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The Role of Medical Cannabis Use in Pain, Sleep, and Mental Health Outcomes Among Older Adults

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THE ROLE OF MEDICAL CANNABIS USE IN PAIN, SLEEP, AND MENTAL HEALTH OUTCOMES AMONG OLDER ADULTS

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ABSTRACT

Older adults represent the fastest growing demographic of cannabis users, and they endorse cannabis use for a variety of reasons including modulation of chronic pain, mental health symptoms, and sleep concerns. Despite escalating patterns of use, current evidence leaves questions of efficacy unanswered among these groups of users. Goals of the present study were to examine the role of medicinal cannabis within subjects at the daily level on the interrelated symptoms of depression, anxiety, sleep, and pain. A final sample of 106 medical cannabis users were recruited nationwide, ranging from 55 to 74 years of age (66.67% female, 82.86% white). A fully within-subject multilevel structural equation model was conducted with use patterns and symptomology broken into four temporal epochs. Subjective intoxication (Epoch 1) averaged across the day was used to predict subsequent anxiety, depression, and pain levels (Epoch 2), which then were used to predict sleep that night (Epoch 3), then subsequent anxiety, depression, and pain levels the following day (Epoch 4) prior to initiation of cannabis use. Results indicated that subjective intoxication negatively predicted post-use anxiety, depression, and pain. There was also a significant indirect effect from subjective intoxication to sleep quality through post-use anxiety. These findings provide evidence of momentary improvement in symptomology, but do not speak to long term changes. Findings are limited by measures used and potential expectancy effects but may help practitioners and patients determine windows for therapeutic use and identify potential development of problematic use as reinforced by momentary improvements in symptomology. Despite its limitations, the results of this study contribute to a growing body of research evaluating the efficacy of medicinal cannabis use for older adults.

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INTRODUCTION

Medicinal cannabis use dates back thousands of years, appearing among a multitude of ancient cultures (Mechoulam, 1983). More recently, overall rates of cannabis use tend to fluctuate throughout the decades, but a strong increase has occurred in recent years, especially among older adults – the fastest growing population of cannabis users (Han & Palamar, 2018, 2020). Medicinal cannabis is used for a variety of conditions among older adults, including pain/arthritis (endorsed, in a sample of $N = 83$ older adults, by 73%), sleep disturbance (29%), anxiety (24%), and depression (17%). Furthermore, common combinations of symptoms endorsed by older adults include both pain and sleep; both depression and anxiety; and pain, sleep, depression, and anxiety altogether (Yang et al., 2021). The list of conditions for which medicinal cannabis may be legally prescribed varies by state, but the preceding conditions often make that list. Within the literature regarding the health effects of cannabis and cannabinoids, the strongest evidence exists to support its use for chronic pain, as well as nausea reduction and spasticity improvement (National Academies of Sciences Engineering and Medicine, 2017).

Less well-supported is the use of cannabis for treating sleep disturbance, among other conditions (National Academies of Sciences Engineering and Medicine, 2017). Very few high-quality studies have been conducted to evaluate the effects of cannabis on depression and anxiety, and yet, these two conditions are very commonly endorsed as motives among medicinal cannabis users. The studies that do exist often report contradictory findings, and as current evidence stands, there is little support for a relationship between cannabis use and depression and/or anxiety in either direction (National Academies of Sciences Engineering and Medicine, 2017). Negative affect may be both a cause and a result of cannabis use (Wycoff et al., 2018).

Likewise, mood is thought to both influence and result from pain (Lumley et al., 2011) and sleep quality/problems (Bao et al., 2017). Older adults in particular are more likely than younger adults to endorse multimorbidity (King et al., 2018) along with polypharmacy (Wastesson et al., 2018). Therefore, in consideration of medicinal cannabis as an option for the management of various health conditions, patients deserve an accurate and evidence-based depiction of cannabinoid efficacy in treatment of these conditions, especially those with complex health profiles. Taken together, it is thus warranted to investigate whether the relationship between cannabis use and anxious and depressive symptomology is direct, or whether health comorbidities more readily influenced by cannabis use (i.e., pain and sleep quality) act as a mechanism that may elucidate this muddled relationship.

Relevance of Medicinal Cannabis

The cannabis plant has been used for its fiber since as early as Neolithic times (Li, 1974), though its use for medicinal purposes was not recorded until much later. The first documented medical use of cannabis was found in the earliest known pharmacopoeia written around the first century A.D. indicating traditional medicinal uses by China's legendary Emperor Shen-Nung around 2000 B.C. (Li, 1974). Historical medicinal purposes varied widely, though some functions included clearing bodily toxins, aiding in the birth process, and relieving rheumatism (Li, 1974; Zias et al., 1993). The earliest physical evidence of medicinal cannabis use dates back to the fourth century A.D. (Zias et al., 1993). In contrast to the longstanding history of medicinal and recreational cannabis consumption, throughout the past century, cannabis use has been met with strong legal opposition. The cannabinoid THC appeared in the United States *Pharmacopoeia* in 1850, though it was removed in 1942, a few years after implementation of the Marihuana Tax Act (Bridgeman & Abazia, 2017). Mandatory legal penalties were introduced by

the Boggs Act in 1952 for cannabis-related offenses, despite shifting cultural perceptions of cannabis use as acceptable, especially in the 1960s (Page et al., 2020). This was followed by federal prohibition in 1970 through the Controlled Substances Act, which categorized cannabis as a Schedule 1 substance, indicating that it has no approved medical use and high potential for abuse (Page et al., 2020). State-wide approval of the medicinal use of cannabis began with California in 1996, and by 2014, Colorado became the first state to approve the sale of cannabis to consumers for recreational purposes (Page et al., 2020).

As of January 2023, cannabis remains illegal at the federal level, though 37 states have legalized the medicinal use of cannabis and 21 have legalized it at the recreational level (Avery, 2023). Attitudes about cannabis use have evolved alongside changing legislation. Some have theorized that birth cohort effects influence the acceptance of cannabis use, and while those born prior to 1945 have greater negative attitudes towards cannabis use and use at much lower rates, period (intracohort) effects appear to have much stronger influence on changing attitudes about cannabis use legalization and acceptability across generations born post-World War II (Felson et al., 2019). While there are some between-group differences in attitudes by political party, gender, and religiosity, for example, overall rates of approval have changed at largely consistent rates across these groups, and across regions of the US (Felson et al., 2019). These changing attitudes can be partially attributed to evolving media portrayal of cannabis use as a medical issue since the 1990s, and can be slightly accounted for by decreasing religious affiliation (Felson et al., 2019).

Since the early 1990s, the nationwide rate of support for cannabis legalization has steadily increased by about 1.5% per year, breaking the 50% threshold in the early 2010s (Felson et al., 2019). In 2020, a record high 68% of Americans were estimated to support cannabis

legalization according to Gallup polls (Brenan, 2020). Among older adults, the increase in rates of cannabis use has been steep. In 2015 and 2016, approximately 9.0% of adults aged 50-64 used cannabis and approximately 2.9% of those age 65 and above used cannabis in the past year (Han & Palamar, 2018). From 2015 to 2018, rates of past-year cannabis use among adults 65 and older increased by approximately 75%, from 2.4% to 4.2% (Han & Palamar, 2020). Many of the health conditions medical cannabis is commonly prescribed for may be relevant to older adults, especially chronic pain and sleep disorders (Yang et al., 2021). Numerous randomized clinical trials have indicated moderate evidence of likely cannabinoid efficacy in treating spasticity and chronic pain, with some low-quality evidence suggesting improvements in sleep disorders, nausea associated with chemotherapy, weight gain in HIV, and Tourette syndrome (Whiting et al., 2015). Common short-term adverse events that may be of particular concern for older adults include, but are not limited to, dizziness, nausea, fatigue, disorientation, drowsiness, confusion, loss of balance, and hallucinations (Whiting et al., 2015). Of adults aged 50 and above who registered as medical cannabis users in the State of Florida, chronic pain and musculoskeletal and spastic disorders were the most common conditions indicating treatment with medical cannabis (Brown et al., 2020). This population was also likely to endorse use of antidepressants (23.8%), benzodiazepines and anxiolytics (23.5%), opioids (28.6%), and cardiovascular agents (27.9%) (Brown et al., 2020), which indicates risk for medication interactions and could potentially exacerbate the risk of adverse events among older adults.

Pharmacology of Cannabis

The cannabis plant is comprised of hundreds of cannabinoids, but the most potent and most often studied are Δ^9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD). Both plant-derived and synthetic cannabinoids primarily act upon the endocannabinoid (eCB) system. The

eCB system is an endogenous network of G-protein-coupled receptors, two of the most prominent being the CB1 receptor (primarily found in the central nervous system with smaller concentrations in the peripheral nervous system) and CB2 receptor (originally thought to be found only in the immune system, but also found in the CNS) (Mechoulam & Parker, 2013). Animal models suggest that CBD exerts anxiolytic properties (Izzo et al., 2009) and appears to counter some adverse effects of THC (Boggs et al., 2018). Though the biological underpinnings of cannabinoid efficacy are beyond the scope of this paper, the theorized actions of THC and CBD on the eCB system provide a framework for the study of the health effects of medicinal cannabis at the clinical level.

Existing reviews of the clinically observable effects of THC and CBD yield relatively mixed findings. In general, findings indicate that higher doses of THC pose greater risks such as dose-dependent increases in heart rate, anxiety, reductions in alertness, psychosis-like effects, and impaired memory and learning (Freeman et al., 2019) while balanced ratios of THC:CBD may protect against some of these adverse outcomes typically thought to be caused by THC alone (some memory impairment, tachycardia, intoxication) and CBD may have some beneficial effects (such as pain relieving and anti-emetic properties) (Englund et al., 2013; Fischer et al., 2017; Russo & Guy, 2006). Many more studies of these effects have been conducted with younger adults alone. Some findings indicate that older adults may experience less sensitivity to some of the cognitive and behavioral effects of THC than younger adults, though rates of anxiety may not differ between age groups (Mueller et al., 2021).

Direct Relationships of Cannabis, Sleep, Pain, and Mental Health

Chronic Pain and Sleep Impairment

The International Association for the Study of Pain characterizes the diagnosis of chronic primary pain by both presence of pain for at least 3 months, and presence of either emotional distress or functional disability (Nicholas et al., 2019). Prior to this conceptualization of chronic pain, definitions varied with considerations of etiology, pathophysiology, and psychological components of pain. While there are copious causes of and definitions for chronic pain, attempts to address the resultant distress and impairment, as well as maintaining factors, both for specific pain conditions and chronic pain more broadly, are warranted. Sleep impairment is often identified as a comorbidity in individuals with chronic pain. Among those with chronic non-cancer pain, pooled prevalence of concurrent sleep disturbance is approximately 75%, though these numbers varied slightly by pain etiology (i.e., lowest among those with rheumatoid arthritis at 65.4%, and highest among those with fibromyalgia at 95.5%) (Sun et al., 2021). In a randomized controlled trial treating chronic pain, the bidirectionality of the pain/sleep relationship was highlighted, with early (1 and 3 month) changes in sleep predicting changes in pain when controlling for depression and anxiety. The reverse relationship was also significant, though weaker, whereby changes in pain predicted changes in sleep (Koffel et al., 2016). The bidirectional relationship of the two constructs is relatively well-supported, though recent reviews tend to highlight a more consistent effect whereby sleep consistently predicts greater pain sensitivity (Herrero Babiloni et al., 2020; Okifuji & Hare, 2011). However, the sleep-pain relationship is complex with many potential confounding factors involved. Poor sleep can impact immune response, specifically exacerbating systemic inflammation, which can then worsen the experience of chronic pain. Additionally, positive and negative affect, mood disorders,

endogenous substances such as dopamine and melatonin, and activation of the HPA axis have all been identified as potential modulators of this relationship (Herrero Babiloni et al., 2020).

Chronic Pain and Mental Health Outcomes

Another intertwined, bidirectional relationship is that of pain and mental health concerns. Pain and depression often co-occur and have some overlapping neurological underpinnings. The Gate Control Theory of Pain explains the role of psychological processes in pain perception (Melzack & Wall, 1965). The theory refers to a gate-like channel in the spinal dorsal horn connecting the brain and spinal cord that controls the transmittance of pain signals through various nerve fibers and modifies the perception of pain. For example, the gate can exacerbate the feeling of pain or attenuate it at the spinal cord before it reaches the brain. Not only can peripheral sensory input open or close the gate, but so too can nerve fibers descending from the brain. This highlights the brain's role in pain perception, such that motivational-affective, sensory-discriminative, and evaluative processes can influence the resultant subjective experience of pain (Melzack, 1993). The Gate Control Theory was the first to identify how psychological factors can play an integral role in the experience of pain (Melzack & Katz, 2013). The reciprocal interplay between pain and depression has been replicated in multiple studies, whereby changes in severity of one domain predicts subsequent changes of severity within the other (Bair et al., 2003; Kroenke et al., 2011). Furthermore, dysregulation of certain cortical networks as a result of pain can perpetuate and exacerbate the emotional experiences associated with persistent pain, including rumination and anxiety about experiencing pain, which can then worsen suffering and disability (Lumley et al., 2011). Consideration of the causal and maintenance factors involved in this bidirectional relationship between chronic pain and emotion can be key in attempting to treat and intervene with both conditions (Meints & Edwards, 2018).

Of particular concern with older adults is functional disability and impairment in daily life, which may originate from or be worsened by chronic health conditions and chronic pain. Specifically, changes in disability strongly predict subsequent depression, and to a lesser extent, depressive changes can predict disability over prolonged time periods; thus persistent depression and/or new disability should be considered as intervention points in this mutually reinforced cycle among older adults (Ormel et al., 2002).

Sleep Impairment and Mental Health Outcomes

Older adults commonly experience changes in sleep architecture and circadian rhythms attributable to physiological and biological factors, and general alterations to sleep due to various comorbid health conditions, which can in turn contribute to poorer overall sleep quality and duration (Neikrug & Ancoli-Israel, 2010). Poor sleep can lead to worsened cognitive functioning in multiple domains, including attention, working memory, long-term memory (Alhola & Polo-Kantola, 2007) and especially depression and anxiety. Sleep difficulties have been linked bidirectionally to depression and anxiety (Alvaro et al., 2013). Sleep difficulties can act as a predisposition to either condition, though more often to depression. In fact, trouble sleeping serves as one of the possible diagnostic criteria for depressive disorders (American Psychiatric Association, 2022). Among older adults, sleep problems can be a contributing causal factor to depression (Baglioni et al., 2011; Riemann, 2003), or a symptom that emerges post-onset of depression (Bao et al., 2017). One hypothesis poses that, rather than separate, independent comorbidities, some of the common factors between anxious and depressive syndromes may explain their link to sleep problems, such as general distress (Magee & Carmin, 2010). The tripartite model of anxiety and depression suggests that the two conditions can be comorbid due to a shared common factor, general affective distress, and two distinct disorder-specific factors,

anxious arousal and/or anhedonia, respectively (Clark & Watson, 1991). Some have similarly posited that insomnia may occur due to an underlying predisposition to hyperarousal, which may explain the overlap between insomnia and anxious/depressive symptoms (Stepanski & Rybarczyk, 2006).

Further complicating this relationship is the role that cognitive factors play in both sleep and mood disorders. For instance, sleep quality among older adults is related to depressive symptoms, though this relationship is mediated by rumination, and the direct link between sleep problems and rumination is moderated by inhibitory control (Brush et al., 2020). Due to the complex, variant patterns and potential causes of comorbidity between insomnia and mental health conditions, there is not one clear way to alleviate symptoms of both. However, in some cases, targeting one condition can indirectly improve the other. For example, treating older adults with comorbid insomnia and depression with an evidence-based psychotherapeutic treatment for insomnia, CBT-I, can improve symptoms of both conditions (Sadler et al., 2018). Similar effects have been seen in those with insomnia and comorbid baseline anxiety and stress (Sweetman et al., 2020). Given the range of conditions for which older adults may use cannabis, consideration of causal factors in individuals' mental health or sleep-related symptomology may be essential in the decision-making process regarding predicted cannabinoid efficacy for treatment of these conditions.

Cannabis and Pain

Many attempts to address the relationship between cannabis and pain have been made, and while some have concluded that cannabis reduces pain, others report little to no effect, or simply indicate an inability to draw conclusions due to a lack of high-quality evidence. In general, cannabis and cannabinoids are commonly reported as slightly effective at relieving pain,

although the conditions for which this applies are largely divergent, and few methodologically rigorous studies exist (Fisher et al., 2021). Consequently, some report that no conclusions can be drawn from the evidence to either support or refute cannabinoid efficacy in treatment of pain (Fisher et al., 2021). In terms of individual cannabinoids, THC:CBD ratios (1:1 or 2:1) may alleviate neuropathic pain in some patients, though there was insufficient evidence to draw conclusions about pain from multiple sclerosis or cancer (Nugent et al., 2017). Contrary to some review papers, the National Academies' 2017 review concluded that substantial evidence supports cannabinoid efficacy in treatment of chronic pain in adults, though this mostly encompassed studies conducted outside of the United States and may not reflect the diverse pool of cannabinoid products and administration routes commercially available in the US (National Academies of Sciences Engineering and Medicine, 2017).

