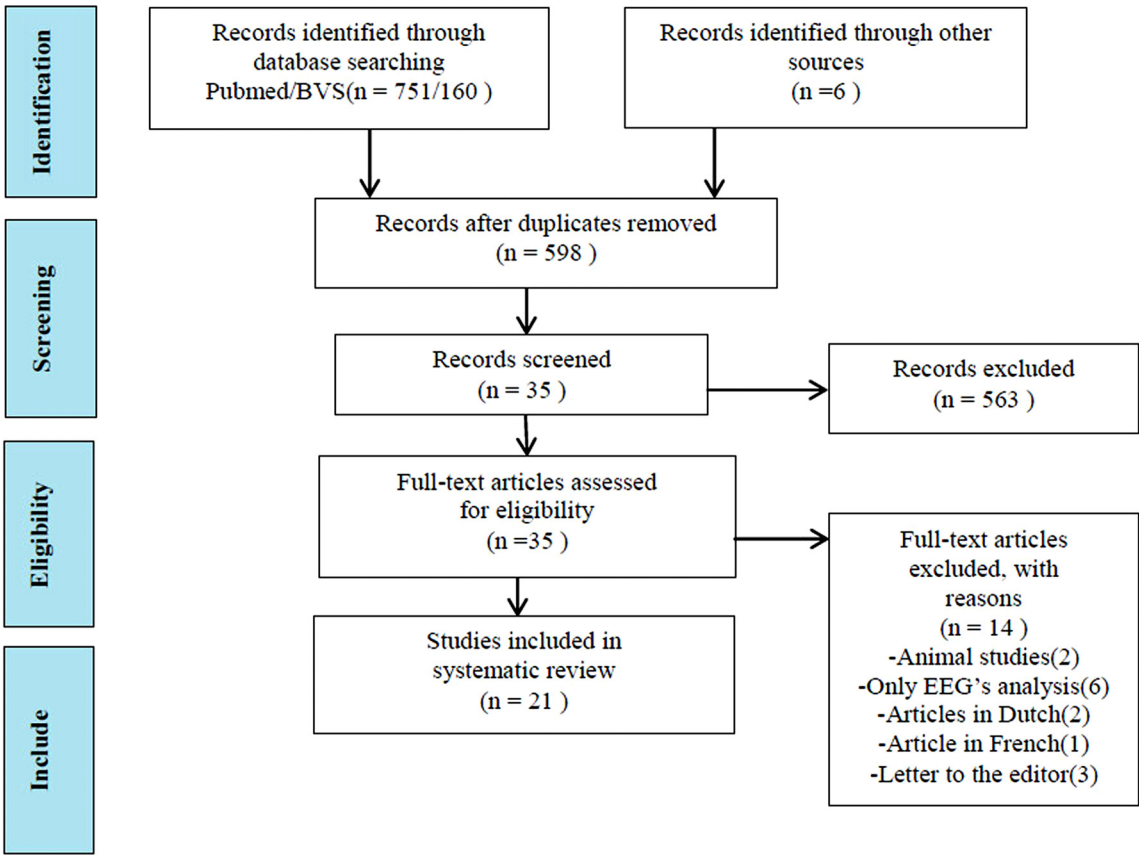

Fig. (1). Prisma flowchart.

On the other hand, long-acting BZDs (12-123 hours) were associated with a reduction in REM and SWS duration. The longer the half-life, the longer the reduction [61]. Only longer half-lives are associated with reduced NREM stage 1 [61]. These previous findings partially agree with our review since the reduction in NREM 1 sleep stage was observed in two studies with intermediate and one with longer half-life [17,29,34]. Some of our studies did not quantify the duration of REM and SWS reductions; therefore, we could not make this comparison. Our most common finding with these long-acting BZDs was the reduction in NREM 2 sleep stage [14-17,22,23,25,27-31,34], a fact that is commonly associated with them [61].

CYP3A4 metabolizes most BZDs, an enzyme from the cytochrome P450, which is inhibited by several antidepressants [62]. Their co-administration can result in higher serum levels of BZDs. Besides that, xanthines (like caffeine) and alcohol can increase sleepiness induced by BZD [63] and consequently cause architecture alterations. These common and possible interactions were not controlled for in most of our included studies.

