

MELATONIN SUPPLEMENTATION IN YOUNG ADULTS:  
ITS PREVALENCE AND EFFECT ON NOCTURNAL SLEEP AND MORNING  
COGNITION

By

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## ABSTRACT

Poor sleep is major health concern facing Americans today, and melatonin supplements are one of the most popular sleep aids in the US. Melatonin is an endogenous hormone produced by the pineal gland in the absence of light that affects circadian rhythmicity. Interestingly, the prevalence of the use of melatonin as a sleep aid and the reasons for its use among young adults are unclear. A question also remains regarding the costs and benefits of the use of melatonin supplements in young adults with healthy sleep. The evidence on whether melatonin affects sleep in young individuals with health sleep is mixed, and some studies have shown that melatonin can impair cognition in individuals with healthy sleep. Therefore, my dissertation includes two studies that aim to better elucidate the prevalence and effects of exogenous melatonin in young adults. Study 1 assessed sleep aid use in undergraduates using an online survey. Participants answered a series of questions about their history using sleep aids, including melatonin, diphenhydramine- and doxylamine-based sleep aids, cannabis, and alcohol. We also measured sleep quality, time of day preferences, insomnia severity, anxiety, and depression to assess individual differences in sleep aid use. Melatonin was the most popular sleep aid- over 57% of participants reporting using melatonin at some point in their life, and the top reasons for use were trouble falling asleep and to prepare for an important commitment the following day. Those who reported using melatonin had worse sleep quality, higher insomnia severity, and higher anxiety and depression, and were more evening-oriented, than those who had never used melatonin. Study 2 used an experimental design to investigate the effect of melatonin on sleep and morning cognition in young adults. Participants completed the Psychomotor Vigilance Task (PVT; a measure of attention), the UNRAVEL task (a measure of placekeeping), and the Paired Associates Learning (PAL) test (a measure of declarative memory) in the evening. Participants

then took a pill, under double-blind conditions, containing melatonin (5mg or 2mg) or placebo, and received an 8-hour sleep opportunity with polysomnography to measure sleep. One hour after waking, participants completed the tasks again. Results showed that melatonin did not affect sleep, but impaired placekeeping and attention in the morning. Thus, the costs of taking melatonin seem to outweigh the benefits for young adults with healthy sleep. These results also suggest that melatonin may not have sleep-promoting effects in young adults, which could be because melatonin does not promote sleep outside of its effect on circadian timing. Taken together, these two studies suggest a potential disconnect between the expected effects of using melatonin as a sleep aid and the observed effects of melatonin on sleep.

This dissertation is dedication to my daughter, Liliana.  
May you always follow your dreams and rise in the face of adversity.

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## LIST OF ABBREVIATIONS

OTC	Over-the-counter
N1	Stage 1 Non-REM sleep
N2	Stage 2 Non-REM sleep
SWS	Stage 3 Non-REM sleep (i.e. 'slow-wave sleep' or N3)
REM	'Rapid eye movement' sleep
PSG	Polysomnography
EEG	Electroencephalography
EOG	Electrooculography
EMG	Electromyography
WASO	Wake after sleep onset
SOL	Sleep onset latency
TST	Total sleep time
SCN	Suprachiasmatic nucleus
CBD	Cannabidiol; the non-psychoactive component in cannabis
THC	Tetrahydrocannabinol; the psychoactive component in cannabis
DSPS	Delayed sleep phase syndrome
PSQI	Pittsburgh Sleep Quality Index; a subjective measure of sleep quality
MEQ	Morningness eveningness questionnaire; a measure of time-of-day preference
SSS	Stanford Sleepiness Scale; a measure of subjective sleepiness
PANAS	Positive and Negative Affect Schedule; a measure of mood
ISI	Insomnia Severity Index; a subjective measure of insomnia severity
BDI	Beck depression inventory; a subjective measure of depressive symptoms

STAI      State Trait Anxiety Scale; a set of subjective measure of current and general feelings of anxiety



## INTRODUCTION

In the United States, approximately 56% of individuals 15 years and older report sleep problems (Leger et al., 2008), and over 35% of adults report sleeping less than the recommended seven hours per night (Center for Disease Control and Prevention, 2014). It is unsurprising that over nine million Americans reported using prescription sleep aids (Center for Disease Control and Prevention, 2013) and that the North America Sleep Aids Market is predicted to reach USD 36.99 billion in worth by the end of 2022 (Market Data Forecaster, 2022). Although prescription sleep medication is an effective option to resolve sleep problems, sleep problems are under-reported and, therefore, undertreated with the help of a medical professional (Estivill, 2002). Over-the-counter (OTC) sleep aids and supplements are an attractive alternative to prescription sleep medications because they are easily accessible. Exogenous melatonin, for example, is sold as a dietary supplement and is one of the most popular sleep aids with over 3.1 million Americans using melatonin (National Institute of Health, 2012) and spending approximately \$408 million dollars on melatonin products (Nutrition Business Journal, 2017). In 2018, adults in the United States reported using twice the amount of sleep aids than 10 years prior, with the use of melatonin supplements increasing five-fold over this period from 0.4% to 2.1% (Li et al, 2022).

Given the popularity of melatonin as a sleep aid, there is a wide range of literature on its efficacy and action in the human body. However, the majority of this research has been conducted on middle-aged and elderly adults, likely because sleep problems are more prevalent later in life (Caskadon et al., 1982; Pandi-Perumal et al., 2002), or in populations with primary or secondary sleep disorders. Primary sleep disorders are sleep disorders that are not associated with another medical condition, psychological disorder or substance abuse (Khoury &

Doghramji, 2015), whereas secondary sleep disorders occur as a symptom of another medical, psychiatric or substance abuse disorder. There is some debate on how melatonin supplementation affects sleep, rather than circadian timing, in humans due to inconsistencies in this literature. This raises the question of whether melatonin supplementation can improve sleep in individuals whose sleep is already healthy, namely young adults.

Research on exogenous melatonin as a sleep aid in young adults is relatively sparse, making it unclear if melatonin can benefit a single night of sleep in individuals with no history of health or sleep problems. Despite ambiguity in the scientific literature, companies that sell melatonin supplements use clever advertising tactics on their packaging (e.g. “Fall asleep faster, stay asleep longer”; “Promotes healthy sleep”; “Improves sleep quality”) to portray melatonin as a magical solution to sleep concerns. This is partly because dietary supplements, such as melatonin, are not FDA-regulated, meaning that the claims made by the manufacturer regarding the contents and effects of the supplement have not been tested or verified by the FDA. Thus, the general public is, in many ways, blind to what melatonin may or may not be doing to their circadian rhythm or sleep. Even for scientists, the details of how melatonin supplements affect sleep, and for whom melatonin supplements are effective, remains elusive. It is also unclear how prevalent melatonin use is among young adults and why young adults choose to use melatonin as a sleep aid. Thus, there is a need for research that both identifies which young adults use melatonin and why they might use melatonin and that provides empirical evidence on whether melatonin should be expected to benefit sleep in young adults.

### The Prevalence of Sleep Aids

Sleep is crucial to achieve optimal physical and mental health and cognitive functioning. Thus, it is not surprising that there is a large market for products that are marketed as being able

to enhance sleep. To date, there have been a handful of studies that assess the prevalence of sleep aid use among Americans, with a focus on prescription sleep aids. For example, one study reported that from 2005 to 2010, 4% of adults older than 20 years old reported using prescription sleep aids, and that the prevalence of sleep aid use increased with age (Chong et al., 2013). Individuals aged 80 and older used sleep aids more frequently (7%), whereas individuals from 20 to 39 years of age used prescription sleep aids the least frequently (1.8%). Given that elderly individuals are more likely to have sleep problems (Caskadon et al., 1982; Pandi-Perumal et al., 2002) and are more likely to take prescription sleep aids, most of the research on over-the-counter sleep aids has focused on elderly individuals (Albert et al., 2017). Research on the specifics of OTC sleep aid use in young adults is sparse.

Even though prescription sleep aid use in young adults is comparatively low to other age groups, young adults may use sleep aids because they do not get enough sleep and make choices that may disrupt their sleep. Over 35% of young adults sleep less than seven hours per night and over 41% report having insomnia (Chen et al., 2013). Relatedly, there are many social and lifestyle factors that can influence sleep and circadian timing in young adults, especially for those in college. College students may be more likely to be exposed to blue light later in the day due to work, class schedules, social activities and social media use (Levenson et al., 2016; Jansen et al. 2020). Young adults also show natural delays in their circadian timing, that are not linked to circadian or sleep disorders, making them more likely to go to bed later in the night and wake up later in the morning (Tonetti et al., 2008; Lange & Randler, 2011). Young adults may also be more likely to use stimulants and substances that disrupt their sleep, such as caffeine, alcohol, nicotine, and other illicit drugs (Schulenberg et al., 2020). Therefore, there are a number of sleep-related factors that may drive young adults to use sleep aids.

Despite the prevalence of factors that can disrupt sleep in young adults, there are also reasons to assume that young adults may not use OTC sleep aids. For example, younger adults should be less likely to experience health-related issues that affect sleep than other age groups (Morphy et al., 2007; Basta et al., 2007; Comijs et al., 2002) and should have a relatively normal endogenous melatonin profile (Zhdanova et al., 1998).

Interestingly, it remains largely unclear how prevalent sleep aid use is in this population, and what types of sleep aids young adults are taking, and why. The current research on the use of sleep aids in college students is sparse and inconsistent ranging from rates of 6.8% (Taylor & Bramoweth., 2010) to 58% (Goodhines et al., 2019a). Another major limitation that likely contributes to this disparity in reported sleep aid use, is that each study focuses on different types of sleep aids. For example, some studies focus primarily on alcohol (Goodhines et al., 2019a) or cannabis (Goodhines et al., 2019b), while other studies look generally at OTC medication, prescription medications, and alcohol and cannabis (Taylor & Bramoweth, 2010; Grigsby et al., 2021). Furthermore, studies that include measures of OTC sleep aid use in young adults often do not classify these sleep aids by their active ingredients and reduce all OTC drugs to one group. There is a wide range of sleep aids, particularly OTC sleep aids, that are available to the public that may serve different purposes and have different effects on sleep based on the active ingredient. Thus, a question remains as to what specific type of sleep aids young adults are using and why young adults take some types of sleep aids over another.

As previously mentioned, one of the most popular OTC sleep aids is melatonin. Melatonin is a hormone produced endogenous by the pineal gland in a number of animal species, including both diurnal and nocturnal animals (Cardinali & Pe'vet, 1998; Reiter, 2003; Claustrat et al., 2005). In all of these species, melatonin synthesis begins in the absence of light and is inhibited

by light. Thus, melatonin synthesis follows a 24-hour cycle and is entrained to the light/dark cycle, reaching its peak concentration between the hours of 02:00 and 04:00 (Arendt & Skene, 2005), giving melatonin its reputation as the “darkness hormone.” Therefore, exogenous melatonin is often marketed as a “natural” sleep aid, which likely contributes to its popularity. Importantly, there is some debate regarding the efficacy of exogenous melatonin as a sleep-promoting agent.

In addition to melatonin, over-the-counter antihistamine-based sleep aids are also widely available in the United States. The active ingredients in these types of sleep aids are diphenhydramine and doxylamine. Diphenhydramine is used in several products, such as ZzzQuil, Benadryl, Advil PM, Tylenol PM, and Aleve PM. Doxylamine is the active ingredient in Unisom SleepTabs and a few other generic brands of sleep aids. Antihistamine-based sleep aids work by binding to acetylcholine receptors in the central and peripheral nervous systems, which causes sedation (Culpepper & Wingertzahn, 2015; Ghossein et al., 2020). There is some evidence that antihistamine-based sleep aids improve sleep when measured by self-report (Rickels et al., 1983; Morin et al., 2005; Glass et al., 2008; Almond et al., 2021); however, there is no evidence to support an objective improvement in sleep using polysomnography (PSG) (Keyatose et al., 2012). Presently, most studies on diphenhydramine and doxylamine focus on use in elderly populations because elderly individuals are particularly at risk for adverse effects such as cognitive impairment, dizziness, and motor impairment (Abraham, Schleiden & Albert, 2017). These studies suggest that as many as 59% of older adults have used antihistamine-based sleep aids at some point (Sproule et al., 1999; Abraham, Schleiden & Albert, 2017), but it is not clear how prevalent the use of these sleep aids is in young adults.

Although there are a number of over-the-counter sleep aids available to individuals in the

United States, some controlled substances are also used as sleep aids, such as alcohol (typically referred to as a “night cap”) and cannabis. Alcohol is a central nervous system depressant and reduces sleep onset latency and increases slow-wave sleep, but also increases disruptions during the second half of sleep and decreases REM sleep (Ebrahim et al., 2013). Research on the use of alcohol in young adults, especially college students, is more prominent than that on other types of sleep aids. These studies suggest that anywhere from 7% (Goodhines et al., 2019a) to 13% (Johnson et al., 1998) of young adults use alcohol specifically as a sleep aid. Cannabis, on the other hand, is a Schedule 1 controlled substance in the United States, but its use is rapidly growing as more states legalize medical and recreational use. There are only three states in the United States that restrict all forms of cannabis (Smolinski et al., 2022). Cannabis contains a number of components, but some of the two most well-known are tetrahydrocannabinol (THC), which is psychoactive and legal to some extent in 37 states (National Conference of State Legislatures, 2022), and cannabidiol (CBD), which is not psychoactive and can also be legally derived from hemp. Although research is sparse, some studies show that cannabis can reduce sleep onset latency (Cousens & DiMacio, 1973; Edwards & Filby, 2021) and wake after sleep onset (Pivik et al., 1972), decrease REM sleep (Feinberg et al., 1975; Feinberg et al., 1976), and increase SWS (Barrat, Beaver & White, 1974; Mondino et al., 2021). However, not all studies have found an effect of cannabis on sleep (Megelin & Ghorayeb, 2017; Collin, 2010; Langford, 2013; Markova, 2019). Importantly, for both alcohol and cannabis, estimates of use among young adults may be under-reported due to issues with the legality. For alcohol, young adults under the age of 21 may be less likely to report use, whereas reports of cannabis use may depend both on the state in which data was collected and participants’ age; in legal states, recreational use is limited to those 21 years and older. Therefore, the prevalence of alcohol and cannabis use,

strictly as a sleep aid, in young adults is not entirely clear.

Given the wide variety of non-prescription sleep aids available to young adults, and the unique lifestyle factors that influence sleep in this population, a question remains as to how the prevalence of sleep aids differs based on the active ingredients. Furthermore, it remains unclear what factors predict sleep aid use and how this varies on the specific sleep aid. Some studies investigating general sleep aid use have indicated those who use sleep aids have greater difficulty falling asleep, more insomnia-related symptoms, and higher daytime sleepiness scores than those who do not use sleep aids (Johnson et al., 1998; Pillitteri et al., 1994). However, there have been some mixed results concerning the relationship between anxiety and depression and sleep aid use, with some studies finding that those who used sleep aids had higher anxiety (Grigsby et al., 2021) and others finding no relationship with anxiety and depression (Goodhines et al., 2019; Sanchez-Ortuno et al., 2009). In the case of melatonin, there is no research that specifically indicates differences between individuals who use melatonin and those who do not. There is no research to date that investigates the specific benefits young adults expect to receive from different sleep aids. These questions are particularly interesting given the rise in popularity of melatonin products, and the ongoing debate on whether or not melatonin directly promotes sleep. Thus, there is a need for more research that provides a more comprehensive look into melatonin use among young adults and the characteristics of individuals who use melatonin.

## Melatonin and Its Effect on Sleep in Humans

### **Basics of Melatonin and Sleep**

Melatonin is naturally occurring exogenous hormone that is produced by the pineal gland in the absence of light. At the onset of dim light and continuing throughout the absence of light, the retina transmits photic information to the suprachiasmatic nucleus (SCN) in the hypothalamus,

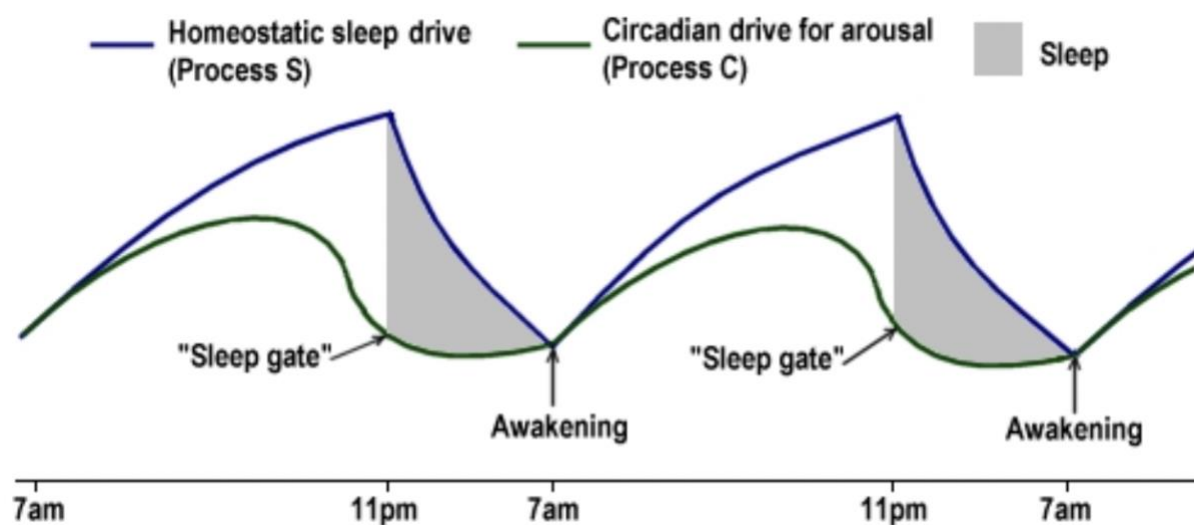
the master circadian clock that regulates the sleep-wake cycle. The SCN then sends signals to the pineal gland to begin melatonin production. Melatonin is then released into cerebrospinal fluid and bloodstream, where it binds to MT1 and MT2 receptors. MT1 receptors are primarily in the SCN and are thought to control the feedback loop. MT2 receptors, on the other hand, are located throughout the central and peripheral nervous systems, including blood vessels, gastrointestinal tract, adipose tissue and skin (Slominski et al., 2012), and help keep a range of biological functions throughout the body entrained to the circadian cycle.