The biological mechanisms of the pain-relieving properties of cannabis and cannabinoids, as well as the general role of the endocannabinoid system in pain perception, is not fully understood and somewhat beyond the scope of this study. However, in general, there are a few cannabinoid-related mechanisms that are considered to influence pain perception. CB1 receptors are primarily expressed in the central nervous system and are abundantly present in brain regions that influence nociceptive perception (Maayah et al., 2020). Furthermore, CB1 receptor activation at presynaptic locations allows for cannabinoid modulation of neurotransmitter release, and activation of these receptors can modulate nociceptive thresholds (Maayah et al., 2020). CB2 receptors, most abundant in peripheral immune and inflammatory cells, both evidently and theoretically play a role in pain perception as well (Maayah et al., 2020). In fact, some CB1, CB2, and non-selective cannabinoid receptor agonists have demonstrated efficacy in pain reduction for both inflammatory and neuropathic pain models, though efficacy is more

consistently demonstrated in neuropathic pain (Haroutounian et al., 2021). The Task Force on Cannabis and Cannabinoid Analgesia has called for more research to further elucidate the pharmacological effects of cannabis and role of the endocannabinoid system in pain processing and analgesic targets (Haroutounian et al., 2021). Overall, based on biological and clinical findings, cannabis likely represents a viable treatment option for pain, and thus, the efficacy of cannabinoid analgesia with consideration of various contextual factors should be further investigated.

Cannabis and Sleep

Various sleep-related outcomes, both beneficial and deleterious, have been tied to cannabinoids for decades, but a strong, conclusive effect of cannabis on sleep has yet to be established. RCTs have revealed that medicinal cannabis and cannabinoids lead to improvements in sleep quality and disturbance among individuals with chronic pain endorsing disturbed sleep at baseline, however, these effects are small in those with non-cancer related pain, and even smaller among those with cancer-related pain (AminiLari et al., 2022). Time may serve as an important explanatory factor regarding cannabis and sleep. Cannabinoids have some efficacy in improving sleep in the short term for certain conditions, including obstructive sleep apnea, fibromyalgia, MS, and chronic pain (National Academies of Sciences Engineering and Medicine, 2017). Overall, studies have commonly reported short-term improvements in sleep onset latency and slow wave sleep, though some have identified differential effects based on constituent cannabinoid concentration and dosage (Babson et al., 2017). In the long term, however, tolerance and dependence appear to develop, as well as disturbed sleep during cannabis withdrawal (Babson et al., 2017), suggesting that cannabis may not be a sustainable, long-term solution to chronic sleep impairment.

The endocannabinoid system appears to play a role in the circadian sleep-wake cycle, and administration of exogenous cannabinoids may impact this process. Endogenous cannabinoids 2-AG and AEA may be associated with wake-promoting and sleep-promoting effects, respectively (Suraev et al., 2020). AEA is a partial agonist at the CB1 receptor, as is THC, which may explain its effects on sleep; CBD on the other hand, is inhibitory of an enzyme, fatty acid amide hydrolase (FAAH) that breaks down AEA, and thus has been theorized to exert effects on sleep indirectly through increased availability of AEA (Suraev et al., 2020). Notably, inhibition of FAAH (and resultant accumulation of AEA) with different inhibitors has resulted in increased wakefulness in some studies (Murillo-Rodriguez et al., 2007) and promotion of sleep in others (Pava et al., 2016). While the endocannabinoid system likely plays some role in sleep, an understanding of the exact mechanisms of this effect has yet to be established and thus, more research is required (Kesner & Lovinger, 2020). At the clinical level, evidence indicates uncertainty about whether cannabinoids result in improved sleep via direct effects on biological sleep-wake processes or alleviation of some other underlying pathology, such as chronic pain (Suraev et al., 2020).

Cannabis and Depression

The relationship between cannabis and mental health symptoms is complex. Cannabis use has been investigated as both a causal factor and a result of mental health symptoms, but there is still a lack of clear evidence for a direct effect in either direction. Within the limited literature of identified methodologically rigorous studies, the effect of cannabinoids on depressive symptoms were only investigated within the context of treatment for another medical condition, such as multiple sclerosis or chronic pain. Results of these studies indicated that cannabis was ineffective in the reduction of depressive symptoms (National Academies of Sciences Engineering and

Medicine, 2017). In this same review, there was also a small but statistically significant finding that cannabis use slightly increases the risk of developing a mood disorder. In a prospective cohort study, baseline cannabis use was significantly associated with elevated levels of depression and anxiety at three-year follow up, although this association was attenuated when controlling for confounding social factors, demographics, and comorbid substance use (Danielsson et al., 2016). Evidence for a bidirectional relationship between cannabis use and depression remains controversial.

The biological and psychological underpinnings of the relationship of cannabis with depression each provide theoretical foundations which may explain both cause and maintenance of this link. The neurotransmitter serotonin (5-HT), and more specifically and simply, low levels thereof, has a well-established role in the pathophysiology of depression (Nemeroff & Owens, 2009). Some evidence has linked the endocannabinoid system with 5-HT, though any role of exogenous cannabinoids is less clear. Within the dorsal raphe nucleus, stimulation of the CB1 receptor via administration of low dose agonists causes an increase in 5-HT firing rates in rat models (similar to the effects of SSRIs used to treat depression), though high-dose agonists decrease this firing rate (Cohen et al., 2019; Langlois et al., 2021). Therefore, it is notable that at the biological level, modulation of the 5-HT system by cannabinoids has been documented (Cohen et al., 2019). However, at the behavioral level, while some case studies and anecdotal evidence support the efficacy of cannabis in treatment of depression, no randomized controlled trials exist to support this theorized therapeutic action (Feingold & Weinstein, 2021). One interpretation of inconsistent findings relating cannabis use with depressive symptoms is that CUD may play a causal role in the development of MDD among the heaviest users (Smolkina et

al., 2017), though the reverse has also been reported – baseline depression may pose as a risk factor for initiation of cannabis use (Langlois et al., 2021).

Among individuals with depression, coping appears to be a common explanatory factor for escalated cannabis use. Some studies have found that individuals using cannabis to cope with baseline mental health concerns such as anxiety and depression experience temporary relief, but elevated levels of depression at follow up (Cuttler et al., 2018). Interestingly, this finding was unique to those who endorsed coping as a motive for use. This may explain the finding that baseline cannabis use predicts more subsequent depression. Furthermore, among cannabis users, difficulty tolerating sad mood states has been shown to predict more frequent cannabis use and greater endorsement of coping motives. Notably, this finding was unique to intolerance of sad mood in this particular sample of undergraduate students, and did not occur with low tolerance of other negative emotions such as anger, anxiety and fear (Hartmann & McLeish, 2022). Individuals experiencing increased life stressors and using cannabis chronically may also be more vulnerable to using for stress-related coping. Chronic cannabis use may additionally alter neurological stress systems by increasing stress response and depleting coping abilities, thus creating a vicious cycle whereby stress leads to cannabis use, which then prompts increased levels of stress and decreased ability to cope with such stress (Hyman & Sinha, 2009). Taken together, cannabis use therefore is likely to potentiate depressive states when used as a coping mechanism, rather than alleviate the aversive feelings the individual was trying to blunt via substance use.

Cannabis and Anxiety

A direct relationship between cannabis and anxiety has been explored in prior studies, though findings are not yet conclusive, perhaps due to the complex, multifaceted role

cannabinoids play in the modulation of anxiety at a biological level coupled with widely varying motives for use. The National Academies' review failed to find many good-quality reviews of cannabinoid efficacy in treatment of anxiety, but identified limited evidence that CBD improves anxiety symptoms in those with social anxiety disorders (2017). Similarly, this review found limited evidence for an association between cannabis use and subsequent development of most anxiety disorders.

The eCB system likely contributes to modulation of anxiety, fear and stress regulation with multiple important roles in regulation of the HPA axis, and is also itself modulated by stress (Morena et al., 2016). However, these stress-respondent effects differ by region and component of the system (i.e., levels of endogenous cannabinoids and receptors), and even by nature of the stressor (Morena et al., 2016). Furthermore, THC appears to have a biphasic role in the modulation of anxiety, such that low doses of THC produce anxiolytic effects whereas high doses are anxiogenic (Viveros et al., 2005). This effect of THC on anxious symptomology may also differ by neuroanatomical region. In rodent models, injection of THC in the prefrontal cortex and ventral hippocampus appears to also have an anxiolytic effect, while injection in the amygdala is anxiogenic (Rubino et al., 2008). CBD, on the other hand, has been shown to have mostly anxiolytic properties that can occur via multiple different neurological routes, though this effect varies by dose and contextual factors (Petrie et al., 2021). Some studies have demonstrated that CBD mitigates the anxiogenic properties of high-dose THC, though this finding does not always replicate (Petrie et al., 2021). Finally, the anxious response humans have demonstrated to cannabis can differ by gender, levels of tolerance, cannabinoid concentration, and route of administration (Petrie et al., 2021), which further complicates this relationship.

Approximately 50% of medical cannabis patients report using for anxiety (Kosiba et al., 2019), and even recreational users endorse self-medicating their anxiety as a motive for use (Osborn et al., 2015). While theoretically, some rationales allude that cannabinoids may be effective in treatment of anxiety disorders, few RCTs exist to support this idea. In fact, out of only 8 RCTs available in 2021, no evidence was identified to support the efficacy of THC or CBD in treatment of anxiety disorders (Stanciu et al., 2021). Some longitudinal studies have examined the inverse – that cannabis use may cause anxiety disorders – yet findings are largely mixed and often null especially when controlling for psychosocial factors, and further limited by lack of methodological rigor (National Academies of Sciences Engineering and Medicine, 2017). However, some studies do report increased odds of anxiety symptoms among cannabis users (Botsford et al., 2020). There is some evidence that cannabis use may cause social anxiety symptoms, especially in older persons (National Academies of Sciences Engineering and Medicine, 2017). Cannabis Use Disorder has a high rate of comorbidity with anxiety disorders such as GAD (Onaemo et al., 2021), though causality in either direction is yet to be clearly established and likely differs by user. Among these groups with substance use disorders and comorbid anxiety disorders, craving was stronger, and thus substance use more frequent, than in those without anxiety disorders in one EMA study (Fatseas et al., 2018).

Despite these controversial findings, individuals still elect to use cannabis in hopes of decreasing their anxiety. It is possible that for some, the perceived efficacy of cannabis in treatment of anxious symptomology may be attributable to negative reinforcement cycles. Higher levels of distress intolerance are related to greater cannabis dependence, problems, and craving (Farris et al., 2016), which suggests that dispositional or trait-like intolerance of anxious distress may be a risk factor for cannabis use, which then likely contributes to maladaptive use and

cannabis-related problems. In fact, prior studies have shown that greater trait-level anxiety, including a greater number of anxiety disorder diagnoses, is associated with increased cannabis use (Wycoff et al., 2018). Consistent with these findings, individuals high in the neuroticism personality trait tend to have higher rates of problematic cannabis use (Winters et al., 2022). Cannabis coping motives mediate the relationship between distress intolerance and cannabis problems (Farris et al., 2016), which will be discussed in greater detail in the following section. Anxiety disorders are often characterized by avoidance behaviors, specifically avoidance of unpleasant, anxious feelings. While avoidance can sometimes be adaptive in truly threatening situations, it often perpetuates anxiety disorders by way of operant conditioning. That is, the removal of unpleasant feelings in the moment (via cannabis use, in this case) only reinforces such avoidance behaviors in the future and worsens symptoms of anxiety over time. Thorndike's law of effect supports this idea as well, stating that behaviors followed by desirable consequences will be repeated (Thorndike, 1927).

Cannabis and Coping

Given that evidence is still inconsistent regarding the direction of causality between cannabis use and depression, despite ongoing investigations of a direct relationship between the two, it is plausible that a third factor responsible for the development and maintenance of this relationship exists. Lazarus and Folkman (1984) introduced the dichotomy of problem-focused and emotion-focused coping. By their definition, problem-focused coping refers to strategies aimed at solving or mitigating the problem that causes the distress, while emotion-focused coping attempts to regulate the emotional response that derives from the problem. Individuals may use either or both strategies. Coping style often varies both between and within persons and situations, and can change by the presenting demands and available resources (Lazarus &

Folkman, 1984). Ideal coping would resolve the problem at the root of the experienced distress and resolve any negative emotions associated with that distress. However, some problems may not be amenable to solutions, therefore, effective coping is complex (Lazarus & Folkman, 1984). Substance use does not typically resolve problems in living, but instead blunts adverse emotional experiences, and so it can be viewed as maladaptive, emotion-focused coping. By comparison to other emotion-focused coping strategies, substance use poses the added burdens of tolerance and withdrawal symptoms. Coping is often considered one of the five main motivators for cannabis use and is endorsed by both recreational and medical users (Bohnert et al., 2018; Simons et al., 1998).

Cannabis is commonly used to treat each of the aforementioned conditions, pain, sleep, depression, and anxiety, but as previously discussed, the causal and maintenance factors of these disorders are broad, and complicated by the common presentation of these conditions in some combination. Whether or not individuals meet full diagnostic criteria for a disorder characterized by these conditions, day-to-day fluctuations in basic symptoms is likely. In combination, these findings indicate several clear research goals. First and foremost, more high-quality clinical trials examining efficacy of therapeutic cannabis for medical and mental health disorders, including sleep impairment and chronic pain, are markedly necessary. The second implication is that, though poor mental health is a common justification for medical cannabis use, this is a complex issue whereby consideration of various comorbidities and motivations for use may be imperative in the process of making treatment decisions. A third implication is that mental health outcomes among older adults may be partially improved by cannabis to the extent that it positively affects sleep quality and pain management. Consideration of patients' motives for use and clinical profile as determined by a thorough medical and psychological screener may constitute a key

component in the medical cannabis prescription process to maximize benefits and minimize iatrogenic effects among all patients, but especially older adults. Integration of these findings resulted in the conceptual framework (Figure 1), whereby investigation of the effects of cannabis use on pain, sleep quality, and mental health symptoms will be explored within subjects at the daily level to establish a clear profile of real-time changes in symptomology before and after cannabis use.

Interrelatedness of Pain, Sleep, and Mental Health, and the Theorized Role of Cannabis

The influential roles of pain, sleep, and mental health as a trifecta may follow similar patterns to the dual relationships described previously. Studies that examine this interplay of symptomology often involve patients with fibromyalgia, a chronic pain condition. Among fibromyalgia patients, early morning reports of poor sleep the previous night have been associated with greater functional disability later in the day, mediated by pain and positive affect, but not negative affect (Kothari et al., 2015). Furthermore, increased levels of pain led to lower positive affect, which then predicted functional impairment (Kothari et al., 2015). Among adult chronic pain patients in general, poor sleep can exacerbate both negative mood and pain, and negative mood mediates the relationship between sleep and pain (O'Brien et al., 2010). The reverse relationship has been demonstrated in community-dwelling older adults, whereby pain inconsistency predicted some aspects of poor sleep, partially mediated by depression (Ravyts et al., 2019).

Investigations of symptom reduction among older adults using medical cannabis for pain and related symptoms (often anxiety, depression, and sleep problems) is an emerging research target. This thesis seeks to address a gap in the literature involving both the interplay of these symptoms, and specifically, the relationship of these things among cohorts restricted to middle-

aged and older adults. As previously discussed, cannabis appears to influence changes most consistently in chronic pain, and older adults commonly endorse pain as a key motive for use (Yang et al., 2021). One study (among adults ages 37-60, $M = 47$) found that increased sleep duration at baseline (potentially itself an indicator of lower sensitivity to pain) and lower depression scores predict greater reductions in pain at 12-month follow-up after medical cannabis initiation (Aviram et al., 2021). This study was not without its limitations (dropout due to inefficacy of medical cannabis, sample characteristics, etc.), but provides an interesting starting point to an understanding of the potential interrelatedness of these symptoms and prediction of cannabinoid efficacy in pain treatment. Another study evaluating the course of chronic pain among individuals ($N = 37$; $M = 54.87$, $SD = 14$) initiating medical cannabis use found reductions in pain after 3, but not 6 months, and related improvements in depression, anxiety, and sleep quality (Gruber et al., 2021). Similarly, 12-month pain reductions in fibromyalgia patients initiating medical cannabis use ($N = 323$; $M = 52$, $SD = 13$) have been postulated to be explained by reductions in negative affect and improvements in sleep (Sotoodeh et al., 2022), though again, this particular study was limited by a very high (75%) dropout rate, and was not likely generalizable to all fibromyalgia patients, let alone all older adults with various etiologies of chronic pain. Finally, another recent study among adults ($M = 55.7$, $SD = 11.9$) found short term improvements in anxiety, pain, and sleep among adults with chronic pain initiating medical cannabis use, and longer term (3-month) maintenance of lower pain levels, reductions in depression, and increased sleep quality, though no long-term improvements in anxiety (Y. Wang et al., 2021). Given the limited, unclear evidence regarding these interactions among cohorts of older adults, further exploration is warranted.

The current study

The goal of this study was to examine the network of hypotheses indicated by Figure 1. Specific hypotheses were as follows:

1. Cannabis use will be negatively associated with (1.a.) post-use anxiety, (1.b.) post-use pain, and (1.c.) post-use depression.
2. Post-use pain will be positively associated with both (2.a.) post-use anxiety and (2.b.) post-use depression.
3. Post-use anxiety (a), post-use pain (b), and post-use depression (c) will be negatively associated with sleep quality (3.a., 3.b., and 3.c., respectively), and (3.d.) cannabis use will be indirectly associated with sleep quality via post-use anxiety, post-use pain, and post-use depression.
4. Cannabis the prior day is associated with pre-use anxiety (4.a.), pre-use pain (4.b.), and pre-use depression (4.c.), via mediated effects through post-use anxiety, pain, depression, and sleep quality the prior night.

