



# Impact of Sleep Disorder as a Risk Factor for Dementia in Men and Women

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## Abstract

Sleep is an essential physiological process, especially for proper brain function through the formation of new pathways and processing information and cognition. Therefore, when sleep is insufficient, this can result in pathophysiologic conditions. Sleep deficiency is a risk factor for various conditions, including dementia, diabetes, and obesity. Recent studies have shown that there are differences in the prevalence of sleep disorders between genders. Insomnia, the most common type of sleep disorder, has been reported to have a higher incidence in females than in males. However, sex/gender differences in other sleep disorder subtypes are not thoroughly understood. Currently, increasing evidence suggests that gender issues should be considered important when prescribing medicine. Therefore, an investigation of the gender-dependent differences in sleep disorders is required. In this review, we first describe sex/gender differences not only in the prevalence of sleep disorders by category but in the efficacy of sleep medications. In addition, we summarize sex/gender differences in the impact of sleep disorders on incident dementia. This may help understand gender-dependent pathogenesis of sleep disorders and develop therapeutic strategies in men and women.

**Key Words:** Sleep disorder, Therapeutics, Sex/gender differences, Dementia risk factor

## INTRODUCTION

Sleep is an essential physiological phenomenon characterized by changes in various physiological functions, including brain activity, respiration, and heart rate. Sleep plays a vital role in the functioning of the brain by forming new pathways and processing information. Many studies have shown that enough sleep helps to improve memory and learning, increase attention and creativity, and assist decision making (Krueger *et al.*, 2016).

The amount of sleep a person needs varies, but adults need an average of seven hours and thirty minutes of sleep per day. Older people require more sleep. Sleep consists of two states that are known as rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. REM is good for memory retention. When in REM, the brain takes information from the short-term memory and transfers it to long-term memory. NREM includes all sleep stages other than REM and is also called atmospheric sleep. Unlike REM sleep, there is usually little or no eye movement. NREM sleep can be broken down

into four stages: stage 1, stage 2, stage 3, and stage 4, and growth hormone production and cell recovery begin (Susic, 2007).

When sleep is insufficient, or sleep quality is poor, this can have various adverse effects on the musculoskeletal system, heart, lungs, and even emotions. This can harm a person's health. Sleep disorders have a high prevalence, affecting 25 to 30% of the population. They are known to cause poor quality of life due not only to secondary physical illnesses but also from psychological stress caused by the sleep disorder (Kiley *et al.*, 2019). Indeed, inadequate sleep has been widely acknowledged to be a risk factor for obesity, diabetes, heart disease, and dementia (Xie *et al.*, 2017). Dementia is a condition associated with a significant decrease in cognitive abilities, including memory deficits, sudden mood changes, problems with normal communication and reasoning. There is increasing research on the close relationship between sleep disorders and cognitive decline, but further investigation is needed (Guarnieri, 2019).

Scientific studies have long focused on one gender, with

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the assumption that studies of one gender would lead to similar results. However, lots of conditions display sex/gender differences in terms of their prevalence and pathogenesis. The gender of patients has shown to affect the risk of getting particular conditions as well as the patient's prognosis (Golden and Voskuhl, 2017).

Additionally, sex/gender differences in the pharmacokinetics of medicines can also affect the efficacy and side effects of certain drugs (Tannenbaum *et al.*, 2016). Moreover, for the concept of personalized medicine, the investigation of sex/gender differences is likely to be critical in developing therapeutic strategies for various conditions (Kim *et al.*, 2018). Increasing evidence indicates that gender factors can affect the pathogenesis of conditions, including sleep disorders and dementia. According to recent studies, insomnia, the most common type of sleep disorder, has a higher prevalence in females than in males (Morphy *et al.*, 2007; Aurora *et al.*, 2010). However, sex/gender differences in other sleep disorders are not thoroughly understood. This review includes a description of the sex/gender differences that exist in the prevalence of sleep disorder subtypes and hypnotic therapeutics. This article further reviews sex/gender differences in seven categories of sleep disorders as a potential risk factor for incident dementia. This includes all-cause dementia and subtypes, such as Alzheimer's dementia (AD) and vascular dementia (VD).

## SEX/GENDER DIFFERENCES IN THE PREVALENCE OF SLEEP DISORDER SUBTYPES

The International Classification of Sleep Disorders identifies seven major categories of sleep disorders. These include insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, sleep-related movement disorders, and parasomnias. The sex/gender differences in the prevalence of sleep disorders have been summarized in Table 1.

### Insomnia

Insomnia is defined as difficulty in starting sleep, maintaining sleep, and waking up early in the morning. Before diagnosing insomnia, sleep disorders that significantly disrupt daily functioning are important factors to consider. Primary insomnia is a symptom of sleep deprivation, not due to medical, mental or environmental causes. The main symptom is having trouble sleeping or not recovering from starting or maintaining sleep for more than a month (Hung *et al.*, 2018). Insomnia accounts for between 30 to 35% of all sleep-related conditions. The frequency of severe or chronic insomnia is between 10 to 15% (Buysse, 2013).

Regarding the sex/gender differences in the prevalence of insomnia, many studies have reported that insomnia occurs more frequently in women (Morphy *et al.*, 2007). Insomnia diagnoses are twice in women than in men in the United States of America. Postmenopausal conditions are associated with increased sleep problems, but not with sleep or fatigue (Phillips and Mannino, 2005). Insomnia symptoms on more than two nights a week were reported in 27.6% of the sample (30.5% in women, 24.5% in men,  $p < 0.001$ ). In the case of chronic insomnia, the incidence was 9.3%. This was higher in women (12.9%) than in men (6.2%) (Singareddy *et al.*, 2012).

In contrast, Breslau *et al.* (1996) reported that the sex/gen-

der differences between insomnia and hypersomnia alone were not significant, but that the lifetime prevalence of insomnia and hypersomnia was 1.9 times higher in women than in men. It was also reported that women over 65 had the highest risk of insomnia (risk rate, 1.73; 95% confidence interval (CI)=1.65-1.83), and women were increasingly at high risk for insomnia as they aged compared to men (Aurora *et al.*, 2010). Another multivariate logistic regression analysis shows that depression is the single most powerful factor for women's gender when it comes to insomnia or sleep disorders. Emphasize that this insomnia is a symptom associated with mental and physical health problems that require proper mental and medical treatment (Bixler *et al.*, 2002). Also, the incidence of depression increased by approximately 1.8 times among those with insomnia symptoms. This could be associated with physical disabilities, sex/gender differences, and former passive occupations (Kim *et al.*, 2009).

### Sleep-related breathing disorders (SBD)

SBD is characterized by abnormal breathing during sleep. These disorders are classified as obstructive sleep apnea, central sleep apnea, sleep-related hypoventilation disorders, and sleep-related hypoxia disorders (Sateia, 2014). The prevalence of SBD has not been well studied in women, since age, body mass index, and menopause have a considerable impact on the outcomes.

Obstructive sleep apnea is defined as at least five apnea low respiration indices per hour and is prevalent in 24% of American adult men and 9% of women (Young *et al.*, 1993). The Apnea-Hypopnea Index (AHI) is an index used to indicate the severity of sleep apnea. Shown as the number of apnea and hypopnea events per hour of sleep (Bonakis *et al.*, 2009) sleep apnea (a pause while breathing) should last for at least 10 seconds. Apnea is associated with reduced blood oxygenation. To determine the apnea severity score, the AHI is calculated by dividing the number of apnea events by the total sleep time. Adult AHI values are classified as normal when they are 5 or less, mild sleep apnea between 5 and 15, moderate sleep apnea between 15 and 30, and severe sleep apnea when 30 and above. One study found that for clinically defined sleep apnea, the prevalence in men and women was 3.9% and 1.2%, respectively, showing 3-fold higher prevalence in men. The prevalence of sleep apnea was significantly lower in premenopausal women (0.6%) and postmenopausal women with hormone replacement therapy (0.5%). These data indicate that menopause is a significant risk factor for sleep apnea in women, and that hormone replacement is associated with reduced risk (Bixler *et al.*, 2001). Snoring occurred in 46% of men and 25% of women and tended to increase with age (Duran *et al.*, 2001). Of adults between 30 and 70 years old, about 13% of men and 6% of women have moderate to severe SBD, which an AHI score of 15 or higher. It was also estimated that 14% of men and 5% of women also had AHI 5 or higher with daytime sleepiness (Peppard *et al.*, 2013). The prevalence of SBD in childhood may also vary by gender, and boys have a higher prevalence at 50-100% than girls (Lumeng and Chervin, 2008). Several studies suggest the length of men's airways as one of the causes of the higher prevalence of sleep apnea in males. Men's airways are more extended than women's, regardless of their body height, which suggests that men's airways may have a greater tendency to collapse (Jordan *et al.*, 2014).

**Table 1.** Sex differences in prevalence/incidence in sleep disorder subtypes

Subtypes of sleep disorders	Sex/gender differences in prevalence/incidence	References
Insomnia	<ul style="list-style-type: none"> <li>• Incident insomnia was 1.5-fold higher in females than in males.</li> <li>• Complaints about insomnia were 9.0% for women, compared to 5.9% for men.</li> <li>• Depression increased approximately 1.8 times among insomnia symptoms in women.</li> <li>• Insomnia diagnosis occurred twice as often in women than in men.</li> <li>• The incidence of chronic insomnia was 9.3%, higher in women (12.9%) than in men.</li> <li>• The gender difference between insomnia alone and hypersomnia alone was not significant. In contrast, the lifetime prevalence of insomnia and hypersomnia was 1.9 times higher in women than in men.</li> </ul>	<p>Morphy <i>et al.</i>, 2007                      Bixler <i>et al.</i>, 2002                      Kim <i>et al.</i>, 2009                      Ohayon <i>et al.</i>, 2002                      Singareddy <i>et al.</i>, 2012                      Breslau <i>et al.</i>, 1996</p>
Sleep-related breathing disorders (SRBD)	<ul style="list-style-type: none"> <li>• The prevalence of sleep apnea was 3.9% for men and 1.2% for women.</li> <li>• Men were 2.0 to 3.7 times more likely to have women with sleep disorder breathing.</li> <li>• Addictive snoring occurred in 46% of men and 25% of women and tended to increase with age.</li> <li>• Of adults 30-70 years old, about 13% of men and 6% of women have moderate to severe SDB (AHI≥15).</li> <li>• 14% of men and 5% of women have daytime sleepiness symptoms ≥AHI5.</li> <li>• The prevalence of childhood SDB can vary by gender, and boys are affected at a rate of 50-100% higher than girls.</li> <li>• Regardless of weight, men's airways are longer than women, suggesting an increased tendency for airway collapse.</li> </ul>	<p>Bixler <i>et al.</i>, 2001                      Young <i>et al.</i>, 1993                      Duran <i>et al.</i>, 2001                      Peppard <i>et al.</i>, 2013                      Lumeng and Chervin, 2008                      Jordan <i>et al.</i>, 2014</p>
Central disorders of hypersomnolence (CDH)	<ul style="list-style-type: none"> <li>• More than a tenth of the Australian adult population is EDS, 10.4% for men and 13.6% for women.</li> <li>• In Korean, the prevalence of EDS was 12.2%, 10.7% for men and 13.7% for women.</li> <li>• The prevalence of EDS was higher in women than in men in the 18-29 and 45-60 age groups.</li> <li>• In Saudi Arabia, the prevalence of EDS was 20.5% (female 22.2%, male 19.5%) with no significant difference between men and women. However, stratified statistical analysis showed that groups with shorter sleep times at night (25.3% for women, 19.0% for men) had a higher prevalence of women than men.</li> <li>• The prevalence of EDS is the same for both men and women (22.2% for women and 19.5% for men).</li> <li>• The prevalence of EDS at age 60 and older was higher among men older than women.</li> <li>• The prevalence of EDS was 14.9% for boys and 18.2% for girls.</li> <li>• The French population's ESS scores indicate that a score of 10 or above is reported by 12% for men and 6% for women.</li> </ul>	<p>Fatani <i>et al.</i>, 2015                      Pallesen <i>et al.</i>, 2007                      Joo <i>et al.</i>, 2005                      Hayley <i>et al.</i>, 2014                      Tsuno <i>et al.</i>, 2007                      Hayley <i>et al.</i>, 2014                      Joo <i>et al.</i>, 2009                      Hara <i>et al.</i>, 2004</p>
Circadian rhythm sleep-wake disorders (CRSD)	<ul style="list-style-type: none"> <li>• Gender differences in adults have not been reported, but adolescents are more common in boys (4.5%) than girls of similar age.</li> <li>• The prevalence of ASPD in New Zealanders ranged from 0.25% to 7.13%, it was high among men and increased with age.</li> <li>• Female crane drivers got less sleep and were more prone to sleepiness at work than men.</li> <li>• Female workers may tend to sleep less than men and become sleepy at work.</li> </ul>	<p>Sack <i>et al.</i>, 2007                      Ohayon <i>et al.</i>, 2002                      Dagan, 2002</p>
Parasomnias	<ul style="list-style-type: none"> <li>• The Academic Sleep Center found an RBD prevalence of 2:1 in males (65%) versus females (35%).</li> <li>• In younger groups under 50, men were higher than women (M:F=1.4:1), but less than older groups over 50 (M:F=3:1).</li> <li>• Behavioral symptoms during sleep were similar in male and female patients. However, female patients were diagnosed with symptoms when they were older than men (72.1 vs 66.4 year).</li> </ul>	<p>Howell, 2012                      Ju <i>et al.</i>, 2011                      Bonakis <i>et al.</i>, 2009                      Wing <i>et al.</i>, 2008</p>
Sleep-related movement disorders (SRMD)	<ul style="list-style-type: none"> <li>• RLS prevalence is twice as high in women as in men.</li> <li>• People with RLS are older than those without RLS, are low-income, unemployed, disabled, non-Hispanic Caucasians, have a higher proportion of women than men, and are less likely to be college educated.</li> <li>• Sleep-related motor disorders are reported to have a higher prevalence than women.</li> <li>• Some studies have reported no difference in prevalence between men and women.</li> </ul>	<p>Howell, 2012                      Ohayon <i>et al.</i>, 2012                      Innes <i>et al.</i>, 2013</p>

### Central disorders of hypersomnolence (CDH)

The main symptom of hypersomnolence is characterized by excessive daytime sleepiness (EDS) despite regular day and nighttime sleep timings (Khan and Trotti, 2015). This affects between 4% to 6% of the population (Dauvilliers and Buguet, 2005). Such sleepiness can be caused by medical conditions, sleep disorders, illegal and prescribed substances, work, and family needs (including shift work), and insufficient time asleep (Khan and Trotti, 2015). This review focuses on the main symptoms of hypersomnolence.