Research on exogenous melatonin became particularly popular in the 1950s when Aaron Lerner, a dermatologist at Yale University, conducted an experiment in which he administered 100 to 200mg of melatonin to participants with the goal of exploring the hormones effect on skin pigmentation (Lerner & Case, 1960). To his surprise, he noted that melatonin had the unintended effect of sedating his participants, meaning that melatonin depressed the central nervous system. This finding led to the hypothesis that melatonin may have specific soporific, or sleep-inducing, effects in humans. Since this discovery, melatonin has been widely studied for its effects on sleep and circadian timing. Despite this abundance of research, experts still debate the efficacy of melatonin as a soporific and the mechanism by which melatonin acts on the human sleep-wake cycle. Based on this research, there seems to be two leading hypotheses to explain the effects of melatonin on sleep in humans. The first is that melatonin acts as a sleep-promoting hormone. The second is that melatonin affects sleep solely through its ability to realign circadian timing.

To best understand these hypotheses, it is important to understand some basics of sleep regulation. There are two processes that are thought to account for sleep regulation, the “two-process model” of sleep regulation: the first is a homeostatic drive for sleep (Process S in Figure 1), and the second is a circadian drive for arousal (Process C in Figure 1) (Borbely, 1982;



Borbely et al., 2016). The homeostatic need for sleep describes the process that occurs when an individual remains awake over time and builds sleep pressure, or the increasing need for sleep to restore the body based on the energy exerted during waking. The circadian drive for arousal, on the other hand, describes a circadian process by which the endogenous circadian rhythm promotes wakefulness. The circadian drive for arousal is thought to be regulated entirely by the SCN, which also regulates melatonin secretion. Although the S and C processes are independent, they work together to coordinate optimal times for sleep and wake. For example, when the circadian drive for arousal is high, the homeostatic sleep drive in a well-rested individual is typically low, although sleep pressure increases throughout the period of wakefulness. As the circadian drive for arousal begins to drop off, typically in the evening, individuals have built up a relatively high need for sleep such that the homeostatic drive for sleep is at or near its peak. When these two processes are at this point- the circadian drive for arousal is low and the homeostatic need for sleep is high- it is said that the “sleep gate” is open and sleep is most likely to occur. After the homeostatic need for sleep has been resolved and returns to baseline, and the circadian drive for arousal begins to climb again, individuals typically wake up from sleep and begin the process again. The two-process model is important to understand when assessing the literature on melatonin and sleep because the two leading hypotheses to explain melatonin’s effect on sleep each target a separate process in this model. Researchers who believe melatonin has a soporific effect seem to suggest that melatonin promotes sleep by affecting homeostatic drive for sleep. On the other hand, researchers who suggest that the effects of melatonin on sleep are primarily based on altering circadian rhythms are suggesting that the effects of melatonin are directly on the circadian drive for arousal. These hypotheses are discussed in further depth in the remainder of this section.



*Figure 1.* A depiction of the two-process model regulating sleep where the blue line corresponds to the homeostatic drive for sleep (Process S) and the green line corresponds to the circadian drive for arousal (Process C). Image taken from: <https://www.mattressadvisor.com/how-two-process/>

### **Melatonin as a Potential Sleep-Promoting Agent**

Early research on melatonin and sleep specifically aimed to investigate melatonin as a sleep-promoting agent, based on Lerner and Case's original finding in 1960. Some of this research suggests that melatonin promotes sleep, even when sleep is not likely to occur (Cramer et al., 1972; Waldhauser et al., 1990). However, these studies include a variety of methodological problems such as small sample sizes and extraordinarily large doses of melatonin (80 – 200mg) that far exceed the concentration of melatonin synthesized endogenously, which is about 0.5mg (Sack, Lewy, Hughes, 1998). Thus, a question remained regarding whether these findings replicated in larger samples and with smaller doses of melatonin.

Interestingly, later studies did not replicate these effects using smaller doses of melatonin (Dijk et al., 1995a; Stone et al., 2000). There is some evidence that lower doses of melatonin can

affect sleep by decreasing sleep-onset latency and increasing sleep duration compared to placebo during daytime sleep opportunities (Dollins et al., 1994; Zhandova et al., 1995; Hughes & Badia, 1997; Vollrath et al., 1981; Tzischinsky & Lavie, 1994; Nave, Peled & Lavie, 1995); however, not all studies have replicated these findings (James et al., 1987). It is possible the soporific effects of melatonin exist but are more prevalent during the day. This could explain why low doses of melatonin affect daytime sleep, whereas only high doses affect nocturnal sleep (Lavie, 1997). During the day, baseline melatonin levels are low, so low doses of exogenous melatonin could significantly increase melatonin circulating in the bloodstream. At night, on the other hand, baseline melatonin levels are higher than during the day, so low doses of exogenous melatonin may not significantly increase melatonin concentrations above baseline, whereas extremely high doses can increase concentrations significantly above baseline.

To explain the potential soporific effects of melatonin on sleep, some researchers have suggested that melatonin affects thermoregulation, such that melatonin decreases core body temperature, which in turn induces sleep to help reduce energy expenditure and maintain homeostasis (Gaskill et al., 2012; Gordon et al., 2014). As such, core body temperature typically starts to drop around 60 minutes before sleep onset (Murphy & Campbell, 1997), with the lowest point occurring around the end of sleep in the early morning (Morf & Schibler, 2013). With regards to sleep, core body temperature is an important factor because sleep typically occurs when core body temperature starts to decline and reaches its lowest point (Glotzback & Heller, 2000; Krauchi et al., 1997). Therefore, changes in core body temperature are correlated with endogenous melatonin profile. When exogenous melatonin is administered, there is some evidence that melatonin leads to decreases in core body temperature (Krauchi et al., 2000; Aizawa, 2002). Although the thermoregulation hypothesis is meant to explain melatonin as a

soporific agent, it is still possible that the effect of melatonin on core body temperature is circadian in nature and dependent on the SCN. The SCN coordinates changes in body temperature throughout the day, following a circadian rhythm. Therefore, exogenous melatonin may simply phase shift circadian rhythms such that drops in body temperature occur earlier than normal, supporting the hypothesis that the effects of melatonin may be circadian and not soporific (Baker et al., 2001; Morf & Schibler, 2013).

Along these same lines, it is possible that the reported effects of melatonin on healthy young adults during daytime sleep opportunities do not directly induce sleep (Dollins et al., 1994; Zhandova et al., 1995; Hughes & Badia, 1997; Vollrath et al., 1981; Tzischinsky & Lavie, 1994; Nave, Peled & Lavie, 1995). Instead, melatonin may lower arousal and the circadian drive for wakefulness. This may explain why melatonin shows a larger effect when the circadian drive for arousal is high (Dijk & Cahochan, 1997). Taken together, this type of evidence would generally suggest a potential soporific effect of melatonin; however, due to the populations and circumstances in which these effects have been documented, the effect of melatonin on sleep may be better explained by alterations to circadian timing.

### **Melatonin as an Agent for Altering Circadian Timing**

The overwhelming majority of studies that have investigated melatonin as a sleep-promoting agent, especially during the day, have found that exogenous melatonin reduces sleep onset latency, while leaving many other measures of sleep unaffected (see Brzezinski et al., 2005 for review). Although this effect could be explained by the hypothesis that melatonin is a sleep-inducing hormone and directly causes sleep, it can also be explained if melatonin does nothing other than affect circadian timing. This is to say that melatonin alters or re-aligns the internal clock and suppresses the circadian drive for arousal. Interestingly, the majority of more recent

findings in the literature on melatonin and sleep provide stronger evidence that melatonin affects circadian timing as opposed to inducing sleep.

Melatonin synthesis occurs in alignment with the sleep/dark cycle, as signals from the retina to the pineal gland through the SCN transmit information about the presence and absence of light in the environment. Importantly, the SCN contains the majority of MT1 receptors, which are the main melatonin receptors in the body and responsible for controlling the circadian drive for arousal (Gobbi & Camai, 2018). Thus, exogenous melatonin should be expected to help resolve issues regarding circadian timing by syncing the brain with desired sleep and wake times.

Some of the most convincing behavioral data to support the argument that melatonin affects sleep by realigning circadian timing comes from studies showing that melatonin helps individuals with primary sleep and circadian disorders, older adults, and individuals experiencing jet lag or who engage in shift work. In individuals with primary sleep disorders, such as insomnia, and circadian-based disorders, such as delayed sleep phase syndrome (DSPS), this is particularly relevant because the primary symptoms are related to difficulties initiating and/or maintaining sleep during the desired time. There have been at least two meta-analyses conducted on the efficacy of exogenous melatonin treatment on resolving primary sleep disorders (sleep disorders that are not associated with another medical condition, concurrent psychological disorder or substance abuse), and both found that melatonin decreased sleep onset latency and increased total sleep time (Buscemi et al., 2005; Ferracioli, Qawasmi & Bloch, 2013). In particular, individuals with insomnia seem to benefit from exogenous melatonin. Insomnia is defined as difficulty initiating or maintaining sleep (Roth & Roehrs, 2003), and affects approximately nine percent of Americans (Chorkroverty, 2010; National Sleep Foundation, 2005). Studies conducted on elderly patients with insomnia show that relatively low doses of

melatonin reduce sleep onset latency and the amount of time spent awake after sleep onset (Haimov et al., 1995; Zisapel, 1999), and increase sleep efficiency (Zhdanova et al., 2001; Lemione & Zisapel, 2012). Thus, melatonin is thought to help restore nocturnal melatonin levels in individuals suffering from insomnia who have deficient endogenous melatonin profiles (Haimov et al., 1995). However, other studies have found that similar doses of melatonin 5mg or less have no effect on insomnia symptoms (James et al., 1990; Ellis, Lemmens & Parkes, 1996; Dawson et al., 1998). One explanation for these mixed effects is that melatonin only affects primary insomnia, which is when insomnia occurs as a primary sleep disorder, as opposed to a secondary sleep disorder (i.e. a sleep disorder that occurs secondarily to another medical, psychiatric or substance abuse disorder). Primary insomnia accounts for only 25% of all patients diagnosed with chronic insomnia (Roth & Roehrs, 2003). This is an important distinction given that melatonin treatment may not be effective for individuals with secondary sleep disorders (Buscemi et al., 2006).

Another possible explanation for these mixed results is that individuals with insomnia who benefit from melatonin actually suffer from a circadian rhythm disorder, such as delayed sleep phase syndrome (DSPS), as opposed to primary insomnia. It is estimated that approximately 10% of patients diagnosed with chronic insomnia actually have DSPS (Ingeborg et al. 2010). DSPS is a circadian rhythm sleep disorder in which an individual's sleep is delayed, such that they fall asleep later in the night and wake later in the morning than the average individual (Micic et al., 2016). Another important characteristic of DSPS is that in addition to sleep being delayed, the circadian rhythm of melatonin synthesis is delayed. In cases of DSPS, exogenous melatonin treatment has been found to advance melatonin onset and sleep onset (Ingeborg et al., 2010; Buscemi et al., 2005; Cummings et al., 2012); thus, effectively re-aligning

circadian timing. Taken together, the available data on the effect of melatonin on individuals with insomnia and DSPS suggest that exogenous melatonin benefits sleep by realigning circadian timing, as opposed to directly inducing sleep.

Evidence of the effectiveness of exogenous melatonin in middle-aged and elderly populations also suggest that melatonin's action in the human body involves circadian realignment, as opposed to having distinct soporific effects. As adults age, individuals experience worse sleep efficiency and have more difficulty maintaining sleep throughout the night (Caskadon et al., 1982; Pandi-Perumal et al., 2002). Elderly individuals, in particular, report difficulty initiating sleep and waking up earlier than desired (Feinsilver, 2003), contributing to this decrease in overall sleep efficiency. One explanation for this increase in sleep problems is that there is a general decline in endogenous melatonin synthesis as adults age (Iguchi et al., 1982; Grad & Rozenzweig, 1993; Mishima et al., 2001). Endogenous melatonin levels gradually start to decline as individuals reach their mid-20s (Karasek, 2004). As such, low doses of melatonin up to 1mg have been shown to increase total sleep time and sleep efficiency in healthy adults as early as in their 40s (Attenburrow, Cowen & Sharpley, 1996). Similar results were found in elderly adults without insomnia with 2mg of melatonin; individuals showed a decrease in sleep onset latency, a decrease in the amount of time spent awake after falling asleep, and increased sleep efficiency (Garfinkel, Laudon & Zisapel, 1995). These improvements have since been replicated in other studies conducted in elderly adults (Fainstein, 1997; Skocbat, Haimov & Lavie, 1998; Valtonen et al., 2005), suggesting that exogenous melatonin may help replace diminished endogenous melatonin profiles and re-align circadian timing to match desired sleep and wake times.

There is also strong evidence that melatonin minimizes symptoms of jet lag (Herxheimer & Petrie, 2002), directly suggesting that exogenous melatonin can benefit sleep by realigning circadian timing. For example, one study evaluated the effect of 5mg of melatonin on jet lag using polysomnography and actigraphy in a double-blind, placebo-controlled study, after travel across seven time zones (Beaumont et al., 2004). Results showed that melatonin helped participants fall asleep faster and maintain sleep better than placebo but did not affect daytime sleepiness. Another study tested the effect of exogenous melatonin administered three days prior to travel, on jet lag symptoms; participants in the melatonin group were able to overcome jet lag and achieve a normal sleep schedule quicker than those in the placebo group (Dawson & Encel, 1993). These results have been replicated in numerous studies, (Arendt et al, 1987, Zisapel, 2001; Zisapel, 2010), suggesting that melatonin has a robust effect on circadian timing after travel across time zones.

A special case of shifts in circadian timing involves night shift workers, who are scheduled to work during the night, and as a result, receive their sleep opportunity during the day. Studies assessing the effect of melatonin on daytime sleep in night shift workers show that, when taken at the desired bedtime, melatonin can improve sleep quality (Folkard, Arendt & Clark, 1993; Jorgensen & Witting, 1998; James et al., 1998). It is important to note, however, that night shift workers self-select their jobs and voluntarily consent to these extreme shifts in circadian rhythm, which introduces selection bias in this research. Therefore, it is possible that melatonin is more effective in these individuals given that their circadian timing may already be altered based on the amount of time they have been working night shifts or individual differences in their preferred time of day and circadian rhythm. As a result, some studies have tested individuals who are not regularly night shift workers and experimentally simulated night shift



work for multiple consecutive nights to better understand the effect of melatonin on dramatic changes to an individual's circadian timing. These studies have also found that melatonin can help improve sleep quality and help individuals adapt to night shift work (James et al., 1998; Sharkey & Eastman, 2000). Taken together, this body of literature suggests that melatonin is an effective treatment for many individuals who need to shift their circadian timing to improve their sleep, including those with disordered sleep, sleep problems associated with old age, jet lag and night shift work.

### **Summary**

To summarize, there are two prominent theories concerning how melatonin affects sleep in humans. The first is that melatonin has soporific or hypnotic effects that directly induce sleep, which may be coordinated by a thermoregulatory response to melatonin. The majority of evidence used to support this hypothesis comes from studies that investigate sleep in healthy young adults and either use extremely high doses of melatonin before nighttime sleep (Cramer et al., 1972, Waldhauser et al., 1990) or low doses of melatonin before daytime sleep (Dollins et al., 1994; Zhandova et al., 1995; Hughes & Badia, 1997; Vollrath et al., 1981; Tzischinsky & Lavie, 1994; Nave, Peled & Lavie, 1995), when sleep propensity is low. These studies show that melatonin can help individuals fall asleep quicker. However, these studies are relatively outdated and pose methodological concerns. Therefore, the evidence supporting the hypothesis that melatonin has direct soporific effects is relatively minimal.

The second theory is that melatonin is regulates circadian rhythmicity via the SCN, which is known to control circadian rhythms in arousal. Thus, one potential explanation for the soporific effects of exogenous melatonin is that it inhibits the natural circadian drive for arousal, which allows any homeostatic drive for sleep to take over, thus promoting sleep. There is also an

abundance of evidence on different populations that make the circadian effect of melatonin on the sleep-wake cycle clearer. Exogenous melatonin can reduce sleep onset latency in individuals with disordered sleep (Ingeborg et al. 2010; Ferracioli, Qawasmi & Bloch, 2013); resolve sleep problems in middle-aged (Attenburrow, Cowen & Sharpley, 1996) and elderly adults (Pandi-Perumal et al., 2005); resolve jet lag (Dawson & Encel, 1993); and help individuals adapt to night shift work (Folkard, Arendt & Clark, 1993; Jorgensen & Witting, 1998; James et al., 1998). Importantly, the underlying issues in these populations can be explained by misalignment of circadian rhythms with desired or optimal sleep and wake times. Thus, the effectiveness of exogenous melatonin in these cases is best explained by the ability of melatonin to re-align circadian timing and adjust one's internal clock.