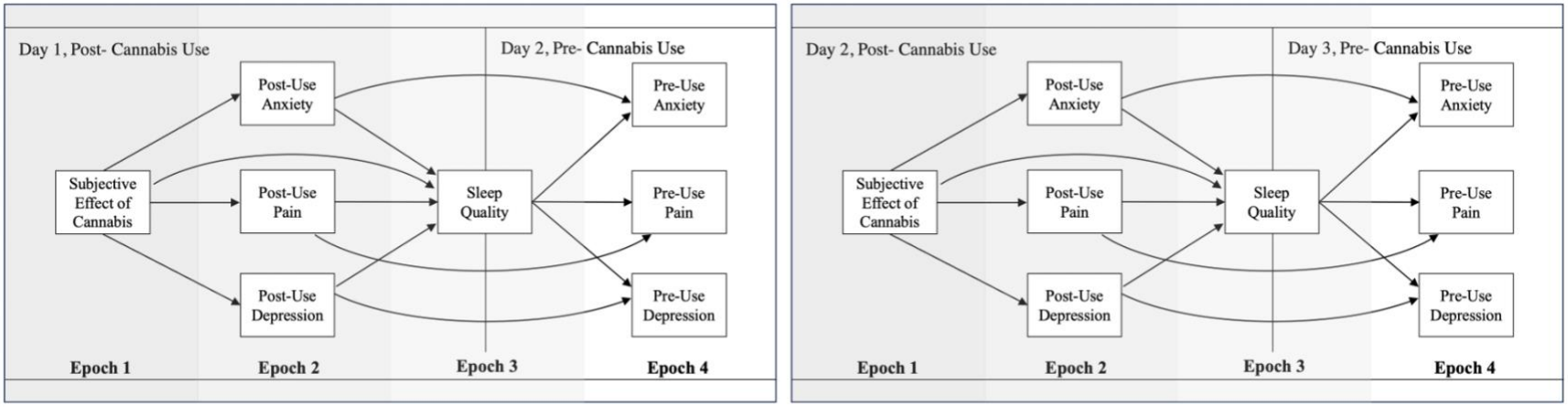


Figure 1. Model depicting structural equation data structure for two nested analysis periods.

METHODS

Participants

Participants were recruited nationwide through social media websites. Inclusionary criteria required participants to be at least 55 years of age, hold a valid medical cannabis card in their state of residence, own a smartphone, and currently use cannabis at least 3 times per week at the time of data collection. Adults who were unable to consent, individuals who were not yet adults, prisoners, and pregnant women were excluded. No other health-related exclusionary criteria were used, as the goal of this study was to maintain external validity by accurately capturing the psychological and medical functioning of the diverse population of medicinal cannabis users. Each participant's information was verified prior to enrollment with their state-issued identification card, thus negating the possibility of multiple enrollments by one individual.

The final sample consisted of $N = 106$ English-speaking participants ranging in age from 55-74 years ($M = 61.06$, $SD = 4.65$), and was thus sufficiently powered (see power calculation above). The sample was primarily White ($n = 87$, 82.86%), and female (66.67%), while 11.32% identified as multiracial ($n = 12$), 2.86% Black ($n = 3$), 1.90% Asian American/Pacific Islander ($n = 2$), and 1.90% indicated "other" or "do not wish to respond" ($n = 2$). Finally, 4.76% of the sample ($n = 5$) endorsed Hispanic/Latino ethnicity.

Measures

Demographics

Demographic data collected for all participants included age, gender, race, ethnicity, and years of education. Information about current medications was collected, but not included in

present analyses. Finally, state of residence was verified for validation of the legality of medicinal cannabis use, and medical cannabis card possession was recorded.

Cannabis use

Participants were asked to self-report a thorough history of cannabis use. Information about cannabis use behavioral patterns were collected through questions about participants' age at the time of their initial use of cannabis, their number of days of lifetime cannabis use, number of days of recent cannabis use, and primary reason for which they use cannabis (physical symptoms, psychiatric symptoms, or both). The source from which cannabis was obtained and the amount of money spent on cannabis were collected, as well as the typical level and highest past-month level of intoxication, and time spent intoxicated from cannabis. At each assessment, the amount of cannabis used since the previous assessment was collected. Participants were asked what form(s) of cannabis they have used since the last prompt and were provided with the options "Smoked, dried cannabis," "vaped cannabis," "edibles," or "other." Dependent upon this answer, participants were prompted with the relevant combination of the following prompts: "How many grams of cannabis did you smoke?" "How many hits did you take when vaping cannabis?" "How many milligrams of THC and CBD were in the edible you consumed?" "What percent THC and CBD is the strain of cannabis you smoked?" and "What percent THC and CBD is the cannabis product that you vaped?" Participants were then prompted to use an 11-point scale to rate how high they were when they last used cannabis, and how high they were at that moment. They were provided with a scale with anchors for 0 (*completely sober*), 1-3 (*somewhat high*), 4-6 (*moderately high*), 7-9 (*very high*) and 10 (*highest I've ever been*).

Current symptoms

At baseline, participants were provided with a list of psychiatric symptoms (anxiety, worry, depressed mood, inability to experience pleasure, stress, difficulty falling asleep, difficulty staying asleep, and difficulty functioning in day-to-day activities due to trauma) and physical symptoms (cancer-related pain, neuropathic pain, abdominal pain, low back pain, fibromyalgia, migraines or headaches, rheumatoid arthritis, gastrointestinal pain, muscle aches and pain, muscle spasms, joint pain, and osteoarthritis) commonly endorsed by medicinal cannabis users and asked to rate the intensity with which they experienced these symptoms within the past month. Items were rated in intensity using an 11-point numeric scale ranging from 0 (*none*) to 10 (*severe*). During the EMA portion of the study, participants were provided with the same psychiatric symptoms and scales and asked about the intensity with which they were "currently experiencing" these symptoms, which has previously been shown to adequately capture negative affect (De Leon et al., 2020). Participants were asked to rate their current overall pain using the same 11-point scale, then were provided with descriptions of different types of pain - for example, "Deep pain (located deep within the body)" and "Sharp pain (feels like a knife, like a spike, piercing, etc.)" – and asked to rate the severity of each type of pain on the 11-point scale. Final analyses included pain, as indicated by participants' rating of overall pain on the 11-point scale; depression, calculated as an average of scores on the items "sad," "depressed," and "blue"; and anxiety, calculated as an average of scores on the items "anxious," "nervous," and "worried."

Sleep Quality

Information about participants' quality of sleep the previous night was collected via questions adapted from the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a self-report instrument intended for use in clinical populations. It contains 19 items assessing sleep quality

and disturbances over a one-month time period (Buysse et al., 1988). When administered to adults aged 20-83 with and without sleep complaints, the PSQI has demonstrated acceptable internal consistency (α = .83), test-retest reliability, and validity (Buysse et al., 1988). However, for the present study, a modified version was implemented. Participants were asked to subjectively rate the previous night's sleep quality, current subjective tiredness, and they were asked to report on various aspects of the timing of their sleep the previous night ("what time did you fall asleep last night?", "how many times did you wake up last night?", etc.). Sleep efficiency was calculated by dividing total minutes asleep by total time in bed. Sleep efficiency, subjective sleep quality, and tiredness were then averaged to create an overall metric, hence forth referred to as sleep quality. This sleep quality variable was used in final analyses.

Procedures

Prior to initiation of this study, approval from the Institutional Review Board at the University of Central Florida was obtained. The present study utilizes data from a larger research project funded by the Consortium for Medical Marijuana Clinical Outcomes Research. Information about this study was advertised to a national audience on social media websites, such as Facebook, stating that medicinal cannabis users may be able to earn up to $100 if they qualify for this study. Participants were provided with a link to complete an initial screening survey (Phase 1) in order to determine if they qualified for participation in Phase 2 of the study. This survey included an initial assessment of demographics, medical cannabis card holder status, frequency and recency of current cannabis use, The Cannabis Use Disorder Identification Test – Revised, CUDIT-R (Adamson & Sellman, 2003); Brief Marijuana Consequences Questionnaire, BMAC-Q (Simons et al., 2012); Protective Behavioral Strategies for Marijuana scale, PBSM (Pedersen et al., 2016); a 10-point intensity scale of symptoms commonly treated with medical

cannabis, motives for using medical cannabis; Pittsburgh Sleep Quality Index, PSQI (Buysse et al., 1988); General Anxiety Disorder-7, GAD-7 (Beard & Bjorgvinsson, 2014; Spitzer et al., 2006); The Alcohol Use Disorder Identification Test, AUDIT (Saunders et al., 1993); The Drug Use Disorder Identification Test, DUDIT (Berman et al., 2002); (notably, many of these items were not used in present analyses, but are described for transparency regarding participant experience and mental load) as well as captcha and multiple validity checks mixed throughout the items in these measures. Participants were asked to provide their phone numbers if they wished to be contacted about Phase 2.

After completion of the screening survey, the research team contacted eligible participants to schedule an enrollment meeting. Those who elected to participate completed a 30-minute video call via a secure online platform with a research team member in which informed consent was obtained. Participants were offered monetary incentive for completion of random interval assessments and morning assessments in the form of a gift card after completion of the study ($1 per random assessment with a $10 bonus offered to those who hit the 80% completion rate, for a total of up to $100). It was made explicitly clear that monetary compensation would not be given for the completion of event-contingent prompts, so as not to compensate for increased patterns of cannabis use.

All eligible, consented participants were given a sample survey to complete. The link to the survey was texted to each participant during the call. Throughout the next 14 days, participants were periodically prompted via text message to answer questions about their most recent cannabis use(s), products, concentrations, and quantities used, motivations for use, and mood, pain, and sleep quality in their natural environments in real time through ecological momentary assessment (Shiffman et al., 2008). Prompts are described in detail below. One

morning assessment was sent per day, followed by a link to the event-contingent assessments in the morning. Subsequently, five random assessments were sent throughout the day. In the early evening, one reminder text was sent with links for the event-contingent assessment.

Morning Assessment

Texts with a link to the morning survey were sent daily, followed by one reminder text prompting participants to "please try to complete this assessment within the next 15 minutes." First, participants were asked about cannabis use the prior night. If use was endorsed, participants were prompted to report last-session cannabis use motives, cannabis quantity, route of administration, and THC/CBD concentration. Morning assessments included the following measures: a subjective 10-point "highness" scale, EMA-adapted PSQI, physical and psychiatric symptoms experienced yesterday, current motives for using cannabis, EMA-adapted B-MACQ, current mood assessment items, and current craving for cannabis.

Random-Interval Assessment

Five random assessment text messages were sent throughout the day, each followed by a prompting text requesting the participant to complete the survey within the next 15 minutes. Similar to the morning assessments, at each random-interval assessment, participants were prompted to report whether they had used cannabis since their last assessment. If they reported use since the last assessment, they were asked to report last-session cannabis use motives, cannabis quantity, route of administration, and THC/CBD concentration. All participants were then prompted with the following measures: subjective 10-point "highness" scale (the key independent variable), current physical and psychiatric symptoms, current motives for cannabis use, current mood assessment items, and current craving for cannabis.

Event-Contingent Assessment

The event-contingent assessment text messages read as follows:

> "*Please make sure to complete this pre-use and post-use survey each time you use cannabis today.*
>
> *Pre-use survey: (link)*
>
> *Post-use survey: (link)"*

No time-sensitive reminder messages followed this message. Instead, this message was sent twice per day, so participants retained easy access to event-contingent surveys throughout the day. The pre-cannabis use survey included current mood assessment items, current craving for cannabis, current physical and psychiatric symptoms, and current motives for cannabis use. Post-cannabis use surveys include current mood assessment items, current craving for cannabis, current physical and psychiatric symptoms, motives for the most recent cannabis use session, cannabis use quantity, route of administration, 10-point subjective "highness" rating, and THC/CBD concentration.

Deviations from Hypothesis 2

Hypothesis 2 originally posited a prospective relationship between pain and anxiety and depression. However, an examination of the data indicated adding an additional Epoch would be potentially problematic given the proximity of use, pain, and depression and anxiety ratings. Thus, we clustered pain, depression, and anxiety in the same Epoch and allowed them to covary. Below, we report the correlations between these variables.

Statistical Analyses

A fully within-subject multilevel structural equation model was specified in *Mplus8.4.* The model was broken up into four epochs based on temporal precedence. The initial time epoch (1) of the model began with the individual's cannabis use, which was assessed subjectively based on a person's rating of cannabis intoxication. The second epoch (2) consisted of post-use anxiety, post-use pain, and post-use depression averaged across the day before the individual went to sleep. At the morning assessment the following day (epoch 3), individuals provided data on their sleep for the prior night (time in and out of bed, time spent asleep and awake, subjective tiredness and sleep quality). From this, the final metric of sleep quality was calculated. Finally (epoch 4), participants provided ratings of anxiety, pain, and depression throughout the day up until the point that they began cannabis use again (these are referred to as "Pre-use" items). Once cannabis use was initiated on this second day, the cannabis use marked the start of a new series of four epochs.

Figure 2 specifies the direct, indirect, and total effects calculated. Notably, due to multiple insignificant direct pathways contained in initially hypothesized indirect effects, some indirect effects were omitted. Final statistical calculations deviated slightly from the initial hypotheses; thus, the power analysis (detailed in the following section) reflects the previously specified model paths. Direct effects from symptomology in Epoch 2 (post-use anxiety, post-use pain, and post-use depression) to their respective (pre-use) counterparts in Epoch 4 were included to reduce multicollinearity within the model. Indirect and total effects of cannabis use (Epoch 1) on sleep quality through post-use anxiety, post-use pain, and post-use depression (Epoch 2) were calculated. Indirect pathways were specified from cannabis use to (pre-use) anxiety, pain, and depression in Epoch 4 through sleep quality (Epoch 3) only. Finally, indirect

effects from cannabis use to each next-day symptom rating through the previous day's ratings of the respective symptom were calculated for all 3 symptom domains (i.e., Epoch 1 cannabis to Epoch 2 post-use anxiety to Epoch 4 pre-use anxiety; see Figure 2).

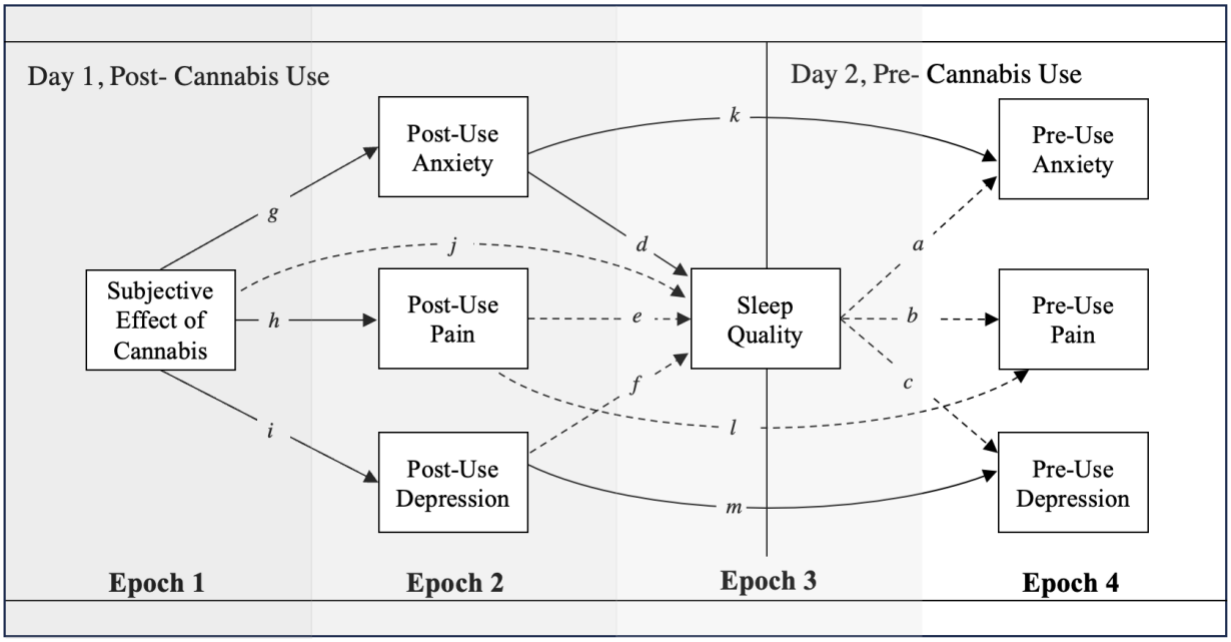


Figure 2. Pathway labels used for calculation of indirect effects.

Note. Indirect and total effects were calculated as follows: CINDANX = (*d***g*), CINDPAIN = (*h***e*), CINDDEP = (*i***f*), CTOTS = (*g***d*)+(*j*)+(*h***e*)+(*i***f*), C_NDANX = (*g***k*), C_NDPAIN = (*j***b*), C_NDDEP = (*i***m*), CS_ANX = (*j***a*), CS_PAIN = (*j***b*), CS_DEP = (*j***c*); Where *CINDANX* = the indirect effect of cannabis on sleep through post-use anxiety, *CINDPAIN* = indirect effect of cannabis on sleep through pain, *CINDDEP* = indirect effect of cannabis on sleep through depression, *CTOTS* = total effect of cannabis on sleep, *C_NDANX* = indirect effect of cannabis on Epoch 4 (pre-use) anxiety through Epoch 2 (post-use) anxiety, *C_NDPAIN* = indirect effect of cannabis on Epoch 4 (pre-use) pain through Epoch 2 (post-use) pain, *C_NDDEP* = indirect effect of cannabis on Epoch 4 (pre-use) depression through Epoch 2 (post-use) depression, *CS_ANX* = indirect effect from cannabis (Epoch 1) to sleep (Epoch 3) to (Epoch 4) pre-use anxiety, *CS_PAIN* = indirect effect from cannabis (Epoch 1) to sleep (Epoch 3) to (Epoch 4) pre-use pain, and *CS_DEP* = indirect effect from cannabis (Epoch 1) to sleep (Epoch 3) to (Epoch 4) pre-use depression.