More than a tenth of the Australian adult population has EDS, 10.4% for men, and 13.6% for women. The prevalence of EDS increases with age, affecting about one-third of people over 80 years old (Hayley *et al.*, 2014). The prevalence of EDS in Koreans was 12.2%, 10.7% for men, and 13.7% for women. EDS is associated with a variety of factors in Korean adults, and habitual snoring or sleep problems increases the risk of EDS (Joo *et al.*, 2009). EDS was reported by 16.8% of participants in a Brazilian town. The prevalence of EDS was higher in women than men in the 18-29 and 45-60 age groups (Hara *et al.*, 2004). The prevalence of EDS was 14.9% for boys and 18.2% for girls in South Korean high school students. The difference in the amount of time asleep reported between boys and girls (6.3 h versus 6.5 h per day) is statistically significant ( $p < 0.001$ ). However, sleep latency in girls, as with the frequency of nightmares ( $p < 0.001$ ), was longer ( $p < 0.01$ ) (Joo *et al.*, 2005). Sex/gender differences in the prevalence of EDS in Norway were significant only in the oldest group (over 60 years), with greater prevalence among men (Pallesen *et al.*, 2007). In results from France using the Epworth Sleepiness Scale (ESS), EDS was reported in 12% of men and 6% of women (Tsuno *et al.*, 2007). In Saudi Arabia, the prevalence of EDS was 20.5% (female 22.2%, male 19.5%,  $p = 0.136$ ) with no significant difference between men and women. However, a stratified statistical analysis showed that women had a higher prevalence of shorter nighttime sleep than men (25.3% for women, 19.0% for men,  $p = 0.036$ ) (Fatani *et al.*, 2015).

### Circadian rhythm sleep-wake disorders (CRSD)

The circadian rhythm is often called the human internal clock and is about 24 h. The migration phase interacts with homeostatic sleep that drives to create waking hours during the day and lasting sleep at night. When this cycle is broken, sleep for 24 h is fragmented and scattered, which leads to sleep problems (Romeijn *et al.*, 2012). CRSDs include delayed sleep phase disorder (DSPD), advanced sleep phase disorder (ASPD), familial advanced sleep phase syndrome, irregular sleep-wake rhythm disorder, shift work sleep disorder and jet lag disorder (Thorpy, 2012).

The prevalence of DSPD is about 1.1-4.5% in adolescents and 0.48-1.5% in adults. Sex/gender differences in the prevalence of DSPD have not been reported in adults, but it is more common in adolescent boys (4.5%) than girls of a similar age (2.7%) (Singer *et al.*, 2016). The prevalence of ASPD in New Zealand ranged from 0.25% to 7.13%, and the prevalence of DSPD ranged from 1.51 to 8.90%. The prevalence of ASPD was higher among men, increased with age, and decreased with age among those living in more deprived areas. The prevalence of DSPD was higher among people living in more deprived areas and decreased with age (Paine *et al.*, 2014). Studies looking at the prevalence of sex/gender differences relating to work sleep disorder are rare. Oginska *et*

*al.* (1993) used questionnaires and self-reporting to find that female crane drivers got less sleep and were more prone to sleepiness at work than men. Subjects on weekly shifts were younger and had a higher proportion of women than the other two groups. Day shift workers reported more difficulty getting to sleep than fixed weekly workers (Ohayon *et al.*, 2002).

Female workers may tend to sleep less than men and become sleepy at work, but the evidence of this is weak. As a potential risk factor for the development of jet lag disorder, gender has not been thoroughly studied, and no definitive conclusions have been drawn. Many studies have included only male subjects, and only one case analyzes gender as a risk factor. Using multiple regression analysis, males were found to be less fatigued after a long flight of more than 10 h. As such, there is not enough data to conclude gender as a risk factor for jet lag disorder (Sack *et al.*, 2007). CRSD patients were younger than patients with other types of insomnia. However, no difference could be found in its prevalence due to gender (Dagan, 2002).

### Parasomnia

Parasomnia is a sleep disorder associated with abnormal movements, behaviors, emotions, perceptions, and dreams that occur between sleep stages or when waking up. Parasomnia is a combination of dissociated sleep states that are partially awakened during the transition between awakening, NREM sleep, and REM sleep (Fleetham and Fleming, 2014). These include sleepwalking, drooling, night terrors, nightmares, diggers, and REM sleep behavior disorders. Each disease varies in its frequency and can occur every night or only a few times a year (Kazaglis and Bornemann, 2016). REM sleep behavior disorder (RBD) is the clinically most relevant REM parasomnia (Howell, 2012).

A review of 115 patients with polysomnogram-identified RBD at the Academic Sleep Center found a 2:1 ratio of males (65%) to females (35%) (Ju *et al.*, 2011). In younger groups under 50, males were more prevalent than females (M:F=1.4:1) but smaller in numbers than older groups over 50 years old (M:F=3:1) (Bonakis *et al.*, 2009). Behavioral symptoms during sleep were similar in male and female patients. However, female patients were diagnosed with symptoms when they were older than men (72.1 vs. 66.4 years,  $p < 0.05$ ) (Wing *et al.*, 2008).

### Sleep-related movement disorders (SRMD)

Sleep-related movement disorders are abnormal movements that occur during sleep or when falling asleep. Sleep-related movement disorders include Restless Leg Syndrome (RLS; Willis-Ekbom Disease), periodic limb movement disorders, rhythmic movement disorders, sleep-related bruxism, and sleep-related leg cramps (Silber, 2013). In the case of RLS, repeated limb movements occur during sleep, but waking paresthesia is the most common symptom (Sateia, 2014). RLS is a common cause of sleep initiation and maintenance failures, affecting about 8-10% of the population (Howell, 2012).

Many studies have reported a higher prevalence of RLS in women than in men (Lopes Da Silva and Storm Van Leeuwen, 1977; Kushida *et al.*, 2006; Anderson and Shneerson, 2009; Patil *et al.*, 2019). The prevalence of RLS was 3.9% to 14.3% for groups that met the minimum diagnostic criteria of the International RLS Study Group. Sex/gender differ-

ences in the prevalence of RLS are about twice as high in women as men. Also, the age of onset increases in Europe and North America, but not in Asian countries. Symptoms of anxiety and depression are consistently associated with RLS (Ohayon *et al.*, 2012). Among the Appalachian care population, people with RLS are older than those without RLS, have lower-incomes, are more likely to be unemployed, disabled, non-Hispanic Caucasians, women and are less likely to be college-educated (Innes *et al.*, 2013). Sleep-related motor disorders are reported to have a higher prevalence in women, but some studies have reported no difference in the prevalence between genders (Tannenbaum *et al.*, 2016; Golden and Voskuhl, 2017).

**SEX DIFFERENCES IN THE EFFICACY OF THERAPEUTICS FOR SLEEP DISORDER**

Sex/gender-related differences at genetic and molecular levels also affect the differences in the degree of drug response (Wang and Huang, 2007). Although sex disparities in the incidence and mortality of disease have been observed for a variety of conditions, chemotherapy has been conducted independently of sex (Keitt *et al.*, 2004; Becker *et al.*, 2005; Zucker and Beery, 2010). Studies involving several animal

models and clinical trials are almost male oriented. Therefore, our accumulated findings support sex-related reactions to chemotherapy. Sleep disorder drugs that indicate sex/gender differences in efficacy are summarize and listed in Table 2. The AASM guided clinical practice recommends Temazepam, Triazolam, Eszopiclone, Zaleplon, Zolpidem, Ramelteon, Doxepin, and Suvorexant for the treatment of chronic insomnia in adults (Sateia *et al.*, 2017).

**Benzodiazepine (BZD)**

BZD, also known as “benzo,” are a type of psychoactive drug whose core chemical structure is the fusion of benzene rings and diazepine rings. Benzodiazepines enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) on the GABA receptors, resulting in sedation, hypnosis (sleep induction), anxiety relief (antianxiety), anticonvulsants, and muscle relaxation. High doses of many short-acting benzodiazepines can also cause pre and post-mortem memory loss and dissociation. This property makes benzodiazepines useful for treating insomnia, anxiety, agitation, seizures, alcohol withdrawal, muscle spasms, and medication before medical or dental procedures (Chen *et al.*, 2016). Benzodiazepines are classified as having short-term, intermediary, or long-term behaviors. Short- and medium-acting benzodiazepines are preferred for the treatment of insomnia whereas long-lasting

**Table 2.** Sex differences in the efficacy of therapeutics for sleep disorder

Medicine	Drug	Note	References
Benzodiazepine	Triazolam	<ul style="list-style-type: none"> <li>• Triazolam removal rates among young women with insomnia averaged 12% higher than young men.</li> <li>• Triazolam clearance rates were higher among young women than young men among CRSD patients.</li> </ul>	Greenblatt <i>et al.</i> , 2004
Non benzodiazepine	Zolpidem	• Zolpidem half-life in women with insomnia was statistically longer than in men.	Guo <i>et al.</i> , 2014
	Zopiclone	• The residual effect of zopiclone in CRSD patients was not significantly different in men and women.	Leufkens and Vermeeren, 2014
Melatonin receptor agonist	Ramelteon	• The difference between ramelteon PK and PD in insomnia patients was not significant, but the clearance was higher in women than in men (no significant).	Greenblatt <i>et al.</i> , 2007 Zammit <i>et al.</i> , 2007
Dual orexin receptor antagonist	Suvorexant	• Suvorexant's effect on insomnia is similar for women and men.	Herring <i>et al.</i> , 2017 Rhynne and Anderson, 2015
CNS stimulant	Modafinil	• The major pharmacokinetic parameters of modafinil acid were higher in women than in men, regardless of their half-life in the CDH and CRSD patient groups.	Guo <i>et al.</i> , 2010
	Amphetamine	• In reinforcing effects of drugs of low dose d-amphetamine acts as a female reinforcer, while high dose d-amphetamine acts as a male reinforcer.	Vansickel <i>et al.</i> , 2010
CNS depressant	Sodium oxybate	• There are no significant differences in the PK parameters assessed for systemic exposure to oxybate between men and women with CDH, but most adverse events have been reported by women.	Borgen <i>et al.</i> , 2003
Dopamine agonist	Pramipexole	• Pramipexole is effective in reducing SRMD symptoms and the incidence of adverse events was not statistically significant between sexes.	Rezvani <i>et al.</i> , 2013
	L-DOPA	• The bioavailability of levodopa was significantly higher in females than in males in SRMD patients.	Martinelli <i>et al.</i> , 2003

benzodiazepines are recommended to treat anxiety (Saías and Gallarda, 2008).

Triazolam among BZDs displays a gender difference when treating sleep disorders. Triazolam is a triazolobenzodiazepine with hypnotic properties for use in insomnia associated with acute or chronic insomnia, inpatient situational insomnia, and other disease states (Pakes *et al.*, 1981). Sixty healthy men and women between 20 and 75 years old received a single dose of 0.25 mg of triazolam, cytochrome P450 (CYP) 3A substrate BZDs, and a placebo in a double-blind crossover study. Among women, age did not have a significant effect on the area in the triazolam plasma concentration curve (Sack *et al.*, 2007) or clearance.

