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Antidepressants, circadian rhythms, and cognition: The effects of SSRIs and SNRIs on circadian rhythms and cognitive performance

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Antidepressants, Circadian Rhythms, and Cognition: The Effects of SSRIs and SNRIs on Circadian Rhythms and Cognitive Performance

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Abstract

It has been well documented that individuals with depression commonly experience sleep disturbances. Decreased sleep quality, diminished sleep efficiency, and increased nighttime awakenings are all typical ailments. Deficits in cognitive functioning often co-occur, including impairments in working memory, learning, inhibition, and set shifting. Many studies have found that upon taking antidepressants (i.e. serotonin agonists), individuals with depression experience normalized sleep and cognitive performance. The impact of antidepressants, especially SSRIs and SNRIs, on sleep stages, particularly REM and slow wave sleep, has been the subject of numerous studies. However, there is currently very limited literature that examines their impact on sleep quality and no literature examining circadian rhythm entrainment. The purpose of the present study was to extend current literature by exploring the effects of antidepressants, specifically SSRIs and SNRIs, on circadian rhythms, entrainment, and cognitive performance. Participants consisted of JMU graduate students who were either taking antidepressants or not taking antidepressants. All participants wore actigraphs and completed morning and evening sleep journals for two consecutive weeks to measure sleep parameters. Cognitive performance was assessed via the Automated Neuropsychological Assessment Metrics (ANAM). No significant differences in sleep parameters, circadian entrainment, or cognitive performance were found between groups. However, within the antidepressant group, years of antidepressant use and dosage demonstrated predictive qualities for certain cognitive measures, and time of antidepressant use predictive qualities for TST and time spent in bed.

Introduction

Prescription anti-depressant use has become commonplace in the United States. From 2015-2018, 13.2% of the U.S. population aged 18 and over used antidepressants in the past month (Brody & Gu, 2020) and their prevalence has increased by over 64% since 1999 (Winerman, 2017). Roughly 6.7% of the U.S. population is affected by major depressive disorder (MDD) with a greater prevalence seen in women than men (Anxiety and Depression Association of America [ADAA], n.d.**)**. Sleep deficiencies often accompany depression and these deficits are correlated with increased suicidal ideation and behaviors (Bernet & Joiner, 2007), as well as decreased cognitive functioning (Alhola & Polo-Kantola, 2007). Research on antidepressants and cognitive performance indicate no decrease in functioning (Goder et al., 2011), but currently there is very limited research that focuses on the impact of antidepressants on circadian rhythmicity. The purpose of this study is to explore the effects of Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) on circadian rhythms and cognitive performance.

Sleep and Depression

In healthy individuals, the typical pattern of sleep consists of four to five cycles, each lasting 90 to 120 minutes on average, of alternating non-rapid eye movement sleep (NREM) and rapid eye movement sleep (REM). NREM is divided into four stages (aptly named stage 1, stage 2, stage 3, and stage 4) with stage 3 and 4 often referred to as slow wave sleep (SWS). The first half of the night is where the majority of SWS occurs, while REM occurs mostly during the second half of the night (Amlan & Fuller, 2009; Argyropoulos & Wilson, 2005). However, when observing the sleep of individuals with

depression, numerous differences are found. People with depression often demonstrate greater sleep fragmentation in the form of increased wakefulness and decreased sleep efficiency. Many individuals also experience a decrease in total sleep time with an increase in sleep latency, which is the time it takes someone to fall asleep (Argyropoulos & Wilson, 2005). An important finding is that REM latency (the time between sleep onset and the first instance of REM sleep) often decreases with a corresponding increase in the duration of REM sleep (Argyropoulos et al., 2009). This is typically accompanied by a decrease in SWS.

The percentage of depressed patients who express difficulties falling asleep is as high as 90%, and there is evidence that these sleep disturbances increase risk factors for poor clinical outcomes (Germain & Kupfer, 2008). Poor sleep quality is associated with poor response to non-pharmacological treatments of depression. One such disturbance that often precedes the onset of depression is insomnia (Germain & Kupfer, 2008; Cole & Dendukuri, 2003). Insomnia has been shown to significantly increase the risk of developing Major Depressive Disorder (MDD), and even an increase in suicidality (Winsper & Tang, 2014; Dryman & Eaton, 1991; Agargun et al., 1997). Poor sleep quality and REM abnormalities post-treatment is associated with recurrence of depressive symptoms, while reported higher sleep quality post-treatment is associated with a lower risk of recurrence (Buysse et al., 1997).

Based on this information, multiple circadian rhythms hypotheses of depression have been proposed. One such model is the phase-shift hypothesis that depressive mood disturbances originate from either a phase advance or delay of our central pacemaker, which regulates circadian rhythms, temperature, cortisol, melatonin, and REM. Another

hypothesis is the internal phase coincidence model. This model postulates that depression is caused by awakening from sleep during a sensitive phase of the circadian rhythm, and thus there is a mismatch in circadian and sleep phases. There are other hypotheses that depression is a REM sleep disorder (as noted by the decrease in REM latency and increase in REM sleep), or a SWS disorder (Germain & Kupfer, 2008).

Depression and Cognitive Functioning

As for depression and cognitive functioning, it has been well documented that depression is associated with numerous deficits in episodic memory and learning (Goodwin et al., 1997). These deficits are seen in both explicit (conscious long-term memory) verbal and visual memory, but not in implicit (unconscious or automatic) memory tasks (Austin et al., 2001). In Austin et al. (1999), individuals with depression demonstrated deficiencies in working memory and tasks reliant on set-shifting. Working memory, which is the retention of small amounts of information in a readily accessible form (Cowan, 2014), was measured using the NAB digits forward/digits backward test, where digit span is assessed by presenting digits forward-facing and backward-facing (reversed) before requiring individuals to recall as many digits as possible. Set-shifting was assessed with the digit symbol substitution task (DSST), where numbers are each paired with a unique symbol. Individuals are provided with a key containing the numbers and corresponding symbols and are tasked with filling in the symbol for each number in an empty list. Doumas et al. (2011) also found working memory impairments on an item recall task in young patients (18-35 years old) with MDD. There have been conflicting results on inhibitory tasks (such as the Stroop test) with some studies indicating no impairments and others showing significant deficiencies (see Murphy et al., 1999). There

have also been numerous conflicting results about the relationship between severity of depression and deficiencies in cognitive performance. Some studies have found significant correlations between severity and task performance while others have not (see Austin et al., 2001).