There is some evidence that the chronic use of BZD is associated with hyperglycemia [64]. This fact should be taken in account in a scenario where Non-Alcoholic Fatty Liver Disease (NAFLD) and diabetes have reached epidemic levels, mainly due to unhealthy western diets and lifestyles [65, 66]. These metabolic changes can cause defective xanthine's metabolism, altered BZD's metabolism, and nutrient deficits, which may be associated with circadian rhythm alterations [65]. Due to these facts, nutrition and liver metabolism should be assessed in future studies.

This review did not assess the risk of bias in individual studies. This risk was also not assessed across studies. Also, it was not possible to handle data and combine the results of studies since the findings were heterogeneous. Another limitation was the selection of studies written in English, Portuguese, and Spanish only. Also, 50% and 57% of the samples included in this review were composed of males and adults only, respectively. This may suggest considering emerging evidence as limited since women, young adults, and seniors were underrepresented. Also, there were small samples involved in clinical trials based on polysomnography [14-34]. However, this was the first systematic review, to our knowledge, that summarized the variations in human sleep architecture induced by BZDs.

CONCLUSION

This systematic review of literature aimed to evaluate variations in human sleep architecture caused by the treatment with BZDs. We may conclude that BZDs use modified sleep architecture in the short and long term. Consistent evidence confirmed an increase in NREM stage 2, decreased stages 3 and 4 of NREM sleep, and a reduction in REM sleep time in a regular nocturnal sleep. The increase in NREM stage 2 possibly leads to a subjective sleep quality improvement, no awakenings, and higher sleep quality sensation, but an increased risk for cardiovascular diseases. There is some evidence that the decrease in stages 3 and 4 may be associated with amyloid-beta pathology. Decreased REM sleep may increase the risk of obesity. Based on these findings, we recommend that benzodiazepines are prescribed with zeal and professional judgment. Physicians should account for the pros and cons of prescribing them with a clinical follow-up of possible side effects in the short- and long-term treatment.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

This systematic review has been performed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

SUPPLEMENTARY MATERIAL

PRISMA checklist is available as supplementary material on the publisher's website along with the published article.

REFERENCES

[1] Antonelli Incalzi R, Marra C, Salvigni BL, *et al.* Does cognitive dysfunction conform to a distinctive pattern in obstructive sleep apnea syndrome? J Sleep Res 2004; 13(1): 79-86. http://dx.doi.org/10.1111/j.1365-2869.2004.00389.x PMID: 14996039

[2] Dauvilliers Y. The major physiological functions during sleep. Sleep. Physiol, Investigat, Med. 2003; pp. 45-60.

[3] Ancoli-Israel S, Cooke JR. Prevalence and comorbidity of insomnia and effect on functioning in elderly populations. J Am Geriatr Soc 2005; 53(7) (Suppl.): S264-71. http://dx.doi.org/10.1111/j.1532-5415.2005.53392.x PMID: 15982375

[4] National institutes of health state of the science conference statement on manifestations and management of chronic insomnia in adults. Sleep 2005; 28(9): 1049-57.

[5] Mellinger GD, Balter MB, Uhlenhuth EH. Insomnia and its treatment. Prevalence and correlates. Arch Gen Psychiatry 1985; 42(3): 225-32. http://dx.doi.org/10.1001/archpsyc.1985.01790260019002 PMID: 2858188

[6] Keenan, S., & Hirshkowitz, M. Monitoring and staging human sleep: In M.H. Kryger, T. Roth, W.C. Dement. Eds. Principles and practice of sleep medicine. 5th ed. St. Louis: Elsevier Saunders 2011; pp 1602-1609. http://dx.doi.org/10.1016/B978-1-4160-6645-3.00002-5

[7] Silva RS. Introdução ao estagiamento do sono humano. Braz J Epilepsy Clin Neurophysiol 1996; 3(2): 187-99.