On the other hand, among men, AUC increases with age, and clearance decreases. However, sex/gender differences in triazolam kinematics were not apparent (Greenblatt *et al.*, 2004). Triazolam removal rates used to treat insomnia in young women averaged 12% higher than in young men. Triazolam removal rates among young women used to treat CRDS were, on average higher than in young men (Greenblatt *et al.*, 2004).

### Non-benzodiazepines (Non-BZD)

Zolpidem, and non-BZD, such as zopiclone and zaleplon, exhibit a hypnotic effect similar to BZDs with good safety profiles. Non-BZDs generally cause less disruption of normal sleep structures than BZDs. In particular, psychomotor and memory disorders can react better to non-BZDs compared to long-lasting BZDs. For the long-term treatment of insomnia, which is not usually recommended, zolpidem and zopiclone are good options because they do not develop resistance quickly and are less likely to be abused (Wagner and Wagner, 2000). Some side effects include anaphylaxis, behavioral changes, withdrawal, and central nervous system (CNS) depression (Bjurstrom and Irwin, 2019; Kim *et al.*, 2019; Sharma *et al.*, 2019). In women with insomnia, zolpidem's half-life was more prolonged than in men at a statistically significant level (Guo *et al.*, 2014). Gender has a significant effect on the cleaning and half-life of zolpidem, and it is necessary to take into account whether sex/gender differences can cause side effects when the same dose is administered to male and female patients.

Zopiclones are cyclopyrrolones that are believed to act on the GABAA receptor complex at sites that are not chemically related to BZDs and are distinct but closely related to the BZD binding site (Wadworth and McTavish, 1993). Unlike zolpidem, the residual effect of zopiclone in CRSD patients was not significantly different among genders (Leufkens and Vermeeren, 2014).

### Dual orexin receptor antagonist

Suvorexant (MK-4305, Merck), an orexin receptor antagonist, was recently approved by the FDA for the treatment of sleep onset and sleep maintenance insomnia (Lee-Iannotti and Parish, 2016). This medication promotes the natural transition from wakefulness to sleep by inhibiting orexin neurons that promote wakefulness. Suvorexant improves sleep initiation and sleep retention and is well tolerated with fewer side effects (Bennett *et al.*, 2014). In patients with insomnia, Suvorexant is comparably effective in women and men (Herring *et al.*, 2017).

### CNS stimulant

CNS stimulants are used for narcolepsy, excessive deficiency disorder, or excessive drowsiness include methylphenadate, atomoxetine, modafinil, armodafinil, and amphetamine. Stimulants that are no longer used for medical conditions include cocaine, ecstasy, and methylenedioxymethamphetamine (MDMA) (George, 2000).

Modafinil is a waking drug that is prescribed to patients with narcolepsy, but it is increasingly being used by healthy individuals, to increase attention spans, and relieve fatigue. The main pharmacokinetic parameters of modafinil acid are higher in women than in men, regardless of their half-life, when compared in patients with CDH and CRSD (Guo *et al.*, 2010). Stimulants such as amphetamines, cocaine, and methylphenidate increase alertness and fight inflammation by increasing levels of endogenous dopamine (Boutrel and Koob, 2004). Their stimulating effect may vary depending on your sexual function. One study found that men are more sensitive to stimulant-enhancing drugs (Chait, 1994). Other studies have shown that women are more sensitive to stimulant-enhancing effects (Gabbay, 2003). In other studies, no gender difference was reported for the enhancing effects of stimulants (Chait, 1993; Evans *et al.*, 1999). Understanding sex/gender differences in the potentiating effects of drugs can help you in drug prevention and treatment efforts by providing the information needed to adjust programs according to gender. In the treatment of CDH, women, and men have different administrations of d-amphetamine. Low dose d-amphetamines act as a potentiator in women, while high dose d-amphetamines act as a potentiator in men. Men also obtained a much larger number of capsules of high-dose d-amphetamine than women (Vansickel *et al.*, 2010).

### CNS depressant

CNS depressants are effective in treating various conditions by slowing brain activity. These drugs affect neurotransmitter GABA, causing side effects such as drowsiness, relaxation, and reduced inhibition (Cordova-Guardia *et al.*, 2019).

Sodium oxybate is a prescription drug used to treat two symptoms of narcolepsy: sudden muscle weakness and EDS (Morgenthaler *et al.*, 2007). Sodium oxybate is a strict risk assessment and mitigation strategy (REMS) program defined by the FDA and was approved for use by the FDA in 2002 to treat narcolepsy symptoms (Mannucci *et al.*, 2018). The United States of America label for sodium oxybate also displays a black box warning as it is a central nervous system inhibitor. When it is used with other CNS inhibitors, such as alcohol, respiratory depression, seizures, lethargy, or even death, can occur.

There was no significant difference ( $p > 0.05$ ) between male and female volunteers for the pharmacokinetic parameters evaluated for systemic exposure to oxybate among CDH patients. However, most side effects have been reported by women (Borgen *et al.*, 2003).

### Melatonin receptor agonist

Melatonin receptor agonists are analogs of melatonin that bind to and activate melatonin receptors. Agents of melatonin receptors have a number of therapeutic uses, including the treatment of sleep disorders and depression (Silvia *et al.*, 2008). Melatonin receptors are G protein-coupled receptors, expressed in various tissues of the body, and there are two sub-

type receptors: melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2) (Pandi-Perumal *et al.*, 2008; Silvia *et al.*, 2008).

Lamelteon is a selective melatonin receptor (MT1 and MT2) agonist approved by the US Food and Drug Administration for the treatment of insomnia, characterized by the difficulty of starting sleep (Erman *et al.*, 2006). Although there is no direct sedative effect, it is the only approved sleep-promoting drug that improves sleep through its effect on sleep control mechanisms within the instrumental nucleus. Ramelteon is not responsible for its abuse, so it is not scheduled as a controlled substance by the US Drug Administration (Neubauer, 2008). The difference between lamelteon pharmacokinetic and pharmacodynamic was not significant in insomnia patients, but the removal rate of lamelteon was higher in women than in men (Greenblatt *et al.*, 2007). This was, however not at a significant level.

### Dopamine agonist

Activation of dopamine agonist receptor is associated with the regulation of several neurobiological processes such as cognition, learning, and memory, motivation, pleasure, and sleep (Moreira *et al.*, 2015; Rangel-Barajas *et al.*, 2015). As dopamine agonists achieve significant improvement, dopamine plays a crucial role in the pathophysiology of RLS. Pramipexole is a virgin compound with selectivity for the D3 dopamine receptor. The drug is very effective in patients with idiopathic and secondary RLS, as well as in patients with treatment resistance, as indicated by double-blind, placebo-controlled studies in adults. For children, the research is much more limited, and RLS is often mistaken for "increasing pain" or attention deficit hyperactivity disorder. Side effects are limited (Benbir and Guilleminault, 2006).

Pramipexole, ropinirole (recommended strength: standard), and dopa decarboxylase inhibitors are recommended for the treatment of patients with RLS. Given the potential for side effects, including heart valve damage, patients with RLS can be treated with cabergoline only if other recommended drugs do not work (Aurora *et al.*, 2012). Pramipexole has shown that women with SRMD having higher rates of severe symptoms. However, the incidence of adverse events was not statistically significant between sexes (Rezvani *et al.*, 2013).

Dopamine agonists and carbidopa/levodopa have become desirable treatments for both RLS and periodic limb movements in sleep. For once-a-day treatment with carbidopa/levodopa, problems associated with increased morning dose recoil of leg movements have been reported to occur in about one-quarter of patients (Allen and Earley, 1996).

In pharmacology, bioavailability is a subcategory of absorption and part of the dosage of unmodified drugs that reaches the systemic circulation, one of the main pharmacokinetic properties of the drug. By definition, the bioavailability is 100% when the drug is administered intravenously. However, if the drug is administered via other routes (for example, orally), bioavailability can generally decrease or vary (due to incomplete absorption and primary metabolism). Bioavailability is one of the essential tools in pharmacokinetics because it must be taken into account when calculating doses for unused routes of administration (Heaney, 2001). Women with PD have greater levodopa bioavailability than men. Sex-related differences in drug disposition may, although statistically significant, be slightly related to drug prescription. Movement disorders were seen in 38 of 33 patients (33%). However, no gender differ-

ence was observed in those with dyskinesia (Martinelli *et al.*, 2003).

## IMPACT OF SLEEP DISORDER AS A RISK FACTOR FOR DEMENTIA IN MEN AND WOMEN

Sleep disturbance has been widely reported to be causatively related to various conditions, including cardiovascular disease, diabetes, and neurological disorders. Although the relationship between sleep disorders and the prevalence of neurogenic diseases has been widely reported, most studies have focused on sleep apnea, and relatively few studies have investigated the relationship between insomnia and neurological disorders (Gu *et al.*, 2010; Crowley, 2011). Besides sleep disturbance, dementia is also one of the most common and significant health problems in older adults. Increasing investigations suggest that sleep disorders can affect the pathogenesis of all-cause dementia or their subtypes, such as AD and VD. As shown in Table 3, we summarize the causative role of seven categories of sleep disorders in the incidence of dementia, including AD and VD, in men and women.

### Insomnia

A recent study from Taiwan's National Health Institute has reported that patients with primary insomnia showed a 2.14-fold (95% confidence interval, 2.01-2.29) increase in dementia risk than those without insomnia. In their study, younger patients under the age of 40 with primary insomnia had a higher incidence of dementia than older patients. Consistently, other recent studies also demonstrated that sleep disturbances could enhance the risk of developing dementia, and insomnia may increase the risk of AD (Shi *et al.*, 2018). Also, another recent study conducted in older adults reported that insomnia was associated with a significantly increased risk of all-cause dementia (de Almondes *et al.*, 2016). Given gender-related differences in the impact of insomnia on the incidence of dementia, a study has reported that male patients with chronic insomnia were associated with an increased risk of cognitive decline independent of depression. After adjustment for possible confounders, nondepressed men with chronic insomnia were 49% more likely to experience cognitive decline than without insomnia. For women, on the other hand, chronic insomnia also tended to be associated with an increased risk of cognitive decline, but only in those who also had high levels of depressive symptoms. In general, for both men and women, those with depressive symptoms showed a higher risk of poor cognitive performance. Subjective reports of insomnia by older persons are correlated with objective sleep disturbances, as documented by polysomnography. However, polysomnographic data indicates that older women may have less objectively disturbed sleep than older men, even though they tend to report more sleep complaints (Bliwise, 1993). One potential explanation for this discrepancy is that men have a higher threshold for reporting sleep complaints, and therefore, those men who report having insomnia could have significantly more disturbed sleep than the women who report insomnia (Cricco *et al.*, 2001). This may explain why the association between chronic insomnia and cognitive decline as observed in men was not in women.

Taken together, these findings elucidate the influence of sleep disturbances on the incidence of dementia both in

**Table 3.** Sleep disturbance as a risk factor for dementia in men and women

Subtype of sleep disorder	Note	References
Insomnia	<ul style="list-style-type: none"> <li>• Patients with primary insomnia had a higher risk of dementia incidence than those without insomnia.</li> <li>• Chronic insomnia increased the risk of incident cognitive decline in older men but not in order women.</li> <li>• Men with sleep disturbances had a higher risk of developing dementia and Alzheimer's disease.</li> </ul>	Cricco <i>et al.</i> , 2001 Shi <i>et al.</i> , 2018 Benedict <i>et al.</i> , 2015
Sleep-related breathing disorders (SRBD)	<ul style="list-style-type: none"> <li>• Incident dementia is greater for patients with SA than those without SA.</li> <li>• Women with SA were more likely to develop dementia than men.</li> <li>• Old (<math>\geq 65</math>) women with SBD had a higher risk of developing cognitive impairment and dementia.</li> <li>• Men with sleep apnea had a higher risk of vascular dementia but not significant.</li> <li>• SA may be a risk factor for subcortical ischemic vascular dementia.</li> </ul>	Chang <i>et al.</i> , 2013 Yaffe <i>et al.</i> , 2011 Elwood <i>et al.</i> , 2011 Culebras and Anwar, 2018
Central disorders of hypersomnolence (CDH)	<ul style="list-style-type: none"> <li>• EDS is a risk factor for dementia in men and women.</li> <li>• REM sleep behavior disorder patients with EDS had an increased risk of developing neurodegenerative diseases particularly PD but not dementia.</li> <li>• Men with daytime sleepiness had a higher risk of vascular dementia.</li> </ul>	Jaussett <i>et al.</i> , 2012 Zhou <i>et al.</i> , 2017 Elwood <i>et al.</i> , 2011
Circadian rhythm sleep-wake disorders (CRSD)	<ul style="list-style-type: none"> <li>• Old (<math>\geq 65</math>) women with decreased circadian rhythm and delayed sleep phases were more likely to develop dementia.</li> <li>• Shorter time in bed (TIB) and later rise time increased the risk of incident dementia in men and women.</li> </ul>	Tranah <i>et al.</i> , 2011 Bokenberger <i>et al.</i> , 2017
Parasomnias	<ul style="list-style-type: none"> <li>• Shorter REM sleep percentage and longer latency to REM sleep were both associated with a higher risk of incident dementia.</li> <li>• PD with REM sleep behavior disorder patients are more likely to be male than female.</li> <li>• The occurrence rate of dementia in the PD group with clinical RBD was significantly higher than that in the PD group with normal REM sleep.</li> </ul>	Pase <i>et al.</i> , 2017 Jacobs <i>et al.</i> , 2016 Romenets <i>et al.</i> , 2012 Nomura <i>et al.</i> , 2013
Sleep-related movement disorders (SRMD)	<ul style="list-style-type: none"> <li>• SRMD patients had a nearly 4 times higher risk of incident all-cause dementia compared with individuals without SRMD.</li> <li>• Female SRMD patients had greater risk to develop all-cause dementia than male.</li> <li>• Restless legs syndrome patients had a higher risk of vascular dementia but not significant.</li> </ul>	Lin <i>et al.</i> , 2015 Elwood <i>et al.</i> , 2011

younger adults and older adults. However, the mechanism underlying the association between primary insomnia and dementia is unclear, and the information about the subtype or level of insomnia necessary to induce dementia is not clear. Therefore, further research in this area is needed to validate these findings.