In a meta-analysis of sixty-nine papers conducted by McDermott and Ebmeir (2009), researchers found there was a significant correlation between depression severity and cognitive performance. Specifically, episodic memory, executive functioning, and processing speed were found to be most affected by this relationship (meaning as severity increased, performance in these domains decreased). They also found that these deficiencies and correlations were independent of slowed psychomotor skills. These findings are supported by a second meta-analysis conducted by Rock et al. (2014) where researchers also found significant deficits in executive functioning, memory, and attention in patients with depression. The deficits discussed in these articles were consistent across the vast majority of studies included in the analyses, and thus provide strong evidence for the relationship between depression severity and cognitive impairments.

Sleep and Cognitive Functioning

As mentioned, diminished sleep quality is a common attribute of depression. Benitez and Gunstad (2012) found that poor sleep quality decreased cognitive functioning, even independent of depression. Their sample consisted of mainly undergraduate females and the Pittsburg Sleep Quality Index (PSQI) was used to measure sleep quality. Attention was assessed via the Adaptive Rate Continuous Performance Test (ARCPT), and the Trailmaking Test part B and FAS were used to assess executive

functioning. The ARCPT is a computerized test where letters of the alphabet randomly appear briefly in the center of the screen. Participants are tasked with responding (pressing the space bar) only when an X follows an A. The Trailmaking Test part B involves participants drawing lines on a sheet of paper that connect letters and numbers in an alternating pattern (ex. 1-A, 2-B, etc.). The FAS test requires participants to produce as many words as possible in 60 seconds to a given letter (F, A, and S). The Minnesota Multiphasic Personality Inventory-2 (MMPI-2) was used as a measure of personality and psychopathology.

Researchers found that individuals who scored higher on parts of the MMPI-2 related to depression and anxiety experienced poorer sleep quality (higher scores on the PSQI). They also found that poor sleep quality was associated with worse executive functioning, and poor sleep duration with worse attention. These findings remained consistent after controlling for MMPI-2 scores (particularly demoralization and emotional reactivity). These findings show that sleep deficiencies and poor sleep quality in and of themselves are associated with decreases in cognitive functioning. Seeing as how trouble sleeping is a common issue reported by individuals with depression (and sometimes their biggest struggle), these findings hold significant implications in the field of cognition and depression.

Sleep and Pharmacology

Selective Serotonin Reuptake Inhibitors (SSRIs) are the most commonly prescribed type of antidepressants (National Institute of Health [NIH], 2020). As their name suggests, SSRIs exert their action by inhibiting the reuptake of serotonin. This occurs at the presynaptic axon terminal by inhibiting the serotonin transporter (SERT),

which in turn increases the amount of serotonin available in the synapse (Xue et al., 2016). SSRIs are generally considered safe, effective, and have minimal effects on other neurotransmitters (National Institute of Health [NIH], 2020). Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) behave in the same way as they block the reuptake of both serotonin and norepinephrine by inhibiting their corresponding transporters (SERT and NET). SNRIs are a relatively newer class of antidepressants and there is some evidence that they have greater efficacy than SSRIs in treating moderate and severe depression (see Lambert & Bourin, 2002).

Cognition

Due to the increase in antidepressant usage in recent years, there has been a push to understand how this may affect cognitive functioning. The most common aspects of cognition studied is attention/alertness and memory and learning. One way of measuring attention is through reaction time tests. These tasks are simple and require the individual to respond as quickly as possible to a specific cue. Reaction time can be used to assess improvements or declines in performance, as well as detect slowed psychomotor abilities and is commonly used with depressed patients. Other common tasks are the Continuous Performance Test (CPT), which involves detecting exact sequences of 2-4 numbers or letters, the Critical Flicker Frequency test (CFF), which evaluates arousal and reactivity by measuring the perception of light frequency over time, and the DSST, which was previously discussed. As for memory and learning, short-term memory (STM) is typically measured via digit span tasks, where individuals are presented either a verbal or written list of numbers and tasked with recalling as many numbers as possible (healthy subjects normally demonstrate a span of 7-9 digits). Long-term memory (LTM) is

typically assessed via word and picture free recall tests, and recognition between original and distractor items (Amado-Boccara et al., 1992).

Through such studies, some SSRIs have been shown to have no cognitive impact while others have demonstrated a positive impact. Amado-Boccara et al., (1995) reviewed the effects of antidepressants on cognitive functions and found that cericlamine, fluvoxamine, and fluoxetine have no impact on the CFF, CPT, reaction time, or psychomotor performances. On the other hand, they found that nomifensine (though now withdrawn), zimeldine (also withdrawn), paroxetine, and sertraline all have been shown to produce positive cognitive effects. Specifically, paroxetine raises the CFF threshold, reduces reaction time, and improves psychomotor task performance. Sertraline also raises the CFF threshold and improves both reaction and choice reaction time (Amado-Boccara et al., 1992). Other studies have explored the effects of long-term antidepressant usage on cognition and have demonstrated that compared to controls, chronic antidepressant users showed no significant decrease in memory tests (Gorenstein et al., 2006). Gorenstein and colleagues compared individuals who had been taking antidepressants for between six months to four years to healthy controls. Participants completed numerous memory and psychomotor tests such as verbal recall, visual recall, digit span, word stem completion, DSST, reaction times, and the symbol copying test. They found no difference between depressed individuals and controls on the vast majority of tests. An interesting discovery was that individuals taking a higher antidepressant dosage were even more similar to controls than those on a low dosage. In Goder et al. (2011), researchers also found no difference in memory or neuropsychological performance in patients prescribed antidepressants. These studies demonstrate that antidepressant usage can ameliorate the

deficiencies in cognitive performance that often occur with depression and increase functioning to levels observed in healthy controls.

Sleep Architecture

Depression as a REM sleep disorder was investigated by Argyropoulos et al. in 2009, where researchers examined the effects of paroxetine and nefazodone on REM and SWS. They proposed that the relationship between REM and depression was not as simple as a decrease in REM latency and an increase is REM sleep, but that it was actually modulated through slow wave activity (SWA). As previously discussed, SWA is typically concentrated towards the beginning of the night before slowly declining throughout the rest of the night. However, individuals with depression often experience a lower peak of SWA in the beginning of the night and smaller spikes throughout. Studies have shown that SSRIs suppress REM and increase sleep continuity (Wilson et al., 2000), but this might not be the whole story. Argyropoulos and colleagues found that over the course of eight weeks, participants who took paroxetine experienced a consolidation of SWA towards the beginning of the night with a subsequent consistent decrease. SWA returned to the distribution typically observed in healthy controls. REM latency was greatly increased (to about 3-4 hours), and time spent in REM decreased. This was due to a significant lengthening of the first cycle of stage 1 and 2 sleep, which allowed for the increase in SWA and suppressed REM. These results show that the use of antidepressants normalize sleep in individuals with depression through not only the suppression of REM, but also redistribution of SWA.