#### Effects of Melatonin on Cognitive Performance

When determining the benefits in melatonin supplementation, it is important to consider the possibility for adverse effects. In other words, what are the consequences of taking exogenous melatonin, and if there are consequences, do they outweigh the benefits? In general, melatonin has been shown to be safe and has very few adverse effects on general health, especially when compared to other sleep aids and hypnotics. For example, there is no evidence of a “hangover” the morning after taking melatonin, such as grogginess or excessive daytime sleepiness, which are common side effects of other sleep aids and benzodiazepines (Zisapel, 2010). Furthermore, melatonin is not toxic, even in very high doses that are not naturally produced by the body (Lerner & Case, 1960; Malhorta, Saehney & Pandi, 2004). Therefore, there is little worry for overdose. There also does not seem to be any serious side effects associated with long-term melatonin use (Anderson et al., 2016). For individuals who suffer from sleep problems and sleep disorders, melatonin seems to be an ideal alternative to prescription sleep medication that are

more likely to be associated with adverse side effects, such as daytime sleepiness and withdrawal symptoms.

Another benefit of exogenous melatonin as a sleep aid is that it improves sleep quality, especially for those who have experienced severe sleep issues. It has been well-documented that sleep is crucial for optimal cognitive performance, especially attention (Lim & Dinges, 2008), working memory (Frenda & Fenn, 2016), and long-term memory (Deak & Stickgold, 2010; Walker, 2008). As such, sleep problems that result in sleep loss can have detrimental effects on attention, working memory, and long-term memory. Importantly, the benefits of exogenous melatonin on improving sleep quality have also been shown to indirectly benefit cognitive performance (Jean-Louis, Gizycki & Zizi, 1998; Peck et al., 2004; Kwon et al., 2015). However, this benefit is specific to individuals who were not obtaining sufficient nightly sleep before starting melatonin treatment.

Interestingly, there is some evidence that melatonin actually impairs working memory and long-term memory performance, but this is specific to situations in which sleep is already healthy prior to taking melatonin. The bulk of this work has been conducted in non-human animals and shows that melatonin impairs memory (Bauman, 2012; Rawashdeh et al., 2007). For example, hamsters naturally have more long-term potentiation in the daytime, when endogenous melatonin is low, compared to at night when melatonin is high (Raghavan et al., 1999), as do zebrafish (Rawashdeh et al., 2007). These findings could both be explained by the direct effect of melatonin on cognitive performance, but also potentially by other differences between physiology and behavior between the day and night. However, it seems more likely this is due to melatonin as higher concentrations of exogenous melatonin have been shown to inhibit long-term potentiation in mice compared to lower doses (Wang et al., 2005). Similarly, rats showed

impaired spatial memory performance after receiving melatonin compared to placebo (Cao et al., 2009), suggesting cognitive impairments are directly caused by melatonin.

Although sparse, similar results have been found in humans (Dollins et al., 1993; Gorfine & Zisapel, 2007). One study found that the hippocampus is less active at night before bedtime than during the afternoon (Gorfine & Zisapel, 2007), suggesting a correlation between memory structures in the brain and melatonin concentration. This study also found similar results in hippocampal activation when exogenous melatonin was administered to individuals in the evening. Decreases in melatonin in the morning also correlate with increases in prefrontal cortex activation, which is important for attention, working memory and long-term memory (Killgore et al., 2018). Relatedly, blue light exposure, which works against melatonin synthesis, can increase activation in the prefrontal cortex to improve memory processes (Alkozei et al., 2016; Alkozei et al., 2017), which is assumed to be due to the suppression of endogenous melatonin. Even more convincing, high doses of melatonin (10 to 80mg) administered to healthy young adults during the day decreased memory performance and increased reaction time, showing a negative effect of melatonin on memory processes (Dollins et al., 1993). However, it is unclear if the effect of melatonin on memory was direct or mediated by sleepiness, which was also higher after taking melatonin than placebo. Either way, in individuals with otherwise healthy sleep, exogenous melatonin has been shown to impair cognitive performance.

Taken together, there is a body of work suggesting that melatonin has some impact on cognitive performance- although some studies show that melatonin benefits performance while others show the opposite. However, there seems to be a fairly clear delineation between these positive and negative effects on exogenous melatonin; when individuals have sleep problems that result in significant sleep loss, which leads to cognitive impairments, melatonin can help restore

sleep so that cognitive performance after sleep is more similar to that of healthy sleepers. Individuals who are already healthy sleepers, on the other hand, do not need more sleep and do not have impairments in cognitive performance due to sleep loss. In these cases, melatonin actually seems to cause cognitive deficits. As such, individuals with generally healthy sleep have little benefit to gain from taking exogenous melatonin. Therefore, it is important that future research assesses the effect of melatonin on sleep and cognition in individuals with healthy sleep to determine whether the benefits of melatonin supplementation outweigh the consequences.

### Methodological Concerns with the Current Literature

The current literature on the effect of melatonin on sleep generally points toward the hypothesis that melatonin shifts an individual's circadian rhythm to benefit sleep, as opposed to having direct soporific effects. However, there are a number of methodological concerns that plague the current literature and make the true efficacy of melatonin in promoting sleep less clear.

The first set of methodological concerns involves the use of melatonin across studies. Although there have been a large number of studies assessing the effect of melatonin on humans, these studies use a wide range of doses, from 0.1mg to 200mg, whereas only 0.5mg is needed to remain within normal endogenous levels of circulating melatonin. Furthermore, over-the-counter melatonin supplements do not always contain the amount of melatonin that is advertised on the packaging; it has been estimated that approximately 70% of melatonin supplements available in stores contain 10% more or less melatonin than the package indicates (Grigg-Damberger & Ianakieva, 2017; Erland & Saxena, 2017). This is because nutritional supplements are not FDA regulated, a consequence of this is that claims made on the packaging have not been evaluated by the FDA and may not be accurate. Thus, if an average consumer purchases a bottle of 10mg

melatonin, there is a 70% chance that the pills might actually contain anywhere from 9mg to 11mg of melatonin. This also makes the findings in the literature more ambiguous because many studies do not report the type of melatonin that was used in a study and may not have a way to verify that the dose they intended to give participants was in fact the dose ingested. Therefore, there is a need for studies to better report and verify the amount of melatonin that is being administered.

To further complicate the interpretations of these findings, these studies have also administered melatonin for different amounts of time- some studies have administered one dose of melatonin on a single night, while others have administered doses across multiple days, up to two weeks. Therefore, it is generally difficult to gain a strong understanding of the optimal dose of melatonin that should be taken by individuals to benefit sleep, depending on the specific issues they are facing (e.g. insomnia, old age, trouble sleeping during the day, etc.).

Finally, there are differences in the mechanism by which pills released melatonin into the bloodstream (i.e. fast-release versus extended-release). Many studies report using fast-release melatonin supplements, which are readily absorbed by the body and deliver melatonin into the bloodstream quickly after ingestion. However, other studies have used extended-release, or sustained-release, melatonin, which release melatonin slowly over the course of multiple hours and more closely model the way endogenous melatonin is synthesized and released from the pineal gland. The type of melatonin pill has been shown to have differential effects on sleep with fast-release pills being more helpful in reducing sleep onset and initiating sleep at the beginning of a sleep opportunity, and extended-release pills being more helpful in maintain sleep across a sleep opportunity and reducing wake after sleep onset (Haimov et al., 1995; Skocbat, Haimov & Lavie, 1998).

Another issue with the majority of previous studies is that sample sizes are quite low, and likely underpowered. Therefore, it is less clear if the effects of melatonin replicate in larger samples. Although some meta-analyses have been conducted and provide evidence that melatonin generally improves sleep in adults with primary sleep disorders (Brzezinski et al., 2005; Buscemi et al., 2005; Ferracioli, Qawasmi & Bloch, 2013), delayed sleep phase syndrome (van Geijlswijk, Korzilius & Smits, 2010), or experiencing jet lag (Herxheimer & Petrie, 2002), the effect of melatonin in other discrete populations is less clear. The use of small sample sizes (i.e. 40 or less) is especially prevalent in earlier studies that investigated the effect of melatonin on young healthy adults. It remains unclear whether or not exogenous melatonin affects sleep in young adults, or other healthy populations with sufficient endogenous melatonin profiles, especially given that the majority of the positive effects of melatonin are most common in individuals with sleep problems and misalignments in circadian timing. If melatonin does not truly have soporific effects, then findings that claim melatonin helps initiate or improve nocturnal sleep in healthy individuals should be further investigated to ensure these effects are not explained by other factors that were not measured (e.g. individual differences in circadian timing, a recent history of sleep deprivation or restriction, etc.).

In addition to the issues with melatonin administration and small samples sizes, a third issue with the literature on melatonin and sleep involves the variety of methods used to measure sleep. Generally, there are three methods used to measure sleep in sleep research. The first and most subjective involves self-report where participants either complete sleep diaries to answer questions about their sleep on given nights or answer survey questions to rate the quality or quantity of their sleep. Subjective self-report measures such as these are notorious for being inaccurate measures of sleep, as participants are likely to over- or underestimate sleep

(Lauderdale et al., 2008; Girschik et al., 2012), and there are individual differences in these estimations. Despite these weaknesses, these subjective measures are still favorable in many ways because they are easy to create and administer and are cost-effective. However, self-report measures in general are far from ideal because responses do not provide accurate estimates of sleep. Another popular measure of sleep is actigraphy, which involves the use of activity monitors to measure movement and determine when an individual is active (i.e. awake) versus inactive (i.e. asleep). Although this method is more objective and accurate than self-report, the specific sleep measures that can be obtained from actigraphy are limited to sleep onset, total sleep time, wake after sleep onset and wake time; actigraphy cannot determine the stage of sleep an individual is in. Furthermore, actigraphy bases its estimates of sleep on the presence or absence of movement, therefore, actigraphy can still result in inaccurate data. The gold-standard of sleep measurement is polysomnography (PSG), which involves the use of electroencephalography (EEG) to measure brain activity, electromyography (EMG) to measure muscle activity, and electrooculography (EOG) to measure eye movements to objectively measure sleep and acquire information about the stages of sleep an individual is in. Importantly, PSG provides the most accurate and detailed information about sleep possible, and is therefore the best method to measure changes in sleep after melatonin is administered. Although there are studies that have showed improvements in sleep using PSG in sleep onset latency and sleep efficiency (Cramer et al., 1974; Waldhauser et al., 1990; Nave et al., 1995; Zhdanova et al., 1995), inconsistencies in the methods used to measure sleep in the current literature could certainly be part of the reason for the mixed effects of melatonin on sleep (see Table 1 in Zhdanova & Wurtman, 1997). Therefore, there is a need for research that takes these



methodological considerations into account to better understand if melatonin directly affects sleep or just circadian timing.

### Overview

Given this information on the benefits and potential consequences of melatonin supplementation, an important question is: who is purchasing and using melatonin supplements and why? For older adults, individuals with primary sleep or circadian rhythm disorders, or those trying to adjust to a foreign time zone of night shift work, the benefits of melatonin supplementation seem to outweigh the potential consequences. Melatonin improves sleep quality in the overwhelming majority of studies involving these populations and helps restore optimal cognitive performance impaired due to sleep problems. Young adults, on the other hand, should not necessarily expect to benefit from exogenous melatonin based on the available data. Because young adults still have relatively normal endogenous melatonin profiles and, in many cases, do not suffer from sleep problems, the effects of melatonin on nocturnal sleep seem to be minimal at best. The more concerning factor to consider is that when sleep is already healthy, melatonin can impair cognition after an individual's sleep opportunity has ended. If taking exogenous melatonin before nocturnal sleep negatively affects performance the following day, then melatonin supplementation may have more costs than benefits for young adults. Thus, it remains unclear why young adults with healthy sleep would use melatonin supplements in the first place. Given the popularity of melatonin products and the unwarranted claims companies print on packaging for melatonin products regarding the "benefits" of melatonin supplements on sleep, it is likely young adults have false hope in melatonin as a sleep aid in situations that may not warrant its use, such as catching up on sleep after one night of poor sleep or trying to improve sleep before an important event. However, there is not much research on the reason for

melatonin use in young adults with healthy sleep, and if the benefits of melatonin use outweigh the consequences in these cases.

Research is needed to better understand melatonin use in young adults. More specifically, there is a need for better information on the consumers of melatonin products. There is also a need for more experimental data on the efficacy of melatonin on sleep in young adults. For my dissertation research, I addressed these concerns in two studies. In Study 1, I surveyed undergraduate students to assess their sleep aid use, the reason for their use, and individual differences related to their use. In Study 2, I conducted an experiment on the effect of melatonin (2mg or 5mg) on sleep, measured via PSG, and on morning cognition in young adults with healthy sleep.

# CHAPTER I: MELATONIN: THE SLEEP AID OF CHOICE AMONG YOUNG ADULTS FOR IMPROVING SLEEP LATENCY AND NEXT-DAY PERFORMANCE

## Study 1

There have been some studies that investigate the prevalence of OTC sleep aid use among adults (Pillitteri et al; 1994; Johnson et al., 1998; Maust et al., 2019; Goodhines et al., 2019); however, the majority of these studies do not specify between different types of these sleep aids (e.g. melatonin, antihistamines, etc.). Therefore, it is largely unclear what percentage of young adults in America use melatonin as a sleep aid, and how melatonin use compares to that of other OTC sleep aids available on the market. A question also remains regarding what factors predict melatonin use and what benefits young adults expect to gain from using melatonin as a sleep aid.

In the present study, we sought to better elucidate sleep aid use in young adults. Using an online survey, we asked undergraduates a series of questions about their use of melatonin, diphenhydramine- and doxylamine-based sleep aids, alcohol, and cannabis across their lifetime and in the past 30 days. We also asked participants to complete a battery of questionnaires to assess individual differences related to sleep aid use. We did not have specific predictions for the prevalence of melatonin. We did predict melatonin use would be higher in individuals with worse overall sleep quality and higher insomnia severity, which would mirror results on overall sleep aid use in previous research (Johnson et al., 1998; Pillitteri et al., 1994). We also predicted melatonin use would be higher for those who were more evening-oriented than morning-oriented, because melatonin may be able to help more evening-oriented individuals fall asleep earlier and obtain more sleep if they are unable to sleep in later in the morning. We also predicted melatonin use would be higher in those with higher anxiety and depression scores than

those with lower scores. This is because both anxiety and depression relate to worse sleep quality and the presence of sleep problems (Alvaro et al., 2013; Nyer et al., 2013), and there is some evidence indicating that individuals who use sleep aids may have higher anxiety and depression scores (Grigsby et al., 2021).

## Methods

### Participants

We recruited 797 (401 females;  $M_{age} = 19.34$ ,  $SD_{age} = 1.36$ ,  $Range_{age} = 18 - 27$ ) native English-speaking undergraduate students from Michigan State University<sup>1</sup>. Of this sample, 66.9% of participants were White, 9.4% were Asian or Pacific Islander, 9.0% were Black or African American, 4.3% were Hispanic or Latino, and 8.0% indicated their ethnicity was mixed or “Other”. The remaining participants (2.4%) preferred not to answer or did not provide their ethnicity. Also, 92.1% of participants had health insurance. The vast majority, 93.2% reported that they had never been diagnosed with a sleep disorder and 89.6% indicated they had never been diagnosed with any other disease or disorder. On average, participants were neither evening- nor morning- oriented (MEQ Scores:  $M = 45.42$ ,  $SD = 8.80$ ,  $Range = 17 - 76$ ) and had healthy sleep quality (PSQI Scores:  $M = 7.53$ ,  $SD = 3.26$ ,  $Range = 0 - 21$ ).

All participants received course credit as compensation and the study was approved by the Michigan State University Institutional Review Board.

### Materials

We administered the following surveys in the order in which they appear below.

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<sup>1</sup>We originally recruited data from 282 participants and then sampled data from another 515 participants. The goal of collecting these extra data was to assess whether our original findings replicated. Because the prevalence of sleep aids was similar, we reported the data as one large sample here.

**Sleep aid questionnaire.** To assess sleep aid use, we developed a questionnaire regarding sleep aid use (Appendix A). The first two questions ask whether the individual has used any of the following sleep aids (i.e, melatonin, diphenhydramine, doxylamine, alcohol, or cannabis) in their lifetime or in the past 30 days. For each sleep aid an individual indicated using, a series of questions were presented to inquire about the details of their use including: the total number of days/nights the sleep aid was used; the number of times per week the sleep aid was used; the dose or amount the individual typically takes; and the specific reason(s) the individual chose to take that sleep aid both generally and specifically the last time the sleep aid was used. To assess the reasons for using sleep aids, we presented individuals with a list of options (i.e. “Trouble falling asleep in general”; “Trouble staying asleep in general”; “Poor sleep the prior night”; “Had an important commitment/appointment the following day”; “Cross time-zone travel/ jet lag”; “Shift work”, “Relieve symptoms of a diagnosed sleep disorder”; and “Other”) and asked them to select as many choices as needed to best represented their reason(s) for taking a given sleep aid.

**Pittsburgh Sleep Quality Index (PSQI).** To assess whether sleep quality relates to sleep aid use in our sample, we used the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI measures sleep quality with seven components, or subscales (i.e. subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction). Scores on each of the components range from zero to three, with higher scores indicating worse sleep quality. The global PSQI score ranges from zero to 21 and is calculated by summing the component scores together. Thus, higher global scores also indicate worse sleep quality.

**Morningness-Eveningness Questionnaire (MEQ).** The Morningness-Eveningness Questionnaire (MEQ) (Horne & Östberg, 1976) assesses chronotype, or time of day preference. The MEQ is a 19-question survey that is used to assess preferred time of day. Based on their responses, individuals are categorized as being a “Definite Evening” (scores of 16-30), “Moderate Evening” (31-41), “Neither” (42-58), or “Moderate Morning” (59-69) type, or “Definite Morning” (70-86). Thus, higher scores indicate being more morning-oriented, whereas lower scores indicate being more evening-oriented.