Power Analysis

A Monte Carlo simulation was conducted in *Mplus, version 1.8.8,* to determine the number of observations needed to adequately power the initially proposed model. 1,000 chain replications were used for this simulation. The proposed sample included 100 participants with

14 days of data maximum for each person. Considering estimated rates of attrition and non-response, $N = 900$ useable observations were assumed. Given the lack of (and inconsistency of) established effect sizes for the proposed pathways within subjects, despite abundant literature detailing relatively robust findings regarding these effects between subjects, a minimum detectable effect size approach was taken for this power analysis (Snijders, 2005). It was assumed that the variance accounted for (R^2) by this model would be no more than 40% for each variable of interest (subjective effect of cannabis, pain intensity, sleep quality, depressive symptoms, and anxious symptoms), thus making each of the respective residual variances 60%. It was specified that with 14 days of data, 100 individuals, and an ICC of roughly .50 (range: .40 -.60) effect sizes of at least $r = .10$ would be necessary for direct effects to be sufficiently powered to detect these effects at .80 or greater. Furthermore, to achieve adequate power within the indirect pathways, an effect size of $r = .15$ was assumed for the relationship between post-use pain and sleep quality. As previously described, findings of an association between pain and sleep are relatively robust. Past literature shows that among patients seeking treatment for chronic pain, pain and sleep disturbance correlate at $r = .26$ (McCracken & Iverson, 2002), so our estimate of $r = .15$ remains acceptable for this conservative model.

Indirect effects were calculated for cannabis use on Day 1 through each of the three primary outcome variables on Day 2 (pre-use pain, pre-use anxiety, and pre-use depression). Figure 3 depicts labeled pathways and formulas used to calculate each indirect effect included in the power analysis. Power was adequate for each pathway (Figure 3: *a* through *k*), ranging from .84 to .99. Additionally, the indirect effects of cannabis use on pre-use anxiety, pre-use pain intensity, and pre-use depression were adequately powered at .81, .82, and .80, respectively. Notably, this power analysis is somewhat inconsistent with the final model. While the

autoregressive effects of day 1 symptoms (pain, sleep, anxiety) on the corresponding day 2 symptoms were anticipated, these effects do not reflect the principle goal of the study and thus, they were not considered when estimating necessary power.

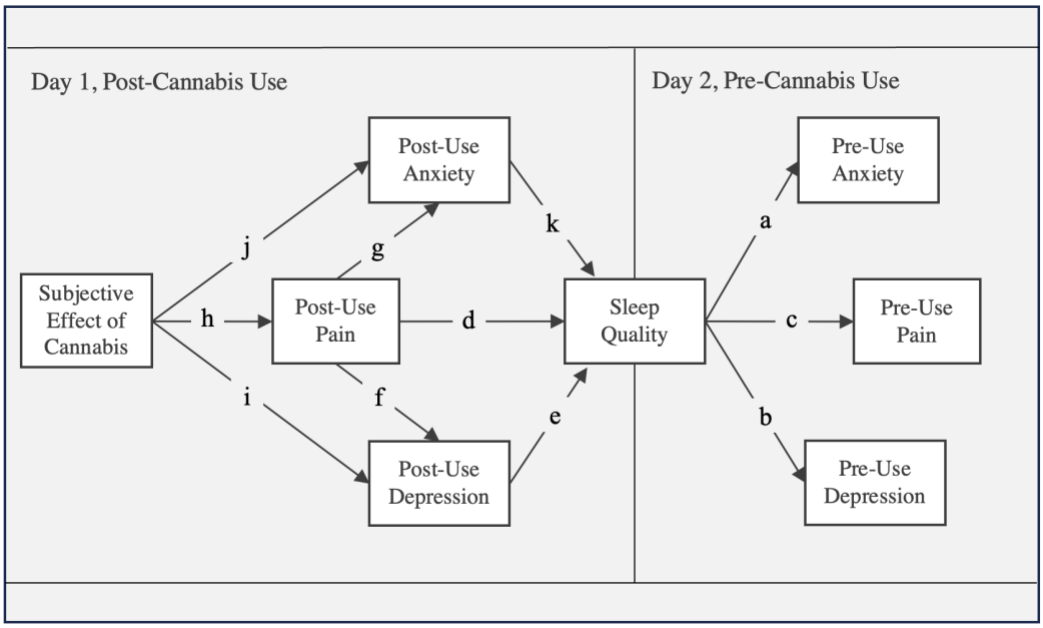


Figure 3. Pathway labels used for power analysis calculation of indirect effects.

Note. Indirect effects included in the power analysis were calculated as follows: INDANX = (a*d*h) + (a*k*j) + (a*k*g*h) + (a*e*i) + (a*e*f*h); INDPN = (c*d*h) + (c*k*j) + (c*k*g*h) + (c*e*i) + (c*e*f*h); INDDEP = (b*d*h) + (b*k*j) + (b*k*g*h) + (b*e*i) + (b*e*f*h); Where *INDANX* = indirect effect on pre-use anxiety, *INDDEP* = indirect effect on pre-use depression, and *INDPN* = indirect effect on pre-use pain.

Diversity Considerations

Goals of this project were to represent the population of adults over age 55 who legally use medicinal cannabis. Because there were no specific hypotheses intended to contrast motivations or patterns of use between ethnic or racial populations, correspondingly, no specific effort was made to power the sample for analyses examining such hypotheses. A standard approach to cultural competency utilizes the ADDRESSING framework, which emphasizes how various diversity considerations (which may often go overlooked) should inform a

multiculturally competent approach to working with individuals across the U.S. (Hayes, 2016). The present study did not seek to stratify subjects by sexual minority status, religion, socioeconomic status, or disability, as these may vary and did not directly relate to primary hypotheses. Furthermore, the primarily white, female composition of the present sample precluded between-subjects analyses stratified by demographics. Table 1 (descriptive statistics) addresses the demographic characteristics of involved participants, however, the goals of the present study were to capture temporal changes in symptomology at the within-subjects level, which does not allow for stratification by demographic covariates, though these questions should be explored in future studies.

Notably, cannabis use has long been associated with racial disparities. Changes to the legal status of cannabis in the mid-to-late twentieth century coincided with increasing negative stigma surrounding cannabis and its consumers. These laws have disproportionately impacted individuals in minority groups. Despite similar rates of use among both black and white individuals, between 2001 and 2010, it was found that a Black person was 3.73 times more likely to be arrested for cannabis possession than a white person (Bunting et al., 2013). Furthermore, disparities of this nature are not attributable to differences by racial group in drug use/sales, community context, or nondrug offending (Mitchell & Caudy, 2013). Though these issues have not been resolved, in recent years, cannabis decriminalization has helped to reduce rates of arrest for possession by over 70% among adults and helped reduce the racial disparity in arrests by 17% (Gunadi & Shi, 2022). These considerations do not reflect the goals of this manuscript, but they do impact the broader environment in which cannabis is prescribed and accessed, and thus represent future directions for research on cannabis use among older adults.

Ethical Considerations

Cannabis use in general, as well as for medicinal purposes, comes with certain ethical considerations, as does research conducted with older adult populations. As detailed previously, the legality of cannabis varies by state and by type of use (i.e., medicinal or recreational). Present protocol required participants to provide verification of medical cannabis card possession corresponding with their official state of residency, as confirmed by brief visual checks of participants' state-issued ID and medical cannabis authorization card. Therefore, to avoid any potential entrapment of participants, it was confirmed that all were using cannabis legally, thus omitting the potential of participants obtaining cannabis illegally to establish eligibility for participation in this study. Furthermore, utilization of medical cannabis comes with certain risks, such as worsened respiratory functioning, development of COPD, and increased risk of motor vehicle crashes (National Academies of Sciences Engineering and Medicine, 2017). The research protocol was designed and conducted with language addressing and describing a suitable response in the event of an adverse outcome such as those described above. Finally, working with older adult participants warrants certain precautions, such as ensuring the mental capability to consent to participate in research due to concerns of age-related cognitive decline and an increasing prevalence of Alzheimer's Disease and related dementias with increased age. In the present study, adults of age 55 and above were recruited. The base rate of dementia occurrence at and below age 60 is estimated to be approximately 1.0% or less (Vieira et al., 2013), though it does increase throughout the next few decades of the lifespan. Among adults aged 70-74, the 2019 prevalence was approximately 2.0%, with steady increases over the consecutive decades (Freedman et al., 2021). An IRB-approved procedure was employed to identify those who could provide consent. Consideration of higher multimorbidity rates is a relevant concern when

working with older participants, especially given the influence medicinal cannabis use could have on such conditions. Because participants possess a medical cannabis card, their use of cannabis is consistent with the standards of care in their respective state. Protocol was approved through the Institutional Review Board at the University of Central Florida (STUDY00004816).

RESULTS

Descriptive Statistics

The final sample consisted of 106 participants in total, with 1,100 independent observations representing participants' cannabis use days (one observation was defined as a single data analysis period, Epochs 1-4). See Table 1 for descriptive statistics.

Primary Analysis

A fully within-subject multilevel structural equation model was specified in *Mplus8.4.* The model was broken up into four epochs based on temporal precedence. The model fit the data well ($\chi^2(10) = 12.30$, $p = .27$; RMSEA = 0.014; CFI = 0.997; TLI = 0.99; SRMR = 0.02). Age was initially added as a level 2 covariate on all variables; however, none of these paths were significant and thus they were removed to reduce model complexity. Interclass correlations for each of the variables in the model were as follows: subjective intoxication ICC = 0.58. The ICC for sleep was 0.46, for post-use anxiety was 0.70, pre-use anxiety 0.71, post-use depression 0.72, pre-use depression 0.75, post-use pain 0.86, and pre-use pain 0.87. Significant effects are discussed below, reflected in Figure 4, and the final model is included in Table 2.

Consistent with hypothesis 1, cannabis intoxication in Epoch 1 was negatively associated with anxiety ($b = -0.04$, $SE = 0.02$, $p = .005$), pain ($b = -0.10$, $SE = 0.02$, $p < .001$), and depression ($b = -0.03$, $SE = 0.01$, $p = .013$) in Epoch 2. Another direct pathway was included

from cannabis use to sleep quality, though this was not statistically significant (b = -0.01, SE = 0.02, p = .63). Hypothesis 2 originally specified direct pathways from post-use pain to both post-use anxiety and post-use depression, respectively, though all three observations overlapped in Epoch 2. These pathways were instead specified as correlated (given they occur in the same epoch), which helped reduce multicollinearity and improved model fit. The correlation between post-use depression and post-use anxiety was r = .58 (p < .001). The correlation between post-use depression and post-use pain was r = .24 (p < .001). The correlation between post-use pain and post-use anxiety was r = .30 (p < .001).

Hypothesis 3 was partially supported. Post-use anxiety (Epoch 2) significantly predicted sleep quality in epoch 3 (b = -0.20, SE = 0.09, p = .03). Furthermore, there was a significant indirect effect of cannabis use (Epoch 1) on sleep quality (Epoch 3) through post-use anxiety (Epoch 2) (b = 0.008, SE = 0.004, p = .046). Other pathways predicted by hypothesis 3 were not statistically significant – neither post-use pain nor post-use depression predicted sleep quality, and thus, indirect effects from cannabis to sleep quality through each of these symptom domains was not statistically significant. Direct effects from sleep quality to pre-use anxiety, pain, and depression were not statistically significant, and thus, the hypothesized indirect effects from cannabis use (Epoch 1) through pre-use symptoms at Epoch 4 were not statistically significant, indicating no support for Hypothesis 4. In the final model, 2 additional indirect effects were specified. There was a significant indirect effect of cannabis use on pre-use (Epoch 4) anxiety through post-use (Epoch 2) anxiety (b = -0.02, SE = 0.01, p = .043), and a significant indirect effect of cannabis use on pre-use (Epoch 4) depression through post-use (Epoch 2) depression (b = -0.02, SE = 0.01, p = .024).

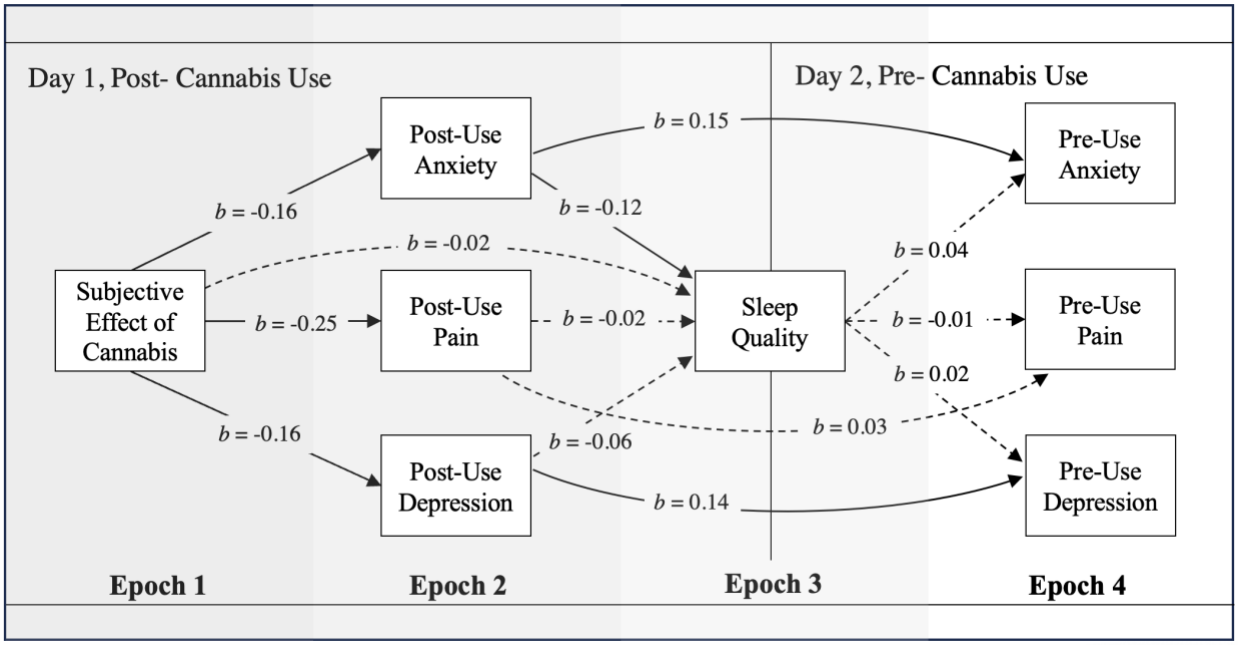


Figure 4. Final model demonstrating unstandardized direct effects.

Note. Solid lines indicate significant relationships ($p < .05$).

Table 1. Descriptive statistics for demographic information.

	Mean (SD) or %	Range
Age	61.06 (4.65)	55-74
Sex (% female)	66.67%	
Race		
White	82.86%	
Black	2.86%	
Asian American/Pacific Islander	1.90%	
Multiracial	11.32%	
Other/Do not wish to respond	1.90%	
Hispanic/Latino ethnicity	4.76%	

Table 2. Within-subjects multilevel structural equation model results.

Model Parameters		*B* (SE)	*p*	95% C.I.
Intercepts				
E1	Subjective high			
E2a	Post-use anxiety	-0.00 (0.01)	.708	(-0.02, 0.01)
E2b	Post-use pain	0.00 (0.00)	.217	(0.00, 0.00)
E2c	Post-use depression	-0.00 (0.00)	.414	(-0.01, 0.01)
E3	Sleep quality	-0.00 (0.00)	.496	(0.00, 0.00)
E4a	Pre-use anxiety	1.69 (0.09)	**<.001**	(1.51, 1.88)
E4b	Pre-use pain	1.34 (0.18)	**<.001**	(0.99, 1.69)
E4c	Pre-use depression	1.50 (0.08)	**<.001**	(1.34, 1.66)
Slopes: Direct effects				
E1 to E2a	High on Post-use anxiety	-0.04 (0.02)	**.005**	(-0.07, -0.01)
E1 to E2b	High on Post-use pain	-0.10 (0.02)	**<.001**	(-0.14, -0.06)
E1 to E2c	High on Post-use depression	-0.03 (0.01)	**.013**	(-0.06, -0.01)
E1 to E3	High on Sleep quality	-0.01 (0.02)	.628	(-0.04, 0.02)
E2a to E3	Post-use anxiety on Sleep quality	-0.20 (0.09)	**.031**	(-0.39, -0.02)
E2b to E3	Post-use pain on Sleep quality	-0.02 (0.05)	.721	(-0.13, 0.09)
E2c to E3	Post-use depression on Sleep quality	-0.12 (0.12)	.294	(-0.36, 0.11)
E3 to E4a	Sleep quality on Pre-use anxiety	0.08 (0.05)	**.091**	(-0.01, 0.18)
E3 to E4b	Sleep quality on Pre-use pain	-0.00 (0.11)	.976	(-0.23, 0.22)
E3 to E4c	Sleep quality on Pre-use depression	0.03 (0.04)	.462	(-0.05, 0.12)
E2a to E4a	Post-use anxiety on Pre-use anxiety	0.45 (0.12)	**<.001**	(0.22, 0.67)
E2b to E4b	Post-use pain on Pre-use pain	0.11 (0.26)	.673	(-0.39, 0.61)
E2c to E4c	Post-use depression on Pre-use depression	0.44 (0.11)	**<.001**	(0.23, 0.66)
Indirect effects				
Subjective high (E1) on Sleep quality (E3)				
E2a	through Post-use anxiety	0.01 (0.00)	**.046**	(0.00, 0.02)
E2b	through Post-use pain	0.00 (0.01)	.718	(-0.01, 0.01)
E2c	through Post-use depression	0.00 (0.00)	.268	(-0.00, 0.01)
Subjective high (E1) on Pre-use anxiety (E4a)				
E2a	through Post-use anxiety	-0.02 (0.01)	**.043**	(-0.04, -0.00)
E3	through Sleep quality	0.00 (0.00)	.645	(0.00, 0.00)
Subjective high (E1) on Pre-use pain (E4b)				
E2b	through Post-use pain	0.00 (0.00)	.976	(0.00, 0.00)

Model Parameters		*B* (SE)	*p*	95% C.I.
E3	through Sleep quality	0.00 (0.00)	.976	(0.00, 0.00)
Subjective high (E1) on Pre-use depression (E4c)				
E2c	through Post-use depression	-0.02 (0.01)	**.024**	(-0.03, -0.00)
E3	through Sleep quality	0.00 (0.00)	.690	(0.00, 0.00)
Total Effects				
Subjective high on Sleep quality		0.01 (0.02)	.657	(-0.03, 0.04)

Note. Significant p-values are bolded.