Some studies have found that SSRIs temporarily decrease sleep quality, but this effect typically diminishes within eight weeks (Argyropoulos & Wilson, 2005). Some

SNRIs, such as duloxetine, and Norepinephrine Reuptake Inhibitors (NRIs), such as reboxetine, suppress REM in the same way SSRIs do while other SNRIs, such as venlafaxine, do not (Wichniak et al., 2017; Lam, 2006). However, SNRIs still demonstrate the same increase in SWA and SWS, and thus a normalized sleep architecture for this population. An interesting finding is that individuals with depression treated with SNRIs often report treatment-emergent insomnia at a higher frequency than those treated with SSRIs. However, overall treatment with SNRIs still demonstrates a decrease in sleep latency, improved sleep efficiency, and increased SWS (Wichniak et al., 2017). While there may be slight short-term deficits, the long-term impact of antidepressants is majority positive. Treatment of depression with SSRIs and SNRIs has strong support for a positive impact on cognitive functioning, sleep quality, and normalized sleep architecture.

Circadian Rhythms

The impact of SSRIs and SNRIs on sleep stages, particularly REM and SWS, has been the subject of numerous studies, but there is currently very limited literature that examines their impact on circadian rhythms. It is well known that individuals with depression often experience sleep disturbances and altered circadian rhythms (Germain & Kupfer, 2008). Our circadian clocks are located in the suprachiasmatic nucleus (SCN), and there is evidence that activation of serotonergic receptors in the SCN is necessary for circadian phase-resetting (Glass, DiNardo, & Ehlen, 2000). Many studies have found that upon taking antidepressants, individuals with depression experience normalized sleep, but this has yet to be examined in terms of wake-sleep patterns. An understanding of how

these patterns are impacted by antidepressant usage has major implications for insomnia and phase delay/advancement that often occurs with depression.

Overview of the Current Study

The purpose of the current study was to explore sleep-wake rhythms, sleep quality, circadian entrainment, and cognitive functioning of James Madison University (JMU) graduate students taking Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) over the course of two consecutive weeks. Antidepressant users were compared to a group of JMU graduate students not taking antidepressants. The antidepressants for this study, SSRIs and SNRIs, were specifically targeted due to their large popularity and high efficacy. As there is a lack of literature on this subject, a greater understanding of how antidepressants impact circadian rhythmicity and cognitive functioning will contribute to the understanding of chronobiology and cognition as a whole, while also providing a guide for further research in this area. It was hypothesized that the cognitive performance of graduate students taking antidepressants would match those of graduate students not taking antidepressants. It was also hypothesized that the circadian rhythms and sleep quality of graduate students taking antidepressants would match those of graduate students not taking antidepressants.

Methodology

Participants

Twenty-eight graduate students were recruited via email (Appendix A) or word-of-mouth from JMU. Two participants (1 AD, 1 Control) withdrew due to reported irritation of their wrists and one (Control) was excluded from analysis due to suspected

delayed sleep-wake phase disorder (DSP), resulting in a final sample size of twenty-five (AD = 13, M_{age} = 27.15 SD = 7.36; Control = 12, M_{age} = 23.58 SD = 1.68). The final sample was comprised of 21 females (AD = 12; Control = 9). 20 participants identified as White/Caucasian, 2 as Hispanic, 2 as Asian, and 1 as Russian (see Table 1 for complete demographics). As incentive for participation, a blind raffle for a $75, $50, or $25 VISA gift card as well as a comprehensive sleep and circadian analysis was offered.

Materials

Interest/Intake/Demographics Survey. The interest form asked participants if they were prescribed antidepressants, detailed the required time and activities that participation entailed, and asked for their signature certifying they were over the age of 18 and agreed to be contacted by the Principal Investigator about participation. The intake form asked participants about their prescribed medications (both antidepressants and others). For those prescribed antidepressants, the name, dosage, frequency of use, and length of use was recorded. Demographic information included participant gender, age, ethnicity, undergraduate GPA, and years of education completed.

Morningness-Eveningness Questionnaire (MEQ). The Morningness-Eveningness Questionnaire (MEQ) is a nineteen item self-report questionnaire that assesses an individual's tendency towards either an "evening-type" or "morning-type". Scores range from 16-86 with scores below 41 indicating an "evening-type", between 42 and 58 indicating an "intermediate-type", and above 59 indicating a "morning-type". This assessment was used to identify correlations between antidepressant use and preferential bed and wake times.

Pittsburgh Sleep Quality Index (PSQI). The Pittsburgh Sleep Quality Index (PSQI) is a nineteen item self-report questionnaire that assesses subjective sleep quality and disturbances over the previous month. It is comprised of seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medicine, and daytime dysfunction that together generate an individual's Global PSQI score. Scores range from 0-21 with 0 indicating no difficulties and 21 representing severe difficulties in all components. A score greater than 5 indicates poor sleep quality and distinguishes between "poor" and "good" sleepers. This assessment was used to compare subjective sleep quality between participants who used antidepressants and those who did not, as well as identify correlations with objective sleep measures.

Patient Health Questionnaire (PHQ-9). The Patient Health Questionnaire (PHQ-9) is a nine item self-report tool that assesses subjective depressive symptoms and is a module of the full PHQ. Scores range from 0-27, with 0 indicating no depressive symptoms, 1-4 minimal symptoms, 5-9 mild symptoms, 10-14 moderate symptoms, 15-19 moderately severe symptoms, and 20-27 severe symptoms. This questionnaire is for monitoring severity of symptoms only and was not designed as a diagnostic tool. This assessment was used to identify participants' severity of depressive symptoms and correlations with sleep and neurocognitive measures.

Sleep Journals. Journals asked for reports of bedtime, wake time, total sleep time, sleep onset latency, wake after sleep onset episodes, naps, actigraph compliance, and antidepressant compliance and time of day their antidepressant was taken. Journals were taken every night before bed and every morning upon waking for the duration of the two-

week period of participation. Sleep journals were used to score actigraphy data by aiding in the determination of sleep onset, sleep onset latency, and morning wake time.