[8] Fernandes RMF. O sono normal. Medicina (Ribeirão Preto) 2006;

39(2): 157-68.
[9] Galduróz JC, Noto AR, Nappo SA, Carlini EA. Use of psychotropic drugs in Brazil: household survey involving the 107 largest cities in the country - 2001. Rev Latino-Am Enfermagem 2005; 13(spe)
http://dx.doi.org/10.1590/S0104-11692005000700017
[10] Sadock BJ, Sadock VA, Ruiz P. Sono normal e transtorno do sono-vigília. Compêndio de Psiquiatria - Ciências do Comportamento e Psiquiatria Clínica. 11th ed. Porto Alegre: Artes Médicas 2017; pp. 533-63.
[11] Woods JH, Katz JL, Winger G. Benzodiazepines: Use, abuse, and consequences. Pharmacol Rev 1992; 44(2): 151-347.
PMID: 1356276
[12] Soldatos CR, Dikeos DG, Whitehead A. Tolerance and rebound insomnia with rapidly eliminated hypnotics: A meta-analysis of sleep laboratory studies. Int Clin Psychopharmacol 1999; 14(5): 287-303.
http://dx.doi.org/10.1097/00004850-199909000-00004 PMID: 10529072
[13] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009; 6(7): e1000097.
http://dx.doi.org/10.1371/journal.pmed.1000097 PMID: 19621072
[14] Uchida S, Okudaira N, Nishihara K, Iguchi Y. Flunitrazepam effects on human sleep EEG spectra: Differences in NREM, REM and individual responses. Life Sci 1996; 58(10): PL199-205.
http://dx.doi.org/10.1016/0024-3205(96)00026-4 PMID: 8602113
[15] Kales A, Bixler EO, Soldatos CR, Jacoby JA, Kales JD. Lorazepam: effects on sleep and withdrawal phenomena. Pharmacology 1986; 32(3): 121-30.
http://dx.doi.org/10.1159/000138160 PMID: 3960963
[16] Gaillard JM, Tissot R. EEG sleep studies of insomniacs under flunitrazepam treatment. Int Pharmacopsychiatry 1975; 10(4): 199-207.
http://dx.doi.org/10.1159/000468195 PMID: 2563
[17] Bixler EO, Kales A, Soldatos CR, Kales JD. Flunitrazepam, an investigational hypnotic drug: Sleep laboratory evaluations. J Clin Pharmacol 1977; 17(10 Pt 1): 569-78.
http://dx.doi.org/10.1177/009127007701701004 PMID: 21199
[18] Jovanović UJ. Polygraphic sleep recordings before and after the administration of flunitrazepam. J Int Med Res 1977; 5(2): 77-84.
http://dx.doi.org/10.1177/030006057700500201 PMID: 17559
[19] Aeschbach D, Dijk DJ, Trachsel L, Brunner DP, Borbély AA. Dynamics of slow-wave activity and spindle frequency activity in the human sleep EEG: effect of midazolam and zopiclone. Neuropsychopharmacology 1994; 11(4): 237-44.
http://dx.doi.org/10.1038/sj.npp.1380110 PMID: 7857498
[20] Zarcone VP Jr, Benson KL, Greene KA, Csernansky JG, Faull KF. The effect of chronic alprazolam on sleep and bioamine metabolites in depression. J Clin Psychopharmacol 1994; 14(1): 36-40.
http://dx.doi.org/10.1097/00004714-199402000-00005 PMID: 7512100
[21] Vgontzas AN, Kales A, Bixler EO, Myers DC. Temazepam 7.5 mg: Effects on sleep in elderly insomniacs. Eur J Clin Pharmacol 1994; 46(3): 209-13.
http://dx.doi.org/10.1007/BF00192550 PMID: 8070501
[22] Feinberg I, Fein G, Walker JM, Price LJ, Floyd TC, March JD. Flurazepam effects on slow-wave sleep: Stage 4 suppressed but number of delta waves constant. Science 1977; 198(4319): 847-8.
http://dx.doi.org/10.1126/science.21453 PMID: 21453
[23] Grözinger M, Kögel P, Röschke J. Effects of Lorazepam on the automatic online evaluation of sleep EEG data in healthy volunteers. Pharmacopsychiatry 1998; 31(2): 55-9.
http://dx.doi.org/10.1055/s-2007-979299 PMID: 9562209
[24] Hemmeter U, Müller M, Bischof R, Annen B, Holsboer-Trachsler E. Effect of zopiclone and temazepam on sleep EEG parameters, psychomotor and memory functions in healthy elderly volunteers. Psychopharmacology (Berl) 2000; 147(4): 384-96.
http://dx.doi.org/10.1007/s002130050007 PMID: 10672632
[25] Uchimura N, Nakajima T, Hayash K, *et al.* Effect of zolpidem on sleep architecture and its next-morning residual effect in insomniac patients: A randomized crossover comparative study with brotizolam. Prog Neuropsychopharmacol Biol Psychiatry 2006; 30(1): 22-9.