DISCUSSION

The goals of this study were to examine the role of medicinal cannabis use on the interrelated symptoms of depression, anxiety, sleep, and pain within subjects at the daily level. Results showed that the subjective effects of medicinal cannabis at the daily level predicted subsequent changes in pain, anxiety, and depression. Furthermore, of all variables investigated at Epochs 1 and 2 in the current study, only post-use anxiety predicted sleep quality (Epoch 3) that night. Furthermore, cannabis exerted an indirect effect on sleep quality via post-use anxiety. Contrary to initial hypotheses, neither post-use pain, post-use depression, nor cannabis use directly predicted sleep quality the following night. Additionally, cannabis significantly predicted both next-day pre-use anxiety and next-day pre-use depression through post-use anxiety and post-use depression, respectively. Interestingly, cannabis also exerted a significant effect on sleep quality through post-use anxiety, indicating that, while cannabis does not influence sleep directly, it does alter anxiety levels, which subsequently influences the individual's sleep the following night. Specifically, as subjective high increased, anxiety levels decreased, and sleep quality increased.

Metrics of cannabis use

Subjective high has been evaluated as a metric for cannabis consumption and prediction of symptom relief in prior studies, though not without some caveats. For instance, some cannabis products may not include THC, though they may still provide symptom relief via other cannabinoids or plant-derived compounds, such as CBD (De Vita et al., 2022; Russo & Guy, 2006), thus limiting the range of utility for this variable. Analysis of secondary data using an 11-point scale indicating subjective high, similar to that used in the present study, found that dosage and percentage of THC consumed each accounted for about 2.5% of the variance in subjective

high (Stith et al., 2023). This finding provides some support for our use of subjective high as a continuous metric of cannabis use and its effect on symptomology and raises interesting questions about the relationship between expectancies of use, product selection, dosing, tolerance, and subjective perceptions of use. Findings reported by Stith et al. (2023) indicated that, though THC is a strong predictor of symptom relief in some models, this effect is attenuated by the inclusion of the perceived high variable, potentially suggesting that THC provides symptom relief when individuals also experience a subjective high. However, perceived high and concentration of THC were also significantly positively associated with increases in negative side effects. They reported that, when controlling for dosage, route of administration, strain, constituent cannabinoids, and starting symptom level, subjective high predicted improvements in pain, fatigue, anxiety, and depression, but did not predict changes in sleep (Stith et al., 2023), which is consistent with our findings.

Direct effect: Pain

Present findings are consistent with previous literature indicating some efficacy of cannabis in the treatment of pain (Haleem & Wright, 2020; Hill et al., 2017; Moore et al., 2021; L. Wang et al., 2021). The endogenous cannabinoid system may play a role in analgesia and modulation of nociceptive thresholds (Haroutounian et al., 2021; Maayah et al., 2020), which may explain the observed effect of cannabis on pain. Major methodological issues often limit the confidence with which conclusions can be made regarding the effect of cannabis on pain (Moore et al., 2021). Clinical trials tend to show small improvements in pain due to cannabis use (Hill et al., 2017), albeit inconsistently. A recent review of randomized clinical trials (RCTs) found that the changes in pain due to cannabis are small, case-specific, and specific to the route of administration (L. Wang et al., 2021). Non-RCTs tend to report stronger effects of cannabis use

on pain (Haleem & Wright, 2020), which aligns with present findings. The present study demonstrated an effect whereby daytime changes in pain were directly related to cannabis use, though these effects did not last through the following day, nor did they impact sleep. A recent meta-analysis identified small but significant improvements in sleep among individuals using cannabis for pain (versus placebo), with a comparatively stronger effect for those with non-cancer pain than those with cancer-related pain (AminiLari et al., 2022). Contrary to some previous evidence and the current hypotheses, cannabis only improved pain directly, but not through improvements in sleep.

Direct effects: Depression and Anxiety

Present findings support prior evidence indicating a direct effect of cannabis on mood in the moment among clinical samples (Cuttler et al., 2018; Wycoff et al., 2018), though these results do not rule out the potentially causal influences of expectancy effects or symptom relief in other domains. The present study specifically identified a pattern whereby anxiety and depression levels were alleviated immediately following cannabis use, though these effects did not last until the following day. Previous literature indicates that mood changes could be related to the medical condition for which individuals endorse cannabis use – for example, when used for the treatment of pain, new cannabis users demonstrate improvements in mood from baseline on average (Y. Wang et al., 2021). The distinction between momentary improvement in depressive and anxious symptoms and long-term mental health status is imperative in the discussion of medical cannabis use. As previously mentioned, cannabis may be ineffective in treating depression and may also serve as a risk factor for the development of a depressive disorder (National Academies of Sciences Engineering and Medicine, 2017). Likewise, RCTs do not support THC or CBD as effective treatment options for anxiety disorders (Stanciu et al.,

2021). Momentary-level cannabis use patterns may differ from longer-term evaluations of its efficacy in the treatment of mental health disorders. In one previous study, individuals perceived momentary improvements in depression, anxiety, and stress after initiation of cannabis use (Cuttler et al., 2018). When comparing tracked sessions across time, however, stress and anxiety levels remained stable, and depression slightly increased (Cuttler et al., 2018). The current study demonstrated similar momentary-level improvements in anxiety and depression after cannabis use, and, interestingly, some lasting impact on next-day depression and anxiety through the previous day's depression/anxiety ratings. The relationships between the prior day's cannabis use and the following day's mental health symptoms are most likely explained by the strength of the relationships between the individual mental health symptoms across days, rather than any meaningful, lasting impact of cannabis use on mental health across time, though these conclusions are speculative. Overall, conclusions cannot be drawn about long-term maintenance, improvement, or worsening of mental health as present data speaks only to smaller-scale day-level effects.

Direct and Indirect Effects on Sleep

Contrary to hypotheses, findings did not indicate any direct effect of cannabis on sleep, though cannabis exerted a significant indirect effect on sleep through reductions in anxiety. Previous literature posits that cannabis may improve sleep among those with certain medical conditions, such as pain, but not among healthy individuals, and effects may differ by cannabinoid concentration and dosage (Babson et al., 2017; National Academies of Sciences Engineering and Medicine, 2017; Velzeboer et al., 2022). The present study did not differentiate cannabis use by product type, and the within-subjects nature of data analysis precluded between-subject factor differentiation. Therefore, heterogeneity within the medical conditions being

treated and the products used may serve as an explanatory factor for the lack of effect of cannabis on sleep. Along these lines, the presence of specific sleep-related disorders was not controlled for, though pathological sleep problems could have influenced the degree of improvement in sleep or the efficacy of cannabis in sleep improvement. Estimates indicate prevalence of sleep disorders among approximately 17% of men and 9% of women aged 50-70 (Peppard et al., 2013). Evidence for any therapeutic potential of cannabis in the treatment of Obstructive Sleep Apnea is limited (National Academies of Sciences Engineering and Medicine, 2017), and use is cautioned against by the American Academy of Sleep Medicine due to limited evidence of efficacy and risk of side effects like daytime sleepiness (Ramar et al., 2018). Furthermore, sleep quality was measured via a modified version of the PSQI. While this metric is a useful self-report measure of subjective sleep quality (Buysse et al., 1988), PSQI scores appear to be either unrelated to objective sleep measures such as actigraphy and polysomnography (Buysse et al., 2008; Scarlata et al., 2013), or only weakly correlated with certain parameters of the objective measures. Therefore, present findings should not be overgeneralized to indicate or disqualify cannabis use in the treatment of sleep disorders. These factors all contextualize the complex relationships between sleep, sleep disorders, and cannabis use, thus indicating several theoretical explanations for the lack of direct effects of cannabis on sleep found in this study.

The influence of cannabis on sleep may be better explained through cannabinoid effects on anxiety, rather than any inherent biological effects exerted on the sleep-wake system or sleep disorders independently, as evinced by the indirect effect found in the present study. One explanation of this is that sleep may be relatively unaffected by cannabis use, except to the extent that cannabis influences anxiety. Thus, it may be that cannabis moderates anxiety symptoms

acutely, which, among other symptoms of anxiety, improves sleep. These results do not suggest cannabis as a panacea for sleep impairment beyond the context of anxiety. As previously discussed, endogenous cannabinoids seem to exert both sleep-promoting and wakefulness-promoting effects, and exogenous cannabinoids may modulate these effects through both agonistic and inhibitory mechanisms, though the evidence is still inconclusive regarding whether cannabis-related sleep improvements are directly related to the circadian system or indirectly result from alleviation of other symptoms (Suraev et al., 2020). Similarly, the eCB system has hypothesized roles in the serotonergic system (Cohen et al., 2019) and stress-regulation (Morena et al., 2016), which could explain the reduction in negative affectivity seen with greater cannabis intoxication. While the neurobiological basis of cannabinoid interaction with sleep and anxiety-related processes is still not fully understood, the interaction of sleep and anxiety independently of endogenous and exogenous cannabinoids lends context to the evident indirect effect.

A multitude of theories have attempted to capture the complex interplay between sleep and anxious arousal. Co-occurrence of sleep disturbance and anxiety may be explained by a common predisposition to hyperarousal (Stepanski & Rybarczyk, 2006), which cannot be ruled out among the present sample. Furthermore, neurobiologically, serotonergic and dopaminergic systems play important regulatory roles in both sleep and affective processes, such that disturbances in one domain may impact the other (Harvey et al., 2011). Thus, a transdiagnostic model of sleep proposes that sleep disorders and psychiatric disturbances are uniquely intertwined, and often have reciprocal relationships that may potentiate disturbances in both (Harvey et al., 2011). As previously discussed, sleep problems and affective disturbance are commonly and effectively treated together by targeting one of the two symptoms, using methods such as CBT-I (Sadler et al., 2018). Given this evidence, our finding that alleviation of anxiety

via cannabis use leads to improvements in sleep the following night may represent a similar phenomenon whereby cannabis effectively reduces anxious arousal, thus breaking the vicious cycle of anxiety and sleep disturbance, at least at the daily level.

Expectancies and Other Considerations

Present findings of cannabis efficacy may be attributable to any of multiple explanations, including cannabis-related expectancies, pharmacological effects of cannabinoids, or other latent mediating factors, such as the release of muscle tension. *Expectancy* is a term often used within the substance-use literature to refer to one of many cognitive and neurophysiological representations of past experiences that influence future behavior (Del Boca et al., 2002). Within the alcohol use literature, expectancies are well-established as predictors of drinking behavior, and they can even be targeted and changed to influence future behaviors (Del Boca et al., 2002; Dunn et al., 2000). Prior studies have shown that expectancies related to a multitude of substances can influence outcomes. One study evaluating remifentanil, an opioid, for pain demonstrated that positive drug expectancies can enhance analgesia, while negative expectancies can abate it (Bingel et al., 2011). The same phenomenon may apply to analgesia associated with cannabis use. Prior placebo-balanced research has demonstrated that expectancies play a role in the relationship between CBD and pain reduction (De Vita et al., 2022). Metrics of cannabis expectancies related to medical symptoms and symptom changes constitute an emergent area of research. One recently developed measure, the CEEQ-M, demonstrated a 2-factor structure of medical cannabis expectancies: symptom relief and unusual beliefs (Weiss et al., 2023). Notably, in this study, baseline expectancies did not predict symptom change; authors also note that while their questionnaire was focused on medical expectancies, users' comprehensive cannabis expectancies may have been formed based on experiences with both medical and recreational

cannabis (Weiss et al., 2023). Furthermore, expectancies were somewhat stable in that study, and while conclusions could not yet be drawn about the persistence of expectancies despite disconfirming evidence, authors note that this may constitute an area of clinical concern (Weiss et al., 2023). While the direct impact of cannabis-related expectancies on symptom change among medical cannabis users is still understudied, it is possible that present findings could have been confounded by participants' expectations for symptom change.

Consideration of tolerance, withdrawal, and adverse events prior to the initiation of medicinal cannabis is especially important among older adults, many of whom may experience polypharmacy and multimorbidity. Precautions should be taken with these populations as some contraindications of cannabis use include unstable cardiovascular disease, respiratory disease, and potential interactions with certain medications – see MacCallum et al. (2021) for detailed descriptions of contraindications. Concerns of tolerance and escalating patterns of use among medical cannabis users should also be considered. Upon repeated administrations of cannabinoids, their effects tend to be less pronounced, suggesting that persistent users are likely to develop tolerance to cannabis (Colizzi & Bhattacharyya, 2018). The present study demonstrated that the greater the reported level of intoxication, the more symptom relief the user experienced, which may be interpreted as negative reinforcement of cannabis use. Prior research indicates that medical cannabis users may be less likely than recreational users to endorse acute adverse effects, but more likely to report unwanted withdrawal symptoms, though this effect differed by age group – adults over 50 reported fewer effects in either category as compared to younger adults (Sexton et al., 2019). While older adults using medical cannabis tend to report fewer adverse events than younger adults, some of these events can include dizziness, nausea,

confusion, and hallucinations (Whiting et al., 2015), and thus should be monitored among these populations.

Placing these Findings in the Context of this Cohort

Studies examining cannabis use and resultant pain and depression at the momentary level to date have been sparse. Of those that exist, many do not address these phenomena in cohorts of older adults, specifically. A review conducted by Wycoff et al. (2018) synthesized findings of studies using EMA with clinical samples to evaluate depressive symptoms following cannabis use and reported inconsistencies between studies. These studies involved young to middle aged adults (mean ages all below 50) with bipolar, depressive, and/or borderline personality disorders, and while two studies found that depressive symptoms decreased after use (Gruber et al., 2012; Sagar et al., 2016), two others found increases in depressive symptoms after use (Trull et al., 2016; Tyler et al., 2015).

Cannabis use and resultant changes in pain at the momentary level has been more often investigated with older cohorts, though results are still mixed, and samples are somewhat heterogeneous. At the within-subjects level, one study of adults (mean age 55.7, *SD* = 11.9) *initiating* cannabis use demonstrated significant momentary reductions in pain (Y. Wang et al., 2021). This study also found momentary improvements in anxiety and sleep, but not depression (Y. Wang et al., 2021). However, another within-subjects analysis conducted with *long-term users* (mean age 43.3, *SD* = 10.6) identified higher pain intensity predicting more cannabis use, but failed to find a direct association of cannabis use with subsequent relief of pain symptoms (Sznitman et al., 2021). Regarding the relationship between anxiety and sleep, the current results were consistent with one previous EMA study utilizing a primarily younger adult sample ranging in age from 21 to 70 years (*M* = 33.15), which also found within-subject improvements in sleep

among individuals with heightened anxiety symptoms on cannabis use days, as compared to non-use days (Sznitman et al., 2024).

A few explanations may be drawn to explain the similarities and differences between these findings and the current study. Of particular importance is the distinctive age cohort evaluated in the current study. The experience of chronic pain often differs by age, such that younger adults are more likely to report pain due to injury and less likely to endorse multimorbidity or treatment for their pain, as compared to older adults (Rustoen et al., 2005). While momentary improvements in pain and depression were observed, these did not lead to resultant changes in sleep. This could either (a) represent some unique component of cannabis use that deviates from typical relationships between pain and sleep and depression and sleep among non-users, (b) provide evidence that these effects are observed at the between-subjects, but not within-subjects, level, (c) reflect some unique age-related differences in the momentary trajectory of cannabis use and the resultant symptoms, or (d) be attributable to other explanations, such as the mood circumplex model (Posner et al., 2005), whereby reductions in anxiety (a high arousal state) may be explained as a mechanism for improvement in sleep (which requires low arousal) whereas reductions in depression (a low arousal state) may not.

The current sample was exclusively age 55 and over, with a mean age of 61.06. The impact of age on THC and CBD uptake, metabolization, and neurocognitive impact all represent critical areas for future research. Inclusion of an age effect in this study produced unnecessary model complexity without any substantive improvement in model fit or variance accounted for. One possibility is that the modeled age effect in this sample was eroded by range restriction on that variable, and another sample representing a broader range of ages may facilitate examination of this effect. While it was thus analytically justifiable to exclude the age effect, future research

should seek to better understand the prospective moderating influence of age on medical cannabis efficacy and user experience.

Limitations

The present study is primarily limited by the nature of the sample and the metrics used to indicate cannabis consumption and sleep quality. The sample size was adequate for the present analysis, but the inclusion of a greater number of participants and/or days of cannabis use would improve the likelihood of accuracy and representativeness of findings. Furthermore, recruitment methods for this study facilitated the collection of a national sample and increased the feasibility of participation for individuals living in rural areas or with other barriers to traveling to a study site. However, given that the study was advertised on social media websites, the sample was self-selected. Individuals who chose to participate in this study may have had numerous reasons for doing so, but some may have biases (expectancies) that could influence their perception of cannabis efficacy or their responses to survey questions. Finally, rather than expectancies or pharmacological effects, some unspecified tertiary factors may explain our results, though these cannot be accounted for based on available data. These may be due to other psychological or physiological phenomena associated with cannabis use, such as coping and negative reinforcement cycles leading to momentary reduction of negative affect, or reduction of muscle tension leading to improved sleep.