Automated Neuropsychological Assessment Metrics (ANAM). The ANAM, distributed exclusively by Vista LifeSciences, is a tool designed to evaluate cognitive function or changes in cognition (vistalifesciences.com/anam-intro). The metric contains 22 different scales that can be customized into specific batteries to meet user needs. Scales encompass cognitive abilities such as inhibition, memory recall, accuracy, and reaction time. There is ample evidence to support the reliability and validity of the various scales that comprise the ANAM (Kane et al., 2007; Short et al., 2007; Kabat et al., 2001). To minimize circadian effects, the ANAM was administered to all subjects between 10:30 AM and 5:00 PM. This assessment was used as a comparison of cognition between participants who used antidepressants and those who did not.

Sleepiness Scale. This is a modified version of the Stanford Sleepiness Scale (SSS-R) that contains seven sentences describing different levels of wakefulness and alertness. Participants select the sentence that best describes how they feel at that moment. This measure assesses state sleepiness and current level of alertness.

Procedural Reaction Time. Participants are presented with a series of numbers ranging from 2-5 and are instructed to respond with the left mouse button if the number is "low" (2 or 3), or the right mouse button if the number is "high" (4 or 5). This task measures speed and efficiency of processing.

Matching Grids. Two 4 x 4 cubes containing colored (checkerboard) patterns are presented side-by-side with patterns either in the same direction or rotated.

Participants respond with the left or right mouse button to indicate whether or not the patterns are the same. This task measures spatial processing and memory.

Logical Relations. The symbols "&#" or "#&" are presented on the screen with a statement above either correctly or incorrectly stating the order of the symbols (i.e. "& is first" or "# is not second"). Participants must indicate if the statement is true or false. This task assesses logical reasoning.

Code Substitution - Learning. Based on the symbol digit-coding paradigm, this task presents participants with pairings of 9 symbols and digits in a "key" on the top of their screen. The bottom of the screen contains a box with one symbol-digit pairing that changes from correct to incorrect pairings. Participants indicate whether or not the pairing matches the above key (right mouse click for correct match, left for incorrect). This task assesses scanning and paired associate learning.

Continuous Performance Test. Participants must monitor their screen in wait for an "X" that infrequently appears and respond with the left mouse button when it does. This task is a measure of sustained attention.

Go-No-Go. Participants are presented with two characters ("x" and "o") and instructed to respond only when "x" is present. This task assesses response inhibition by measuring their ability to correctly respond to "x" while inhibiting their response to "o".

Simple Reaction Time. Participants are presented with a series of * (star) symbols and are instructed to respond with the left mouse button as quickly as possible whenever the * appears on the screen. This task measures pure reaction time.

Stroop Test. This test is composed of three sub-tasks. In the first task (Color), participants are presented with the words Red, Green, or Blue in black and white and respond with the number keys that correspond with the name of the color (1 for Red, 2 for Green, and 3 for Blue). In the second task (Word), four Xs are presented in one of the three colors and participants must press the key that corresponds with the color of the Xs. In the third task (ColorWord), the words Red, Green, or Blue are presented again in mismatched colors with their meanings. Participants must press the key that corresponds to the color of the letters, not the meaning of the word. This task is a measure of cognitive interference inhibition.

Actigraphs. Small watch-like devices that measure wrist activity and reliably infer sleep and circadian parameters from that information. Motionlogger actigraphs from Ambulatory Monitoring Inc. (Ardsley, NY) were used. This data was first analyzed using Action-W 2 software with epochs and sampling mode set to one-minute and zero crossing mode (ZCM), respectively. To assess circadian entrainment, data was analyzed using Action4 software. Actigraph data was averaged over the 14 day period for all group comparisons.

Procedure

Intake. Graduate students were asked to come in-person to the Sleep and Actigraphy Laboratory at James Madison University. After the details of the study and what participation would involve was covered in-depth, all participants signed an informed consent form. Upon consent, participants completed the brief intake survey about their demographics and medication use followed by the MEQ, PSQI, and PHQ-9. After these were completed, the ANAM was administered. During the ANAM,

researchers stepped out of the lab in order to avoid serving as a distraction. Once the ANAM was completed, participants were given an actigraph, verbal and written instructions for actigraph care and use, and information on the JMU Counseling Center.

Check-in. One week (seven days) after their first visit to the lab, an email was sent to participants in order to check in, answer any questions, and ensure there were no negative side effects occurring. In this email, participants' final lab session was scheduled.

Final Lab Session. Two weeks (fourteen days) after their first lab sessions, participants returned to the lab at the same time of day as their initial visit. Their actigraph was collected and data downloaded. The ANAM was then administered a second time while researchers stepped out of the lab. Upon completion, participants were debriefed and asked if they would like to receive an analysis of their sleep.

COVID-19 Precautions. As this study took place during the COVID-19 pandemic, special precautions were taken to ensure the safety of both participants and researchers. Before participants arrived at the Sleep and Actigraphy Lab, all tables, desks, chairs, door handles, and computers were sanitized using the disinfectant spray provided by JMU. Both participants and researchers were required to wear masks at all times and were seated at separate desks over six feet apart. Prior to each intake session, all relevant materials were placed in a manila folder on the participants' table along with their disinfected actigraph. Participants were asked to use their own pen to sign the informed consent form. Sanitized pens were provided upon request and were sanitized again after use. With the exception of the ANAM, all surveys and assessments were completed virtually on the participants' own phone in order to keep contact to a minimum. The

ANAM is a commercial instrument, so it required the use of the lab computer. Upon completion of the ANAM, the computer, keyboard, mouse, desk, and chair were disinfected. After participants left the lab, all surfaces were once again disinfected. These cleaning and social distancing guidelines were followed for each lab visit.

Results

All participants displayed 100% compliance by wearing their actigraph for the duration of their two-week participation in the study. Only one participant reported using an SNRI, so the SNRI and SSRI groups were combined into one single antidepressant group (AD). No participants in the control group reported using any antidepressant or antianxiety medication. Within the antidepressant group, 11 participants showed 100% compliance with antidepressant use by taking their prescribed dosage every day, 1 participant showed 93% compliance, and 1 participant showed 86% compliance. The median length of time participants had been using antidepressants was 4 years (SD = 7.32 years, Min = 2 months, Max = 27 years). The average years of education completed for the AD group was 16.83 (SD = .59) and 17.08 (1.46) for the control group. Controls had an average undergraduate GPA of 3.67 (SD = .20), and the AD group displayed an average of 3.53 (.34). Average PSQI scores were 10.08 (SD = 4.09) for the AD group and 7.83 (2.41) for controls. Scores on the MEQ indicated that all participants were categorized as intermediate chronotypes (AD = 50.38, SD = 4.59, Control = 48.43, SD = 4.28). No significant differences were found between groups when comparing their years of education completed, GPA, PSQI, or MEQ scores, suggesting that all participants had similar educational backgrounds and preferred sleep-wake schedules. The average PHQ-9 score for the AD group was 12.15 (SD = 7.45) and 7.25 (SD = 4.25) for the control

group. While these scores did not statistically differ from each other likely due to the small sample size, $t(23) = 1.99$, $p = .06$, the effect size for the difference was large ($d = .81$) indicating that participants in the AD group experienced more severe depressive symptoms than the control group at the time of this study.