### Sleep-related breathing disorders (SBD)

SBD, a disorder characterized by recurrent arousals from sleep and intermittent hypoxemia, is common among older adults and affects up to 60% of older adults (Yaffe *et al.*, 2011). A number of adverse health outcomes, including hypertension, cardiovascular disease, and diabetes have been associated with SBD (Young and Peppard, 2000; Ip *et al.*, 2002; Punjabi *et al.*, 2004). Cognitive impairment has also been linked to SBD, but the majority of studies have been cross-sectional or have relied on non-objective measures of SBD, therefore limiting the ability to conclude the directionality of association. The data from the National Health Insurance Research Database, which is managed by the Taiwanese National Health Research Institutes have shown that the hazard ratio (HR) of dementia is 1.44 times greater for patients with SA. It has also been reported that female (HR: 2.38, 95% CI=1.51-3.74;  $p <$

0.001), but not male, SA patients were more likely to develop dementia within a 5-year follow-up period (Chang *et al.*, 2013). When SA patients were divided into 4 groups according to age (40-49, 50-59, 60-69,  $\geq 70$ ), those in the 50-59 group, 60-69 group, and  $\geq 70$  groups displayed a greater risk of developing dementia. This statistical significance persisted in the 50-59 group and  $\geq 70$  groups after adjusting for potential confounders (50-59 group, adjusted HR 3.63, 95% CI=1.67-7.88;  $\geq 70$  groups, adjusted HR 1.53, 95% CI=1.01-2.33). For females with SA, the risk of dementia increased after age 50 (Chang *et al.*, 2013).

One prospective cohort study that used overnight polysomnography confirmed that women aged 65 years or older with SBD had a higher risk of developing cognitive impairment and dementia as compared with women without SBD (Yaffe *et al.*, 2011). Measures of sleep fragmentation (arousal index and wake after sleep onset) or sleep duration (total sleep time) were not associated with a risk of cognitive impairment. The increased risk for cognitive impairment related to SBD opens a new avenue for additional research on the risk of developing dementia and the exploration of preventive strategies that target sleep quality, including SBD.

A study (Chang *et al.*, 2013) focusing on the impact of SA

on the risk of developing the two most common forms of dementia, AD and VD, reported that SA could increase the risk of VD (adjusted HR: 1.93, 95% CI=1.00-3.77;  $p<0.005$ ). A recent study (Culebras and Anwar, 2018) further demonstrated that older women (mean age 82.3 years) with moderate to severe obstructive sleep apnea were more likely to develop mild cognitive impairment or VD (adjusted odds ratio [AOR], 1.85; 95% CI=1.11-3.08). Hypoxia is the main feature of SA affecting cognition, and microinfarcts are the major lesions of VD. Recent observations indicate that the frontal cortex in patients with SA suffering hypoxia may be abnormally thin (Macey *et al.*, 2018). Although the authors suggest direct hypoxic damage of the cortical cells, a thin cortex might be the consequence of transneuronal degeneration as a result of a disconnection at the periventricular white matter level. Therefore, SA may be a risk factor for subcortical ischemic VD, also known as Binswanger disease, a form of VD in the elderly (Roman, 1987). Uncontrolled SA of moderate to severe intensity may accelerate neurological deterioration during acute stroke stages and worsen the prognosis for recovery during rehabilitation. There is also compelling and mounting evidence that SA with chronic intermittent hypoxia underlies VD resulting from subcortical ischemic disease. Proper management of SA may decrease the clinical impact of stroke risk factors, improve the neurological outcomes after stroke, and lessen the progression of subcortical ischemic vascular disease.

### Central disorders of hypersomnolence (CDH)

In addition to insomnia, EDS is one of the most frequently reported sleep disruptions in older adults (Foley *et al.*, 1995). Among several longitudinal studies performed in community-dwelling elderly, EDS has been reported to be associated with an increased risk (30%) in cognitive impairment using the MMSE score, independently of clinical characteristics and the APOE genotype. Consistently, some prospective epidemiologic research have reported a link between EDS and cognitive impairment in the elderly. One longitudinal study performed for older Japanese-American men has also reported an association between EDS and dementia incidence over a 3 year follow-up period (Foley *et al.*, 2001). In addition, EDS has been suggested to be strongly predictive for VD in men, but not as a predictor for non-VD (Elwood *et al.*, 2011). Other studies confirm this finding in both genders, within a larger sample number of older adults and more extended follow-up period (Jausset *et al.*, 2012).

EDS is one of the well-known nonmotor symptoms of Parkinson's disease (PD), affecting up to 50% of patients with PD (Hobson *et al.*, 2002). In 8 years of follow-up longitudinal study, a significant increase has been shown in the prevalence of EDS from 4.1% to 40.8% in the patients with PD, suggesting that EDS increases progressively with PD (Gjerstad *et al.*, 2006; Tholfsen *et al.*, 2015). In addition, an epidemiologic research has indicated that EDS may be associated with a 3-fold increase in the incident PD, suggesting EDS as a pre-clinical marker for PD. Since RBD has been considered as a marker of  $\alpha$ -synucleinopathies (Wing *et al.*, 2015; Iranzo *et al.*, 2016), there has been attention focused on developing new markers for the progress of RBD toward PD, such as loss of olfactory function (Fantini *et al.*, 2006; Mahlke *et al.*, 2015), defected color vision (Postuma *et al.*, 2015a), depression (Wing *et al.*, 2012), and cognitive decline (Molano *et al.*, 2010). Furthermore, a recent study indicated that EDS patient

with RBD would have potential for a rapid conversion to PD (Arnulf *et al.*, 2015). From these results, EDS is suggested to be a possible biomarker for neurodegeneration in RBD. Further studies are need to clarify the neurochemical and neural circuitry underlying EDS in RBD.

### Circadian rhythm sleep-wake disorders (CRSD)

During waking, there has been known to be rhythms in synaptic plasticity (Chaudhury *et al.*, 2005) and behavioral flexibility (Aston-Jones and Cohen, 2005) Aging has been known to be linked with alteration of circadian rhythms, such as decreased amplitude (peak activity), fragmentation of rhythms, altered entrainment (Hofman and Swaab, 2006). The timing of circadian activity is also reported to advance with age, leading to an earlier onset time of sleepiness in the evening, and an earlier waking in the morning (Czeisler *et al.*, 1992). Abnormalities of sleep-wake rhythm in the elderly patient with dementia have been suggested to show a shorter life span (Gehrman *et al.*, 2004) and increased risk for AD (Satlin *et al.*, 1995). So far, little information is available regarding the causes of age-dependent changes in circadian activity in older adults without dementia and the following results on health. It has been reported that older ( $\geq 65$ ) women and men of community-dwelling with disturbed circadian activity show an increased risk for mortality (Paudel *et al.*, 2010; Tranah *et al.*, 2011). In a prospective study examining the relationship of sleep-associated characteristics during late adulthood and subsequent incidence of dementia up to 17 years later, increased incident dementia was shown in the group of short ( $\leq 6$  h) and extended ( $> 9$  h) TIB as well as in the group of later rise time (Bokenberger *et al.*, 2017). However, there has been no clear evidence supporting a link between increased risk of dementia with bedtime, sleep quality, or heavy snoring. The mechanism underlying the increased dementia risk implicated from short TIB might be a decreased interstitial clearance of metabolic waste linked to decreased time of sleep, subsequently leading to elevated level of extraneuronal  $\beta$ -amyloid (Kang *et al.*, 2009; Spira *et al.*, 2013). Later riser, which may indicate delayed circadian activity rhythm has been reported to show an atypical feature in the cognitively impaired elderly (Bokenberger *et al.*, 2017).

From these reports, it is suggested that circadian activity rhythms may be biomarkers for advanced aging and dementia even though further study is need to understand the mechanism for this link.

### Parasomnias

RBD has been reported to be a preclinical symptom of  $\alpha$ -synucleinopathies, such as dementia with Lewy bodies (DLB) and PD (Schenck *et al.*, 1996). RBD has been also implicated as a possible risk factor for aggravation of autonomic function and cognition in PD patients (Postuma *et al.*, 2011). In addition, the occurrence of RBD in PD patients can be higher in patient dementia than those without dementia (Marion *et al.*, 2008). Thus, the existence of clinical RBD could be associated with deteriorated motor and autonomic function, and incidence of dementia in PD patients.

Based on a prospective study of a population-based sample, shorter REM sleep percentage and longer latency to REM sleep were shown to be independently associated with a higher risk of incident dementia (Pase *et al.*, 2017). Greater wake after sleep onset, a measure of difficulty maintaining sleep,

was also associated with an increased risk of dementia, but only in a fully adjusted statistical model. Stages of non-REM sleep were not associated with dementia incidence in our sample. The mechanisms linking REM sleep to incident dementia are yet to be determined. It has been reported that the association between REM sleep percentage and dementia is independent of numerous confounders such as pharmacologic intervention for mood disorders, which adversely interfere with REM sleep (Pase *et al.*, 2017). REM sleep is thought to promote synaptic consolidation and to upregulate the activity of immediate early genes implicated in synaptic plasticity (Diekelmann and Born, 2010). Thus, REM sleep can buffer from synaptic loss and cognitive impairment by supporting the formation of new networks. Though there are biologically plausible mechanisms to explain these results, more studies are needed to explore the mechanisms linking REM sleep to AD pathology and incident dementia.

Individuals suffering from RBD tend to be male with symptoms starting in later middle age. Idiopathic RBD is a robust prodromal marker of synuclein-dependent neurodegenerative disorder, such as DLB and PD. Pathologic studies have demonstrated that patients with RBD have a more diffuse and severe deposition of synuclein (Postuma *et al.*, 2015b). PD patients with RBD is more likely to occur in males than females. From these results, it is implicated that PD patients with clinical RBD symptoms may develop dementia in a shorter period of time than those with normal REM sleep, suggesting the clinical RBD symptoms as a preclinical marker for dementia incidence.

### Sleep-related movement disorders (SRMD)

SRMD is considered to be a class of sleep disorders, which is characterized by simple, stereotyped repetitive movements during sleep. Patients with SRMD are reported to experience fragmented sleep, disturbance of sleep initiation, and excessive daytime sleepiness, resulting in decreased quality of life (Pigeon and Yurcheshen, 2009). Among SRMD, periodic limb movement disorder and restless legs syndrome are the most common sleep complaints, which involve nocturnal involuntary limb movements. The prevalence of periodic limb movement disorder and RLS has been reported to affect 3 to 10% of the general population, increasing with age (Ohayon and Roth, 2002). Both conditions have been reported to be associated with several physical disorders and mental abnormalities. They have been linked to poorer quality of life through fatigue, compromised work performance, and impaired social and family life (Earley and Silber, 2010). It has been suggested that SRMD is a common complication and comorbidity of neurodegenerative disorders such as PD. However, the relationship of SRMD, such as periodic limb movement disorder and RLS with cognitive impairments like dementia, remains unclear. Researches investigating the relationship between sleep disorders and cognitive illness have predominantly focused on sleep behavior disorders and degenerative dementia. A recent longitudinal study using data from the National Health Insurance Research Database showed that individuals with SRMD had 3.952 times (95% CI=1.124-4.767) higher risk of developing all-cause dementia as compared with individuals without SRMD (Lin *et al.*, 2015). These results showed that SRMD patients aged between 45 and 64 years old exhibited the highest risk of developing all-cause dementia (HR: 5.320, 95% CI=1.770-5.991), followed by patients age

>65 (HR: 4.123, 95% CI=2.066-6.972) and <45 (HR: 3.170, 95% CI=1.050-4.128), respectively (Lin *et al.*, 2015). Females with SRMD had a higher risk of developing all-cause dementia (HR: 4.372, 95% CI=1.175-5.624), compared to men (HR: 2.567, 95% CI=1.006-2.977). The impact of SRMD on dementia risk progressively increased by various follow-up time intervals (<1 year, 1-2 years, and >2 years). Furthermore, RLS patients had a higher risk of VD (OR: 2.39, 95% CI=1.10-5.20,  $p=0.029$ ). However, this was not statistically significant.