**Insomnia Severity Index (ISI).** The insomnia severity index (ISI) (Bastien, Vallières & Morin, 2001) measures the severity of insomnia symptoms. The ISI is composed of seven questions that ask participants to rate the extent to which they are experiencing trouble with their sleep (difficulty falling asleep, difficulty staying asleep, and problems waking up too early), the effect of these sleep problems, and individuals’ satisfaction with their sleep. Responses to each of these questions are scored from zero to four, with higher scores indicating more severe insomnia. Scores on each question are then summed together for the total ISI score. Scores from 0-7 indicate “no clinically significant insomnia”, 8-14 indicates “subthreshold insomnia”, 15-21 indicates “clinical insomnia (moderate severity)”, and 22-28 indicates “clinical insomnia (severe)”.

**State-Trait Anxiety Inventory (STAI).** The STAI (Spielberger et al., 1983) includes two subscales; one that measures state and another that measures trait anxiety. Participants completed the STAI to assess if either of these two measures, or both, related to sleep aid use in our sample. The STAI includes 40 total questions, 20 for the state subscale and 20 for the trait subscale. To measure state anxiety, participants respond to a series of prompts (e.g. “I am worried”, “I feel upset”, “I feel secure”) by indicating the extent to which they agree with each in

the given moment. For trait anxiety, participants respond similarly to prompts regarding how they generally feel (e.g. “I feel satisfied with myself”, “I lack self-confidence”, “I feel nervous and restless”). Scores on each subscale range from 20-80, where higher scores mean higher anxiety. Based on their responses, individuals are classified as having “no or low anxiety” (20-37), “moderate anxiety” (38-44), or “high anxiety” (45-80). This value is calculated once for state anxiety and then separately for trait anxiety.

**Beck Depression Inventory (BDI).** We used the BDI (Beck, Steer, Brown, 1996) to measure depression. The BDI is a 21-item self-report questionnaire that asks participants to select statements that best describe how they felt during the past two weeks. Responses to each of these questions are scored from zero to three, where higher scores indicate a greater severity of depression. Scores from 0-9 typically indicate “minimal depression”, 10-18 indicates “mild depression”, 19-29 indicates “moderate depression, and 30-63 indicates “severe depression”. We removed one of the questions (#9), which refers to thoughts and feelings of suicide.

**Sleep diary.** We administered a sleep diary to participants to subjectively measure sleep in the days leading up to the study. Participants received a sleep diary via email upon signing up for the study and were instructed to use the sleep diary to record details of their sleep for three nights before their session. For each entry, the diary contains a set of seven questions regarding the quantity and quality of their sleep (e.g. time to bed, estimated sleep time, number of awakenings, time to rise, napping behavior, etc.) (Appendix B).

## **Procedure**

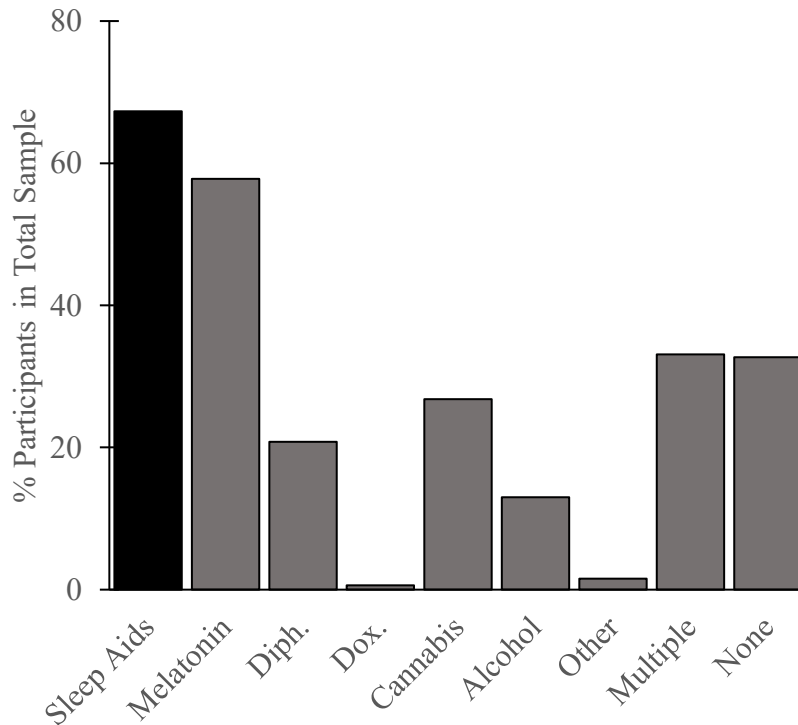
Participants signed up for our study via our online subject pool and immediately received an email with a sleep log and a link to the study survey on Qualtrics. We titled our study “Things You Do Everyday” to avoid selection bias or recruiting participants based on their interest in

sleep or health. In the study email, we instructed participants to complete the whole survey in one sitting within a two-week period of receiving the study email. The survey included the sleep aid questionnaire, the PSQI, MEQ, ISI, the STAI, and BDI. Finally, participants recorded their sleep diary responses into the survey and answered questions about their general health and demographics. Participants were allowed to complete this survey at any time of the day, as long as they completed the study in one sitting.

## Results

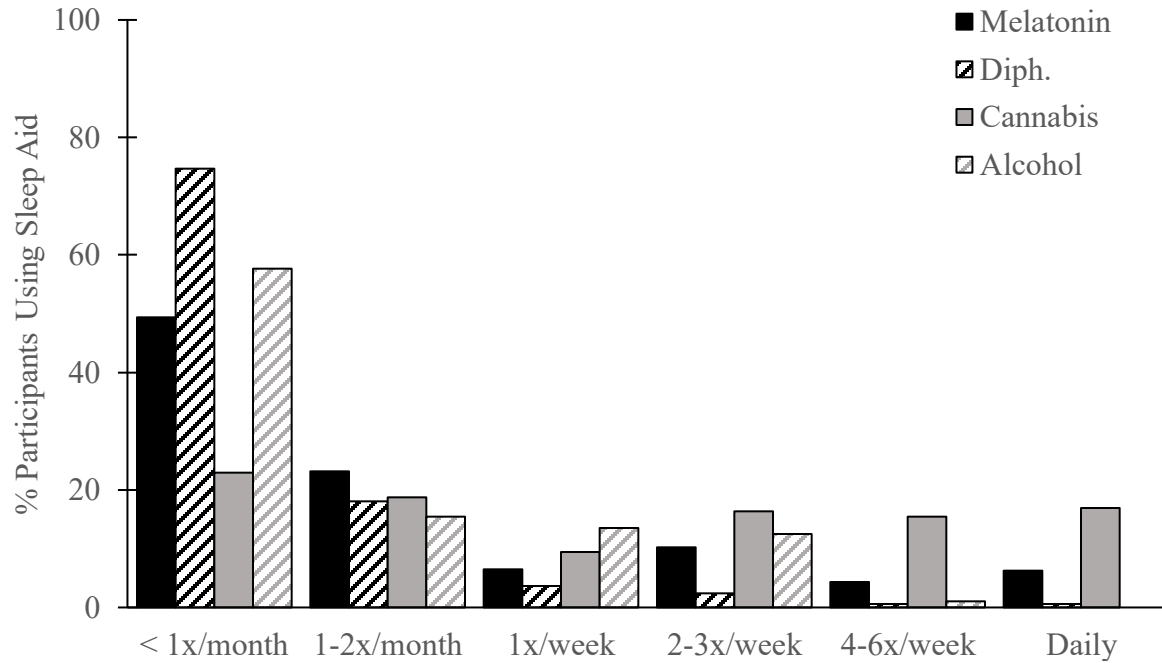
**Descriptive statistics on sleep aid use.** We first calculated descriptive statistics on the percent of participants who had taken sleep aids at some point, and then further broke this down by the specific sleep aid participants had taken. Overall, 67.3% of our sample indicated that they had used sleep aids at some point in their lives, and 33.1% of the sample reported using multiple sleep aids. Melatonin was the most popular sleep aid, with 57.8% of the sample reporting use (Figure 2). The next most popular sleep aids were cannabis (26.8% reporting use) and diphenhydramine (20.8%). Another 13.0% reported using alcohol as a sleep aid, 0.6% reported using doxylamine, and 1.5% reported using some other sleep aid. We also asked participants about their sleep aid use in the past 30 days. Again, melatonin was the most popular sleep aid, with 26.2% of the sample using melatonin in the last month, followed by cannabis (19.1%), diphenhydramine (5.8%), alcohol (5.5%), and doxylamine (0.3%).



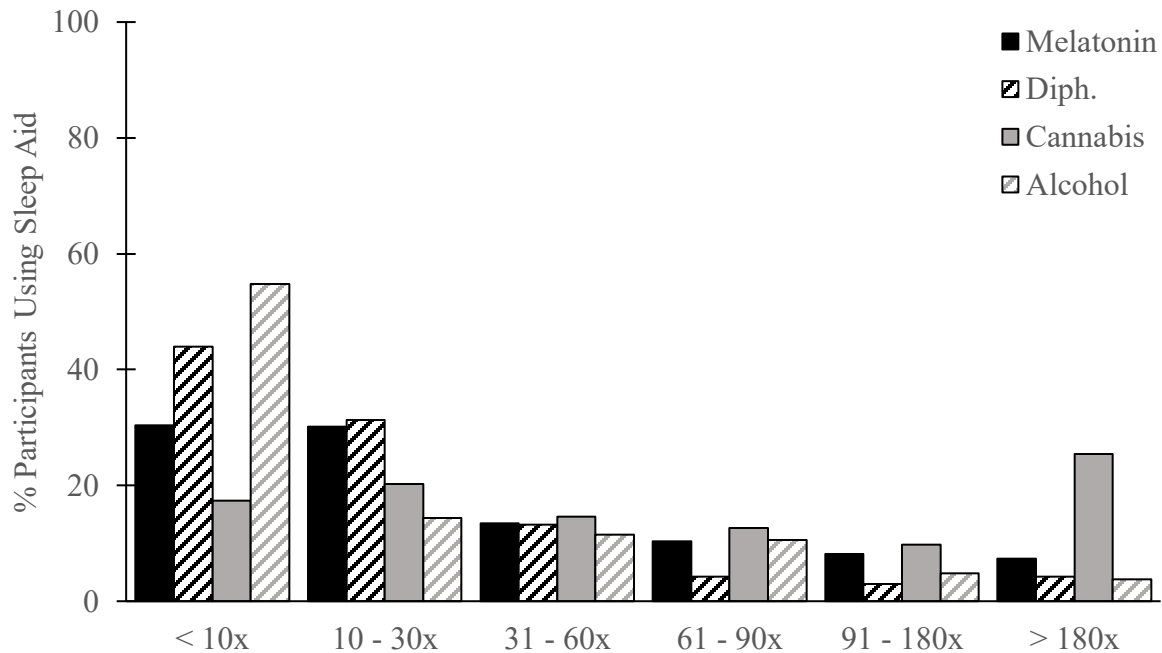


*Figure 2.* The percent of participants in the sample who indicated using sleep aids in general (i.e. striped bar), each sleep aid (i.e. gray bars), multiple sleep aids (i.e. black bar) or no sleep aids (i.e. white bar) in their lifetime.

We calculated descriptive statistics on how frequently participants used each of these sleep aids (Tables 1 and 2). Because so few participants indicated using doxylamine and “other” sleep aids, we did not include these sleep aids in our further analyses.



*Figure 3.* The percent of participants in the sample who responded to each answer option to describe the frequency of their use of melatonin (i.e. solid black bar), diphenhydramine (i.e. striped black bar), cannabis (i.e. solid gray bar) and alcohol (i.e. striped gray bar).



*Figure 4.* The percent of participants in the sample who responded to each answer option to describe the frequency of their use of melatonin (i.e. solid black bar), diphenhydramine (i.e. striped black bar), cannabis (i.e. solid gray bar) and alcohol (i.e. striped gray bar).

We also wanted to better understand the reasons participants use sleep aids by asking participants indicate the most common reason they have used each type of sleep aid in the past. Of the options provided, participants were able to select as many as they saw fit (see Table 1). Of the participants who reported using melatonin, the two most common reason were trouble falling asleep (74.8%) and having an important commitment the following day (26.0%). Of those who had previously used diphenhydramine, 62.5% reported using it due to trouble falling asleep. When participants selected “Other”, there were asked to specify this response by providing more detail in a text box. When we looked into these responses for those who chose diphenhydramine, we discovered that 20.3% of those using diphenhydramine described using it as a sleep aid to help alleviate the symptoms of a sickness or allergies that interfering with sleep. For those who

reported using cannabis, participants said they used cannabis because of trouble falling asleep (76.0%) or trouble staying asleep (22.5%). For those who used alcohol as a sleep aid, the most common reasons for use were trouble falling asleep (57.6%) and poor sleep the prior night (9.1%)

Table 1

*Percentage of participants who responded to each reason for using each sleep aid in general.*

<b>Sleep Aid</b>	<b>Trouble falling asleep (%)</b>	<b>Trouble staying asleep (%)</b>	<b>Poor sleep prior night (%)</b>	<b>Commit- ment the following day (%)</b>	<b>Jet lag/ cross time- zone travel (%)</b>	<b>Shift work (%)</b>	<b>Alleviate sleep disorder symptom (%)</b>	<b>Other (%)</b>
<b>Melatonin</b>	80.7	24.9	23.6	26.5	4.6	3.9	2.6	2.2
<b>Diph.</b>	59.7	21.7	18.1	11.4	1.1	1.8	7.2	30.1
<b>Cannabis</b>	81.8	32.2	19.2	8.9	2.3	4.7	2.3	8.9
<b>Alcohol</b>	59.6	16.3	12.5	1.9	-	1.9	2.9	21.1

**Individual differences in sleep aid use.** The main sleep aid we wanted to focus on was melatonin; therefore, we assessed individual differences in melatonin use first. To do this, we conducted a series of *t*-tests comparing global PSQI, MEQ, ISI, STAI state and trait, and BDI scores between participants who did and did not use melatonin. Because of the number of tests we ran, we adjusted our *p*-value using the Bonferroni correction; therefore, we rejected the null hypothesis at an alpha-level of 0.0083 ( $\alpha/n$ , where  $\alpha = 0.05$  and  $n$  (the number of comparisons) = 6). Results of these *t*-tests are reported in Table 2. In general, individuals who reported using melatonin had higher global PSQI scores,  $t(794) = 7.22, p < .001, d = 0.52$ ; higher MEQ scores,  $t(794) = 4.30, p < .001, d = 0.31$ ; and higher ISI scores,  $t(791) = 6.52, p < .001, d = 0.47$ . Thus, participants who take melatonin have worse sleep quality, higher insomnia severity, and are more evening-oriented than individuals who have not used melatonin. Undergraduates who used melatonin also had marginally higher STAI state,  $t(794) = 2.65, p = .008, d = 0.19$ , and trait scores,  $t(280) = 4.17, p < .001, d = 0.30$ ; and higher BDI scores,  $t(788) = 4.84, p = .002, d = 0.35$ , than those who reported never using melatonin. A correlation matrix displaying relationships between our individual difference measures are included in Table 3.

Table 2

*Results from a series of t-tests conducted between individuals who have and have not used melatonin on measures of sleep quality (Global PSQI), chronotype (MEQ), insomnia severity (ISI), state anxiety (STAI- State), trait anxiety (STAI-trait), and depression (BDI).*

	Have Used Melatonin	Have Not Used Melatonin	<i>t</i>	<i>p</i>
	<i>M (SD)</i>	<i>M (SD)</i>		
<b>Global PSQI</b>	8.47 (4.57)	6.44 (2.77)	7.22	< .001
<b>MEQ</b>	44.10 (8.98)	46.79 (8.32)	4.30	< .001
<b>ISI</b>	9.75 (4.11)	7.89 (3.80)	6.52	< .001
<b>STAI- State</b>	40.40 (12.20)	38.15 (11.41)	2.65	.008
<b>STAI- Trait</b>	46.17 (11.11)	42.93 (10.41)	4.17	< .001
<b>BDI</b>	12.72 (9.76)	9.51 (8.36)	4.84	< .001

We conducted similar analyses for diphenhydramine, cannabis, and alcohol, using the same Bonferroni correction to account for multiple tests ( $\alpha = 0.0083$ ). For diphenhydramine, individuals who reported using diphenhydramine as a sleep aid had worse sleep quality,  $t(794) = 4.73, p < .001, d = 0.41$ ; higher insomnia severity,  $t(791) = 5.33, p < .001, d = 0.46$ ; higher state,  $t(794) = 2.93, p = .003, d = 0.26$ , and trait anxiety,  $t(790) = 5.04, p < .001, d = 0.44$ ; higher depression scores,  $t(788) = 4.95, p < .001, d = 0.43$ , than those who never used diphenhydramine. There was no difference in chronotype between individuals who had and had not used melatonin before,  $t(794) = 1.48, p = .14$ . For cannabis, we found similar results. Individuals who reported using cannabis has worse sleep quality,  $t(794) = 4.64, p < .001, d =$

0.37; insomnia severity  $t(791) = 4.10, p < .001, d = 0.33$ ; state,  $t(794) = 3.16, p = .002, d = 0.25$ , and trait anxiety scores,  $t(790) = 4.22, p < .001, d = 0.34$ ; and depression scores,  $t(788) = 4.55, p < .001, d = 0.36$ , than those who reported never using cannabis as a sleep aid. Additionally, those who had used cannabis were more evening oriented than those who had not,  $t(794) = 3.02, p = .003, d = 0.24$ . Lastly, participants who reported using alcohol had worse sleep quality,  $t(794) = 4.81, p < .001, d = 0.51$ ; insomnia severity  $t(791) = 3.34, p < .001, d = 0.35$ ; state,  $t(794) = 2.68, p = .008, d = 0.28$ , and trait anxiety scores,  $t(790) = 2.79, p = .005, d = 0.29$ ; and depression scores,  $t(788) = 2.99, p = .003, d = 0.32$ , and trended towards being more evening-oriented chronotype,  $t(794) = 2.63, p = .009, d = 0.28$ , than those who reported never using alcohol as a sleep aid. However, the comparison for chronotype did not reach significance between those who did and did not report using alcohol as a sleep aid.