Cognition

Paired t-tests were conducted to evaluate if there were any differences between time 1 and time 2 of ANAM administration. Significant differences were found for reaction time on the Logical Relations task (Time1 = 1959.88, SD = 477.36; Time2 = 1751.07, SD = 373.21), $t(23) = 2.39$, $p = .03$, $d = .49$, Matching Grid task (Time1 = 1703.95, SD = 442.53; Time2 = 1460.66, SD = 372.08), $t(23) = 4.25$, $p < .001$, $d = .60$, Code Substitution – Learning task (Time1 = 1066.64, SD = 236.05; Time2 = 943.90, SD = 135.78), $t(16) = 4.78$, $p < .001$, $d = .64$, and the Stroop Test, Color (Time1 = 542.73, SD = 110.72; Time2 = 511.34, SD = 90.31): $t(23) = 2.37$, $p = .03$, $d = .31$, Word (Time1 = 619.39, SD = 112.24; Time2 = 586.59, SD = 97.73): $t(23) = 2.19$, $p = .04$, $d = .31$, ColorWord (Time1 = 738.88, SD = 160.82; Time2 = 673.64, SD = 138.91): $t(23) = 2.37$, $p = .03$, $d = .43$. No differences in these patterns between groups were found. As such, these tasks were left separate as time 1 and time 2 in all subsequent analyses. Averages of time 1 and time 2 were used for all other tasks where no differences between time of administration were found.

No significant between group differences were found on any of the ANAM tasks. However, higher antidepressant dosage negatively correlated with reaction time for Logical Relations time 1 ($r = -.66$, $p = .03$), Procedural Reaction Time ($r = -.78$, $p < .001$), Matching Grid correct responses ($r = -.82$, $p < .001$), correct responses on Go-No-Go ($r =$

-.80, p <.001), and Simple Reaction Time (r = -.674 p <.01). Greater number of years taking antidepressants positively correlated with reaction time for Matching Grid time 1 (r = .74, p <.01), time 2 (r = .76, p <.01), and negatively correlated with Code Substitution – Learning (r = -.64, p = .03). For the AD group only, MEQ scores positively correlated with Procedural Reaction Time (r = .64 p = .02) and Code Substitution – Learning (r = .70 p = .01). No correlations between the PSQI and PHQ-9 for either groups were found. To further investigate these correlations, multiple regression was used to evaluate the predictive quality of years of antidepressant use and antidepressant dosage on these ANAM tasks. In order to analyze potential interactions, variables were mean-centered to reduce multicollinearity among predictors.

The model containing years of antidepressant use and antidepressant dosage significantly predicted reaction time on the 2nd administration of the Logical Relations task and an interaction was found between the predictors [R^2 = .84, $F_{change}(1,7)$ = 6.05, p = .04]. The interaction accounted for 68% of the variance in reaction times (b = -5.36, p = .04, sr^2 = -.68). Antidepressant dosage significantly contributed to the model (b = -27.36, p = .02, sr^2 = -.76), while years of antidepressant use did not (b = -47.77, p = .49, sr^2 = -.26). However, the interaction term indicates that as years of antidepressant use increases, the relationship between antidepressant dosage and reaction time becomes more negative.

The model containing years of antidepressant use and antidepressant dosage significantly predicted Procedural Reaction time [$F(2,9)$ = 19.72, p <.01] and accounted for 81% of the variance in reaction time (R^2 = .81). Both years of antidepressant use and dosage significantly contributed to the model, accounting for 70% and 81% of the variance, respectively [b_{yoad} = -10.74, p = .02, sr^2 = -.70; $b_{ADdosage}$ = -1.102, p <.01, sr^2 = -

.81]. As indicated by the negative slopes and squared semipartial correlation coefficients, both participants who have used antidepressants for a greater amount of time and those who take higher dosages demonstrate slower procedural reaction times. No interaction between years of use and dosage was found.

Years of use, dosage, and their interaction also predicted Matching Grid performance [$F_{change}(1,8) = 10.54$, $p = .01$] and accounted for 98% of the variance in correct responses ($R^2 = .98$). The interaction accounted for 75% of the variance in correct responses ($b = -.02$, $p = .01$, $sr^2 = -.75$). Antidepressant dosage significantly contributed to the model ($b = -.118$, $p < .01$, $sr^2 = -.89$), while years of antidepressant use did not ($b = -.617$, $p = .21$, $sr^2 = -.26$). However, the interaction term indicates that as years of antidepressant use increases, the relationship between antidepressant dosage and matching grid performance becomes more negative. This model was not a significant predictor of reaction time for time 1 [$R^2 = .53$, $F(2,8) = 1.584$, $p = .26$] or time 2 [$R^2 = .54$, $F(2,9) = 1.86$, $p = .21$].

Years of antidepressant use, dosage, and their interaction also predicted correct responses on the Go-No-Go task [$F_{change}(1,8) = 6.36$, $p = .04$] and accounted for 97% of the variance ($R^2 = .97$). The interaction accounted for 67% of the variance in correct responses ($b = -.03$, $p = .04$, $sr^2 = -.67$). Antidepressant dosage significantly contributed to the model ($b = -.15$, $p < .01$, $sr^2 = -.84$), while years of antidepressant use did not ($b = -.94$, $p = .23$, $sr^2 = -.42$). However, the interaction term indicates that as years of antidepressant use increases, the relationship between antidepressant dosage and correct responses on the Go-No-Go task becomes more negative. However, this relationship was

not found for incorrect or missing responses, indicating that these factors did not impact cognitive inhibition.