## IMPACT OF THERAPUTICS FOR SLEEP DISORDERS ON COGNITIVE IMPAIRMENT IN MEN AND WOMEN

Research into the mechanism of BZDs and the risk of dementia is ongoing. Well known mechanisms are the dynamic balance of the cholinergic and glutamate systems in the CNS, and the inhibitory action of GABA signaling through the GABA receptor (Rissman *et al.*, 2007). Increased GABAergic transmission associated with BZD is opposed to the detrimental effects of neurotoxic transmitter glutamate, which may be related to the appearance of dementia (Green *et al.*, 2003). It has been shown that hyperpolarize neuronal cell membranes impair synaptic plasticity, impairing their ability to form new memories (Wan *et al.*, 2004).

Another mechanism is the downregulation of GABA receptors after prolonged BZD exposure, which induces cognitive impairment (Shimohama *et al.*, 1988; Hutchinson *et al.*, 1996; Ihara *et al.*, 2004; Lanctot *et al.*, 2004). Studies on the effects of sex/gender differences are still insufficient. Therefore, a study was conducted on sex/gender differences between the use of BZDs and non-BZDs and the risk of dementia. Firstly, four papers on sex/gender differences in the use of BZDs and the risk of developing dementia did not show significant differences between the use of BZDs and the risk of dementia. We summarize in Table 4 the Impact of BZD and Non-BZD use on the risk of cognitive impairment in men and women.

In a preliminary PAQUID (Personnes Agees Quid) study, 253 cases of dementia were identified after 15 years in 1063 men and women (average 78.2 years) who had no dementia and had not started BZDs until at least the third year of follow-up. That is, new use of BZD is associated with an increased risk of dementia, but no significant association was found between taking BZDs and gender ( $p=0.23$  for interaction) (de Gage *et al.*, 2012).

Islam *et al.* (2016) examined the association between dementia risk and sex/gender differences following using BZDs. As a result, people who used BZDs had a 78% higher risk of dementia than those who did not use BZDs (OR: 1.78, 95% CI=1.33-2.38). Also, women were at higher risk of developing dementia than men, but the results were not significant; female OR: 1.16, 95% CI=1.00-1.36, male: OR 1.00 95% CI=0.96-1.04.

A 10-year follow-up in the VISAT (Vieillessement, Santé, Travail) cohort study found that the long-term consumption of BZDs negatively affected cognitive abilities. Male cognitive abilities were not affected but affected female's long-term memory (Boeuf-Cazou *et al.*, 2011). Paterniti assessed the impact on cognitive function in 1999 by comparing male, female, and non-users of psychotropic drugs (Paterniti *et al.*, 1999). As a result, cognitive decline associated with psychoactive

**Table 4.** Impact of BZD & Non-BZD use on the risk of cognitive impairment in men and women

Medicine	Risk of cognitive impairment		Note	References
	Men	Women		
BZD	+	+	• No significant effect modification of the association between starting BZD and incident dementia by sex was found (P for interaction=0.23).	de Gage <i>et al.</i> , 2012
	+	+	• BZD use and risk of developing dementia tended to be higher in women and in men, but there was no statistical significance. • There was no significant gender-specific BZD use and risk of developing dementia.	Islam <i>et al.</i> , 2016
	N.S.	+	• The analysis revealed a significant alteration of long-term memory in women whereas there was no significant association in men.	Boeuf-Cazou <i>et al.</i> , 2011
	N.S.	+	• Psychotropic drug use was associated with lower cognitive scores in both sexes whereas was no significant association in man.	Paterniti <i>et al.</i> , 1999
Non-BZD	+	++	• Women had a higher risk of developing Alzheimer’s dementia than men.	Lee <i>et al.</i> , 2018
	+	+	• There was no significant difference between dementia risk for zolpidem user and non-user in men and women, and there was no significant difference in the risk of dementia by gender.	Cheng <i>et al.</i> , 2017
	+	+	• Both male patients and female patients with hypnotic usage had higher risks of dementia, but there were no significant differences between them.	Chen <i>et al.</i> , 2012

+, increases dementia risk; ++, increases dementia risk to a great extent; N.S., not significant risk.

drug use was statistically significant for women. In men, anxiety and depressive symptoms had a significant association independent of most cognitive abilities, independent of psychoactive drug use, and in women, the relationship between anxiety or depression and cognitive function disappeared after adjustments to psychotic drug use. In other words, psychoactive drug use resulted in low cognitive scores in both men and women.

From several studies on the use of non-BZD and sex/gender differences in the risk of developing dementia, no significant differences were found between non-BZD use and dementia risk. Zolpidem, a non-BZD hypnotic, is often used for short-term treatment of insomnia (Cheng *et al.*, 2017). The pharmacological mechanism of zolpidem, including anxiolytic, muscle relaxant, sedative, and anticonvulsant effects, has been shown to act through 1, 2, 3, and 5 subunits of GABAA receptors (Sancar *et al.*, 2007; Yayeh *et al.*, 2018). Unlike BZDs, zolpidem has a high binding capacity to the  $\alpha 1$  subunit, which provides more specific soothing properties than BZDs (Sancar *et al.*, 2007). Non-BZDs have fewer side effects similar to BZDs but can increase the risk of cognitive and psychomotor decline, leading to long-term memory loss (Berdyeva *et al.*, 2014). The use of BZDs and zolpidem is associated with memory loss and decreased cognitive function (Pat McAndrews *et al.*, 2003; Tannenbaum *et al.*, 2012). Although zolpidem use has been reported to be associated with an increased risk of dementia (Shih *et al.*, 2015), studies on sex/gender differences and the effects of dementia have not been actively conducted. In a retrospective cohort study on the use of sedative-hypnotics and the risk of AD, AD risk increased when exposed to BZDs or zolpidem’s, particularly when exposed to 360-defined daily dose or longer-acting BZDs (HR: 1.77, 95% CI=1.65-1.89). However, in secondary results, women had a higher risk of developing dementia than men (male HR: 1, female HR: 1.17, 95% CI=1.14-1.19) (Lee

*et al.*, 2018).

Zolpidem exposure, dementia effects, and sex/gender differences were studied in a retrospective cohort study using data from the National Health Insurance Research Database from 2001 to 2011. This study showed that psychoactive drug use was significantly and independently associated with cognitive function in older people. The use of high cumulative doses of zolpidem increased the risk of AD in older adults living in Taiwan, but there were no significant differences between men and women (male HR: 1.32, 95% CI=0.56-3.09, female HR: 1.38, 95% CI=0.80-2.38) (Cheng *et al.*, 2017). To determine the risk of hypnotics and dementia, a population-based reverse transcription cohort study was performed, in patients aged 50 years and older who were first diagnosed with insomnia between 2002 and 2007. After adjusting for high blood pressure, diabetes, hyperlipidemia, and stroke, the risk of dementia was significantly higher in patients with long-term insomnia. As a result, the use of hypnotics with long half-lives and high prescription doses was expected to increase the risk of dementia, but the sex/gender differences regarding dementia risk were not significant (male HR: 2.28, 95% CI=1.68-3.10, female HR: 2.39, 95% CI=1.85-3.09) (Chen *et al.*, 2012).

The drugs used in several studies mainly included BZDs and zolpidem, but there was a limitation in that no evaluation of the sex/gender differences between individual drugs. Six of the seven papers that studied sex/gender differences relating to dementia risk between BZD and non-BZDs had insignificant results. Only one paper showed significant results in the sex/gender differences between hypnotics and the risk of developing dementia. Therefore, future studies on the use of BZD and non-BZDs should take into account individual drug studies on sex/gender differences in the risk of developing dementia. This is due to differences in the cognitive and metabolic capacity of men and women.

## CONCLUSION

As describe in this review, the prevalence/incidence of sleep disorders and the efficacy of therapeutics of sleep disorders are significantly different by sex/gender. Sleep medications may only work for one gender or may have different benefits for men and women. There are very few drugs with a prescription difference between men and women even in the guidelines for drugs prescribed for sleep disorders. Sex plays a crucial role in improving individual pharmacogenomics and in developing personalized therapeutic medicines. Pharmacogenomic differences between the sexes might play a significant role in chemotherapy in the future. Further studies are needed to provide greater insight into sex differences in sleep disorders and their therapeutics.

As further describe in this review, the impact of sleep disorders on incident dementia was likely to be different by sex/gender, even though sex differences are not fully elucidated by each type of diseases. In fact, both male and female patients were included in many studies, however, most studies did not consider sex/gender issue separately. Because life span of women is longer than men in most countries, the impact of the risk factors on dementia may be more meaningful in women. In the context, sleep medications may have different impact in view of efficacy or side effect between men and women. Future studies of new therapeutics for sleep disorders should take into account intentional stratification by sex/gender, and appropriate sample sizes are needed to individually test the efficacy of treatment in men and women. In addition, further research is needed to understand the sex/gender specific effects of sleep disorders as a risk factor for the development of dementia and to investigate the underlying mechanisms of gender/gender differences.

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## REFERENCES

Allen, R. P. and Earley, C. J. (1996) Augmentation of the restless legs syndrome with carbidopa/levodopa. *Sleep* **19**, 205-213.

Anderson, K. N. and Shneerson, J. M. (2009) Drug treatment of REM sleep behavior disorder: the use of drug therapies other than clonazepam. *J. Clin. Sleep Med.* **5**, 235-239.

Arnulf, I., Neutel, D., Herlin, B., Golmard, J. L., Leu-Semenescu, S., Cochen de Cock, V. and Vidailhet, M. (2015) Sleepiness in idiopathic REM sleep behavior disorder and parkinson disease. *Sleep* **38**, 1529-1535.

Aston-Jones, G. and Cohen, J. D. (2005) An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal per-

formance. *Annu. Rev. Neurosci.* **28**, 403-450.

Aurora, R. N., Kristo, D. A., Bista, S. R., Rowley, J. A., Zak, R. S., Casey, K. R., Lamm, C. I., Tracy, S. L., Rosenberg, R. S.; American Academy of Sleep Medicine (2012) The treatment of restless legs syndrome and periodic limb movement disorder in adults--an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. *Sleep* **35**, 1039-1062.

Aurora, R. N., Zak, R. S., Maganti, R. K., Auerbach, S. H., Casey, K. R., Chowdhuri, S., Karippot, A., Ramar, K., Kristo, D. A., Morgenthaler, T. I.; Standards of Practice Committee; American Academy of Sleep Medicine (2010) Best practice guide for the treatment of REM sleep behavior disorder (RBD). *J. Clin. Sleep Med.* **6**, 85-95.

Becker, J. B., Arnold, A. P., Berkley, K. J., Blaustein, J. D., Eckel, L. A., Hampson, E., Herman, J. P., Marts, S., Sadee, W., Steiner, M., Taylor, J. and Young, E. (2005) Strategies and methods for research on sex differences in brain and behavior. *Endocrinology* **146**, 1650-1673.

Benbir, G. and Guilleminault, C. (2006) Pramipexole: new use for an old drug - the potential use of pramipexole in the treatment of restless legs syndrome. *Neuropsychiatr. Dis. Treat.* **2**, 393-405.

Benedict, C., Byberg, L., Cedernaes, J., Hogenkamp, P. S., Giedratitis, V., Kilander, L., Lind, L., Lannfelt, L. and Schiöth, H. B. (2015) Self-reported sleep disturbance is associated with Alzheimer's disease risk in men. *Alzheimers Dement.* **11**, 1090-1097.

Bennett, T., Bray, D. and Neville, M. W. (2014) Suvorexant, a dual orexin receptor antagonist for the management of insomnia. *P T* **39**, 264-266.

Berdyeva, T., Otte, S., Aluisio, L., Ziv, Y., Burns, L. D., Dugovic, C., Yun, S., Ghosh, K. K., Schnitzer, M. J., Lovenberg, T. and Bonaventure, P. (2014) Zolpidem reduces hippocampal neuronal activity in freely behaving mice: a large scale calcium imaging study with miniaturized fluorescence microscope. *PLoS ONE* **9**, e112068.

Bixler, E. O., Vgontzas, A. N., Lin, H. M., Ten Have, T., Rein, J., Vela-Bueno, A. and Kales, A. (2001) Prevalence of sleep-disordered breathing in women: effects of gender. *Am. J. Respir. Crit. Care Med.* **163**, 608-613.

Bixler, E. O., Vgontzas, A. N., Lin, H. M., Vela-Bueno, A. and Kales, A. (2002) Insomnia in central Pennsylvania. *J. Psychosom. Res.* **53**, 589-592.

Bjurstrom, M. F. and Irwin, M. R. (2019) Perioperative pharmacological sleep-promotion and pain control: a systematic review. *Pain Pract.* **19**, 552-569.

Bliwise, D. L. (1993) Sleep in normal aging and dementia. *Sleep* **16**, 40-81.