Table 3

*A correlation matrix showing the relationships between our individuals difference factors: sleep quality (Global PSQI), chronotype (MEQ; higher scores indicate being more morning-oriented, lower scores indicate being more evening-oriented); insomnia severity (ISI), state and trait anxiety (STAI), depression (BDI) and sleep measures from participant's sleep diaries (Sleep onset latency, No. of Awakenings, and total sleep time).*

	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>	<i>9</i>
<b>1. Sleep quality</b>	1.00	-	-	-	-	-	-	-	-
<b>2. Chronotype</b>	-.16***	1.00	-	-	-	-	-	-	-
<b>3. Insomnia severity</b>	.48***	-.14***	1.00	-	-	-	-	-	-
<b>4. State anxiety</b>	.37***	-.05	.42***	1.00	-	-	-	-	-
<b>5. Trait anxiety</b>	.40***	-.22***	.50***	.71***	1.00	-	-	-	-
<b>6. Depression</b>	.39***	-.22***	.50***	.55***	.68***	1.00	-	-	-
<b>7. Sleep onset latency</b>	.21***	-.06	-.17***	.19***	.13***	.16***	1.00	-	-
<b>8. No. of Awakenings</b>	.19***	.02	.33***	.17***	.18***	.25***	.22***	1.00	-
<b>9. Total Sleep Time (TST)</b>	-.14***	-.01	.24***	-.15***	-.11***	-.15***	-.13***	-.122***	1.00

*Note:  $p < .05$  \*,  $p < .01$  \*\*,  $p < .001$*

We also analyzed participant's sleep diary responses and assessed how sleep patterns differed between those who take melatonin, diphenhydramine, and cannabis and those who do not. We calculated participants total sleep time (TST), number of awakenings per night, and sleep onset latency (i.e. the amount of time it take for an individual to fall asleep). For melatonin, there was a trend for individuals who used melatonin to have a longer sleep time than those who had never used melatonin,  $t(776) = 1.94, p = .053, d = 0.14$ , and to take longer to fall asleep,  $t(780) = 1.92, p = .055, d = 0.14$ ; however, neither of these reached significance. there was no difference in the number of reported awakenings per night between those who had and had not taken melatonin,  $t(781) = 1.39, p = .16$ . Individuals who had used diphenhydramine before reported having more awakenings,  $t(781) = 4.16, p < .001, d = 0.37$ , and taking longer to fall asleep,  $t(780) = 2.22, p = .03, d = 0.20$ . There was no difference in TST,  $t(776) = 0.37, p = .71$ . Individuals who had used cannabis before had more awakenings per night,  $t(781) = 3.05, p = .002, d = 0.25$ , but there was no difference in sleep latency,  $t(780) = 1.10, p = .002$ , or TST,  $t(776) = 0.83, p = .41$ .

## Discussion

The general aims of this study were to assess: 1) the prevalence of melatonin use in young adults as well as other sleep aids; 2) the individual differences between those who do and do not use sleep aids, specifically for melatonin; and 3) the reasons young adults use melatonin. We found that over two-thirds of undergraduates reported using sleep aids, which is similar to the 58% estimate that Goodhines and colleagues found in 2019. Thus, melatonin was the most popular sleep aid among undergraduates, and cannabis and diphenhydramine were the second and third most popular sleep aids. We also found that individuals who use melatonin tend to have worse sleep quality and more severe insomnia symptoms, are more evening-oriented, and have

higher state and trait anxiety, as well as depression scores. Finally, our results showed that the top reasons for using melatonin were to help reduce sleep onset latency, to improve sleep the night before an important commitment, to help maintain sleep throughout the night, and to make up for a poor night of sleep.

Although melatonin was the most prevalent sleep aid, the results regarding individual differences in melatonin use were similar to those for other sleep aids. Worse sleep quality, insomnia severity, anxiety, and depression predicted participants' use of melatonin, diphenhydramine, cannabis and alcohol. The only exception was chronotype, which predicted use of all sleep aids except for diphenhydramine. However, the direction of the relationship between MEQ and sleep aid use was in the same direction for diphenhydramine use as for the other sleep aids; those who reported using sleep aids trended towards being more evening-oriented than those who had not used sleep aids. These results replicate previous findings showing that sleep aid use relates to worse sleep quality (Johnson et al., 1998; Pillitteri et al., 1994; Goodhines et al., 2019a) and higher anxiety (Grigsby et al., 2021).

Although sleep quality, chronotype, anxiety and depression all related to sleep aid use in our sample, the direction of these relationships is not clear from our data. A question remains as to whether individuals who use sleep aids do so because they are already experiencing troubles with sleep, anxiety, and depression; if the use of sleep aids is contributing to these factors; or if there is a spurious variable that explains this relationship, such as increased or chronic stress (Lund et al., 2010; Van Laethem et al., 2015). A likely explanation for our results is that pre-existing sleep problems (i.e. higher PSQI and ISI scores) cause individuals to be more likely to use sleep aids. It is even less clear how anxiety and depression scores relate to sleep aid use. One possibility is that individuals with worse sleep quality also have higher anxiety and depression

(Mayers et al., 2009; Alvaro et al., 2013), which was also true in our study. As such, anxiety and depression are indirectly related to sleep aid use via their relationship with sleep quality.

We also found that the main reasons that young adults use melatonin were trouble falling asleep, an important commitment the following day, trouble staying asleep, and poor sleep the night prior (i.e. to make up for lost sleep). Importantly, it remains largely unclear whether melatonin affects sleep in young adults, and whether melatonin can help achieve the results young adults desire when they choose to take melatonin. As discussed earlier, the results regarding the effect of melatonin on nocturnal sleep in young adults are mixed. Some studies show that melatonin benefits sleep (Cramer et al., 1972; Waldhauser et al., 1990; Dollins et al., 1994; Zhandova et al., 1995; Hughes & Badia, 1997; Vollrath et al., 1981; Tzischinsky & Lavie, 1994; Nave, Peled & Lavie, 1995) and others show that there is no effect (Dijk et al., 1995a; Stone et al., 2000; James et al., 1987). There are also mixed results on the effect of melatonin on cognition; melatonin can impair morning cognition in healthy sleepers (Killgore et al., 2018; Dollins et al., 1993) and aid cognition in those who have poor sleep (Jean-Louis, Gizycki & Zizi, 1998; Peck et al., 2004; Kwon et al., 2015). This is particularly interesting because the second most popular response for the reasons individuals used melatonin was “due to an important commitment the following day.” If there is a potential that melatonin impairs morning cognitive performance in healthy young adults, then individuals who are simply looking to boost their sleep for a night may be taking melatonin and gaining no benefit.

Given the popularity of melatonin and the uncertainty of its effects, an important question is whether young adults even benefit from the melatonin they ingest. In Study 2, we assess the effects of exogenous melatonin on sleep and morning cognition, in young adults with healthy sleep.

CHAPTER II: THE BENEFITS AND COSTS OF NIGHTTIME MELATONIN  
SUPPLEMENTATION: MELATONIN DOES NOT AFFECT SLEEP BUT IMPAIRS  
MORNING COGNITION IN YOUNG ADULTS WITH HEALTHY SLEEP

Study 2

Melatonin is marketed as a supplement that promotes sleep. However, there is an ongoing debate on whether melatonin induces sleep or realigns circadian timing in a way that improves sleep in some individuals (e.g. individuals with primary sleep disorders, elderly individuals, those experiencing jet lag, etc). Given the mixed results on melatonin as a soporific, an important question regarding melatonin supplementation is whether melatonin benefits sleep in individuals who do not experience circadian disruption (e.g. young adults with healthy sleep). The primary goal for Study 2 is to assess the effect of exogenous melatonin on nocturnal sleep in young adults. Additionally, we aim to investigate the effect of exogenous melatonin on morning cognition in this population, given that sleep quality is healthy.

We asked 120 undergraduates to participate in a double-blind, placebo-controlled study on the effect of melatonin on sleep. Participants completed cognitive tasks in the evening and took a pill containing 2mg or 5mg of melatonin or placebo. Participants then received an 8-hour sleep opportunity with partial PSG to measure sleep. In the morning, participants completed the same cognitive tasks as in the evening again.

If melatonin has a soporific effect, then individuals who take melatonin should fall asleep faster and stay asleep more than those who take placebo. If melatonin does not directly promote sleep, then individuals who take melatonin should sleep similarly to those who take placebo. Regarding the effect of melatonin on cognition, we predict that individuals who take melatonin will have more lapses in attention in the morning than those who received a placebo. We also

predict that those who receive melatonin will have more placekeeping errors during normal task flow and after interruptions than those who receive placebo because placekeeping involves both vigilant attention (Stepan, Altmann & Fenn, 2019) and working memory (Burgoyne, Hambrick & Altmann, 2019; 2020). Finally, we predict that those who take melatonin will have worse recall on the PAL test compared to those who take placebo.

## Methods

### Participants

We recruited 122 undergraduate students from Michigan State University. All participants were native English speaking U.S. citizens with no history of memory or sleep disorders, and have normal hearing and vision, including color vision. Participants were neither morning- nor evening-oriented with MEQ scores between 42 – 58, and had generally healthy sleep quality (PSQI global scores between 0 – 12). Participants also had a regular bedtime between 23:00 and 01:00, which means that their habitual bedtime was within one hour of the bedtime in our experiment (00:00). Participants were not regular users of sleep aids. We also asked participants to adhere to the following study restrictions: obtain at least 6 hours of sleep the night before their study session, wake by 09:00 the day of the study, refrain from napping the day of the study, and refrain from consuming caffeine, alcohol, and drugs 24 hours prior to the start of the study session. Of our initial sample, six were excluded from analysis for various reasons, including attrition ( $n = 4$ ), software issues ( $n = 1$ ), and oversleeping during the study ( $n = 1$ ). Therefore, our final sample included 116 participants (78 females;  $M_{\text{age}} = 18.75$ ,  $SD_{\text{age}} = 0.93$ ,  $\text{Range}_{\text{age}} = 18 - 22$ ). We completed a post-hoc power analysis in G-Power to assess the observed power in our study to detect an effect of melatonin on sleep (i.e. wake after sleep onset;  $d = .26$ ). Results of this power analysis showed that power in our study was 24% ( $1 - \beta = .24$ ).

We completed a similar post-hoc analysis for the effect of melatonin on post-interruption errors (our main cognitive measure), which revealed an observed power of 60%.

All participants provided informed consent and were compensated with course credit.

This study was approved by the Michigan State University Institutional Review Board.

## **Materials**

Participants completed the following tasks during the experiment.

**Prescreen Questionnaire.** We administered a short survey to all participants to ensure they followed the study restrictions. The survey contained questions regarding how much sleep they obtained the night before the study, when they woke up the morning of the study, if they napped at all during the day of the study, and if they consumed any caffeine, alcohol or drugs 24 hours prior to the study. To pass the prescreen, participants needed to obtain at least 6 hours of sleep, wake up by 09:00, not nap, and not consume any caffeine, alcohol, or drugs 24 hours prior to the start of the study session.

**Stanford Sleepiness Scale (SSS).** The SSS is a measure of subjective sleepiness using a single-item questionnaire that asks individuals to rate their feelings of sleepiness on a seven-point scale, ranging from 1 (“Feeling active, vital, alert, or wide awake”) to 7 (“No longer fighting sleep, sleep onset soon; having dream-like thoughts”; Hoddes et al., 1973). We administered the SSS to assess sleepiness at multiple timepoints throughout the session (22:00, 08:15, 08:30, 08:45, 09:00, 10:00) to assess the effect of melatonin on sleepiness in the morning.

### **International Positive and Negative Affect Schedule- Short Form (I-PANAS-SF).**

The I-PANAS-SF (PANAS) is a 10-item questionnaire that assesses positive and negative affect (Thompson, 2007). Participants are given 10 adjectives (i.e. Upset, Hostile, Alert, Ashamed, Inspired, Nervous, Determined, Attentive, Afraid, Active) and respond the degree to which they

are currently feeling each, on a 5-point Likert scale ranging from “Not at all” (1) to “Very much” (5). Therefore, the highest score for both positive and negative affect is 25. We used the PANAS to measure mood in the evening and morning sessions and assess the effect of melatonin on mood.

**Psychomotor Vigilance Task (PVT).** The PVT is a timed, 10-minute task that measures vigilant attention. In this task, a blank white screen is displayed on the computer monitor with a fixation cross in the middle. At random intervals throughout the 10-minute period, a red dot appears on the screen. Participants must monitor the screen and click the mouse as quickly as possible each time they see a red dot appear. The red dot remains on the screen until a response is made. After each response, participants receive feedback on their performance. The response latency (in milliseconds) is numerically presented in the middle of the screen in place of the fixation cross, and then the next trial begins. The primary measure of performance in this task is the number of attentional lapses that occur within the 10-minute period. Attentional lapses are defined as response latencies greater than 500 milliseconds. Thus, a higher number of attentional lapses corresponds to worse performance and more errors in vigilant attention.

**UNRAVEL.** UNRAVEL is a measure of placekeeping, where the term UNRAVEL serves as an acronym for a seven-step procedure (see illustration in Figure 5). Each letter of the acronym represents one of the seven steps in the order in which they are meant to be performed. The seven steps are defined as follows: U represents the “Underlined” or “Italicized” rule; N represents the “Near to” or “Far from” the start of the alphabet rule; R represents the “Red” or “Yellow” rule; A represents the “Above” or “Below” the gray box rule; V represents the “Vowel” or “Consonant” rule; E represents the “Even” or “Odd” rule; and L represents the “Less than” or “More than” five rule. On each trial, participants see a stimulus and must make a two-



option forced choice response corresponding with the rule associated with the current step (or letter) of the UNRAVEL sequence. Importantly, each step of the UNRAVEL sequence can be applied to each stimulus. For each trial, a unique stimulus appears on the screen containing a letter and a digit, a font style applied to one of these characters (underline or italic) as well as a font color (red or yellow), and a box outlined in gray with a character appearing either above or below the box.

Step	Rule	Answer
U	Underlined or Italicized	U
N	Near to or Far from the start of the alphabet	F
R	Red or Yellow	Y
A	Above or Below the box	A
V	Vowel or Consonant	V
E	Even or Odd	O
L	Less than or More than 5	M

Enter code #1: bruenlmyiocafv **bruen**

*Figure 5.* An illustration of the UNRAVEL placekeeping task. The panel on the left shows an example stimulus. The top right panel shows the rule for each step of the UNRAVEL sequence as well as the correct answer options for each step for the stimulus on the left. The bottom right panel shows an example of the interruption task.

On the first trial of the task, participants see a unique stimulus and must respond correctly using the U step by determining whether a character in the display is underlined or italicized. If a character is underlined, the correct response option is “U”, and participants should respond by pressing the “U” key on the keyboard. If the character is italicized, the correct response option is “I”. After responding, the next trial begins, and participants are presented with a novel stimulus.

On this trial, participants must respond using the N step. Each trial, participants receive a new stimulus and must respond according to the next step in the UNRAVEL sequence. Once a participant has completed the “L” step, they should start the cycle over again by performing the “U” step on the next trial.

A critical aspect of placekeeping is the ability to execute the procedure correctly, even when task flow is interrupted. As such, an interruption will occur during this task every six trials, on average, such that interruption trials occur on various steps in the UNRAVEL procedure. Each interruption consists of the same task. Participants are asked to type out and enter a “code” comprised of all of the letters that made up the response options for the UNRAVEL procedure (i.e. U, I, N, F, R, Y, A, B, V, C, E, O, L, and M). Participants must successfully type two codes using the keyboard to continue with the UNRAVEL task. If the participant does not type in a code correctly, a new code is generated, and participants must type in the new code.

There are two main measures of performance derived from this study. Both measures are sequence errors, which are defined as repetitions (e.g. completing the “N” step on two consecutive trials) or omissions to the UNRAVEL sequence (e.g. skipping the “A” step between the “R” and “V” steps). If a participant uses the correct step in the sequence, but chooses the incorrect response option (e.g. “I” instead of “U”), these are errors but we do not consider them sequence errors. The first type of sequence error we measured is “non-interruption errors”, or sequence errors that occur during normal task flow, on trials where there is not an interruption. We also measured “post-interruption errors”, which are sequence errors that occur on the trial immediately following an interruption.

**Paired Associates Learning (PAL) Task.** The paired associates learning task measures declarative memory and consists of four parts: the study phase, a cued recall test with feedback, a

cued recall test without feedback, and a final cued recall test. In the study phase, participants are asked to memorize 24 unrelated word pairs (e.g. *stove* – *duck*) presented on the screen, one pair at a time. After seeing all of the 24 word pairs, participants complete the first cued recall memory test, in which they will be given the first word in each word pair (e.g. *stove* - ?) and asked to recall the second word by typing the word using the keyboard. Participants receive feedback after each response. Regardless of their response, the correct word appears on the center of the screen. Participants then complete another cued recall test, except this time, participants do not receive any feedback. In the morning, participants complete the final cued recall test. For our dependent variable for this task, we calculated a change in accuracy by subtracting the number of correct responses from the final cued recall test in the evening from the number of correct responses in the morning.