Future Directions

Future studies should seek to replicate and clarify the nature of present findings, address the limitations described above, and contrast present findings with the influence of cannabis cessation or abstinence on sleep, pain, and negative affect. The present study did not differentiate by pain subtypes, such as neuropathic, cancer-related, or pain from multiple sclerosis, despite

previous findings indicating potential differences (Nugent et al., 2017), which therefore reflects a future direction of investigation. Additionally, prior studies have demonstrated that cessation of cannabis use can lead to worsened sleep (Babson & Bonn-Miller, 2014; Babson et al., 2017; Cranford et al., 2017; Sullivan et al., 2022) especially in the short term, though among adolescent and young adult individuals, a return to baseline and no difference in sleep as compared to controls has been demonstrated after sustained abstinence of about 2 weeks (Sullivan et al., 2022). Given the present indirect effect, this begs the question of how withdrawal may impact pain and negative affect through worsened sleep. Withdrawal-induced sleep disturbances may also increase the likelihood of resurgent cannabis use to alleviate symptoms (Babson & Bonn-Miller, 2014), thus, if medicinal cannabis users choose to discontinue use, they and their practitioners should be aware of potential withdrawal effects including worsened symptoms, potentially among all three symptom domains. Even in the absence of acute withdrawal, the current study did not evaluate sleep, affect and pain data on non-use days, thus, individual differences in these symptoms on use and non-use days should be investigated in the future.

Implications

Results of this study and future studies within this emerging line of research may help inform practitioners and patients in their decision-making regarding the utility of treatment with medicinal cannabis. This study provided evidence for momentary improvements in symptoms of pain, anxiety, and depression among older adults using for medical reasons, and uniquely identified improvements in sleep only following reductions in anxiety, but not directly through intoxication. These findings are largely limited by measures and the potential implications of expectancy effects, and do not provide information about long-term outcomes for treatment, but uniquely speak to the momentary patterns in medical symptomology at the acute, daily level.

Any substance can be overused, and this study (along with others like it) may help provide groundwork for delineation between therapeutic use and problematic use by identifying ways in which problem use may be maintained by momentary improvements in symptomology. Despite its limitations, the results of this study contribute to a growing body of research evaluating the efficacy of medicinal cannabis use for older adults and serve to help inform moderate use guidelines for this population.

APPENDIX A: UCF IRB APPROVAL LETTERS

UNIVERSITY OF CENTRAL FLORIDA

Institutional Review Board
FWA00000351
IRB00001138, IRB00012110
Office of Research
12201 Research Parkway
Orlando, FL 32826-3246

APPROVAL

October 27, 2022

Dear Robert Dvorak:

On 10/27/2022, the IRB reviewed the following submission:

Type of Review:	Initial Study, Expedited category 7
Title:	Efficacy of Medical Cannabis
Investigator:	Robert Dvorak
IRB ID:	STUDY00004816
Funding:	Name: Consortium for Medical Marijuana Clinical Outcomes Research
Grant ID:	
IND, IDE, or HDE:	None
Documents Reviewed:	• MC Phase I Consent 2.0.pdf, Category: Consent Form; • MC Phase II Consent 3.0.pdf, Category: Consent Form; • MC Screen (5).docx, Category: Survey / Questionnaire; • MC Study Protocol 2.0 10-25 (1).docx, Category: IRB Protocol; • MC_Morning_PII (1).docx, Category: Survey / Questionnaire; • MC_Morning_Survey (1).docx, Category: Survey / Questionnaire; • MC_Post-Use_PII (1).docx, Category: Survey / Questionnaire; • MC_Post-Use_Survey (1).docx, Category: Survey / Questionnaire; • MC_Pre-Use_PII (1).docx, Category: Survey / Questionnaire; • MC_Pre-use_Survey (1).docx, Category: Survey / Questionnaire; • MC_RandomDaily_PII (1).docx, Category: Survey / Questionnaire; • MC_RandomDaily_Survey (1).docx, Category: Survey / Questionnaire; • MC_Screen_PII (1).docx, Category: Survey /

	Questionnaire; • recrutiment materials 2.0.docx, Category: Recruitment Materials; • ResearchPlan.pdf, Category: Sponsor Attachment; • Standard Operating Procedures for Studies with Personally Identifiable Information (1).docx, Category: Other;

The IRB approved the protocol on 10/27/2022.

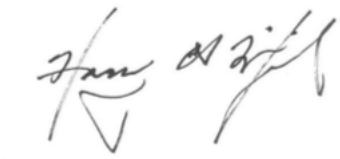
In conducting this protocol, you are required to follow the requirements listed in the Investigator Manual (HRP-103), which can be found by navigating to the IRB Library within the IRB system. Guidance on submitting Modifications and a Continuing Review or Administrative Check-in is detailed in the manual. If continuing review is required and approval is not granted before the expiration date, approval of this protocol expires on that date.

Use of the stamped version of the consent form is required.To document consent, use the consent documents that were approved and stamped by the IRB. Go to the Documents tab to download them.

When you have completed your research, please submit a Study Closure request so that IRB records will be accurate.

If you have any questions, please contact the UCF IRB at 407-823-2901 or irb@ucf.edu. Please include your project title and IRB number in all correspondence with this office.

Sincerely,



Harry Wingfield
Designated Reviewer

Subject: IRB From Thesis
Date: Sunday, March 31, 2024 at 2:45:28 PM Eastern Daylight Time
From: Robert Dvorak <dvorak@ucf.edu>
To: Madison Maynard <Madison.Maynard@ucf.edu>
Attachments: photo_2024-03-31 13.42.18.jpeg

This thesis research conducted by Madison Maynard is connected to IRB Approval STUDY00004816. She is also on the IRB protocol (see below).

Rob

Robert D. Smith-Dvorak, PhD, ABPP
Professor of Clinical Psychology, Department of Psychology, College of Science
Professor of Medicine, Department of Clinical Sciences, College of Medicine
Co-Director, Substance Use Research Group
Director, REALE-TIME Lab
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robert.dvorak@ucf.edu
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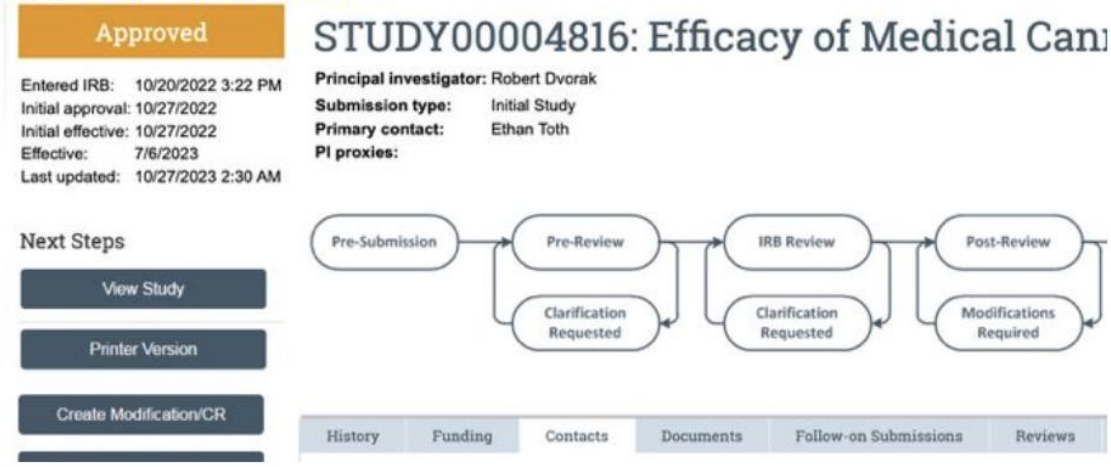
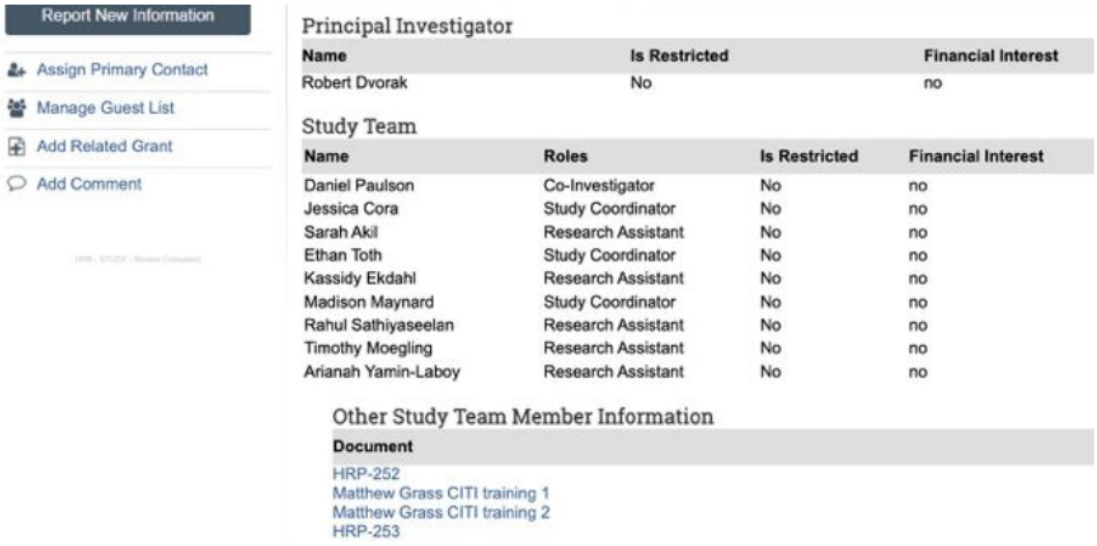
To book a meeting with me:
https://calendly.com/rob-d-dvorak/30min




Report New Information
Assign Primary Contact
Manage Guest List
Add Related Grant
Add Comment
Principal Investigator
Name
Is Restricted
Financial Interest
Robert Dvorak
No
no
Study Team
Name
Roles
Is Restricted
Financial Interest
Daniel Paulson
Co-Investigator
No
no
Jessica Cora
Study Coordinator
No
no
Sarah Akil
Research Assistant
No
no
Ethan Toth
Study Coordinator
No
no
Kassidy Ekdahl
Research Assistant
No
no
Madison Maynard
Study Coordinator
No
no
Rahul Sathiyaseelan
Research Assistant
No
no
Timothy Moegling
Research Assistant
No
no
Arianah Yamin-Laboy
Research Assistant
No
no
Other Study Team Member Information
Document
HRP-252
Matthew Grass CITI training 1
Matthew Grass CITI training 2
HRP-253

REFERENCES

Adamson, S. J., & Sellman, J. D. (2003). A prototype screening instrument for cannabis use disorder: the Cannabis Use Disorders Identification Test (CUDIT) in an alcohol-dependent clinical sample. *Drug and Alcohol Review*, *22*(3), 309-315. https://doi.org/10.1080/0959523031000154454

Alhola, P., & Polo-Kantola, P. (2007). Sleep deprivation: Impact on cognitive performance. *Neuropsychiatric Disease and Treatment*, *3*(5), 553–567.

Alvaro, P. K., Roberts, R. M., & Harris, J. K. (2013). A Systematic Review Assessing Bidirectionality between Sleep Disturbances, Anxiety, and Depression. *Sleep*, *36*(7), 1059-1068. https://doi.org/10.5665/sleep.2810

American Psychiatric Association. (2022). *Diagnostic and Statistical Manual of Mental Disorders: DSM-5-TR* (5th ed.). American Psychiatric Association Publishing. https://doi.org/https://doi.org/10.1176/appi.books.9780890425787

AminiLari, M., Wang, L., Neumark, S., Adli, T., Couban, R. J., Giangregorio, A., Carney, C. E., & Busse, J. W. (2022). Medical cannabis and cannabinoids for impaired sleep: a systematic review and meta-analysis of randomized clinical trials. *Sleep*, *45*(2). https://doi.org/10.1093/sleep/zsab234

Avery, D. (2023). *Marijuana Laws by State: Where Is Weed Legal?* CNET (Computer Network). Retrieved 5 March 2023 from https://www.cnet.com/news/politics/marijuana-laws-by-state-where-is-weed-legal/

Aviram, J., Pud, D., Gershoni, T., Schiff-Keren, B., Ogintz, M., Vulfsons, S., Yashar, T., Adahan, H. M., Brill, S., Amital, H., Goor-Aryeh, I., Robinson, D., Green, L., Segal, R., Fogelman, Y., Tsvieli, O., Yellin, B., Vysotski, Y., Morag, O., . . . Eisenberg, E. (2021).

Medical cannabis treatment for chronic pain: Outcomes and prediction of response. *European Journal of Pain*, *25*(2), 359-374. https://doi.org/10.1002/ejp.1675

Babson, K. A., & Bonn-Miller, M. O. (2014). Sleep Disturbances: Implications for Cannabis Use, Cannabis Use Cessation, and Cannabis Use Treatment. *Current Addiction Reports*, *1*(2), 109-114. https://doi.org/10.1007/s40429-014-0016-9

Babson, K. A., Sottile, J., & Morabito, D. (2017). Cannabis, Cannabinoids, and Sleep: a Review of the Literature. *Current Psychiatry Reports*, *19*(4), 23. https://doi.org/10.1007/s11920-017-0775-9

Baglioni, C., Battagliese, G., Feige, B., Spiegelhalder, K., Nissen, C., Voderholzer, U., Lombardo, C., & Riemann, D. (2011). Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *Journal of Affective Disorders*, *135*(1-3), 10-19. https://doi.org/10.1016/j.jad.2011.01.011

Bair, M. J., Robinson, R. L., Katon, W., & Kroenke, K. (2003). Depression and pain comorbidity: a literature review. *Archives of Internal Medicine*, *163*(20), 2433-2445. https://doi.org/10.1001/archinte.163.20.2433

Bao, Y. P., Han, Y., Ma, J., Wang, R. J., Shi, L., Wang, T. Y., He, J., Yue, J. L., Shi, J., Tang, X. D., & Lu, L. (2017). Cooccurrence and bidirectional prediction of sleep disturbances and depression in older adults: Meta-analysis and systematic review. *Neuroscience and Biobehavioral Reviews*, *75*, 257-273. https://doi.org/10.1016/j.neubiorev.2017.01.032

Beard, C., & Bjorgvinsson, T. (2014). Beyond generalized anxiety disorder: psychometric properties of the GAD-7 in a heterogeneous psychiatric sample. *Journal of Anxiety Disorders*, *28*(6), 547-552. https://doi.org/10.1016/j.janxdis.2014.06.002

Berman, A. H., Bergman, H., Palmstierna, T., & Schlyter, F. (2002). Drug Use Disorders Identification Test (DUDIT). *APA PsycTests*. https://doi.org/https://doi.org/10.1037/t02890-000

Bingel, U., Wanigasekera, V., Wiech, K., Ni Mhuircheartaigh, R., Lee, M. C., Ploner, M., & Tracey, I. (2011). The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. *Science Translational Medicine*, *3*(70), 70ra14. https://doi.org/10.1126/scitranslmed.3001244

Boggs, D. L., Nguyen, J. D., Morgenson, D., Taffe, M. A., & Ranganathan, M. (2018). Clinical and Preclinical Evidence for Functional Interactions of Cannabidiol and Delta(9)-Tetrahydrocannabinol. *Neuropsychopharmacology*, *43*(1), 142-154. https://doi.org/10.1038/npp.2017.209

Bohnert, K. M., Bonar, E. E., Arnedt, J. T., Conroy, D. A., Walton, M. A., & Ilgen, M. A. (2018). Utility of the comprehensive marijuana motives questionnaire among medical cannabis patients. *Addictive Behaviors*, *76*, 139-144. https://doi.org/10.1016/j.addbeh.2017.08.001

Botsford, S. L., Yang, S., & George, T. P. (2020). Cannabis and Cannabinoids in Mood and Anxiety Disorders: Impact on Illness Onset and Course, and Assessment of Therapeutic Potential. *The American Journal on Addictions*, *29*(1), 9-26. https://doi.org/10.1111/ajad.12963

Brenan, M. (2020, November 9). Support for Legal Marijuana Inches Up to New High of 68%. *Gallup*. https://news.gallup.com/poll/323582/support-legal-marijuana-inches-new-high.aspx

Bridgeman, M. B., & Abazia, D. T. (2017). Medicinal Cannabis: History, Pharmacology, And Implications for the Acute Care Setting. *Pharmacy and Therapeutics*, *42*(3), 180-188. https://www.ncbi.nlm.nih.gov/pubmed/28250701

Brown, J. D., Costales, B., van Boemmel-Wegmann, S., Goodin, A. J., Segal, R., & Winterstein, A. G. (2020). Characteristics of Older Adults Who Were Early Adopters of Medical Cannabis in the Florida Medical Marijuana Use Registry. *Journal of Clinical Medicine*, *9*(4). https://doi.org/10.3390/jcm9041166

Brush, D. M., Paulson, D., Legon, M. J. H., James, N. T., Scheurich, J. A., Stevenson, B. L., & Dvorak, R. D. (2020). Sleep disturbance and depressive symptoms in later-life: Cross-sectional examination of cognitive mechanisms. *Neurology, Psychiatry and Brain Research*, *37*, 6-14. https://doi.org/10.1016/j.npbr.2020.05.001

Bunting, W. C., Garcia, L. R., & Edwards, E. (2013). *The War on Marijuana in Black and White*. American Civil Liberties Union. https://www.aclu.org/publications/report-war-marijuana-black-and-white

Buysse, D. J., Hall, M. L., Strollo, P. J., Kamarck, T. W., Owens, J., Lee, L., Reis, S. E., & Matthews, K. A. (2008). Relationships Between the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and Clinical/Polysomnographic Measures in a Community Sample. *Journal of Clinical Sleep Medicine*, *04*(06), 563-571. https://doi.org/10.5664/jcsm.27351

Buysse, D. J., Reynolds III, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1988). The Pittsburgh Sleep Quality Index: A New Instrument for Psychiatric Practice and Research. *Psychiatry Research*, *28*, 193-213.