Boeuf-Cazou, O., Bongue, B., Ansiau, D., Marquié, J. C. and Lapeyre-Mestre, M. (2011) Impact of long-term benzodiazepine use on cognitive functioning in young adults: the VISAT cohort. *Eur. J. Clin. Pharmacol.* **67**, 1045-1052.

Bokenberger, K., Ström, P., Dahl Aslan, A. K., Johansson, A. L., Gatz, M., Pedersen, N. L. and Åkerstedt, T. (2017) Association between sleep characteristics and incident dementia accounting for baseline cognitive status: a prospective population-based study. *J. Gerontol. A Biol. Sci. Med. Sci.* **72**, 134-139.

Bonakis, A., Howard, R. S., Ebrahim, I. O., Merritt, S. and Williams, A. (2009) REM sleep behaviour disorder (RBD) and its associations in young patients. *Sleep Med.* **10**, 641-645.

Borgen, L. A., Okerholm, R., Morrison, D. and Lai, A. (2003) The influence of gender and food on the pharmacokinetics of sodium oxybate oral solution in healthy subjects. *J. Clin. Pharmacol.* **43**, 59-65.

Boutrel, B. and Koob, G. F. (2004) What keeps us awake: the neuropharmacology of stimulants and wakefulness-promoting medications. *Sleep* **27**, 1181-1194.

Breslau, N., Roth, T., Rosenthal, L. and Andreski, P. (1996) Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol. Psychiatry* **39**, 411-418.

Buyse, D. J. (2013) Insomnia. *JAMA* **309**, 706-716.

Chait, L. D. (1993) Factors influencing the reinforcing and subjective effects of d-amphetamine in humans. *Behav. Pharmacol.* **4**, 191-199.

Chait, L. D. (1994) Factors influencing the reinforcing and subjective

- effects of ephedrine in humans. *Psychopharmacology (Berl.)* **113**, 381-387.
- Chang, W. P., Liu, M. E., Chang, W. C., Yang, A. C., Ku, Y. C., Pai, J. T., Huang, H. L. and Tsai, S. J. (2013) Sleep apnea and the risk of dementia: a population-based 5-year follow-up study in Taiwan. *PLoS ONE* **8**, e78655.
- Chaudhury, D., Wang, L. M. and Colwell, C. S. (2005) Circadian regulation of hippocampal long-term potentiation. *J. Biol. Rhythms* **20**, 225-236.
- Chen, L., Bell, J. S., Visvanathan, R., Hilmer, S. N., Emery, T., Robson, L., Hughes, J. M. and Tan, E. C. (2016) The association between benzodiazepine use and sleep quality in residential aged care facilities: a cross-sectional study. *BMC Geriatr.* **16**, 196.
- Chen, P. L., Lee, W. J., Sun, W. Z., Oyang, Y. J. and Fuh, J. L. (2012) Risk of dementia in patients with insomnia and long-term use of hypnotics: a population-based retrospective cohort study. *PLoS ONE* **7**, e49113.
- Cheng, H. T., Lin, F. J., Erickson, S. R., Hong, J. L. and Wu, C. H. (2017) The association between the use of zolpidem and the risk of Alzheimer's disease among older people. *J. Am. Geriatr. Soc.* **65**, 2488-2495.
- Cordova-Guardia, S., Lardelli-Claret, P., Vilar-López, R., López-Espuela, F., Guerrero-López, F. and Fernández-Mondéjar, E. (2019) The effect of central nervous system depressant, stimulant and hallucinogenic drugs on injury severity in patients admitted for trauma. *Gac. Sanit.* **33**, 4-9.
- Cricco, M., Simonsick, E. M. and Foley, D. J. (2001) The impact of insomnia on cognitive functioning in older adults. *J. Am. Geriatr. Soc.* **49**, 1185-1189.
- Crowley, K. (2011) Sleep and sleep disorders in older adults. *Neuropsychol. Rev.* **21**, 41-53.
- Culebras, A. and Anwar, S. (2018) Sleep apnea is a risk factor for stroke and vascular dementia. *Curr. Neurol. Neurosci. Rep.* **18**, 53.
- Czeisler, C. A., Dumont, M., Duffy, J. F., Steinberg, J. D., Richardson, G. S., Brown, E. N., Sánchez, R., Ríos, C. D. and Ronda, J. M. (1992) Association of sleep-wake habits in older people with changes in output of circadian pacemaker. *Lancet* **340**, 933-936.
- Dagan, Y. (2002) Circadian rhythm sleep disorders (CRSD). *Sleep Med. Rev.* **6**, 45-55.
- Dauvilliers, Y. and Buguet, A. (2005) Hypersomnia. *Dialogues Clin. Neurosci.* **7**, 347-356.
- de Almondes, K. M., Costa, M. V., Malloy-Diniz, L. F. and Diniz, B. S. (2016) Insomnia and risk of dementia in older adults: systematic review and meta-analysis. *J. Psychiatr. Res.* **77**, 109-115.
- de Gage, S. B., Bégaud, B., Bazin, F., Verdoux, H., Dartigues, J. F., Pérès, K., Kurth, T. and Pariente, A. (2012) Benzodiazepine use and risk of dementia: prospective population based study. *BMJ* **345**, e6231.
- Diekelmann, S. and Born, J. (2010) The memory function of sleep. *Nat. Rev. Neurosci.* **11**, 114-126.
- Duran, J., Esnaola, S., Rubio, R. and Iztueta, A. (2001) Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am. J. Respir. Crit. Care Med.* **163**, 685-689.
- Earley, C. J. and Silber, M. H. (2010) Restless legs syndrome: understanding its consequences and the need for better treatment. *Sleep Med.* **11**, 807-815.
- Elwood, P. C., Bayer, A. J., Fish, M., Pickering, J., Mitchell, C. and Gallacher, J. E. (2011) Sleep disturbance and daytime sleepiness predict vascular dementia. *J. Epidemiol. Community Health* **65**, 820-824.
- Erman, M., Seiden, D., Zammit, G., Sainati, S. and Zhang, J. (2006) An efficacy, safety, and dose-response study of Ramelteon in patients with chronic primary insomnia. *Sleep Med.* **7**, 17-24.
- Evans, S. M., Haney, M., Fischman, M. W. and Foltin, R. W. (1999) Limited sex differences in response to "binge" smoked cocaine use in humans. *Neuropsychopharmacology* **21**, 445-454.
- Fantini, M. L., Postuma, R. B., Montplaisir, J. and Ferini-Strambi, L. (2006) Olfactory deficit in idiopathic rapid eye movements sleep behavior disorder. *Brain Res. Bull.* **70**, 386-390.
- Fatani, A., Al-Rouqi, K., Al Towairky, J., Ahmed, A. E., Al-Jahdali, S., Ali, Y., Al-Shimemeri, A., Al-Harbi, A., Baharoon, S., Khan, M. and Al-Jahdali, H. (2015) Effect of age and gender in the prevalence of excessive daytime sleepiness among a sample of the Saudi population. *J. Epidemiol. Glob. Health* **5**, S59-S66.
- Fleetham, J. A. and Fleming, J. A. (2014) Parasomnias. *CMAJ* **186**, E273-E280.
- Foley, D., Monjan, A., Masaki, K., Ross, W., Havlik, R., White, L. and Launer, L. (2001) Daytime sleepiness is associated with 3-year incident dementia and cognitive decline in older Japanese-American men. *J. Am. Geriatr. Soc.* **49**, 1628-1632.
- Foley, D. J., Monjan, A. A., Brown, S. L., Simonsick, E. M., Wallace, R. B. and Blazer, D. G. (1995) Sleep complaints among elderly persons: an epidemiologic study of three communities. *Sleep* **18**, 425-432.
- Gabbay, F. H. (2003) Variations in affect following amphetamine and placebo: markers of stimulant drug preference. *Exp. Clin. Psychopharmacol.* **11**, 91-101.
- Gehrman, P., Marler, M., Martin, J. L., Shochat, T., Corey-Bloom, J. and Ancoli-Israel, S. (2004) The timing of activity rhythms in patients with dementia is related to survival. *J. Gerontol. A Biol. Sci. Med. Sci.* **59**, 1050-1055.
- George, A. J. (2000) Central nervous system stimulants. *Baillieres Best Pract. Res. Clin. Endocrinol. Metab.* **14**, 79-88.
- Gjerstad, M. D., Alves, G., Wentzel-Larsen, T., Aarsland, D. and Larsen, J. P. (2006) Excessive daytime sleepiness in Parkinson disease: is it the drugs or the disease? *Neurology* **67**, 853-858.
- Golden, L. C. and Voskuhl, R. (2017) The importance of studying sex differences in disease: the example of multiple sclerosis. *J. Neurosci. Res.* **95**, 633-643.
- Green, R. C., Cupples, L. A., Kurz, A., Auerbach, S., Go, R., Sadvnick, D., Duara, R., Kukull, W. A., Chui, H., Edeki, T., Griffith, P. A., Friedland, R. P., Bachman, D. and Farrer, L. (2003) Depression as a risk factor for Alzheimer disease: the MIRAGE Study. *Arch. Neurol.* **60**, 753-759.
- Greenblatt, D. J., Harmatz, J. S. and Karim, A. (2007) Age and gender effects on the pharmacokinetics and pharmacodynamics of ramelteon, a hypnotic agent acting via melatonin receptors MT1 and MT2. *J. Clin. Pharmacol.* **47**, 485-496.
- Greenblatt, D. J., Harmatz, J. S., von Moltke, L. L., Wright, C. E. and Shader, R. I. (2004) Age and gender effects on the pharmacokinetics and pharmacodynamics of triazolam, a cytochrome P450 3A substrate. *Clin. Pharmacol. Ther.* **76**, 467-479.
- Gu, D., Sautter, J., Pipkin, R. and Zeng, Y. (2010) Sociodemographic and health correlates of sleep quality and duration among very old Chinese. *Sleep* **33**, 601-610.
- Guarnieri, B. (2019) Sleep disorders and cognitive alterations in women. *Maturitas* **126**, 25-27.
- Guo, T., Mao, G., Zhao, L., Xia, D. and Yang, L. (2014) Comparative pharmacokinetics of zolpidem tartrate in five ethnic populations of China. *Acta Pharm. Sin. B* **4**, 146-150.
- Guo, T., Zhao, L. S. and Xia, D. Y. (2010) Pharmacokinetic study of modafinil in relation to gender and ethnicity in healthy young Chinese volunteers. *J. Pharm. Pharm. Sci.* **13**, 443-449.
- Hara, C., Lopes Rocha, F. and Lima-Costa, M. F. (2004) Prevalence of excessive daytime sleepiness and associated factors in a Brazilian community: the Bambui study. *Sleep Med.* **5**, 31-36.
- Hayley, A. C., Williams, L. J., Kennedy, G. A., Berk, M., Brennan, S. L. and Pasco, J. A. (2014) Prevalence of excessive daytime sleepiness in a sample of the Australian adult population. *Sleep Med.* **15**, 348-354.
- Heaney, R. P. (2001) Factors influencing the measurement of bioavailability, taking calcium as a model. *J. Nutr.* **131**, 1344S-1348S.
- Herring, W. J., Connor, K. M., Snyder, E., Snavely, D. B., Zhang, Y., Hutzelmann, J., Matzura-Wolfe, D., Benca, R. M., Krystal, A. D., Walsh, J. K., Lines, C., Roth, T. and Michelson, D. (2017) Clinical profile of suvorexant for the treatment of insomnia over 3 months in women and men: subgroup analysis of pooled phase-3 data. *Psychopharmacology (Berl.)* **234**, 1703-1711.
- Hobson, D. E., Lang, A. E., Martin, W. R., Razmy, A., Rivest, J. and Fleming, J. (2002) Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. *JAMA* **287**, 455-463.
- Hofman, M. A. and Swaab, D. F. (2006) Living by the clock: the circa-