**Polysomnography.** We used partial polysomnography (PSG) to measure sleep and place 14 electroencephalographic (EEG) electrodes, according to the international 10-20 system (Jasper, 1985). We placed recording electrodes at *F3*, *F4*, *C3*, *C4*, *O1*, *O2*, with *FpZ* as ground. Reference electrodes were placed on each mastoid (*M1*, *M2*). We also placed two electrooculogram (EOG) electrodes, one on each eye, and three electromyogram (EMG) electrodes on the chin. We recorded data continuously using the Philips Respironics Alice 6 LDx Diagnostic sleep system (Koninklijke Philips N.V., Eindhoven, Netherlands) and Sleepware G3 software. We scored each 30-second epoch based on standard criteria (American Academy of Sleep Medicine, 2018), and the individual scoring the data was blind to condition. We also measured spindle count and spindle density using the EEGLAB toolbox (Delorme et al., 2004) in MATLAB (MATLAB, R2020b), adapted from Wamsley et al. (2012). This procedure uses the

electrode at C3 to detect spindles during NREM sleep with a frequency of 11Hz - 16Hz and a duration of 0.5 seconds or greater.

**Pills.** Because this study was placebo-controlled we created 3 types of pills: placebo, 2mg melatonin and 5mg melatonin. We chose to use REMfresh brand melatonin because it has been used in a peer-reviewed studies that show this brand contains the dose indicated on the packaging and to keep plasma levels of melatonin elevated above 1000 pg/mL for a median of 6.7 hours to mimic endogenous melatonin production throughout the night compared to 3.7 hours for immediate release melatonin (Seiden & Shah, 2019). REMfresh has also been shown to improve sleep in individuals with short sleep duration (Seiden, Bridner & Shah, 2021). REMfresh contains two components in each of its pills: an immediate-release layer that administers melatonin to the system within 15 minutes via the gastrointestinal lining of the stomach, and an extended-release layer that administers melatonin into the system continuously for up to 7 hours. For our placebo pills, we chose to use vitamin C pills because there is evidence that vitamin C pills can increase alertness (Kubala and Katz, 1960), and because they are safe.

To ensure the participants and researchers did not know what types of pills were being administered during a given session, the melatonin and vitamin C pills were placed inside an opaque gelatin capsule. We constructed three types of pills. For each pill, we first placed half of a 1000mg vitamin C pill in a gelatin capsule. This was all that was placed inside of our placebo pills. For our melatonin pills we also put one pill of either 2mg or 5mg REMfresh inside of the gelatin capsules with the vitamin C.

The pills for this study were assembled by a researcher who had no involvement in the data collection or data analysis project. When pills were being assembled, the researcher placed each pill inside of a plastic bag labeled with a 3-letter code (e.g. 'XGR'). Therefore, the

researchers involved in the study and the participants did not know which codes were associated with which condition.

## **Procedure**

Participants arrived at our lab at 21:30 for their scheduled study session. We ran either one or two participants per night, which was limited by the number of bedrooms in our lab. Upon arrival, we asked participants to complete the prescreen questionnaire. Individuals who passed the questionnaire were allowed to continue with the study session, while those who did not pass all questions on the questionnaire were rescheduled and sent home.

Participants who adhered to the study restrictions started their evening tasks. They completed the SSS and PANAS surveys, the 10-minute PVT task, four blocks of the UNRAVEL task, and the paired associated learning (PAL) test. For the PAL, participants completed the study phase, the cued recall test with feedback, and the cued recall test without feedback.

Once participants finished these tasks, we gave them until 23:30 to get ready for bed before beginning the PSG set-up. At 23:30, a trained researcher set up each participant up with partial polysomnography. At 00:00, we told the participants to turn off their lights to sleep for the night. A trained researcher stayed in the lab with participants overnight to ensure the PSG set-up remains intact and for the participants' safety.

At 08:00, or eight hours after lights out, participants were woken up by the researcher, and had until 09:00 to get ready for the day and overcome sleep inertia (Wertz et al. 2006). At 08:15, 08:30, and 08:45, participants completed the SSS to monitor changes in sleepiness during that first hour awake. At 09:00, participants complete the SSS and PANAS again, the final cued recall test on the paired associates, four blocks of UNRAVEL, and the PVT. Although participants completed PAL last in the evening session, we had participants complete the final

test for the PAL task first in the morning to reduce interference that could impair their memory retrieval. Importantly, we also conducted a passive drool saliva assay (Salimetrics, LLC) in a subset of our participants to assess morning salivary melatonin concentrations. After completing the PVT, participants will be given a passive drool saliva assay kit and be asked to provide a sample of 0.25µm of saliva. These samples were stored in a freezer and sent back to the Salimetrics lab for analysis upon completion of the study. All participants then completed a demographic survey.

## Results

### Sleep

A primary aim of this study was to assess the effect of melatonin on sleep in young adults with healthy sleep. Thus, we compared sleep measures obtained via PSG [duration in N1, N2, N3, and REM sleep; wake after sleep onset (WASO); sleep onset latency; total sleep time (TST); number of spindles and spindle density, and sleep efficiency (i.e. [total sleep time/total sleep opportunity] \*100) between participants who took melatonin and placebo. Descriptive statistics for these measures can be found in Table 4, and results from the t-tests are presented in Table 5. Surprisingly, there were no differences between the sleep measures we assessed based on whether participants were in the Melatonin or Placebo group,  $t$ 's < 1.30,  $p$ 's > .20. However, there was a general trend for melatonin to decrease sleep onset latency,  $t(104) = .87, p = .38, d = 0.18$ , and wake after sleep onset,  $t(103) = 1.29, p = .20, d = 0.26$ , and thus increase sleep efficiency,  $t(103) = 1.81, p = .07, d = 0.37$ .

Table 4

Summary sleep data averaged across all participants in our sample, including the amount of time (in minutes) in Stage 1 (N1), Stage 2 (N2), Stage 3 (N3 or slow-wave sleep), and REM sleep; sleep onset latency (in minutes); the amount of time spent awake after sleep onset (WASO); total sleep time (TST); the number of spindles and spindle density; and sleep efficiency (%).

	<i><b>M</b></i>	<i><b>SD</b></i>	<i><b>%</b></i>
<b>N1 (mins)</b>	27.41	15.13	6.77
<b>N2 (mins)</b>	207.70	43.41	48.86
<b>N3 (mins)</b>	102.76	29.52	24.86
<b>REM (mins)</b>	88.66	26.50	15.67
<b>Sleep onset latency (mins)</b>	15.76	13.41	-
<b>WASO (mins)</b>	26.22	20.00	7.37
<b>TST (mins)</b>	426.22	64.02	90.19
<b>No. of Spindles</b>	208.57	150.62	-
<b>Spindle Density</b>	0.61	0.43	-
<b>Sleep efficiency (%)</b>	90.55	9.98	-

Table 5

Results from the independent samples t-test assessing the effect of melatonin on various sleep measures: the amount of time (in minutes) in Stage 1 (N1), Stage 2 (N2), Stage 3 (N3 or slow-wave sleep), and REM sleep; sleep onset latency (in minutes); the amount of time spent awake after sleep onset (WASO); total sleep time (TST); the number of spindles and spindle density.

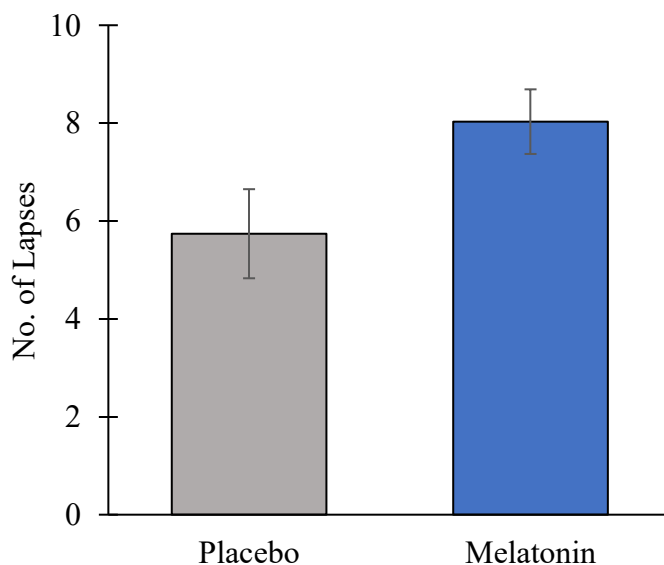
	<b>Placebo</b> <i>M (SD)</i>	<b>Melatonin</b> <i>M (SD)</i>	<i>t</i>	<i>p</i>
<b>N1</b>	27.81 (16.14)	27.19 (14.67)	0.20	.84
<b>N2</b>	205.55 (49.89)	208.90 (39.74)	0.37	.71
<b>N3</b>	101.69 (35.80)	103.34 (25.74)	0.27	.79
<b>REM</b>	86.01 (26.85)	90.10 (26.40)	0.74	.40
<b>Sleep Onset</b>	17.31 (15.28)	14.92 (12.33)	0.87	.38
<b>WASO</b>	29.71 (23.99)	24.32 (17.35)	1.30	.20
<b>TST</b>	420.41 (77.91)	429.39 (55.41)	0.48	.63
<b>No. of Spindles</b>	198.76 (128.52)	214.42 (163.20)	0.48	.63
<b>Spindle Density</b>	0.59 (0.39)	0.62 (0.46)	0.38	.71
<b>Sleep Efficiency</b>	88.18 (15.34)	91.84 (4.85)	1.81	.07

### Cognitive Performance

**Vigilant Attention.** We assessed the effect of melatonin on vigilant attention by conducting an ANCOVA on the number of morning PVT lapses with Pill (Placebo, Melatonin) as a between-subject factor and evening PVT lapses as a covariate. This analysis revealed that



participants who took melatonin had a higher number of PVT lapses in the morning than those who took placebo,  $F(1, 111) = 4.11, p = .045, \eta_p^2 = .04$  (Figure 6). Thus, melatonin impaired attention by increasing morning lapses in attention. Evening lapses were also a significant predictor of morning lapses,  $F(1, 111) = 65.04, p < .001, \eta_p^2 = .37$ ; those who had more lapses in the evening also had more lapses in the morning,  $r(114) = .59, p < .001$ .



*Figure 6.* The number of lapses (response latencies > 500ms) in the Psychomotor Vigilance Task (PVT) for the placebo (gray bar) and melatonin group (blue bar). Error bars represent S.E.M.

Because melatonin affected morning PVT performance, we conducted an analysis to assess whether the effect of melatonin was similar throughout the entire task. Therefore, we calculated the number of lapses that occurred in the first and second halves (or blocks) of the 10-minute PVT task. We then conducted a MANCOVA with Pill as a between-subjects factor, block (1, 2) as a within-subjects factor, and evening lapses across the entire task as a covariate. There was no effect of block or interactions between block and Pill,  $F$ 's < 1.10,  $p$ 's > .30.

We also conducted similar analyses on mean reaction time (RT) and median RT to assess whether melatonin impaired general performance across trials. Melatonin and placebo participants performed similarly on the PVT for mean RT,  $F(1, 111) = 1.00, p = .32$ , and median RT,  $F(1, 111) = 2.30, p = .13$ . Thus, the effect of melatonin on PVT performance was specific to the number of attentional lapses that occurred in the morning throughout the entire task.

**Placekeeping.** To assess the effect of melatonin on placekeeping, we conducted two separate ANCOVAs with Pill (Placebo, Melatonin): one for post-interruption errors and one for non-interruption errors (Figure 7). For both analyses, we used the corresponding measure of evening performance (post-interruption or non-interruption) as a covariate<sup>2</sup>. For post interruption errors, results showed that participants who took melatonin has higher errors than those who took placebo,  $F(1, 102) = 4.49, p = .04, \eta_p^2 = .04$ . Evening post-interruption errors were also a significant predictor of morning post-interruption errors,  $F(1, 111) = 65.04, p < .001, \eta_p^2 = .04$ ; those who had more errors in the evening also had more errors in the morning,  $r(105) = .67, p < .001$ .

Given this effect of melatonin on post-interruption errors, we conducted a supplementary analysis to investigate whether the effect of melatonin was similar across the entire task duration, or if the effect changed over time (i.e. across each of the four blocks of the task). Therefore, we used a MANCOVA with Pill (Placebo, Melatonin) as a between-subjects factor, block (1, 2, 3, 4) as a within-subjects factor, and evening performance- averaged across all four evening blocks- as a covariate. However, there was no effect of block,  $F(1, 102) = 0.48, p = .69$ , or interaction

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<sup>2</sup> For all of our UNRAVEL analyses, we excluded participants whose accuracy was below chance in the evening session. The threshold for chance performance was defined as a sequence error rate of 0.814. Therefore, participants who had a sequence error rate above 81.4% ( $n = 3$ ) were excluded.

between block and pill,  $F(1, 102) = 0.48, p = .70$ . There was still an effect of pill,  $F(1, 102) = 4.49, p = .04, \eta_p^2 = .04$ ; melatonin led to higher post-interruption errors than placebo.

For non-interruption errors, we found that there was not an effect of melatonin on morning errors,  $F(1, 102) = 0.83, p = .36$ . Evening non-interruption errors were a significant predictor of morning non-interruption errors,  $F(1, 102) = 12.76, p < .001, \eta_p^2 = .11$ , such that those who had more errors in the evening also had more errors in the morning,  $r(105) = .33, p < .001$ . Taken together, these UNRAVEL results suggest melatonin specifically impairs placekeeping performance on trials right after an interruption, but not on non-interruption trials.

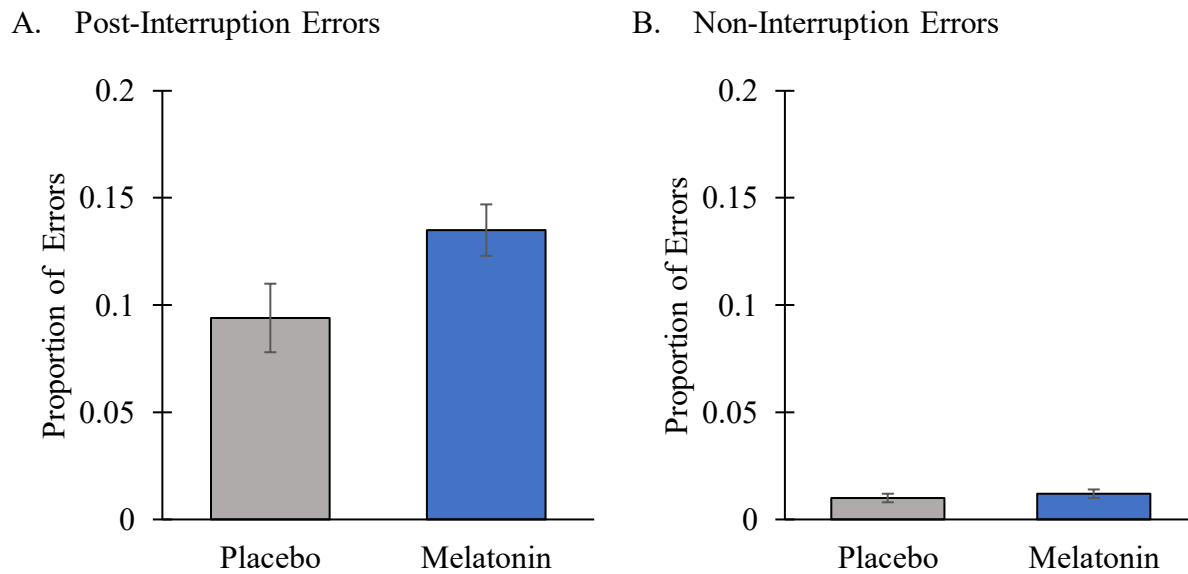
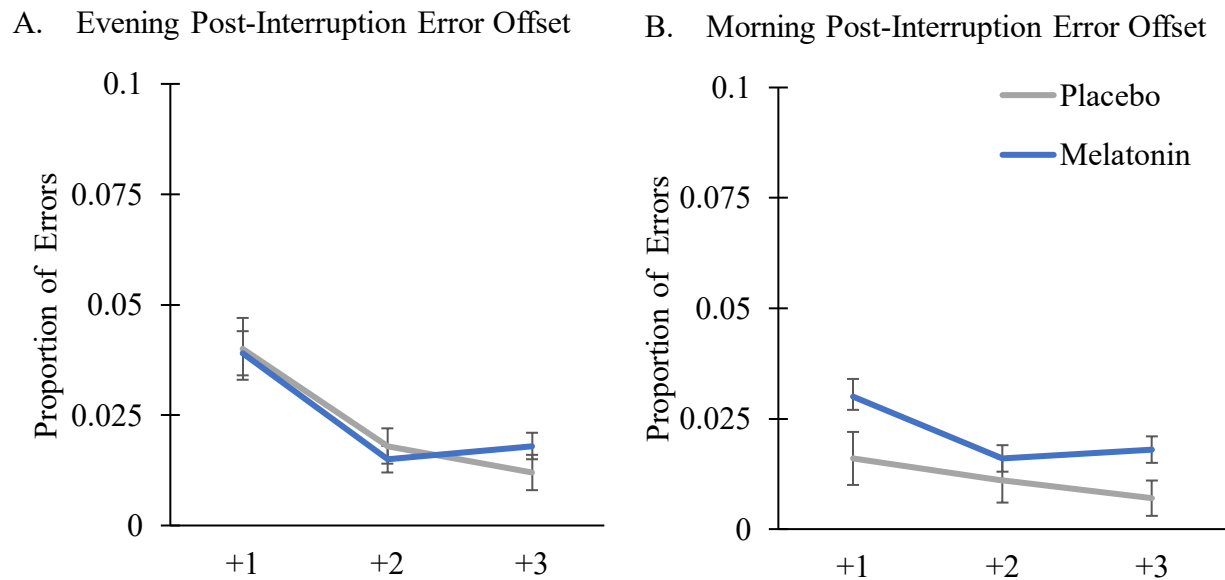


Figure 7. UNRAVEL performance in the placebo (gray bar) and melatonin group (blue bar) for A) post-interruption errors, and B) non-interruption errors. Error bars represent S.E.M.