http://dx.doi.org/10.1016/j.pnpbp.2005.06.018 PMID: 16048734
[26] Roehrs T, Zorick F, Kaffeman M, Sicklesteel J, Roth T. Flurazepam for short-term treatment of complaints of insomnia. J Clin Pharmacol 1982; 22(7): 290-6.
http://dx.doi.org/10.1002/j.1552-4604.1982.tb02677.x PMID: 7107976
[27] Calvo JM. La neurobiología del sueño en animals experimentales y en el hombre. Salud Ment 1996; 19(3): 58-65.
[28] Declerck AC, Ruwe F, O'Hanlon JF, Vermeeren A, Wauquier A. Effects of zolpidem and flunitrazepam on nocturnal sleep of women subjectively complaining of insomnia. Psychopharmacology (Berl) 1992; 106(4): 497-501.
http://dx.doi.org/10.1007/BF02244821 PMID: 1579623
[29] Feinberg I, Maloney T, Campbell IG. Effects of hypnotics on the sleep EEG of healthy young adults: New data and psychopharmacologic implications. J Psychiatr Res 2000; 34(6): 423-38.
http://dx.doi.org/10.1016/S0022-3956(00)00038-8 PMID: 11165310
[30] Freemon FR, Al-Marashi MSH, Lee JCM. The effect of a new benzodiazepine on the polygraphically monitored sleep of normal volunteers. J Clin Pharmacol 1977; 17(7): 398-401.
http://dx.doi.org/10.1002/j.1552-4604.1977.tb04622.x PMID: 18491
[31] Nicholson AN, Stone BM, Clarke CH. Effect of diazepam and fosazepam (a soluble derivative of diazepam) on sleep in man. Br J Clin Pharmacol 1976; 3(4): 533-41.
http://dx.doi.org/10.1111/j.1365-2125.1976.tb04872.x PMID: 22216491
[32] Risberg AM, Henricsson S, Ingvar DH. Evaulation of the effect of fosazepam (a new benzodiazepine), nitrazepam and placebo on sleep patterns in normal subjects. Eur J Clin Pharmacol 1977; 12(2): 105-9.
http://dx.doi.org/10.1007/BF00645130 PMID: 200435
[33] Monti JM, Debellis J, Gratadoux E, Alterwain P, Altier H, D'Angelo L. Sleep laboratory study of the effects of midazolam in insomniac patients. Eur J Clin Pharmacol 1982; 21(6): 479-84.
http://dx.doi.org/10.1007/BF00542042 PMID: 7075654
[34] Tan X, Uchida S, Matsuura M, Nishihara K, Kojima T. Long-, intermediate- and short-acting benzodiazepine effects on human sleep EEG spectra. Psychiatry Clin Neurosci 2003; 57(1): 97-104.
http://dx.doi.org/10.1046/j.1440-1819.2003.01085.x PMID: 12519461
[35] Peigneux P, Laureys S, Fuchs S, *et al.* Are spatial memories strengthened in the human hippocampus during slow wave sleep? Neuron 2004; 44(3): 535-45.
http://dx.doi.org/10.1016/j.neuron.2004.10.007 PMID: 15504332
[36] McNamara P, Johnson P, McLaren D, Harris E, Beauharnais C, Auerbach S. REM and NREM sleep mentation. Int Rev Neurobiol 2010; 92: 69-86.
http://dx.doi.org/10.1016/S0074-7742(10)92004-7 PMID: 20870063
[37] Roehrs T, Roth T. Drug-related sleep state changes: functional significance and clinical relevance. Sleep Med Clin 2010; 5(4): 559-70.
http://dx.doi.org/10.1016/j.jsmc.2010.08.002 PMID: 21344068
[38] Song Y, Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Stone KL. Relationships between sleep stages and changes in cognitive function in older men: the MrOS Sleep Study. Sleep (Basel) 2015; 38(3): 411-21.
http://dx.doi.org/10.5665/sleep.4500 PMID: 25325465
[39] Martynas Z, Vanda L, Ramune G, Raminta M, Osvaldas R. Arousals and macrostructure of sleep: importance of NREM stage 2 reconsidered. Sleep Sci 2013; 6(3): 91-7.
[40] Madsen PL, Schmidt JF, Holm S, Vorstrup S, Lassen NA, Wildschiødtz G. Cerebral oxygen metabolism and cerebral blood flow in man during light sleep (stage 2). Brain Res 1991; 557(1-2): 217-20.
http://dx.doi.org/10.1016/0006-8993(91)90137-K PMID: 1747754
[41] Maquet P, Dive D, Salmon E, *et al.* Cerebral glucose utilization during stage 2 sleep in man. Brain Res 1992; 571(1): 149-53.
http://dx.doi.org/10.1016/0006-8993(92)90522-B PMID: 1611488