- dian pacemaker in older people. *Ageing Res. Rev.* **5**, 33-51.
- Howell, M. J. (2012) Parasomnias: an updated review. *Neurotherapeutics* **9**, 753-775.
- Hung, C. M., Li, Y. C., Chen, H. J., Lu, K., Liang, C. L., Liliang, P. C., Tsai, Y. D. and Wang, K. W. (2018) Risk of dementia in patients with primary insomnia: a nationwide population-based case-control study. *BMC Psychiatry* **18**, 38.
- Hutchinson, M. A., Smith, P. F. and Darlington, C. L. (1996) The behavioural and neuronal effects of the chronic administration of benzodiazepine anxiolytic and hypnotic drugs. *Prog. Neurobiol.* **49**, 73-97.
- Ihara, M., Tomimoto, H., Ishizu, K., Mukai, T., Yoshida, H., Sawamoto, N., Inoue, M., Doi, T., Hashikawa, K., Konishi, J., Shibasaki, H. and Fukuyama, H. (2004) Decrease in cortical benzodiazepine receptors in symptomatic patients with leukoaraiosis: a positron emission tomography study. *Stroke* **35**, 942-947.
- Innes, K. E., Flack, K. L., Selfe, T. K., Kandati, S. and Agarwal, P. (2013) Restless legs syndrome in an appalachian primary care population: prevalence, demographic and lifestyle correlates, and burden. *J. Clin. Sleep Med.* **9**, 1065-1075.
- Ip, M. S., Lam, B., Ng, M. M., Lam, W. K., Tsang, K. W. and Lam, K. S. (2002) Obstructive sleep apnea is independently associated with insulin resistance. *Am. J. Respir. Crit. Care Med.* **165**, 670-676.
- Iranzo, A., Santamaria, J. and Tolosa, E. (2016) Idiopathic rapid eye movement sleep behaviour disorder: diagnosis, management, and the need for neuroprotective interventions. *Lancet Neurol.* **15**, 405-419.
- Islam, M. M., Iqbal, U., Walther, B., Atique, S., Dubey, N. K., Nguyen, P. A., Poly, T. N., Masud, J. H., Li, Y. J. and Shabbir, S. A. (2016) Benzodiazepine use and risk of dementia in the elderly population: a systematic review and meta-analysis. *Neuroepidemiology* **47**, 181-191.
- Jacobs, M. L., Dauvilliers, Y., St Louis, E. K., McCarter, S. J., Romanets, S. R., Pelletier, A., Cherif, M., Gagnon, J. F. and Postuma, R. B. (2016) Risk factor profile in Parkinson's disease subtype with REM sleep behavior disorder. *J. Parkinsons Dis.* **6**, 231-237.
- Jausse, I., Bouyer, J., Ancelin, M. L., Berr, C., Foubert-Samier, A., Ritchie, K., Ohayon, M. M., Besset, A. and Dauvilliers, Y. (2012) Excessive sleepiness is predictive of cognitive decline in the elderly. *Sleep* **35**, 1201-1207.
- Joo, S., Baik, I., Yi, H., Jung, K., Kim, J. and Shin, C. (2009) Prevalence of excessive daytime sleepiness and associated factors in the adult population of Korea. *Sleep Med.* **10**, 182-188.
- Joo, S., Shin, C., Kim, J., Yi, H., Ahn, Y., Park, M., Kim, J. and Lee, S. (2005) Prevalence and correlates of excessive daytime sleepiness in high school students in Korea. *Psychiatry Clin. Neurosci.* **59**, 433-440.
- Jordan, A. S., McSharry, D. G. and Malhotra, A. (2014) Adult obstructive sleep apnoea. *Lancet* **383**, 736-747.
- Ju, Y. E., Larson-Prior, L. and Duntley, S. (2011) Changing demographics in REM sleep behavior disorder: possible effect of autoimmunity and antidepressants. *Sleep Med.* **12**, 278-283.
- Kang, J. E., Lim, M. M., Bateman, R. J., Lee, J. J., Smyth, L. P., Cirrito, J. R., Fujiki, N., Nishino, S. and Holtzman, D. M. (2009) Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. *Science* **326**, 1005-1007.
- Kazaglis, L. and Bornemann, M. A. C. (2016) Classification of parasomnias. *Curr. Sleep Medicine Rep.* **2**, 45-52.
- Keitt, S. K., Fagan, T. F. and Marts, S. A. (2004) Understanding sex differences in environmental health: a thought leaders' roundtable. *Environ. Health Perspect.* **112**, 604-609.
- Khan, Z. and Trotti, L. M. (2015) Central disorders of hypersomnolence: focus on the narcolepsies and idiopathic hypersomnia. *Chest* **148**, 262-273.
- Kiley, J. P., Twery, M. J. and Gibbons, G. H. (2019) The National Center on Sleep Disorders Research-progress and promise. *Sleep* **42**, zsz105.
- Kim, H. I., Lim, H. and Moon, A. (2018) Sex differences in cancer: epidemiology, genetics and therapy. *Biomol. Ther. (Seoul)* **26**, 335-342.
- Kim, H. M., Gerlach, L. B., Van, T., Yosef, M., Conroy, D. A. and Zivin, K. (2019) Predictors of long-term and high-dose use of zolpidem in Veterans. *J. Clin. Psychiatry* **80**, 18m12149.
- Kim, J. M., Stewart, R., Kim, S. W., Yang, S. J., Shin, I. S. and Yoon, J. S. (2009) Insomnia, depression, and physical disorders in late life: a 2-year longitudinal community study in Koreans. *Sleep* **32**, 1221-1228.
- Krueger, J. M., Frank, M. G., Wisor, J. P. and Roy, S. (2016) Sleep function: toward elucidating an enigma. *Sleep Med. Rev.* **28**, 46-54.
- Kushida, C. A., Littner, M. R., Hirshkowitz, M., Morgenthaler, T. I., Alessi, C. A., Bailey, D., Boehlecke, B., Brown, T. M., Coleman, J., Jr., Friedman, L., Kapen, S., Kapur, V. K., Kramer, M., Lee-Chiong, T., Owens, J., Pancer, J. P., Swick, T. J. and Wise, M. S.; American Academy of Sleep Medicine (2006) Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. *Sleep* **29**, 375-380.
- Lancot, K. L., Herrmann, N., Mazzotta, P., Khan, L. R. and Ingber, N. (2004) GABAergic function in Alzheimer's disease: evidence for dysfunction and potential as a therapeutic target for the treatment of behavioural and psychological symptoms of dementia. *Can. J. Psychiatry* **49**, 439-453.
- Lee-Iannotti, J. K. and Parish, J. M. (2016) Suvorexant: a promising, novel treatment for insomnia. *Neuropsychiatr Dis. Treat.* **12**, 491-495.
- Lee, J., Jung, S. J., Choi, J. W., Shin, A. and Lee, Y. J. (2018) Use of sedative-hypnotics and the risk of Alzheimer's dementia: a retrospective cohort study. *PLoS ONE* **13**, e0204413.
- Leufkens, T. R. and Vermeeren, A. (2014) Zopiclone's residual effects on actual driving performance in a standardized test: a pooled analysis of age and sex effects in 4 placebo-controlled studies. *Clin. Ther.* **36**, 141-150.
- Lin, C. C., Chou, C. H., Fan, Y. M., Yin, J. H., Chung, C. H., Chien, W. C., Sung, Y. F., Tsai, C. K., Lin, G. Y., Lin, Y. K. and Lee, J. T. (2015) Increased risk of dementia among sleep-related movement disorders: a population-based longitudinal study in Taiwan. *Medicine (Baltimore)* **94**, e2331.
- Lopes Da Silva, F. H. and Storm Van Leeuwen, W. (1977) The cortical source of the alpha rhythm. *Neurosci. Lett.* **6**, 237-241.
- Lumeng, J. C. and Chervin, R. D. (2008) Epidemiology of pediatric obstructive sleep apnea. *Proc. Am. Thorac. Soc.* **5**, 242-252.
- Macey, P. M., Haris, N., Kumar, R., Thomas, M. A., Woo, M. A. and Harper, R. M. (2018) Obstructive sleep apnea and cortical thickness in females and males. *PLoS ONE* **13**, e0193854.
- Mahlknecht, P., Iranzo, A., Högl, B., Frauscher, B., Müller, C., Santamaria, J., Tolosa, E., Serradell, M., Mitterling, T., Gschliesser, V., Goebel, G., Brugger, F., Scherfler, C., Poewe, W. and Seppi, K.; Sleep Innsbruck Barcelona Group (2015) Olfactory dysfunction predicts early transition to a Lewy body disease in idiopathic RBD. *Neurology* **84**, 654-658.
- Mannucci, C., Pichini, S., Spagnolo, E. V., Calapai, F., Gangemi, S., Navarra, M. and Calapai, G. (2018) Sodium oxybate therapy for alcohol withdrawal syndrome and keeping of alcohol abstinence. *Curr. Drug Metab.* **19**, 1056-1064.
- Marion, M. H., Qurashi, M., Marshall, G. and Foster, O. (2008) Is REM sleep behaviour disorder (RBD) a risk factor of dementia in idiopathic Parkinson's disease? *J. Neurol.* **255**, 192-196.
- Martinelli, P., Contin, M., Scaglione, C., Riva, R., Albani, F. and Baruzzi, A. (2003) Levodopa pharmacokinetics and dyskinesias: are there sex-related differences? *Neurol. Sci.* **24**, 192-193.
- Molano, J., Boeve, B., Ferman, T., Smith, G., Parisi, J., Dickson, D., Knopman, D., Graff-Radford, N., Geda, Y., Lucas, J., Kantarci, K., Shiung, M., Jack, C., Silber, M., Pankratz, V. S. and Petersen, R. (2010) Mild cognitive impairment associated with limbic and neocortical Lewy body disease: a clinicopathological study. *Brain* **133**, 540-556.
- Moreira, F. A., Jupp, B., Belin, D. and Dalley, J. W. (2015) Endocannabinoids and striatal function: implications for addiction-related behaviours. *Behav. Pharmacol.* **26**, 59-72.
- Morgenthaler, T. I., Kapur, V. K., Brown, T., Swick, T. J., Alessi, C., Aurora, R. N., Boehlecke, B., Chesson, A. L., Jr., Friedman, L., Maganti, R., Owens, J., Pancer, J. and Zak, R.; Standards of Practice Committee of the American Academy of Sleep Medicine (2007) Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep* **30**, 1705-1711.