The same model predicted Simple Reaction time [$F(2,9) = 24.15$, $p < .001$] accounting for 84% of the variance in reaction times ($R^2 = .84$). Both years of antidepressant use and dosage significantly contributed to the model, accounting for 81% and 78% of the variance, respectively [$b_{yoad} = -7.36$, $p < .01$, $sr^2 = -.81$; $b_{ADdosage} = -.49$, $p < .01$, $sr^2 = -.78$]. As indicated by the negative slopes and squared semipartial correlation coefficients, participants who have used antidepressants for a greater amount of time and those who take higher dosages demonstrate slower reaction times. No interaction between years of use and dosage was found.

For the first administration of the Stroop Test, years of antidepressant use and dosage predicted each sub task [Color: $R^2 = .91$, $F(2,9) = 21.71$, $p < .001$; Word: $R^2 = .84$, $F(2,9) = 10.55$, $p < .01$; ColorWord: $R^2 = .70$, $F(2,9) = 10.47$, $p < .01$]. For the Color and ColorWord subtasks, both years of antidepressant use and dosage significantly contributed to the model [Color: $b_{yoad} = -1.92$, $p < .01$, $sr^2 = -.77$; $b_{ADdosage} = -.15$, $p < .01$, $sr^2 = -.79$; ColorWord: $b_{yoad} = -2.30$, $p = .03$, $sr^2 = -.67$; $b_{ADdosage} = -.15$, $p = .04$, $sr^2 = -.63$]. As indicated by the negative slopes and squared semipartial correlation coefficients, participants who have used antidepressants for a greater amount of time and those who take higher dosages demonstrate slower reaction times on the Color and ColorWord tasks. Only years of antidepressant use significantly contributed to the model for the Word sub task [$b_{yoad} = -2.37$, $p = .02$, $sr^2 = -.70$], indicating that those who have taken antidepressants for a greater amount of time demonstrate slower reaction times on the

Word sub task. No interactions between years of use and dosage were found for any subtasks.

Circadian Rhythms

Analyses using multiple regression were conducted to determine whether years of antidepressant use and antidepressant dosage predicted circadian rhythm alterations in the AD group. These results were non-significant [$F(2,9) = 2.80$, $p = .11$]. The average sleep-wake rhythms for the AD group ($R^2 = .58$) and control group ($R^2 = .57$) did not significantly differ in their fit to the cosine model, $t(23) = .09$, $p = .93$, $d = .03$, indicating that both groups were equally entrained to 24-hr model.

Sleep

No significant differences on any sleep parameters were found between the AD and control groups. Effect sizes were calculated using Cohen's d, with most parameters falling below .2 in size. However, the effect sizes for wake after sleep onset (AD: 49.01 min, SD = 70.04 min; Control: 35.02 min, SD = 79.94 min) and sleep efficiency (AD: 83.93%, SD = 10.93; Control: 87.69%, SD = 8.00) were .37 and .39, respectively. While there is no literature to compare the size of these effects to, they indicate that there could be at least a moderate difference in WASO and sleep efficiency not found to be statistically significant due to the small sample size. Average sleep parameters for each group are depicted in Table 4.

Time of day that participants took their antidepressant was positively correlated and TST ($r = .72$, $p = .02$) and time spent in bed ($r = .74$, $p = .01$), indicating that participants who took their antidepressant later in the day slept longer and spent more

time in bed. Multiple regressions were conducted in order to further evaluate these relationships.

A model containing years of antidepressant use, antidepressant dosage, and time of antidepressant use was used to predict TST. The overall model was non-significant [R2 = .64, $F(3,6) = 3.61$, $p = .09$]. However, time of antidepressant use did significantly contribute to the model and accounted for 79% of the variance in TST [$b = .003$, $p = .02$, $sr^2 = .79$]. This indicates that participants who took their antidepressant later in the day experienced greater TST. The same model significantly predicted total time in bed [$F(3,6) = 5.03$, $p = .04$] and accounted for 72% of the variance ($R^2 = .72$). Only time of antidepressant use significantly contributed to the model and accounted for 75% of the variance in bed duration [$b = .002$, $p = .03$, $sr^2 = .75$]. This indicates that participants who took their antidepressant later in the day spent more time in bed, whether or not this time was spent asleep. No other correlations or relationships between antidepressant variables and sleep parameters were found.

Discussion

The goal of this study was twofold: to investigate the effects of SSRIs and SNRIs on circadian rhythmicity and entrainment; and examine their impact on cognition. I provided some evidence that there are no differences in circadian rhythmicity, entrainment, or cognition between individuals taking antidepressants and those who do not. Previous literature foreshadowed these results; however, this study was the first to actively investigate the circadian properties of antidepressants that act upon serotonergic systems in human subjects. While no differences between groups were found, a number of variables displayed predictive qualities within the AD group.

The current study indicated that participants in both the AD and control groups were equally entrained to the traditional 24-hr Cosinor model, and no significant differences in mean bed-wake times, TST, sleep efficiency, WASO (wake after sleep onset), or other circadian parameters were found. While effect sizes indicated a potential difference in sleep efficiency and WASO with the AD group performing poorer in each, the difference is only about 4% in sleep efficiency and 14 minutes in WASO. In light of the lack of statistical or practical differences in TST, sleep latency, time in bed, and mean bed-wake times, these differences in WASO and sleep efficiency are likely not noticeable to the sleeper. As such, these results suggest that antidepressants have a positive impact on circadian rhythmicity and can enable users to achieve sleep schedules and quality equivalent to those of individuals not experiencing depression. However, I found some evidence that the time of day participants took their antidepressant impacted TST and time spent in bed. Those who took their antidepressant later in the day spent more time in bed and experienced greater TST. While I lacked the power to explore this relationship in more depth, the interplay between time of antidepressant use and circadian parameters warrants further investigation.

As for the cognitive measures, no differences between groups were found. The negative cognitive effects of depression have been well-established (Cowin, 2014; Austin et al. 2001; Doumas et al., 2011), so these results indicate that antidepressants can enable users to perform at the same level of individuals without depression and are consistent with previous literature (Goder et al., 2011; Gorenstein et al., 2006; Amado-Boccara et al., 1995). In addition, I found evidence that antidepressant dosage and its interaction with years of antidepressant use can play a factor in certain cognitive areas such as spatial

processing, logical reasoning, and procedural reaction times. My results depicted that higher dosages of SSRIs and SNRIs alone predict poorer performance on simple reaction times and some aspects of cognitive inhibition.