[42] Wulff K, Gatti S, Wettstein JG, Foster RG. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. Nat Rev Neurosci 2010; 11(8): 589-99. http://dx.doi.org/10.1038/nrn2868 PMID: 20631712

[43] Wulff K, Porcheret K, Cussans E, Foster RG. Sleep and circadian rhythm disturbances: multiple genes and multiple phenotypes. Curr Opin Genet Dev 2009; 19(3): 237-46. http://dx.doi.org/10.1016/j.gde.2009.03.007 PMID: 19423332

[44] Mesrine S, Gusto G, Clavel-Chapelon F, Boutron-Ruault MC, Fournier A. Use of benzodiazepines and cardiovascular mortality in a cohort of women aged over 50 years. Eur J Clin Pharmacol 2018; 74(11): 1475-84. http://dx.doi.org/10.1007/s00228-018-2515-4 PMID: 29971451

[45] Billioti de Gage S, Pariente A, Bégaud B. Is there really a link between benzodiazepine use and the risk of dementia? Expert Opin Drug Saf 2015; 14(5): 733-47. http://dx.doi.org/10.1517/14740338.2015.1014796 PMID: 25691075

[46] Patorno E, Glynn RJ, Levin R, Lee MP, Huybrechts KF. Benzodiazepines and the risk of all-cause mortality in older patients. Innov Aging 2018; 2(1): 852-3. http://dx.doi.org/10.1093/geroni/igy023.3178

[47] Osler M, Jørgensen MB. Associations of benzodiazepines, z-drugs, and other anxiolytics with subsequent dementia in patients with affective disorders: a nationwide cohort and nested case-control study. Am J Psychiatry 2020; 177(6): 497-505. http://dx.doi.org/10.1176/appi.ajp.2019.19030315 PMID: 32252539

[48] Rasch B, Born J. About sleep's role in memory. Physiol Rev 2013; 93(2): 681-766. http://dx.doi.org/10.1152/physrev.00032.2012 PMID: 23589831

[49] Mander BA, Marks SM, Vogel JW, *et al.* β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. Nat Neurosci 2015; 18(7): 1051-7. http://dx.doi.org/10.1038/nn.4035 PMID: 26030850

[50] Aly M, Moscovitch M. The effects of sleep on episodic memory in older and younger adults. Memory 2010; 18(3): 327-34. http://dx.doi.org/10.1080/09658211003601548 PMID: 20182945

[51] Scullin MK. Sleep, memory, and aging: the link between slow-wave sleep and episodic memory changes from younger to older adults. Psychol Aging 2013; 28(1): 105-14. http://dx.doi.org/10.1037/a0028830 PMID: 22708533