Clark, L. A., & Watson, D. (1991). Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology*, *100*(3), 316-336. https://doi.org/10.1037//0021-843x.100.3.316

Cohen, K., Weizman, A., & Weinstein, A. (2019). Modulatory effects of cannabinoids on brain neurotransmission. *European Journal of Neuroscience*, *50*(3), 2322-2345. https://doi.org/10.1111/ejn.14407

Colizzi, M., & Bhattacharyya, S. (2018). Cannabis use and the development of tolerance: a systematic review of human evidence. *Neuroscience and Biobehavioral Reviews*, *93*, 1-25. https://doi.org/10.1016/j.neubiorev.2018.07.014

Cranford, J. A., Arnedt, J. T., Conroy, D. A., Bohnert, K. M., Bourque, C., Blow, F. C., & Ilgen, M. (2017). Prevalence and correlates of sleep-related problems in adults receiving medical cannabis for chronic pain. *Drug and Alcohol Dependence*, *180*, 227-233. https://doi.org/10.1016/j.drugalcdep.2017.08.017

Cuttler, C., Spradlin, A., & McLaughlin, R. J. (2018). A naturalistic examination of the perceived effects of cannabis on negative affect. *Journal of Affective Disorders*, *235*, 198-205. https://doi.org/10.1016/j.jad.2018.04.054

Danielsson, A. K., Lundin, A., Agardh, E., Allebeck, P., & Forsell, Y. (2016). Cannabis use, depression and anxiety: A 3-year prospective population-based study. *Journal of Affective Disorders*, *193*, 103-108. https://doi.org/10.1016/j.jad.2015.12.045

De Leon, A. N., Dvorak, R. D., Kramer, M. P., Peterson, R., Pinto, D. A., Leary, A. V., & Magri, T. D. (2020). Daily Patterns of Emotional Functioning on Drinking and Nondrinking Days. *Alcoholism: Clinical and Experimental Research*, *44*(12), 2598-2610. https://doi.org/10.1111/acer.14480

De Vita, M. J., Maisto, S. A., Gilmour, C. E., McGuire, L., Tarvin, E., & Moskal, D. (2022). The effects of cannabidiol and analgesic expectancies on experimental pain reactivity in healthy adults: A balanced placebo design trial. *Experimental and Clinical Psychopharmacology*, *30*(5), 536-546. https://doi.org/10.1037/pha0000465

Del Boca, F. K., Darkes, J., Goldman, M. S., & Smith, G. T. (2002). Advancing the Expectancy Concept via the Interplay Between Theory and Research. *Alcoholism: Clinical and Experimental Research*, *26*(6), 926-935. https://doi.org/10.1111/j.1530-0277.2002.tb02623.x

Dunn, M. E., Lau, H. C., & Cruz, I. Y. (2000). Changes in activation of alcohol expectancies in memory in relation to changes in alcohol use after participation in an expectancy challenge program. *Experimental and Clinical Psychopharmacology*, *8*(4), 566-575. https://doi.org/10.1037//1064-1297.8.4.566

Englund, A., Morrison, P. D., Nottage, J., Hague, D., Kane, F., Bonaccorso, S., Stone, J. M., Reichenberg, A., Brenneisen, R., Holt, D., Feilding, A., Walker, L., Murray, R. M., & Kapur, S. (2013). Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *Journal of Psychopharmacology*, *27*(1), 19-27. https://doi.org/10.1177/0269881112460109

Farris, S. G., Metrik, J., Bonn-Miller, M. O., Kahler, C. W., & Zvolensky, M. J. (2016). Anxiety Sensitivity and Distress Intolerance as Predictors of Cannabis Dependence Symptoms, Problems, and Craving: The Mediating Role of Coping Motives. *Journal of Studies on Alcohol and Drugs*, *77*(6), 889-897. https://doi.org/10.15288/jsad.2016.77.889

Fatseas, M., Serre, F., Swendsen, J., & Auriacombe, M. (2018). Effects of anxiety and mood disorders on craving and substance use among patients with substance use disorder: An

ecological momentary assessment study. *Drug and Alcohol Dependence*, *187*, 242-248. https://doi.org/10.1016/j.drugalcdep.2018.03.008

Feingold, D., & Weinstein, A. (2021). Cannabis and Depression. In E. Murillo-Rodriguez, S. R. Pandi-Perumal, & J. M. Monti (Eds.), *Cannabinoids and Neuropsychiatric Disorders*. https://doi.org/10.1007/978-3-030-57369-0_5

Felson, J., Adamczyk, A., & Thomas, C. (2019). How and why have attitudes about cannabis legalization changed so much? *Social Science Research*, *78*, 12-27. https://doi.org/10.1016/j.ssresearch.2018.12.011

Fischer, B., Russell, C., Sabioni, P., van den Brink, W., Le Foll, B., Hall, W., Rehm, J., & Room, R. (2017). Lower-Risk Cannabis Use Guidelines: A Comprehensive Update of Evidence and Recommendations. *American Journal of Public Health*, *107*(8), e1-e12. https://doi.org/10.2105/AJPH.2017.303818

Fisher, E., Moore, R. A., Fogarty, A. E., Finn, D. P., Finnerup, N. B., Gilron, I., Haroutounian, S., Krane, E., Rice, A. S. C., Rowbotham, M., Wallace, M., & Eccleston, C. (2021). Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomised controlled trials. *Pain*, *162*(Suppl 1), S45-S66. https://doi.org/10.1097/j.pain.0000000000001929

Freedman, V. A., Cornman, J. C., & Kasper, J. D. (2021). *National Health and Aging Trends Study Trends Chart Book: Key Trends, Measures and Detailed Tables.* Institute for Social Research. micda.isr.umich.edu/research/nhats-trends-dashboards

Freeman, A. M., Petrilli, K., Lees, R., Hindocha, C., Mokrysz, C., Curran, H. V., Saunders, R., & Freeman, T. P. (2019). How does cannabidiol (CBD) influence the acute effects of delta-

9-tetrahydrocannabinol (THC) in humans? A systematic review. *Neuroscience and Biobehavioral Reviews*, *107*, 696-712. https://doi.org/10.1016/j.neubiorev.2019.09.036

Gruber, S. A., Sagar, K. A., Dahlgren, M. K., Olson, D. P., Centorrino, F., & Lukas, S. E. (2012). Marijuana impacts mood in bipolar disorder: a pilot study. *Mental Health and Substance Use*, *5*(3), 228-239. https://doi.org/10.1080/17523281.2012.659751

Gruber, S. A., Smith, R. T., Dahlgren, M. K., Lambros, A. M., & Sagar, K. A. (2021). No pain, all gain? Interim analyses from a longitudinal, observational study examining the impact of medical cannabis treatment on chronic pain and related symptoms. *Experimental and Clinical Psychopharmacology*, *29*(2), 147-156. https://doi.org/10.1037/pha0000435

Gunadi, C., & Shi, Y. (2022). Cannabis decriminalization and racial disparity in arrests for cannabis possession. *Social Science & Medicine*, *293*, 114672. https://doi.org/10.1016/j.socscimed.2021.114672

Haleem, R., & Wright, R. (2020). A Scoping Review on Clinical Trials of Pain Reduction With Cannabis Administration in Adults. *Journal of Clinical Medicine Research*, *12*(6), 344-351. https://doi.org/10.14740/jocmr4210

Han, B. H., & Palamar, J. J. (2018). Marijuana use by middle-aged and older adults in the United States, 2015-2016. *Drug and Alcohol Dependence*, *191*, 374-381. https://doi.org/10.1016/j.drugalcdep.2018.07.006

Han, B. H., & Palamar, J. J. (2020). Trends in Cannabis Use Among Older Adults in the United States, 2015-2018. *JAMA Internal Medicine*, *180*(4), 609-611. https://doi.org/10.1001/jamainternmed.2019.7517

Haroutounian, S., Arendt-Nielsen, L., Belton, J., Blyth, F. M., Degenhardt, L., Di Forti, M., Eccleston, C., Finn, D. P., Finnerup, N. B., Fisher, E., Fogarty, A. E., Gilron, I.,

Hohmann, A. G., Kalso, E., Krane, E., Mohiuddin, M., Moore, R. A., Rowbotham, M., Soliman, N., . . . Rice, A. S. C. (2021). International Association for the Study of Pain Presidential Task Force on Cannabis and Cannabinoid Analgesia: research agenda on the use of cannabinoids, cannabis, and cannabis-based medicines for pain management. *Pain*, *162*(Suppl 1), S117-S124. https://doi.org/10.1097/j.pain.0000000000002266

Hartmann, S. A., & McLeish, A. C. (2022). Tolerance for specific negative affective states and coping-oriented cannabis use motives among college student cannabis users. *Journal of American College Health*, *70*(3), 911-917. https://doi.org/10.1080/07448481.2020.1781135

Harvey, A. G., Murray, G., Chandler, R. A., & Soehner, A. (2011). Sleep disturbance as transdiagnostic: Consideration of neurobiological mechanisms. *Clinical Psychology Review*, *31*(2), 225-235. https://doi.org/10.1016/j.cpr.2010.04.003

Hayes, P. A. (2016). *Addressing Cultural Complexities in Practice: Assessment, Diagnosis, and Therapy* (3 ed.). American Psychological Association. https://doi.org/https://doi.org/10.1037/14801-000

Herrero Babiloni, A., De Koninck, B. P., Beetz, G., De Beaumont, L., Martel, M. O., & Lavigne, G. J. (2020). Sleep and pain: recent insights, mechanisms, and future directions in the investigation of this relationship. *Journal of Neural Transmission*, *127*(4), 647-660. https://doi.org/10.1007/s00702-019-02067-z

Hill, K. P., Palastro, M. D., Johnson, B., & Ditre, J. W. (2017). Cannabis and Pain: A Clinical Review. *Cannabis and Cannabinoid Research*, *2*(1), 96-104. https://doi.org/10.1089/can.2017.0017

Hyman, S. M., & Sinha, R. (2009). Stress-related factors in cannabis use and misuse: implications for prevention and treatment. *Journal of Substance Abuse Treatment*, *36*(4), 400-413. https://doi.org/10.1016/j.jsat.2008.08.005

Izzo, A. A., Borrelli, F., Capasso, R., Di Marzo, V., & Mechoulam, R. (2009). Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends in Pharmacological Sciences*, *30*(10), 515-527. https://doi.org/10.1016/j.tips.2009.07.006

Kesner, A. J., & Lovinger, D. M. (2020). Cannabinoids, Endocannabinoids and Sleep. *Frontiers in Molecular Neuroscience*, *13*, 125. https://doi.org/10.3389/fnmol.2020.00125

King, D. E., Xiang, J., & Pilkerton, C. S. (2018). Multimorbidity Trends in United States Adults, 1988-2014. *Journal of the American Board of Family Medicine*, *31*(4), 503-513. https://doi.org/10.3122/jabfm.2018.04.180008

Koffel, E., Kroenke, K., Bair, M. J., Leverty, D., Polusny, M. A., & Krebs, E. E. (2016). The bidirectional relationship between sleep complaints and pain: Analysis of data from a randomized trial. *Health Psychology*, *35*(1), 41-49. https://doi.org/10.1037/hea0000245

Kosiba, J. D., Maisto, S. A., & Ditre, J. W. (2019). Patient-reported use of medical cannabis for pain, anxiety, and depression symptoms: Systematic review and meta-analysis. *Social Science & Medicine*, *233*, 181-192. https://doi.org/10.1016/j.socscimed.2019.06.005

Kothari, D. J., Davis, M. C., Yeung, E. W., & Tennen, H. A. (2015). Positive affect and pain: mediators of the within-day relation linking sleep quality to activity interference in fibromyalgia. *Pain*, *156*(3), 540-546. https://doi.org/10.1097/01.j.pain.0000460324.18138.0a

Kroenke, K., Wu, J., Bair, M. J., Krebs, E. E., Damush, T. M., & Tu, W. (2011). Reciprocal relationship between pain and depression: a 12-month longitudinal analysis in primary care. *The Journal of Pain*, *12*(9), 964-973. https://doi.org/10.1016/j.jpain.2011.03.003

Langlois, C., Potvin, S., Khullar, A., & Tourjman, S. V. (2021). Down and High: Reflections Regarding Depression and Cannabis. *Frontiers in Psychiatry*, *12*, 625158. https://doi.org/10.3389/fpsyt.2021.625158

Lazarus, R. S., & Folkman, S. (1984). *Stress, Appraisal and Coping*. Springer Publishing Company, Inc.

Li, H.-L. (1974). The Origin and Use of Cannabis in Eastern Asia Linguistic-Cultural Implications. *Economic Botany*, *28*(3), 293-301. http://www.jstor.org/stable/4253516

Lumley, M. A., Cohen, J. L., Borszcz, G. S., Cano, A., Radcliffe, A. M., Porter, L. S., Schubiner, H., & Keefe, F. J. (2011). Pain and emotion: a biopsychosocial review of recent research. *Journal of Clinical Psychology*, *67*(9), 942-968. https://doi.org/10.1002/jclp.20816

Maayah, Z. H., Takahara, S., Ferdaoussi, M., & Dyck, J. R. B. (2020). The molecular mechanisms that underpin the biological benefits of full-spectrum cannabis extract in the treatment of neuropathic pain and inflammation. *Biochimica et Biophysica Acta - Molecular Basis of Disease*, *1866*(7), 165771. https://doi.org/10.1016/j.bbadis.2020.165771

MacCallum, C. A., Lo, L. A., & Boivin, M. (2021). "Is medical cannabis safe for my patients?" A practical review of cannabis safety considerations. *European Journal of Internal Medicine*, *89*, 10-18. https://doi.org/10.1016/j.ejim.2021.05.002

Magee, J. C., & Carmin, C. N. (2010). The relationship between sleep and anxiety in older adults. *Current Psychiatry Reports*, *12*(1), 13-19. https://doi.org/10.1007/s11920-009-0087-9

McCracken, L. M., & Iverson, G. L. (2002). Disrupted sleep patterns and daily functioning in patients with chronic pain. *Pain Research and Management*, *7*(2), 75-79. https://doi.org/10.1155/2002/579425

Mechoulam, R. (1983). *Cannabinoids as Therapeutic Agents*. https://doi.org/10.1201/9780429260667

Mechoulam, R., & Parker, L. A. (2013). The endocannabinoid system and the brain. *Annual Review of Psychology*, *64*, 21-47. https://doi.org/10.1146/annurev-psych-113011-143739

Meints, S. M., & Edwards, R. R. (2018). Evaluating psychosocial contributions to chronic pain outcomes. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *87*(Pt B), 168-182. https://doi.org/10.1016/j.pnpbp.2018.01.017

Melzack, R. (1993). Pain: past, present and future. *Canadian Journal of Experimental Psychology*, *47*(4), 615-629. https://doi.org/10.1037/h0078871

Melzack, R., & Katz, J. (2013). Pain. *WIREs Cognitive Science*, *4*(1), 1-15. https://doi.org/10.1002/wcs.1201

Melzack, R., & Wall, P. D. (1965). Pain Mechanisms: A New Theory. *Science*, *150*(3699), 971-979.