Given the effect of melatonin on sequence errors, particularly post-interruption errors, we wanted to assess whether or not melatonin affected the patterns of errors. More specifically, we wanted to assess how off participants were in the UNRAVEL sequence when a sequence error

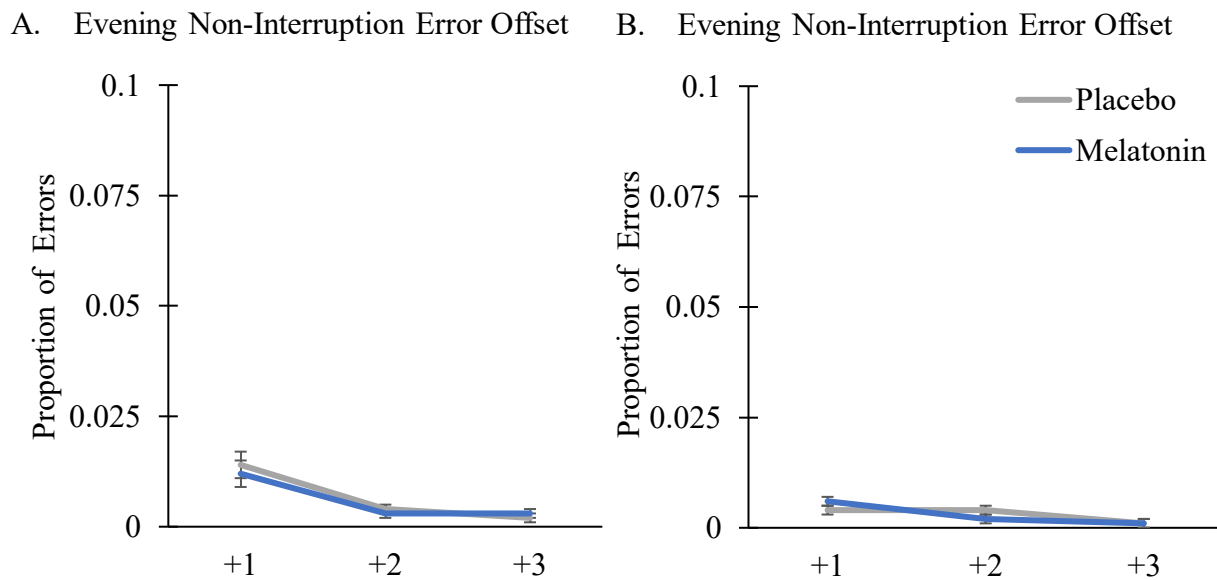
was made (i.e. the distance or offset between the correct step in the sequence and the executed step in the sequence). To do this, we analyzed the error gradients in our UNRAVEL data (Figure 8) in a mixed ANOVA using Pill as the between-subjects factor and session (Evening, Morning) and error offset from the correct step (+1, +2, +3) as a within-subject factors. There were main effects of session,  $F(1, 206) = 10.68, p = .003, \eta_p^2 = .09$ , and offset,  $F(1, 206) = 29.73, p < .001, \eta_p^2 = .22$ , but there was not a main effect of Pill,  $F(1, 103) = 1.61, p = .21$  (Figure 8).

Participants had higher errors in the evening than the morning, and error offsets were twice as high for +1 step from the correct step in the UNRAVEL sequence as for the +2 and +3 steps. There were not any significant interactions,  $F$ 's  $< 3.19, p$ 's  $> .08$ , except an interaction between session and offset,  $F(1, 103) = 6.58, p = .002, \eta_p^2 = .06$ , which was not relevant to our research question.



*Figure 8.* Error gradient for post-interruption errors in UNRAVEL in the placebo (gray line) and melatonin group (blue line) in the A) evening, and B) morning. X-axis is the number of steps away incorrect responses were from the correct response. Error bars represent S.E.M.

We conducted a similar analysis on the error gradient for non-interruption errors (Figure 9). There were main effects of session,  $F(1, 206) = 13.99, p < .001, \eta_p^2 = .12$ , and offset,  $F(1, 206) = 42.67, p < .001, \eta_p^2 = .29$ , but there was not a main effect of Pill,  $F(1, 103) = 0.03, p = .86$ . Participants had higher errors in the evening than the morning, and error offsets were over four times as high for +1 step from the correct step in the UNRAVEL sequence as for the +2 and +3 steps. There were not any significant interactions,  $F$ 's  $< 1.05, p$ 's  $> .35$ , except another interaction between session and offset,  $F(1, 103) = 10.08, p < .001, \eta_p^2 = .09$ , that again was not relevant to our research question.

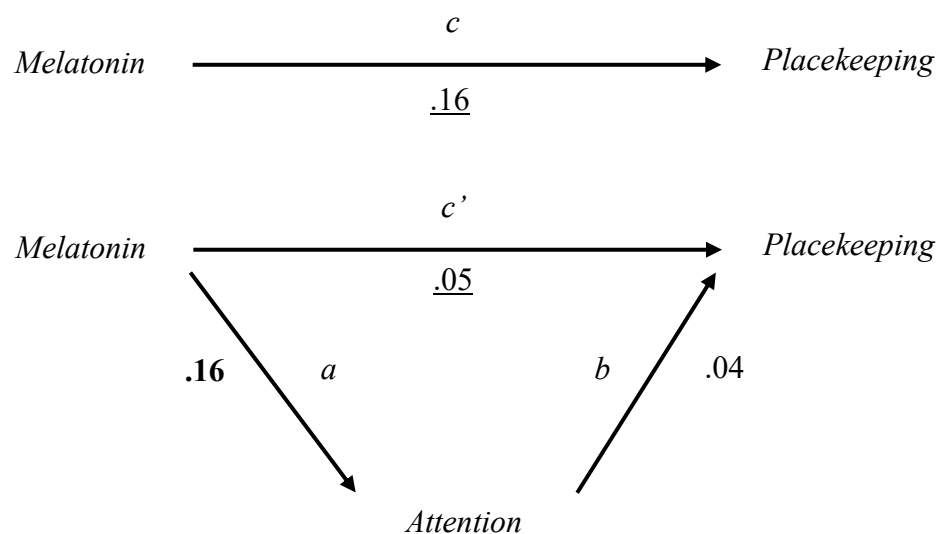


*Figure 9.* The error gradient for non-interruption errors in the UNRAVEL task in the placebo (gray line) and melatonin group (blue line) in the A) evening, and B) morning. The x-axis categories pertain to the numbers of steps away a participant's incorrect response was from the correct response. Error bars represent S.E.M.

We also analyzed the effect of melatonin on non-sequence errors (i.e. entering the

incorrect response for the correct step) in a ANCOVA with Pill (Placebo, Melatonin) as the between-subjects factor. Importantly, melatonin did not affect non-sequence errors in the UNRAVEL task,  $F(1, 102) = 0.28, p = .60$ . Those who took a placebo pill had similar error rates ( $M = .006, SD = .009$ ) as those who took a melatonin pill ( $M = .006, SD = .01$ ).

**Mediation analysis.** There is some evidence that higher-order cognition, such as placekeeping performance, is at least partially mediated by attention (Lim & Dinges, 2010; Stepan, Altmann & Fenn, 2019). Given the effect of melatonin on post-interruption placekeeping performance and vigilant attention, we assessed whether the effect of melatonin on placekeeping was mediated by attention, using a model used by Stepan and colleagues (2019) paper (Figure 10).



*Figure 10.* Hypothesized mediation model on the role of attention in the relationship between melatonin and placekeeping (post-interruption errors). Independent variable: Melatonin; Dependent variable: Placekeeping; Hypothesized Mediator: Attention. Numbers are standardized regression coefficients ( $\beta$ ). **Bold**,  $p < .01$ . Underline,  $p < .05$ .

To do this, we first assessed the effect of melatonin on morning PVT lapses in a hierarchical regression, in which the first step accounted for evening PVT lapses (Table 6). As expected, evening PVT lapses significantly predicted morning PVT lapses,  $t(102) = 7.94, p < .001$ , but melatonin affected morning performance over and above evening performance,  $\Delta R^2 = .03, p = .04$ . Thus, we know melatonin affects attention.

Table 6

*Hierarchical regression for morning PVT lapses (Path a in Figure 10).*

	<i>B</i>	<i>SE<sub>B</sub></i>	<i>β</i>	<i>t</i>	<i>p</i>	<i>R<sup>2</sup></i>	<i>Δ R<sup>2</sup></i>
<b>Step 1</b>							
Evening PVT lapses	0.50	0.06	.62	7.94	< .001	.38	
<b>Step 2</b>							
Pill (Placebo, Melatonin)	2.44	1.17	.16	2.09	.04	.41	.03*

*Note: All statistics are from the full model;  $p < .06$  †,  $p < .05$  \*,  $p < .01$  \*\*,  $p < .001$  \*\*\**

We then conducted a similar hierarchical regression to assess the effect of melatonin on morning post-interruption placekeeping errors, with evening post-interruption errors accounted for in the first step (Table 7). Again, evening post-interruption error rates significantly predicted morning post-interruption error rates,  $t(103) = 9.20, p < .001$ , and melatonin affected morning performance over and above evening performance,  $\Delta R^2 = .02, p = .04$ . Therefore, melatonin affects placekeeping performance.

Table 7

*Hierarchical regression for morning post-interruption errors, unmediated by attention (Path c in Figure 10).*

	<i>B</i>	<i>SE<sub>B</sub></i>	$\beta$	<i>t</i>	<i>p</i>	<i>R</i> <sup>2</sup>	$\Delta R^2$
<b>Step 1</b>							
Evening post-interruption errors	0.60	0.07	.67	9.28	< .001	.45	
<b>Step 2</b>							
Pill (Placebo, Melatonin)	0.04	0.02	.16	2.12	.04	.47	.02*

*Note: All statistics are from the full model;  $p < .06$  †,  $p < .05$  \*,  $p < .01$  \*\*,  $p < .001$  \*\*\**

Finally, we conducted the final component of the mediation analysis using a hierarchical regression on morning post-interruption errors. Our model accounted for evening post-interruption errors in Step 1, morning PVT lapses in Step 2, and Pill (Placebo, Melatonin) in Step 3 (Table 8). Interestingly, we found that evening post-interruptions errors predicted morning errors,  $t(102) = 9.05$ ,  $p < .001$ ; however, morning PVT lapses did not significantly predict morning post-interruption errors, as we had predicted it might,  $t(103) = 0.54$ ,  $p = .59$ . Melatonin, on the other hand, did still predict morning post-interruption errors,  $t(103) = 2.07$ ,  $p = .04$ . Thus, the effect of melatonin on placekeeping was direct, or at least not mediated by attention.



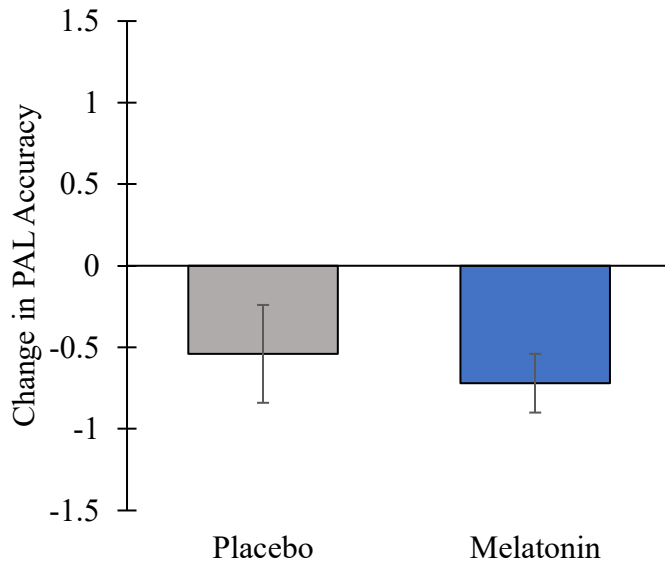
Table 8

*Hierarchical regression for morning post-interruption errors (Path c' in Figure 10).*

	<i>B</i>	<i>SE<sub>B</sub></i>	<i>β</i>	<i>t</i>	<i>p</i>	<i>R<sup>2</sup></i>	<i>Δ R<sup>2</sup></i>
<b>Step 1</b>							
Evening post-interruption errors	0.60	0.07	.66	9.05	< .001	.45	
<b>Step 2</b>							
Morning PVT lapses	0.001	0.001	.04	0.54	.59	.45	.002
<b>Step 3</b>							
Pill (Placebo, Melatonin)	0.04	0.02	.15	2.07	.04	.47	.02*

*Note: All statistics are from the full model;  $p < .06$  †,  $p < .05$  \*,  $p < .01$  \*\*,  $p < .001$  \*\*\**

**Declarative Memory.** We assessed the effect of melatonin on declarative memory by conducting a t-test on PAL performance with Pill (Placebo, Melatonin) as the independent variable (Figure 11). For word pairs, our main measure was change in accuracy across sessions (i.e. the proportion of correctly recalled pairs in the morning minus the proportion of correctly recalled pairs in the evening). Thus, negative numbers indicate a loss of information across time and positive numbers indicate a gain in information. Results showed no difference in PAL performance between Melatonin and Placebo participants,  $t(109) = 0.52$ ,  $p = .60$ .



*Figure 11.* Change in accuracy on the Paired Associates Learning (PAL) task from the morning to the evening in the placebo (gray bar) and melatonin group (blue bar). Positive scores indicate an increase in accuracy from the evening to the morning and negative scores indicate a decrease in accuracy (or loss of information). Error bars represent S.E.M.

**Correlations between tasks.** We conducted a collection of bivariate correlations between our morning performance variables: UNRAVEL post-interruption errors, non-interruption errors, PVT lapses, PVT mean response latency, and proportion correct for the PAL test (Table 9). UNRAVEL post-interruption error rates correlated positively with non-interruption errors,  $r(105) = .32, p < .001$ ; those with higher post-interruption errors also had higher non-interruption errors. Post-interruption errors also correlated negatively with the proportion correct of recalled word pairs in the PAL test,  $r(103) = -.32, p < .001$ , and there was a similar trend between non-interruption errors and proportion correct on the PAL test,  $r(103) = -.32, p < .001$ , that did not reach significance. Thus, those with more sequence errors, specifically, post-interruption errors also recalled fewer word pairs. PVT lapses correlated positively with

PVT mean RT, as expected,  $r(104) = .83, p < .001$ , but more interestingly, mean RT in the PVT correlated negatively with proportion correct in PAL,  $r(103) = -.21, p = .03$ . Thus, those with longer RTs in the PVT- a marker of poorer performance- had fewer correct on the PAL test in the morning.

Table 9

*A correlation matrix showing the relationships between our morning performance variables: PVT lapses, PVT mean response latency, UNRAVEL post-interruption errors, non-interruption errors, and proportion correct for the PAL test.*

	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
<b>1. PVT Lapses</b>	1.00	-	-	-	-
<b>2. PVT Mean RT</b>	.83***	1.00	-	-	-
<b>3. UNRAVEL Post-Interruption Errors</b>	.12	.11	1.00	-	-
<b>4. UNRAVEL Non-Interruption Errors</b>	.02	.01	.32***	1.00	-
<b>5. PAL Proportion Correct</b>	-.13	-.21*	-.32***	-.19 <sup>†</sup>	1.00

*Note:  $p < .06$  <sup>†</sup>,  $p < .05$  \*,  $p < .01$  \*\*,  $p < .001$  \*\*\**

## Salivary melatonin

In a subset of our participants ( $n = 31$ ), we administered a saliva assay to assess the effect of exogenous melatonin on salivary melatonin. Although 31 participants is only about 25% of our sample, a sample of size of 30 is on the upper end for studies that have been previously conducted on the effect of melatonin on sleep (Lethringer, 2009; Zhdanova, 2001; Haimov, 1995). Of the participants in our sample who provided a saliva sample, ten had a concentration of melatonin that came back as “> 100”; we replaced these values with “101”. One participant’s assay came back as containing a “non-detectable” amount of melatonin, and this value was replaced with “0”. We conducted an independent-samples  $t$ -test on the salivary melatonin concentration (measured in mg/mL) using Pill (Placebo, Melatonin) as the independent variable (Figure 12). Participants who took melatonin in the evening had higher melatonin concentrations in the morning than those who took a placebo pill,  $t(17) = 3.22, p < .01, d = 1.53$ . Thus, the melatonin supplement we administered caused participants to have elevated melatonin levels until at least over 10 hours after taking a pill. However, there were no correlations between melatonin concentrations and any of our dependent variables,  $r$ ’s  $< .28, p$ ’s  $> .24$ . However, this is likely because nearly one-third of our sample of assays came back as “> 101”, meaning that there was an upper limit in our sample for a substantial number of participants that limited the true range of salivary melatonin concentration.