When it comes to procedural reaction times and spatial processing, the relationship between dosage and performance was modulated by years of antidepressant use, meaning that those who were prescribed higher dosages displayed poorer performance the longer they had been using their antidepressant. These results stand in contrast to previous literature that indicated chronic antidepressant users displayed no decrease in cognitive functioning (Gorenstein et al., 2006). However, previous literature focused on memory tasks whereas the differences in this study pertain to spatial processing and procedural reaction time and I included dosage as an additional variable. This interaction was not found for tasks related to cognitive inhibition or simple reaction time. While these variables accounted for large amounts of variance in performance, their effects were not large enough to produce significant between-group differences. The interaction between dosage and years of use is also difficult to interpret considering that the exact type of SSRI or SNRI was not constant for all participants. Other variables, such as the specific half-lives and affinities for serotonergic receptors, could impact this relationship. The interaction found in this study should not be taken out of context and interpreted to mean that higher dosages of antidepressants have negative cognitive effects but rather should be explored further in a more controlled setting where specific types of SSRIs or SNRIs are held constant. Overall, these results provide further evidence that antidepressants can have positive impacts on the cognitive abilities of individuals with depression and bring performance levels back up to pre-depressive states.

The fact that I found statistically and practically significant differences on a number of tasks between time 1 and time 2 of ANAM administration is somewhat baffling. The ANAM is typically considered robust to practice effects (Vincent et al., 2017; Roebuck-Spencer et al., 2007), yet participants in the AD and control group both performed better during the second administration (with no differences between groups). While I have no concrete explanation for why this occurred, there are a few factors that could have influenced their performance. First, a number of technical issues with the first administration of the ANAM occurred where an error message appeared on screen before the code substitution-learning task. This distraction could have impacted participants' initial performance. However, only half of the participants actually experienced this error message and the sample as a whole still performed better on the second administration. The second factor at play is purely anecdotal evidence. After the second administration of the ANAM, all participants were asked how they felt about the tasks and their performance. All participants responded by saying they felt more comfortable the second time as they knew what to expect and were able to focus more on the tasks. This suggests that there could be some form of first-lab effects, but this would require more substantial and concrete evidence in order to draw any conclusions.

The most obvious limitation of this study is the small sample size I was able to recruit, and due to the small sample size I was unable to control for other medications or tease apart potential differences between SSRIs and SNRIs. A number of technical difficulties with the ANAM also might have introduced confounding variables in the data. Another major limitation is the fact that data collection occurred during the COVID-19 pandemic. COVID-19 has had a major negative impact on not only economics

(Fernandes, 2020) but also mental health (Salari et al., 2020). There has been a marked increase in stress and anxiety due to COVID-19 (Xiong et al., 2020; Horesh & Brown, 2020), both of which have negative impacts on sleep (Van Reeth et al., 2000). Given this information, there is no certainty that the same pattern of results would be found outside of pandemic times. However, the values for the variables of interest in this study are not abnormal and this would suggest that my findings should not be considered simply byproducts of the pandemic.

It is important to note that the medication use of the AD group was not limited to one single brand of SSRI or SNRI as many participants were prescribed multiple antidepressant and antianxiety medications. While antidepressant-free, participants in the control group were not completely medication-free. However, rates of use of some of these medications were comparable between groups. It is possible that the circadian effects found in this study are at least partially due to other medications or interactions among a number of substances. However, in light of the ample evidence available of the cognitive and sleep deficits that accompany depression (Bernet & Joiner, 2007; Alhola & Polo-Kantola, 2007; Argyropoulos et al. 2009; Germain & Kupfer, 2008; Doumas et al., 2011; Goodwin et al., 1997) and the overall shortage of literature on this subject, my lack of finding differences between the AD and control groups provides some evidence that antidepressant have a positive impact on circadian rhythmicity and cognition, and can possibly ameliorate previous deficits due to depression.

Future Directions

While this study raises more questions than answers and the results are merely suggestive, the patterns found here are of great interest and require further investigation

to fully understand the circadian effects of antidepressants. Future studies should control for other medications and recruit a larger sample of both SSRI and SNRI users. A sample of non-college students should be recruited to aid in the generalizability of these results. As previously stated, this data was collected during the COVID-19 pandemic so these results warrant investigation in non-pandemic times. I found some evidence that the time of day antidepressants are taken can impact TST and time in bed, so future studies should further explore these relationships in a more controlled setting. The interaction between years of antidepressant use and dosage should also be further explored in the context of their effects on spatial processing and procedural reaction times.

With an ever-increasing prevalence of anxiety and depression in college students (Duffy et al., 2019) as well as significant increases in antidepressant use (Winerman, 2017; Brody & Gu, 2020), the need for a comprehensive understanding of the impact antidepressants have on students' daily lives is crucial. The COVID-19 pandemic has seen an even steeper increase in anxiety and depression rates in college students (The Healthy Minds Network & American College Health Association, 2020), yet there is still a major lack of literature that examines the effect of antidepressants on circadian rhythms and entrainment. This study was the first to investigate the relationship between antidepressants that act on serotonergic systems and circadian entrainment in a human population and provided evidence for the positive impact these antidepressants can have on the circadian and cognitive deficiencies that commonly accompany depression. There are still many unanswered questions, but this study serves as a starting point for future investigation.

Table 1.

Demographics

	N	Age	Gender	YOEC	GPA	YOAD
AD	13	27.15	12 (F)	16.85	3.53	4
Control	12	23.58	9 (F)	17.08	3.637	-
Total	25	25.44	21 (F)	16.96	3.60	-

Table 2.

Antidepressants by Classification

	N	Classification
Primary Antidepressant		
Citalopram	1	SSRI
Desvenlafaxine	1	SNRI
Escitalopram	3	SSRI
Fluoxetine	1	SSRI
Paroxetine	1	SSRI
Sertraline	6	SSRI
Secondary Prescription		
Aripiprazole	1	Atypical Antipsychotic
Alprazolam	2	Benzodiazepine
Bupropion	4	NDRI
Buspirone	1	Anxiolytic

Table 3.

Prescription Medication use by Group

	AD	Control
Albuterol	1	-
Atomoxetine	1	-
Amphetamine Salts	-	1
Birth Control	6	6
Clonazepam	1	-
Levothyroxine	-	1
Metoprolol	1	-
Montelukast	1	-
Propranolol	1	1
Sumatriptan	-	1

Note: Numbers indicate the number of participants prescribed each medication

Table 4.

Average Sleep Parameters by Group

	Sleep onset	Wake Time	TST	SLAT	Sleep Efficiency	WASO
AD	0:32(70.04)	8:14(84.06)	419.1(71.98)	30.34(29.29)	83.93%(10.93)	49.01(42.29)
Control	0:53(78.94)	8:34(70.86)	429.3(46.35)	30.45(23.14)	87.69%(8.00)	35.02(32.61)

Table 5.