Mitchell, O., & Caudy, M. S. (2013). Examining Racial Disparities in Drug Arrests. *Justice Quarterly*, *32*(2), 288-313. https://doi.org/10.1080/07418825.2012.761721

Moore, R. A., Fisher, E., Finn, D. P., Finnerup, N. B., Gilron, I., Haroutounian, S., Krane, E., Rice, A. S. C., Rowbotham, M., Wallace, M., & Eccleston, C. (2021). Cannabinoids,

cannabis, and cannabis-based medicines for pain management: an overview of systematic reviews. *Pain*, *162*(Suppl 1), S67-S79. https://doi.org/10.1097/j.pain.0000000000001941

Morena, M., Patel, S., Bains, J. S., & Hill, M. N. (2016). Neurobiological Interactions Between Stress and the Endocannabinoid System. *Neuropsychopharmacology*, *41*(1), 80-102. https://doi.org/10.1038/npp.2015.166

Mueller, R. L., Ellingson, J. M., Bidwell, L. C., Bryan, A. D., & Hutchison, K. E. (2021). Are the Acute Effects of THC Different in Aging Adults? *Brain Sciences*, *11*(5). https://doi.org/10.3390/brainsci11050590

Murillo-Rodriguez, E., Vazquez, E., Millan-Aldaco, D., Palomero-Rivero, M., & Drucker-Colin, R. (2007). Effects of the fatty acid amide hydrolase inhibitor URB597 on the sleep-wake cycle, c-Fos expression and dopamine levels of the rat. *European Journal of Pharmacology*, *562*(1-2), 82-91. https://doi.org/10.1016/j.ejphar.2007.01.076

National Academies of Sciences Engineering and Medicine. (2017). *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. The National Academies Press. https://doi.org/https://doi.org/10.17226/24625

Neikrug, A. B., & Ancoli-Israel, S. (2010). Sleep disorders in the older adult - a mini-review. *Gerontology*, *56*(2), 181-189. https://doi.org/10.1159/000236900

Nemeroff, C. B., & Owens, M. J. (2009). The role of serotonin in the pathophysiology of depression: as important as ever. *Clinical Chemistry*, *55*(8), 1578-1579. https://doi.org/10.1373/clinchem.2009.123752

Nicholas, M., Vlaeyen, J. W. S., Rief, W., Barke, A., Aziz, Q., Benoliel, R., Cohen, M., Evers, S., Giamberardino, M. A., Goebel, A., Korwisi, B., Perrot, S., Svensson, P., Wang, S. J., Treede, R. D., & Pain, I. T. f. t. C. o. C. (2019). The IASP classification of chronic pain

for ICD-11: chronic primary pain. *Pain*, *160*(1), 28-37. https://doi.org/10.1097/j.pain.0000000000001390

Nugent, S. M., Morasco, B. J., O'Neil, M. E., Freeman, M., Low, A., Kondo, K., Elven, C., Zakher, B., Motu'apuaka, M., Paynter, R., & Kansagara, D. (2017). The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms: A Systematic Review. *Annals of Internal Medicine*, *167*(5), 319-331. https://doi.org/10.7326/M17-0155

O'Brien, E. M., Waxenberg, L. B., Atchison, J. W., Gremillion, H. A., Staud, R. M., McCrae, C. S., & Robinson, M. E. (2010). Negative mood mediates the effect of poor sleep on pain among chronic pain patients. *The Clinical Journal of Pain*, *26*(4), 310-319. https://doi.org/10.1097/AJP.0b013e3181c328e9

Okifuji, A., & Hare, B. D. (2011). Do sleep disorders contribute to pain sensitivity? *Current Rheumatology Reports*, *13*(6), 528-534. https://doi.org/10.1007/s11926-011-0204-8

Onaemo, V. N., Fawehinmi, T. O., & D'Arcy, C. (2021). Comorbid Cannabis Use Disorder with Major Depression and Generalized Anxiety Disorder: A Systematic Review with Meta-analysis of Nationally Representative Epidemiological Surveys. *Journal of Affective Disorders*, *281*, 467-475. https://doi.org/10.1016/j.jad.2020.12.043

Ormel, J., Rijsdijk, F. V., Sullivan, M., van Sonderen, E., & Kempen, G. I. (2002). Temporal and reciprocal relationship between IADL/ADL disability and depressive symptoms in late life. *The Journals of Gerontology: Series B*, *57*(4), P338-347. https://doi.org/10.1093/geronb/57.4.p338

Osborn, L. A., Lauritsen, K. J., Cross, N., Davis, A. K., Rosenberg, H., Bonadio, F., & Lang, B. (2015). Self-Medication of Somatic and Psychiatric Conditions Using Botanical

Marijuana. *Journal of Psychoactive Drugs*, *47*(5), 345-350. https://doi.org/10.1080/02791072.2015.1096433

Page, R. L., II, Allen, L. A., Kloner, R. A., Carriker, C. R., Martel, C., Morris, A. A., Piano, M. R., Rana, J. S., & Saucedo, J. F. (2020). Medical Marijuana, Recreational Cannabis, and Cardiovascular Health: A Scientific Statement From the American Heart Association. *142*(10), e131-e152. https://doi.org/10.1161/CIR.0000000000000883

Pava, M. J., Makriyannis, A., & Lovinger, D. M. (2016). Endocannabinoid Signaling Regulates Sleep Stability. *PLoS One*, *11*(3), e0152473. https://doi.org/10.1371/journal.pone.0152473

Pedersen, E. R., Hummer, J. F., Rinker, D. V., Traylor, Z. K., & Neighbors, C. (2016). Measuring Protective Behavioral Strategies for Marijuana Use Among Young Adults. *Journal of Studies on Alcohol and Drugs*, *77*(3), 441-450. https://doi.org/10.15288/jsad.2016.77.441

Peppard, P. E., Young, T., Barnet, J. H., Palta, M., Hagen, E. W., & Hla, K. M. (2013). Increased prevalence of sleep-disordered breathing in adults. *American Journal of Epidemiology*, *177*(9), 1006-1014. https://doi.org/10.1093/aje/kws342

Petrie, G. N., Nastase, A. S., Aukema, R. J., & Hill, M. N. (2021). Endocannabinoids, cannabinoids and the regulation of anxiety. *Neuropharmacology*, *195*, 108626. https://doi.org/10.1016/j.neuropharm.2021.108626

Posner, J., Russell, J. A., & Peterson, B. S. (2005). The circumplex model of affect: An integrative approach to affective neuroscience, cognitive development, and psychopathology. *Development and Psychopathology*, *17*(03). https://doi.org/10.1017/s0954579405050340

Ramar, K., Rosen, I. M., Kirsch, D. B., Chervin, R. D., Carden, K. A., Aurora, R. N., Kristo, D. A., Malhotra, R. K., Martin, J. L., Olson, E. J., Rosen, C. L., Rowley, J. A., & American Academy of Sleep Medicine Board of, D. (2018). Medical Cannabis and the Treatment of Obstructive Sleep Apnea: An American Academy of Sleep Medicine Position Statement. *Journal of Clinical Sleep Medicine*, *14*(4), 679-681. https://doi.org/10.5664/jcsm.7070

Ravyts, S. G., Dzierzewski, J. M., Grah, S. C., Buman, M. P., Aiken-Morgan, A. T., Giacobb, P. R., Jr., Roberts, B. L., Marsiske, M., & McCrae, C. S. (2019). Pain inconsistency and sleep in mid to late-life: the role of depression. *Aging & Mental Health*, *23*(9), 1174-1179. https://doi.org/10.1080/13607863.2018.1481929

Riemann, D. (2003). Primary insomnia: a risk factor to develop depression? *Journal of Affective Disorders*, *76*(1-3), 255-259. https://doi.org/10.1016/s0165-0327(02)00072-1

Rubino, T., Guidali, C., Vigano, D., Realini, N., Valenti, M., Massi, P., & Parolaro, D. (2008). CB1 receptor stimulation in specific brain areas differently modulate anxiety-related behaviour. *Neuropharmacology*, *54*(1), 151-160. https://doi.org/10.1016/j.neuropharm.2007.06.024

Russo, E., & Guy, G. W. (2006). A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Medical Hypotheses*, *66*(2), 234-246. https://doi.org/10.1016/j.mehy.2005.08.026

Rustoen, T., Wahl, A. K., Hanestad, B. R., Lerdal, A., Paul, S., & Miaskowski, C. (2005). Age and the experience of chronic pain: differences in health and quality of life among younger, middle-aged, and older adults. *The Clinical Journal of Pain*, *21*(6), 513-523. https://doi.org/10.1097/01.ajp.0000146217.31780.ef

Sadler, P., McLaren, S., Klein, B., Harvey, J., & Jenkins, M. (2018). Cognitive behavior therapy for older adults with insomnia and depression: a randomized controlled trial in community mental health services. *Sleep*, *41*(8). https://doi.org/10.1093/sleep/zsy104

Sagar, K. A., Dahlgren, M. K., Racine, M. T., Dreman, M. W., Olson, D. P., & Gruber, S. A. (2016). Joint Effects: A Pilot Investigation of the Impact of Bipolar Disorder and Marijuana Use on Cognitive Function and Mood. *PLoS One*, *11*(6), e0157060. https://doi.org/10.1371/journal.pone.0157060

Saunders, J. B., Aasland, O. G., Babor, T. F., De La Fuente, J. R., & Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption-II. *Addiction*, *88*(6), 791-804. https://doi.org/10.1111/j.1360-0443.1993.tb02093.x

Scarlata, S., Pedone, C., Curcio, G., Cortese, L., Chiurco, D., Fontana, D., Calabrese, M., Fusiello, R., Abbruzzese, G., Santangelo, S., Zito, A., & Incalzi, R. A. (2013). Pre-polysomnographic assessment using the Pittsburgh Sleep Quality Index questionnaire is not useful in identifying people at higher risk for obstructive sleep apnea. *Journal of Medical Screening*, *20*(4), 220-226. https://doi.org/10.1177/0969141313511591

Sexton, M., Cuttler, C., & Mischley, L. K. (2019). A Survey of Cannabis Acute Effects and Withdrawal Symptoms: Differential Responses Across User Types and Age. *The Journal of Alternative and Complementary Medicine*, *25*(3), 326-335. https://doi.org/10.1089/acm.2018.0319

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annual Review of Clinical Psychology*, *4*, 1-32. https://doi.org/10.1146/annurev.clinpsy.3.022806.091415

Simons, J., Correia, C. J., Carey, K. B., & Borsari, B. E. (1998). Validating a five-factor marijuana motives measure: Relations with use, problems, and alcohol motives. *Journal of Counseling Psychology*, *45*(3), 265-273. https://doi.org/https://doi.org/10.1037/0022-0167.45.3.265

Simons, J. S., Dvorak, R. D., Merrill, J. E., & Read, J. P. (2012). Dimensions and severity of marijuana consequences: development and validation of the Marijuana Consequences Questionnaire (MACQ). *Addict Behav*, *37*(5), 613-621. https://doi.org/10.1016/j.addbeh.2012.01.008

Smolkina, M., Morley, K. I., Rijsdijk, F., Agrawal, A., Bergin, J. E., Nelson, E. C., Statham, D., Martin, N. G., & Lynskey, M. T. (2017). Cannabis and Depression: A Twin Model Approach to Co-morbidity. *Behavior Genetics*, *47*(4), 394-404. https://doi.org/10.1007/s10519-017-9848-0

Snijders, T. A. B. (2005). Power and sample size in multilevel modeling. In B. S. Everitt & D. C. Howell (Eds.), *Encyclopedia of Statistics in Behavioral Science* (Vol. 3, pp. 1570–1573). Wiley.

Sotoodeh, R., Waldman, L. E., Vigano, A., Moride, Y., Canac-Marquis, M., Spilak, T., Gamaoun, R., Kalaba, M., Hachem, Y., Beaulieu, P., Desroches, J., Ware, M. A., Perez, J., Shir, Y., Fitzcharles, M. A., & Martel, M. O. (2022). Predictors of Pain Reduction Among Fibromyalgia Patients Using Medical Cannabis: A Long-Term Prospective Cohort Study. *Arthritis Care & Research*. https://doi.org/10.1002/acr.24985

Spitzer, R. L., Kroenke, K., Williams, J. B., & Lowe, B. (2006). A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. *Archives of Internal Medicine*, *166*(10), 1092-1097. https://doi.org/10.1001/archinte.166.10.1092

Stanciu, C. N., Brunette, M. F., Teja, N., & Budney, A. J. (2021). Evidence for Use of Cannabinoids in Mood Disorders, Anxiety Disorders, and PTSD: A Systematic Review. *Psychiatric Services*, *72*(4), 429-436. https://doi.org/10.1176/appi.ps.202000189

Stepanski, E. J., & Rybarczyk, B. (2006). Emerging research on the treatment and etiology of secondary or comorbid insomnia. *Sleep Medicine Reviews*, *10*(1), 7-18. https://doi.org/10.1016/j.smrv.2005.08.002

Stith, S. S., Li, X., Brockelman, F., Keeling, K., Hall, B., & Vigil, J. M. (2023). Understanding feeling "high" and its role in medical cannabis patient outcomes. *Frontiers in Pharmacology*, *14*. https://doi.org/10.3389/fphar.2023.1135453

Sullivan, R. M., Wallace, A. L., Stinson, E. A., Montoto, K. V., Kaiver, C. M., Wade, N. E., & Lisdahl, K. M. (2022). Assessment of Withdrawal, Mood, and Sleep Inventories After Monitored 3-Week Abstinence in Cannabis-Using Adolescents and Young Adults. *Cannabis and Cannabinoid Research*, *7*(5), 690-699. https://doi.org/10.1089/can.2021.0074

Sun, Y., Laksono, I., Selvanathan, J., Saripella, A., Nagappa, M., Pham, C., Englesakis, M., Peng, P., Morin, C. M., & Chung, F. (2021). Prevalence of sleep disturbances in patients with chronic non-cancer pain: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *57*, 101467. https://doi.org/10.1016/j.smrv.2021.101467

Suraev, A. S., Marshall, N. S., Vandrey, R., McCartney, D., Benson, M. J., McGregor, I. S., Grunstein, R. R., & Hoyos, C. M. (2020). Cannabinoid therapies in the management of sleep disorders: A systematic review of preclinical and clinical studies. *Sleep Medicine Reviews*, *53*, 101339. https://doi.org/10.1016/j.smrv.2020.101339

Sweetman, A., Lovato, N., Micic, G., Scott, H., Bickley, K., Haycock, J., Harris, J., Gradisar, M., & Lack, L. (2020). Do symptoms of depression, anxiety or stress impair the effectiveness of cognitive behavioural therapy for insomnia? A chart-review of 455 patients with chronic insomnia. *Sleep Medicine*, *75*, 401-410. https://doi.org/10.1016/j.sleep.2020.08.023

Sznitman, S. R., Martin-Willett, R., Ma, W., Karoly, H. C., & Bidwell, L. C. (2024). Daily diary study of associations between alcohol, cannabis, co-use and sleep quality in individuals with intentions to use cannabis to cope with anxiety. *Drug and Alcohol Review*, *43*(2), 501-511. https://doi.org/10.1111/dar.13778

Sznitman, S. R., Rosenberg, D., Vulfsons, S., Meiri, D., & Greene, T. (2021). Medical Cannabis Use and Pain: An Experience Sampling Study. *Frontiers in Psychiatry*, *12*. https://doi.org/10.3389/fpsyt.2021.728283

Thorndike, E. L. (1927). The Law of Effect. *The American Journal of Psychology*, *39*(1/4). https://doi.org/10.2307/1415413

Trull, T. J., Wycoff, A. M., Lane, S. P., Carpenter, R. W., & Brown, W. C. (2016). Cannabis and alcohol use, affect and impulsivity in psychiatric out-patients' daily lives. *Addiction*, *111*(11), 2052-2059. https://doi.org/10.1111/add.13471

Tyler, E., Jones, S., Black, N., Carter, L. A., & Barrowclough, C. (2015). The relationship between bipolar disorder and cannabis use in daily life: an experience sampling study. *PLoS One*, *10*(3), e0118916. https://doi.org/10.1371/journal.pone.0118916

Velzeboer, R., Malas, A., Boerkoel, P., Cullen, K., Hawkins, M., Roesler, J., & Lai, W. W. (2022). Cannabis dosing and administration for sleep: a systematic review. *Sleep*, *45*(11). https://doi.org/10.1093/sleep/zsac218

Vieira, R. T., Caixeta, L., Machado, S., Silva, A. C., Nardi, A. E., Arias-Carrion, O., & Carta, M. G. (2013). Epidemiology of early-onset dementia: a review of the literature. *Clinical Practice and Epidemiology in Mental Health*, *9*, 88-95. https://doi.org/10.2174/1745017901309010088

Viveros, M. P., Marco, E. M., & File, S. E. (2005). Endocannabinoid system and stress and anxiety responses. *Pharmacology Biochemistry & Behavior*, *81*(2), 331-342. https://doi.org/10.1016/j.pbb.2005.01.029

Wang, L., Hong, P. J., May, C., Rehman, Y., Oparin, Y., Hong, C. J., Hong, B. Y., AminiLari, M., Gallo, L., Kaushal, A., Craigie, S., Couban, R. J., Kum, E., Shanthanna, H., Price, I., Upadhye, S., Ware, M. A., Campbell, F., Buchbinder, R., . . . Busse, J. W. (2021). Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. *The BMJ*, *374*, n1034. https://doi.org/10.1136/bmj.n1034

Wang, Y., Jean Jacques, J., Li, Z., Sibille, K. T., & Cook, R. L. (2021). Health Outcomes among Adults Initiating Medical Cannabis for Chronic Pain: A 3-month Prospective Study Incorporating Ecological Momentary Assessment (EMA). *Cannabis*, *4*(2), 69-83. https://doi.org/10.26828/cannabis/2021.02.006

Wastesson, J. W., Morin, L., Tan, E. C. K., & Johnell, K. (2018). An update on the clinical consequences of polypharmacy in older adults: a narrative review. *Expert Opinion on Drug Safety*, *17*(12), 1185-1196. https://doi.org/10.1080/14740338.2018.1546841

Weiss, J. H., Tervo-Clemmens, B., Potter, K. W., Evins, A. E., & Gilman, J. M. (2023). The Cannabis Effects Expectancy Questionnaire-Medical (CEEQ-M): Preliminary

psychometric properties and longitudinal validation within a clinical trial. *Psychological Assessment*, *35*(8), 659-673. https://doi.org/10.1037/pas0001244

Whiting, P. F., Wolff, R. F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A. V., Keurentjes, J. C., Lang, S., Misso, K., Ryder, S., Schmidlkofer, S., Westwood, M., & Kleijnen, J. (2015). Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *The Journal of the American Medical Association*, *313*(24), 2456-2473. https://doi.org/10.1001/jama.2015.6358

Winters, A. M., Malouff, J. M., & Schutte, N. S. (2022). The association between the five-factor model of personality and problem cannabis use: A meta-analysis. *Personality and Individual Differences*, *193*. https://doi.org/10.1016/j.paid.2022.111635

Wycoff, A. M., Metrik, J., & Trull, T. J. (2018). Affect and cannabis use in daily life: a review and recommendations for future research. *Drug and Alcohol Dependence*, *191*, 223-233. https://doi.org/10.1016/j.drugalcdep.2018.07.001

Yang, K. H., Kaufmann, C. N., Nafsu, R., Lifset, E. T., Nguyen, K., Sexton, M., Han, B. H., Kim, A., & Moore, A. A. (2021). Cannabis: An Emerging Treatment for Common Symptoms in Older Adults. *Journal of the American Geriatrics Society*, *69*(1), 91-97. https://doi.org/10.1111/jgs.16833

Zias, J., Stark, H., Sellgman, J., Levy, R., Werker, E., Breuer, A., & Mechoulam, R. (1993). Early medical use of cannabis. *Nature*, *363*(6426), 215. https://doi.org/10.1038/363215a0