[52] Schneider-Helmert D. Why low-dose benzodiazepine-dependent insomniacs can't escape their sleeping pills. Acta Psychiatr Scand 1988; 78(6): 706-11. http://dx.doi.org/10.1111/j.1600-0447.1988.tb06408.x PMID: 2906215

[53] Horne JA. Human REM sleep: Influence on feeding behaviour, with clinical implications. Sleep Med 2015; 16(8): 910-6. http://dx.doi.org/10.1016/j.sleep.2015.04.002 PMID: 26122167

[54] Shechter A, O'Keeffe M, Roberts AL, Zammit GK, RoyChoudhury A. St-Onge MP. Alterations in sleep architecture in response to experimental sleep curtailment are associated with signs of positive energy balance. Am J Physiol - Reg Integ Comp Physiol 2012; 303: R883-9.

[55] Gonnissen HK, Hursel R, Rutters F, Martens EA, Westerterp-Plantenga MS. Effects of sleep fragmentation on appetite and related hormone concentrations over 24 h in healthy men. Br J Nutr 2012; 8: 1-9.

[56] Goldstein AN, Walker MP. The role of sleep in emotional brain function. Annu Rev Clin Psychol 2014; 10: 679-708. http://dx.doi.org/10.1146/annurev-clinpsy-032813-153716 PMID: 24499013

[57] Wiesner CD, Pulst J, Krause F, *et al.* The effect of selective REM-sleep deprivation on the consolidation and affective evaluation of emotional memories. Neurobiol Learn Mem 2015; 122: 131-41. http://dx.doi.org/10.1016/j.nlm.2015.02.008 PMID: 25708092

[58] Gaillard J-M, Auhert C. (1075): Specificity of benzodiazepine action on human sleep confirmed. Another contribution of automatic analysis of polygraph recordings. Biol Psychiatry 10: 185-97.

[59] Jouvet M. Biogenic amines and the states of sleep. Science 1969; 163(3862): 32-41. http://dx.doi.org/10.1126/science.163.3862.32 PMID: 4303225

[60] Chen L, Bell JS, Visvanathan R, *et al.* The association between benzodiazepine use and sleep quality in residential aged care facilities: A cross-sectional study. BMC Geriatr 2016; 16(1): 196. http://dx.doi.org/10.1186/s12877-016-0363-6 PMID: 27888835

[61] Hümpel M, Nieuweboer B, Milius W, Hanke H, Wendt H. Kinetics and biotransformation of lormetazepam. II. Radioimmunologic determinations in plasma and urine of young and elderly subjects: first-pass effect. Clin Pharmacol Ther 1980; 28(5): 673-9. PMID: 6108174

[62] Tanaka E. Clinically significant pharmacokinetic drug interactions with benzodiazepines. J Clin Pharm Ther 1999; 24(5): 347-55. http://dx.doi.org/10.1046/j.1365-2710.1999.00247.x PMID: 10583697

[63] Wlaź P, Roliński Z, Kleinrok Z, Czuczwar SJ. Influence of chronic aminophylline on antielectroshock activity of diazepam and aminophylline-induced convulsions in mice. Pharmacol Biochem Behav 1994; 49(3): 609-13. http://dx.doi.org/10.1016/0091-3057(94)90076-0 PMID: 7862714

[64] Moghadamnia AA, Moudi S, Tamaskani N, Saleki M, Hamidia A, Mouodi M. Effects of alprazolam and clonazepam on blood sugar in patients with panic disorder. Cyprus J Med Sci 2019; 4(3): 195-200. http://dx.doi.org/10.5152/cjms.2019.716

[65] Martins IJ. Nutrition therapy regulates caffeine metabolism with relevance to nafld and induction of type 3 diabetes. J Diabetes Metab Disord 2017; 4: 019.

[66] Martins IJ. Sirtuin 1, a Diagnostic protein marker and its relevance to chronic disease and therapeutic drug interventions. EC Pharmacology and Toxicology 2018; 6(4): 209-15.