Performance on ANAM by Group.

Metric	AD	Control
Continuous performance task	442.35 (31.34)	451.34 (35.40)
Code substitution - learning	88.66 (19.10)	76.39 (25.11)
Go-No-Go # correct	108.50 (16.68)	106.90 (15.82)
Go-No-Go # incorrect	5.85 (2.76)	6.92 (4.01)
Go-No-Go # missed	.65 (1.81)	.58 (.67)
Logical relations % correct	89.26 (16.77)	92.01 (8.13)
Logical relations reaction time (1)	1934.97 (480.63)	1984.78 (494.07)
Logical relations reaction time (2)	1695.40 (374.80)	1811.40 (378.20)
Matching Grid % correct	91.92 (12.84)	93.33 (6.34)
Matching grid reaction time (1)	1629.10 (337.80)	1778.80 (532.10)
Matching grid reaction time (2)	1509.40 (299.10)	1407.80 (445.60)
Procedural reaction time	578.10 (99.25)	580.90 (60.21)
Simple reaction time	282.30 (47.05)	292.50 (25.78)
Stroop test - color (1)	519.50 (75.14)	565.90 (137.20)
Stroop test - color (2)	502.00 (57.03)	523.03 (119.28)
Stroop test - word (1)	588.50 (67.38)	650.30 (140.40)
Stroop test - word (2)	567.86 (78.73)	606.29 (117.57)
Stroop test - color/word (1)	721.10 (121.70)	756.70 (196.40)
Stroop test - color/word (2)	679.79 (99.82)	682.91 (169.96)

Mean reaction times for correct trials depicted in milliseconds for continuous performance task, logical relations, matching grid, procedural and simple reaction time, and stroop test. Percent correct depicted for code substitution – learning, logical relations, and matching grid. Correct, incorrect, and missed responses depicted for Go-No-Go. Standard deviations shown in parentheses.

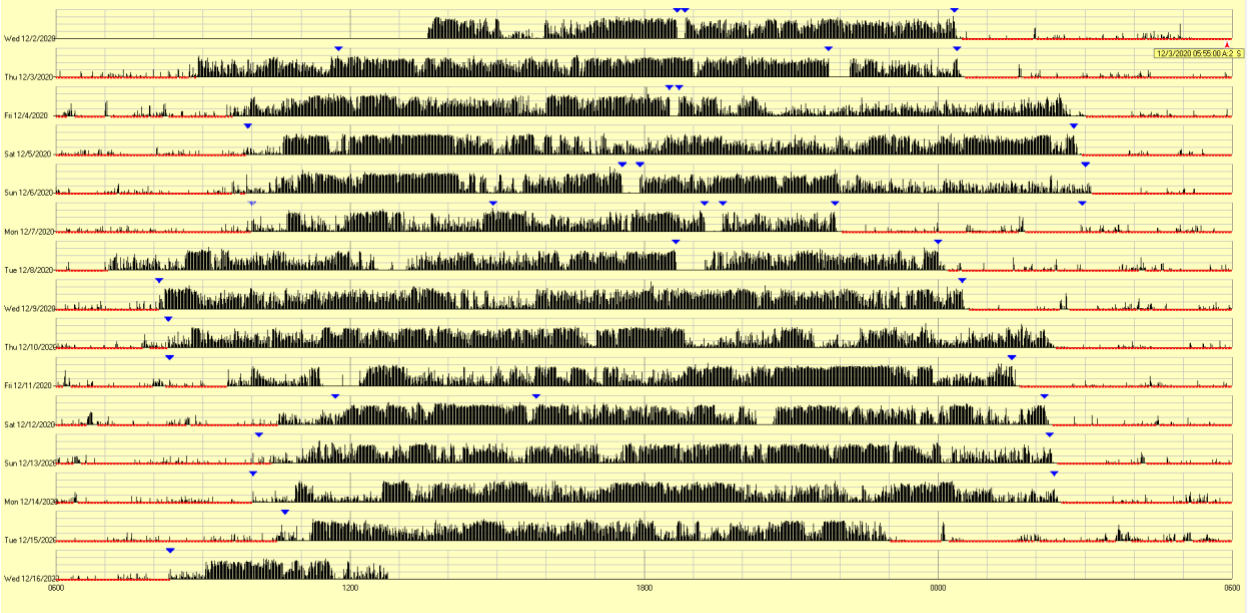

Figure 1. Example of actigraph data.

Appendix A

Participant recruitment email

"Interested in learning more about your sleep? Participate in a sleep study!

Researchers in the Sleep and Actigraphy Lab are seeking graduate students to participate in a study examining the effect of antidepressants on sleep behaviors and cognitive performance. This study will serve as the researcher's Master's Thesis.

Participation entails wearing an actigraph watch for two consecutive weeks to measure sleep behaviors. A 30-45 minutes intake session at the beginning of the study, a 10 minute mid-study check-in, and a 30-45 minute debrief session at the end of the study is required and involves coming in person to the Sleep and Actigraphy Lab located in Miller Hall. Per JMU guidelines, all social distancing, mask-wearing, and sanitization protocols will be followed.

Participants will be entered into a raffle at the end of the study for a chance to win one of three prepaid VISA gift cards worth either $75, $50, or $25."

Appendix B

Intake Survey

Participant Identification Number: _____

Gender:_____

Age: _____

1. Are you prescribed any antidepressants (yes/no)? _____

1a. If yes: What antidepressants are you taking? _____

1b. What is your prescribed dosage?_____

1c. How often do you take your antidepressant?_____

2. Are you prescribed any other medications (yes/no)?_____

2a. If yes: What other medications are you taking?_____

Appendix C

Sleep Journal

Participant Identification Number _____

To be filled out just before you go to bed: Date:_____

1. Did you take any naps? _____

1a. If yes: When? _____ How long? _____

2. Did you take the actigraph off for any period during the day? If so when and for how long?_____

3. If applicable, did you take your prescribed antidepressant today (if so, please record the time)?_____

To be filled out upon waking up in the Morning: Date: _____

1. What time did you first try to go to sleep last night? _____

2. How long did it take you to fall asleep last night? _____

3. How many times did you wake up during the night? _____

3a. How many total minutes were you awake last night after you first fell asleep? _____

4. What time did you wake up this morning? _____

5. How many total hours of sleep did you get last night? _____

6. Did the actigraph impact your ability to sleep?_____

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