- Morphy, H., Dunn, K. M., Lewis, M., Boardman, H. F. and Croft, P. R. (2007) Epidemiology of insomnia: a longitudinal study in a UK population. *Sleep* **30**, 274-280.
- Neubauer, D. N. (2008) A review of ramelteon in the treatment of sleep disorders. *Neuropsychiatr. Dis. Treat.* **4**, 69-79.
- Nomura, T., Inoue, Y., Kagimura, T. and Nakashima, K. (2013) Clinical significance of REM sleep behavior disorder in Parkinson's disease. *Sleep Med.* **14**, 131-135.
- Oginska, H., Pokorski, J. and Ogiński, A. (1993) Gender, ageing, and shiftwork intolerance. *Ergonomics* **36**, 161-168.
- Ohayon, M. M., Lemoine, P., Arnaud-Briant, V. and Dreyfus, M. (2002) Prevalence and consequences of sleep disorders in a shift worker population. *J. Psychosom. Res.* **53**, 577-583.
- Ohayon, M. M., O'Hara, R. and Vitiello, M. V. (2012) Epidemiology of restless legs syndrome: a synthesis of the literature. *Sleep Med. Rev.* **16**, 283-295.
- Ohayon, M. M. and Roth, T. (2002) Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. *J. Psychosom. Res.* **53**, 547-554.
- Paine, S. J., Fink, J., Gander, P. H. and Warman, G. R. (2014) Identifying advanced and delayed sleep phase disorders in the general population: a national survey of New Zealand adults. *Chronobiol. Int.* **31**, 627-636.
- Pakes, G. E., Brogden, R. N., Heel, R. C., Speight, T. M. and Avery, G. S. (1981) Triazolam: a review of its pharmacological properties and therapeutic efficacy in patients with insomnia. *Drugs* **22**, 81-110.
- Pallesen, S., Nordhus, I. H., Omvik, S., Sivertsen, B., Tell, G. S. and Bjorvatn, B. (2007) Prevalence and risk factors of subjective sleepiness in the general adult population. *Sleep* **30**, 619-624.
- Pandi-Perumal, S. R., Trakht, I., Srinivasan, V., Spence, D. W., Maestroni, G. J., Zisapel, N. and Cardinali, D. P. (2008) Physiological effects of melatonin: role of melatonin receptors and signal transduction pathways. *Prog. Neurobiol.* **85**, 335-353.
- Pase, M. P., Himali, J. J., Grima, N. A., Beiser, A. S., Satizabal, C. L., Aparicio, H. J., Thomas, R. J., Gottlieb, D. J., Auerbach, S. H. and Seshadri, S. (2017) Sleep architecture and the risk of incident dementia in the community. *Neurology* **89**, 1244-1250.
- Pat McAndrews, M., Weiss, R. T., Sandor, P., Taylor, A., Carlen, P. L. and Shapiro, C. M. (2003) Cognitive effects of long-term benzodiazepine use in older adults. *Hum. Psychopharmacol.* **18**, 51-57.
- Paterniti, S., Dufouil, C., Bissesse, J. C. and Alépovitch, A. (1999) Anxiety, depression, psychotropic drug use and cognitive impairment. *Psychol. Med.* **29**, 421-428.
- Patil, S. P., Ayappa, I. A., Caples, S. M., Kimoff, R. J., Patel, S. R. and Harrod, C. G. (2019) Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine clinical practice guideline. *J. Clin. Sleep Med.* **15**, 335-343.
- Paudel, M. L., Taylor, B. C., Ancoli-Israel, S., Blackwell, T., Stone, K. L., Tranah, G., Redline, S., Cummings, S. R. and Ensrud, K. E.; Osteoporotic Fractures in Men (MrOS) Study (2010) Rest/activity rhythms and mortality rates in older men: MrOS Sleep Study. *Chronobiol. Int.* **27**, 363-377.
- Peppard, P. E., Young, T., Barnett, J. H., Palta, M., Hagen, E. W. and Hla, K. M. (2013) Increased prevalence of sleep-disordered breathing in adults. *Am. J. Epidemiol.* **177**, 1006-1014.
- Phillips, B. and Mannino, D. (2005) Correlates of sleep complaints in adults: the ARIC study. *J. Clin. Sleep Med.* **1**, 277-283.
- Pigeon, W. R. and Yurcheshen, M. (2009) Behavioral sleep medicine interventions for Restless Legs Syndrome and Periodic Limb Movement Disorder. *Sleep Med. Clin.* **4**, 487-494.
- Postuma, R. B., Adler, C. H., Dugger, B. N., Hentz, J. G., Shill, H. A., Driver-Dunckley, E., Sabbagh, M. N., Jacobson, S. A., Belden, C. M., Sue, L. I., Serrano, G. and Beach, T. G. (2015a) REM sleep behavior disorder and neuropathology in Parkinson's disease. *Mov. Disord.* **30**, 1413-1417.
- Postuma, R. B., Gagnon, J. F., Bertrand, J. A., Génier Marchand, D. and Montplaisir, J. Y. (2015b) Parkinson risk in idiopathic REM sleep behavior disorder: preparing for neuroprotective trials. *Neurology* **84**, 1104-1113.
- Postuma, R. B., Montplaisir, J., Lanfranchi, P., Blais, H., Rompré, S., Colombo, R. and Gagnon, J. F. (2011) Cardiac autonomic denervation in Parkinson's disease is linked to REM sleep behavior disorder. *Mov. Disord.* **26**, 1529-1533.
- Punjabi, N. M., Shahar, E., Redline, S., Gottlieb, D. J., Givelber, R. and Resnick, H. E.; Sleep Heart Health Study Investigators (2004) Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. *Am. J. Epidemiol.* **160**, 521-530.
- Rangel-Barajas, C., Coronel, I. and Florán, B. (2015) Dopamine receptors and neurodegeneration. *Aging Dis.* **6**, 349-368.
- Rezvani, M., Zamani, B. and Fereshtehnejad, S. M. (2013) Factors affecting the efficacy of pramipexole in patients with restless legs syndrome. *Acta Med. Iran.* **51**, 377-385.
- Rhyne, D. N. and Anderson, S. L. (2015) Suvorexant in insomnia: efficacy, safety and place in therapy. *Ther. Adv. Drug Saf.* **6**, 189-195.
- Rissman, R. A., De Blas, A. L. and Armstrong, D. M. (2007) GABA(A) receptors in aging and Alzheimer's disease. *J. Neurochem.* **103**, 1285-1292.
- Roman, G. C. (1987) Senile dementia of the Binswanger type. A vascular form of dementia in the elderly. *JAMA* **258**, 1782-1788.
- Romeijn, N., Raymann, R. J., Møst, E., Te Lindert, B., Van Der Meijden, W. P., Fronczek, R., Gomez-Herrero, G. and Van Someren, E. J. (2012) Sleep, vigilance, and thermosensitivity. *Pflugers Arch.* **463**, 169-176.
- Romenets, S. R., Gagnon, J. F., Latreille, V., Panniset, M., Chouinard, S., Montplaisir, J. and Postuma, R. B. (2012) Rapid eye movement sleep behavior disorder and subtypes of Parkinson's disease. *Mov. Disord.* **27**, 996-1003.
- Saïas, T. and Gallarda, T. (2008) Aggressive reactions under benzodiazepines: a review of the literature. *Encephale* **34**, 330-336.
- Sack, R. L., Auckley, D., Auger, R. R., Carskadon, M. A., Wright, K. P., Jr., Vitiello, M. V. and Zhdanova, I. V.; American Academy of Sleep Medicine (2007) Circadian rhythm sleep disorders: part I, basic principles, shift work and jet lag disorders. An American Academy of Sleep Medicine review. *Sleep* **30**, 1460-1483.
- Sancar, F., Ericksen, S. S., Kucken, A. M., Teissère, J. A. and Czajkowski, C. (2007) Structural determinants for high-affinity zolpidem binding to GABA-A receptors. *Mol. Pharmacol.* **71**, 38-46.
- Sateia, M. J. (2014) International classification of sleep disorders-third edition: highlights and modifications. *Chest* **146**, 1387-1394.
- Sateia, M. J., Buysse, D. J., Krystal, A. D., Neubauer, D. N. and 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. *J. Clin. Sleep Med.* **13**, 307-349.
- Satlin, A., Volicer, L., Stopa, E. G. and Harper, D. (1995) Circadian locomotor activity and core-body temperature rhythms in Alzheimer's disease. *Neurobiol. Aging* **16**, 765-771.
- Schenck, C. H., Bundlie, S. R. and Mahowald, M. W. (1996) Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. *Neurology* **46**, 388-393.
- Sharma, M. K., Kainth, S., Kumar, S., Bhardwaj, A., Agarwal, H. K., Maiwall, R., Jamwal, K. D., Shasthry, S. M., Jindal, A., Choudhary, A., Anand, L., Dhamija, R. M., Kumar, G., Sharma, B. C. and Sarin, S. K. (2019) Effects of zolpidem on sleep parameters in patients with cirrhosis and sleep disturbances: a randomized, placebo-controlled trial. *Clin. Mol. Hepatol.* **25**, 199-209.
- Shi, L., Chen, S. J., Ma, M. Y., Bao, Y. P., Han, Y., Wang, Y. M., Shi, J., Vitiello, M. V. and Lu, L. (2018) Sleep disturbances increase the risk of dementia: a systematic review and meta-analysis. *Sleep Med. Rev.* **40**, 4-16.
- Shih, H. I., Lin, C. C., Tu, Y. F., Chang, C. M., Hsu, H. C., Chi, C. H. and Kao, C. H. (2015) An increased risk of reversible dementia may occur after zolpidem derivative use in the elderly population: a population-based case-control study. *Medicine (Baltimore)* **94**, e809.
- Shimohama, S., Taniguchi, T., Fujiwara, M. and Kameyama, M. (1988) Changes in benzodiazepine receptors in Alzheimer-type dementia. *Ann. Neurol.* **23**, 404-406.
- Silber, M. H. (2013) Sleep-related movement disorders. *Continuum (Minneapolis, Minn.)* **19**, 170-184.
- Silvia, R., Mor, M., Bedini, A., Spadoni, G. and Tarzia, G. (2008) Melatonin receptor agonists: SAR and applications to the treatment of

- sleep-wake disorders. *Curr. Top. Med. Chem.* **8**, 954-968.
- Singareddy, R., Vgontzas, A. N., Fernandez-Mendoza, J., Liao, D., Calhoun, S., Shaffer, M. L. and Bixler, E. O. (2012) Risk factors for incident chronic insomnia: a general population prospective study. *Sleep Med.* **13**, 346-353.
- Singer, H. S., Mink, J. W., Gilbert, D. L. and Jankovic, J. (2016) Chapter 19 - Movements that occur in sleep. In *Movement Disorders in Childhood* (2nd ed.) (H. S. Singer, J. W. Mink, D. L. Gilbert and J. Jankovic, Eds.), pp. 427-451. Academic Press, Boston.
- Spira, A. P., Gamaldo, A. A., An, Y., Wu, M. N., Simonsick, E. M., Bilgel, M., Zhou, Y., Wong, D. F., Ferrucci, L. and Resnick, S. M. (2013) Self-reported sleep and beta-amyloid deposition in community-dwelling older adults. *JAMA Neurol.* **70**, 1537-1543.
- Susic, V. (2007) Normal sleep. *Glas - Srpska Akademija Nauka I Umetnosti* **49**, 1-6.
- Tannenbaum, C., Greaves, L. and Graham, I. D. (2016) Why sex and gender matter in implementation research. *BMC Med. Res. Methodol.* **16**, 145.
- Tannenbaum, C., Paquette, A., Hilmer, S., Holroyd-Leduc, J. and Carnahan, R. (2012) A systematic review of amnesic and non-amnesic mild cognitive impairment induced by anticholinergic, antihistamine, GABAergic and opioid drugs. *Drugs Aging* **29**, 639-658.
- Tholfsen, L. K., Larsen, J. P., Schulz, J., Tysnes, O. B. and Gjerstad, M. D. (2015) Development of excessive daytime sleepiness in early Parkinson disease. *Neurology* **85**, 162-168.
- Thorpy, M. J. (2012) Classification of sleep disorders. *Neurotherapeutics* **9**, 687-701.
- Tranah, G. J., Blackwell, T., Stone, K. L., Ancoli-Israel, S., Paudel, M. L., Ensrud, K. E., Cauley, J. A., Redline, S., Hillier, T. A., Cummings, S. R. and Yaffe, K.; SOF Research Group (2011) Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. *Ann. Neurol.* **70**, 722-732.
- Tsuno, N., Jaussent, I., Dauvilliers, Y., Touchon, J., Ritchie, K. and Besset, A. (2007) Determinants of excessive daytime sleepiness in a French community-dwelling elderly population. *J. Sleep Res.* **16**, 364-371.
- Vansickel, A. R., Stoops, W. W. and Rush, C. R. (2010) Human sex differences in d-amphetamine self-administration. *Addiction* **105**, 727-731.
- Wadsworth, A. N. and McTavish, D. (1993) Zopiclone. A review of its pharmacological properties and therapeutic efficacy as an hypnotic. *Drugs Aging* **3**, 441-459.
- Wagner, J. and Wagner, M. L. (2000) Non-benzodiazepines for the treatment of insomnia. *Sleep Med. Rev.* **4**, 551-581.
- Wan, H., Warburton, E. C., Zhu, X. O., Koder, T. J., Park, Y., Aggleton, J. P., Cho, K., Bashir, Z. I. and Brown, M. W. (2004) Benzodiazepine impairment of perirhinal cortical plasticity and recognition memory. *Eur. J. Neurosci.* **20**, 2214-2224.
- Wang, J. and Huang, Y. (2007) Pharmacogenomics of sex difference in chemotherapeutic toxicity. *Curr. Drug Discov. Technol.* **4**, 59-68.
- Wing, Y. K., Lam, S. P., Li, S. X., Yu, M. W., Fong, S. Y., Tsoh, J. M., Ho, C. K. and Lam, V. K. (2008) REM sleep behaviour disorder in Hong Kong Chinese: clinical outcome and gender comparison. *J. Neurol. Neurosurg. Psychiatry* **79**, 1415-1416.
- Wing, Y. K., Lam, S. P., Zhang, J., Leung, E., Ho, C. L., Chen, S., Cheung, M. K., Li, S. X., Chan, J. W., Mok, V., Tsoh, J., Chan, A. and Ho, C. K. (2015) Reduced striatal dopamine transmission in REM sleep behavior disorder comorbid with depression. *Neurology* **84**, 516-522.
- Wing, Y. K., Li, S. X., Mok, V., Lam, S. P., Tsoh, J., Chan, A., Yu, M. W., Lau, C. Y., Zhang, J. and Ho, C. K. (2012) Prospective outcome of rapid eye movement sleep behaviour disorder: psychiatric disorders as a potential early marker of Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* **83**, 470-472.
- Xie, Z., Chen, F., Li, W. A., Geng, X., Li, C., Meng, X., Feng, Y., Liu, W. and Yu, F. (2017) A review of sleep disorders and melatonin. *Neurol. Res.* **39**, 559-565.
- Yaffe, K., Laffan, A. M., Harrison, S. L., Redline, S., Spira, A. P., Ensrud, K. E., Ancoli-Israel, S. and Stone, K. L. (2011) Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA* **306**, 613-619.
- Yayeh, T., Leem, Y. H., Kim, K. M., Jung, J. C., Schwarz, J., Oh, K. W. and Oh, S. (2018) Administration of alphas1-casein hydrolysate increases sleep and modulates GABAA receptor subunit expression. *Biomol. Ther. (Seoul)* **26**, 268-273.
- Young, T., Palta, M., Dempsey, J., Skatrud, J., Weber, S. and Badr, S. (1993) The occurrence of sleep-disordered breathing among middle-aged adults. *N. Engl. J. Med.* **328**, 1230-1235.
- Young, T. and Peppard, P. (2000) Sleep-disordered breathing and cardiovascular disease: epidemiologic evidence for a relationship. *Sleep* **23**, S122-S126.
- Zammit, G., Erman, M., Wang-Weigand, S., Sainati, S., Zhang, J. and Roth, T. (2007) Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. *J. Clin. Sleep Med.* **3**, 495-504.
- Zhou, J., Zhang, J., Lam, S. P., Chan, J. W., Mok, V., Chan, A., Li, S. X., Liu, Y., Tang, X., Yung, W. H. and Wing, Y. K. (2017) Excessive daytime sleepiness predicts neurodegeneration in idiopathic REM sleep behavior disorder. *Sleep* **40**, doi: 10.1093/sleep/zsx041.
- Zucker, I. and Beery, A. K. (2010) Males still dominate animal studies. *Nature* **465**, 690.