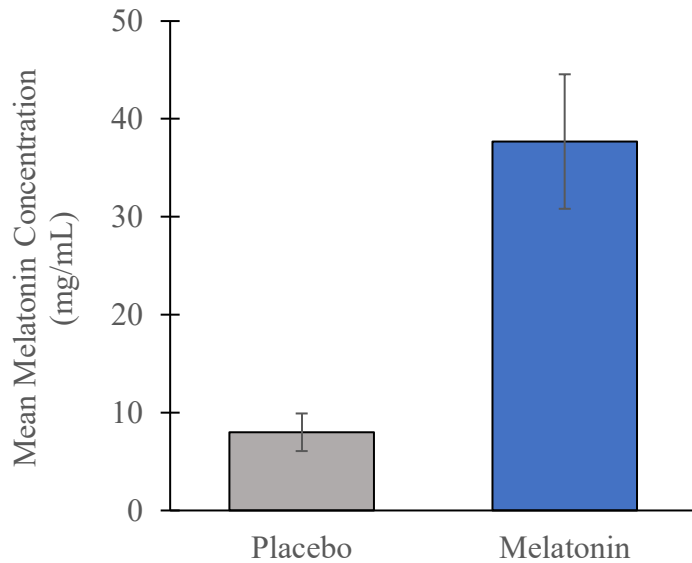


Figure 12. Salivary concentration of melatonin in the morning after completing tasks for participants in the placebo (gray bar) and melatonin group (blue bar). Error bars represent S.E.M.

**Subjective Sleepiness.** We assessed the effect of melatonin of subjective sleepiness in the morning by conducting a mixed ANOVA on SSS scores with Pill (Placebo, Melatonin) as a between-subject factor and Time (08:15, 08:30, 08:45, 09:00, 10:00) as a within-subject factor. Results are depicted in Figure 13. There was an effect of time on sleepiness,  $F(1, 97) = 53.74$ ,  $p < .001$ ,  $\eta_p^2 = .36$ ; participants were the most sleepy at 08:15 right after waking up, they were less sleepy at 08:30, and then their sleepiness leveled off from 08:45 – 10:00. However, sleepiness did not differ between participants in the Melatonin and Placebo groups,  $F(1, 97) = 1.97$ ,  $p = .16$ , and there was no an interaction between Pill and Time,  $F(1, 97) = 0.38$ ,  $p = .82$ .

We also analyzed sleepiness data across separately within each Pill group. Therefore, we conducted two separate MANCOVAs with evening sleepiness (at 21:00) as a covariate and time in the morning (08:15, 08:30, 08:45, 09:00 and 10:00) as the within-subjects factor. For both placebo and melatonin participants, there was a significant effect of time,  $F(1, 136) = 7.41$ ,  $p <$

.001,  $\eta_p^2 = .18$ , and  $F(1, 136) = 4.85, p < .001, \eta_p^2 = .08$ , respectively.

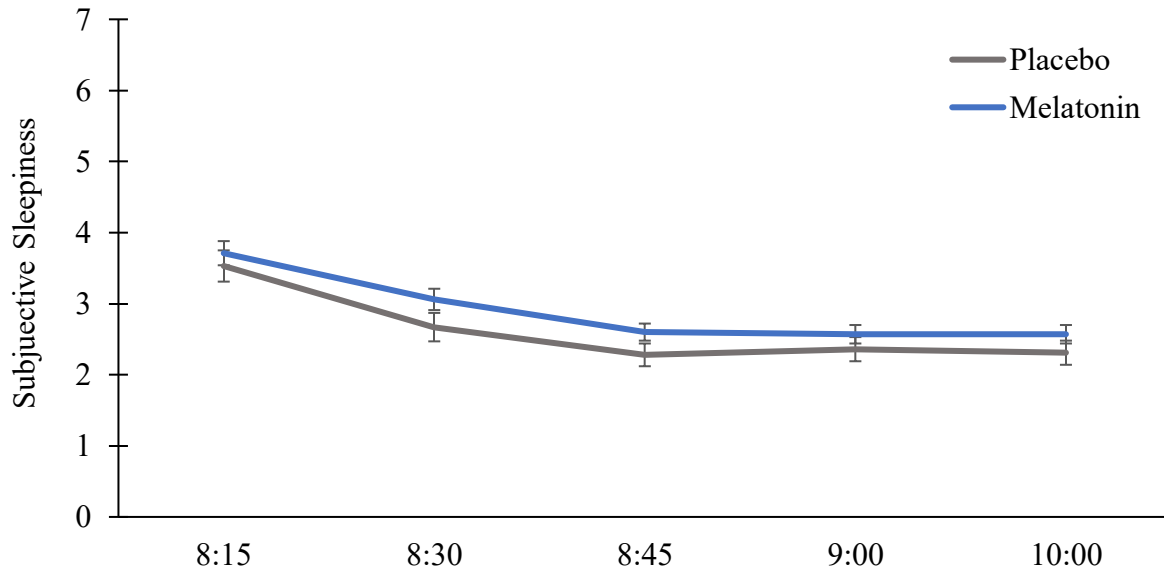


Figure 13. Line chart of subjective sleepiness (SSS scores) across the morning session for the placebo group (gray line) and the melatonin group (blue line). Error bars represent S.E.M.

Finally, we ran bivariate correlations between sleepiness scores and performance on our cognitive tasks. In the sample as a whole, we found that sleepiness scores correlated with performance on the word pair task,  $r(101) = -.24, p = .02$ , and non-sequence errors in the UNRAVEL task,  $r(99) = -.24, p = .02$ , and PVT lapses,  $r(109) = .25, p = .01$ . Thus, higher sleepiness scores in the morning correlated with worse task performance on the PAL task and PVT. However, higher sleepiness scores correlated with lower non-sequence errors, suggesting being more sleepy helped performance, which was against our predictions.

We also conducted these correlations within each pill group. For placebo participants, sleepiness scores correlated with morning PAL performance,  $r(36) = -.36, p = .03$ , and non-interruption errors in the UNRAVEL task,  $r(109) = .34, p = .04$ . For melatonin participants,

sleepiness correlated with PAL performance,  $r(101) = -.31, p = .01$ , non-sequence errors in the UNRAVEL task,  $r(99) = -.31, p = .01$ , and PVT lapses,  $r(109) = -.28, p = .02$ .

## Discussion

The general aims of this study were to assess the effects of exogenous melatonin on nocturnal sleep and next-morning cognition in young adults. Interestingly, we found that melatonin did not affect sleep, but impaired vigilant attention and placekeeping after interruptions in the morning. Melatonin did not affect memory performance in our sample.

There are a few possible explanations that melatonin may not have affected sleep in our sample of participants. First, melatonin may not affect sleep in young adults, which has been suggested by some studies (Dijk et al., 1995a; Stone et al., 2000). We only sampled participants who had a generally healthy sleep quality, were neither morning- nor evening-oriented, and had no history of sleep or memory disorders. Thus, melatonin may not have affected sleep much in this sample because sleep was already healthy and average sleep efficiency was over 90% for the sample. However, it is also possible that melatonin does affect sleep in young adults with healthy sleep, but we did not find evidence of this effect in our study (i.e. a Type II error). Importantly, there were trends in our data suggesting melatonin helped individuals initiate and maintain sleep, although these trends were not significant. It is also possible that benefits to sleep might have been better observed if participants were allowed to sleep as long as they wanted instead of being cut off after eight hours. This is to say a longer sleep opportunity (e.g. nine or ten hours) might exaggerate any possible effects of melatonin on sleep (Rajaratnam et al., 2004). It is also possible a higher dose of melatonin (i.e. 10mg) may have allowed for a larger and more robust effect of melatonin on sleep in our sample.

Although our study did not reveal any effects of melatonin on sleep, there were effects of

melatonin on cognition the following morning. Melatonin impaired placekeeping performance on trials after an interruption, which involves working memory unlike non-interruption errors, and increased attentional lapses in the PVT. However, there were no effects on consolidation of retrieval memory processes or non-interruption errors, which are thought to rely on priming processes (Altmann et al., 2017). A question remains regarding the underlying mechanism. One explanation for impairments caused by melatonin is that melatonin impairs prefrontal cortex (PFC) functioning (Killgore et al., 2018). If this is the case, then performance should suffer on PFC-dependent tasks when melatonin is taken. This hypothesis could explain why melatonin impaired post-interruption errors and attentional lapses and not declarative memory in the PAL task, which should be more mediated by the hippocampus as a memory task (Mayes et al., 2001; Jun et al., 2019) Since we did not collect the neural data necessary to investigate this hypothesis in our study, this question remains open. Another explanation is that taking exogenous melatonin delays circadian rhythmicity such that the normal increase in arousal and performance in the morning (Borbely, 1982; Borbely et al., 2016) was delayed. Participants who took melatonin in our study had elevated salivary melatonin in the morning than placebo participants. Therefore, it is possible that circadian rhythmicity was altered in the morning by this excess melatonin.



### CHAPTER III: OVERALL DISCUSSION

The overall aims of this dissertation were to survey sleep aid use in undergraduates and assess the effect of exogenous melatonin on sleep and cognition in young adults. In Study 1, we found that melatonin was the most popular sleep aid among undergraduates and that the top reasons for using melatonin were to help individuals fall and stay asleep and to get better sleep before an important commitment or event the following day. Additionally, melatonin use was relatively sparse; most participants we surveyed indicated that they used melatonin on occasion, not regularly. These findings suggest that young adults consume melatonin supplements to benefit sleep on a single night and in the hope that these benefits might translate to performance gains the following day.

Surprisingly, in Study 2, we found that exogenous melatonin did not affect sleep, which has been shown previously in some studies (Lavie, 1997; Dijk et al., 1995a; Stone et al., 2000). In general, these findings have been used as evidence in support of the hypothesis that melatonin only affects sleep via its effect on circadian timing and does not directly promote sleep. Although this is a likely explanation for our findings, as well as the majority of findings in the melatonin and sleep literature, there are other reasons melatonin may not have affected sleep in our experiment.

Importantly, there was a general, albeit insignificant, trend for melatonin to reduce sleep onset latency, wake after sleep onset, and sleep efficiency. Therefore, it is possible that melatonin does affect sleep in young adults with already healthy sleep, but that we did not detect this effect in our study. For example, in young adults, higher doses of melatonin might be needed to significantly affect sleep at night. Because young adults are likely to have sufficient

endogenous levels of melatonin, it may take a higher dose to increase melatonin levels above pre-existing endogenous levels.

Although melatonin did not significantly affect sleep in Study 2, melatonin did impair morning placekeeping and attention. These findings replicate previous studies showing that melatonin can impair cognition when sleep quality is already healthy (Dollins et al., 1993; Gorfine & Zisapel, 2007; Killgore et al., 2018). It is possible the increase in circulating melatonin levels in the morning either delay or suppress the drive for circadian arousal in the morning (Graw et al., 2001; Van Dongen & Dinges, 2005), suggesting that cognitive processes such as attention, working memory, and placekeeping have a circadian rhythm. In fact, there is evidence that prefrontal cortex (PFC) functioning correlates negatively with morning melatonin levels; as melatonin declines in the morning, PFC functioning increases (Killgore et al., 2018). Thus, melatonin may exert circadian effects on cognition by inhibiting neural functioning in regions such as the PFC, especially given the concentration of melatonin (i.e. MT1) receptors in the PFC (Seitheikurippu et al., 2008). This effect is particularly interesting in our study because melatonin was administered at 23:15 at night and the morning tasks began at 09:00, which is nearly ten hours later. Importantly, if the effects of taking exogenous melatonin, particularly slow- or extended- release melatonin, can impair cognitive functioning for an extended period of time after ingestion, then consumers of melatonin supplements should wait to complete cognitive until melatonin levels return to baseline.

Although the results of these studies have shed light on melatonin use in young adults, they also leave a number of outstanding questions that would make successful avenues for future research. The first outstanding question is about the timeline of the cognitive effects of melatonin. In our study, one of the last steps of the participants completed was the saliva assay,

and at this point in our study, melatonin concentrations were still elevated in the melatonin group. Therefore, the effects of the melatonin we administered to participants continued until after our study ended, making it unclear exactly how long melatonin affected cognitive performance and left melatonin concentrations in the body elevated. Future research should better gauge the timeline of melatonin levels and effect of performance in the morning by administering cognitive tasks and collecting salivary assays multiple times throughout the morning to assess changes over time.

A related question is how cognitive performance compares between those who took melatonin and placebo once melatonin levels decline to baseline in the melatonin group. Some studies have reported performance benefits after taking melatonin (Jean-Louis, Gizycki & Zizi, 1998; Peck et al., 2004; Kwon et al., 2015). One possibility is that performance was measured in these studies once melatonin levels had already declined in the morning. Thus, it is possible that melatonin ultimately does improve cognitive performance once melatonin levels normalize.

Another important consideration is how the melatonin we chose for this study affected our results. In Study 2, we used a brand of melatonin that has both a fast-acting layer that delivers melatonin quickly and an extended-release layer that administers melatonin over an extended period of time. As such, it is likely that the cognitive impairments we observed in the morning is that the extended-release component of the pill instead of the fast-acting component. If this is the case, then individuals may be able to avoid the cognitive impairments associated with melatonin after sleep by avoiding extended-release melatonin supplements. Thus, an important avenue for future research is to assess the differences between fast-acting and slow-release melatonin supplements on sleep and morning cognition.

In conclusion, we found that more than half of undergraduates use melatonin as a sleep aid, making it the most popular sleep aid among undergraduates. We also found that individuals most commonly take melatonin as a sleep aid to help them fall asleep and to prepare for a next-day commitment or event. However, our findings also showed that melatonin did not affect sleep and impaired morning cognition in young adults with healthy sleep. Therefore, the results of our two studies suggest there is likely a disconnect between the benefits young adults expect to gain from taking a melatonin supplement and the actual effects of melatonin on sleep and cognition. As such, young adults should take melatonin supplements cautiously so the consequences of melatonin supplementation outweigh the benefits.

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## APPENDIX A: SLEEP AID USE QUESTIONNAIRE

The questions asked on the Sleep Aid Questionnaire for each sleep aid a participant indicated using.

1. “Have you ever used any of the following over-the-counter medications or supplements to help you sleep? Please select all that apply.”

[Melatonin; Diphenhydramine (i.e. Benadryl, ZzzQuil, Aleve PM, etc.);

Doxylamine (i.e. Unisom); Cannabis/Marijuana; Alcohol; Prescription sleep

medication(s) (Please enter the specific names of your prescriptions below); Other

(Please specify); I have never used an over-the-counter or prescription

medications or supplements to help me sleep]

2. “In the past 30 days, have you taken \_\_\_\_\_ to help your sleep?”

(Yes; No)

3. “What is the total number of days/nights you used \_\_\_\_\_ to help you sleep?”

(Less than 10 times; 10-29 times; 30-59 times; 60-89 times; 90-180 times; more than 180 times)

4. “Think back to the first time you used \_\_\_\_\_ to help you sleep. How long have you started using \_\_\_\_\_ as a sleep aid?”

(Less than a month; Over a month, but less than a year, 1-2 year, 2-5 years, 5-10 years, more than 10 years)

5. “On average, how long before going to bed do you take \_\_\_\_\_ to help you sleep?

Please write your answer in minutes. (Ex. If you took \_\_\_\_\_ at 9:30 PM and go to bed at 10:00 PM, you should enter “30”.)

(Text entry to respond)

6. “When you use \_\_\_\_\_ as a sleep aid, how do you determine what dose you should take? Please select all that apply.”

[Take recommended dose listed on the packaging; Consult with a medical professional; Determine the dose on my own; Research the appropriate dose via the internet, or some other source; Other (please specify)]

7. “What brand(s) of \_\_\_\_\_ have you used in the past? Please type in the brand names below.”

(Text entry to respond)

8. “Think back to the last time you used \_\_\_\_\_ to help you sleep. What was the specific reason you used \_\_\_\_\_?”

(Trouble falling asleep; Trouble staying asleep; Poor sleep the prior night; Had an important commitment/appointment the following day; Cross time-zone travel/ jet lag; Shift work; Relieve symptoms of a diagnosed sleep disorder; Other (please specify))

9. “Think about all of the times you have used \_\_\_\_\_ to help you sleep, or as many as you can recall. Most commonly, what was the specific reason you used \_\_\_\_\_?”

(Trouble falling asleep; Trouble staying asleep; Poor sleep the prior night; Had an important commitment/appointment the following day; Cross time-zone travel/ jet lag; Shift work; Relieve symptoms of a diagnosed sleep disorder; Other (please specify))

## APPENDIX B: SLEEP DIARY

Example of a sleep diary entry.

Evening of (Fill in the date):

1. Time you went to bed: \_\_\_\_\_
2. Approximately how long did it take you to fall asleep? \_\_\_\_\_
3. Time that you got out of bed in the morning: \_\_\_\_\_
4. Did you feel well-rested when you awoke? Yes    No
5. Approximately how many times did you awake last night? \_\_\_\_\_
  - a) What was the total amount of time that you were awake (approximately)? \_\_\_\_\_
6. What is the total amount of time that you slept? \_\_\_\_\_
7. Did you nap at all during the day (following this evening)? Yes    No
  - a) What is the total amount of time that you slept during this nap? \_\_\_\_\_

## APPENDIX C: STANFORD SLEEPINESS SCALE (SSS)

The Stanford Sleepiness Scale (SSS), our measure of subjective sleepiness.

A. Please circle the number which best describes how you feel right now.

1. *feeling active and vital; alert; wide awake*
  2. *functioning at a high level, but not at peak; able to concentrate*
  3. *relaxed; awake; not at full alertness; responsive*
  4. *a little foggy, not at peak; let down*
  5. *fogginess; beginning to lose interest in remaining awake; slowed down*
  6. *sleepiness; prefer to be lying down; fighting sleep, woozy*
  7. *almost in reverie; sleep onset soon; lost struggle to remain awake*
  - X. *asleep*
-