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# Cannabis Use Moderates the Relationship between Pain and Negative Affect in Adults with Opioid Use Disorder

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## Abstract

**Introduction:** Adults in Medication-Assisted Treatment (MAT) for opioid addiction are at risk for substance use relapse and opioid overdose. They often have high rates of cannabis use and comorbid symptoms of pain, depression, and anxiety. Low levels of self-efficacy (confidence that one can self-manage symptoms) are linked to higher symptom burdens and increased substance use. The effects of cannabis use on symptom management among adults with MAT are currently unclear. Therefore, the primary purpose of this study is to examine whether cannabis use moderates the relationships between pain and negative affect (i.e., depression and anxiety) and whether self-efficacy influences symptom interactions.

**Methods:** A total of 150 adults receiving MAT and attending one of two opioid treatment program clinics were administered a survey containing measures of pain, depression, anxiety, self-efficacy, and cannabis use.

**Results:** Cannabis use frequency moderated the relationships between pain and depression as well as pain and anxiety. Specifically, as cannabis use frequency increased, the positive relationships between pain and depression and pain and anxiety grew stronger. However, cannabis use was no longer a significant moderator after controlling for self-efficacy.

**Conclusions:** Results suggest that cannabis use strengthens, rather than weakens, the relationships between pain and depression and pain and anxiety. These effects appear to be driven by decreased self-efficacy in cannabis users. It is important to understand how self-efficacy can be improved through symptom self-management interventions and whether self-efficacy can improve distressing symptoms for people in MAT.

**Keywords:** Anxiety, Cannabis Use, Depression, Opioid Addiction, Pain, Self-Efficacy

## 1. Introduction

The number of Americans with an opioid use disorder related to prescription pain relievers climbed from 1.4 million to 1.9 million in the last 10 years (Substance Abuse and Mental Health Services Administration [SAMHSA], 2015). Opioid overdose death rates have more than tripled in the past two decades and are now the second leading cause of accidental death in the United States (U.S.) (Centers for Disease Control and Prevention [CDC], 2017). Death certificate data indicate that states with legalized medical cannabis have 25% lower annual opioid-related deaths (Bachhuber, Saloner, Cunningham, & Barry, 2014). While the root cause of this relationship is unknown, it has been hypothesized that the ability to obtain cannabis easily may reduce opioid use (Bradford & Bradford, 2016; Miller, 2016) and that cannabis may be used as a substitute drug (Corroon, Mischley, & Sexton, 2017). Still, more robust research is needed to assess positive and negative effects of cannabis prior to endorsing its use as a harm reduction strategy to reduce opioid overdose deaths. Unmeasured factors could account for improvements in death rates, such as concomitant reductions in opioid prescribing and policy changes (Hall & Weier, 2015).

Widespread use of cannabis has been documented among adults in Medication-Assisted Treatment (MAT) for opioid use disorders (Bawar, 2015). Individuals prone to opioid misuse often use substances, including cannabis, to “self-medicate” disturbing symptoms (Alford et al., 2016). While as many as 62% of adults in MAT present with co-existing chronic pain (Dunn, Brooner, & Clark, 2014), little is known about their cannabis use in relation to pain and management of other symptoms. Some studies indicate that adults in MAT experience co-occurring depression and anxiety at the respective rates of 19-22% and 44% (Batki, Canfield, & Ploutz-Snyder, 2011; Savant et al., 2013). Still lacking is sufficient empirical understanding of

opioid-cannabis interactions related to symptom relief. More specifically, a dearth of knowledge exists about cannabis' effects on pain and affective symptoms among adults receiving MAT. Because the relapse rates for people in MAT are high (up to 86%) (Termorshuizen et al. 2005; Tkacz, Severt, Cacciola, & Ruetsch, 2012), and the risk for overdose is three times greater post-treatment (Cornish, Macleod, Strang, Vickerman, & Hickman, 2010; Davoli et al., 2007), it is important to consider whether adjuncts, including cannabis, could assist in reducing distressing symptoms of pain and affect, opioid dosages, risk of overdose deaths, and/or relapses. Such information is essential to guide patients regarding risks and benefits of cannabis, particularly as clinicians strive to limit opioid dosages and follow recommendations to reduce overdose risk for people with pain and/or opioid use disorders (National Institute on Drug Abuse, 2015).

Medical cannabis patients primarily report using cannabis to manage three conditions: pain, anxiety, and depression (Sexton, Cuttler, Finnell, & Mischley, 2016). A consensus committee of the U.S. National Academy of Sciences, Engineering, and Medicine (2017) concluded that there is "substantial" evidence for cannabis use to relieve chronic pain symptoms. The strongest evidence they cite comes from a systematic review that includes 28 randomized controlled studies and concludes that moderate quality evidence exists supporting cannabinoids to improve chronic pain (Whiting et al., 2015). Yet, little substantial evidence exists on cannabis use and pain relief that is specific to MAT populations. Rodent models suggest that agonists targeting the cannabinoid 2 and mu opioid receptors act synergistically to reverse inflammatory, post-operative, and neuropathic pain while preventing opioid-induced reward behaviors (Grenald et al., 2017). In addition, findings from animal studies indicate that activating the endocannabinoid system may help minimize stress and depression (Haj-Dahmane & Shen, 2014). Despite frequent reports of cannabis use to alleviate negative affect, limited evidence

supports its use for improving either depression or anxiety in human trials (National Academy of Sciences, Engineering, and Medicine, 2017). Intermittent cannabis use has been found to diminish opioid withdrawal symptoms for individuals in naloxone treatment (Raby et al., 2009), and medical cannabis patients report that they are able to decrease amounts of opioids they consume when they use cannabis for pain (Reiman, Welty, & Solomon, 2017). While these outcomes are encouraging, it is critical to ascertain if using cannabis to self-manage symptoms may lead to untoward effects, especially due to the insufficiency of research in this area.

Self-efficacy is an important attribute in self-management of symptoms and is linked to reductions in disability, pain intensity, and affective symptoms (Jackson, Wang, Wang, & Fan, 2014; Wilson, Roll, Corbett, & Barbosa-Leiker, 2015). Through mastery experiences that build confidence, or self-efficacy, people can incorporate effective symptom-management strategies, such as relaxation, distraction, and self-talk (Lorig, Ritter, Laurent, & Plant, 2008). Self-efficacy is a strong predictor of coping behaviors and perseverance in the face of difficult problems (Kadden & Litt, 2011). Numerous studies on substance use populations find that self-efficacy can predict drug use and post-treatment abstinence (Kadden & Litt, 2011). Findings suggest that for individuals struggling with nicotine addiction, a sense of greater self-efficacy to quit smoking coupled with a perceived control over withdrawal symptoms were predictors of abstinence after concluding nicotine dependence treatment (Schnoll et al., 2011). Moreover, a cross-sectional study in Australia among 1,514 adults taking opioids for chronic non-cancer pain found worse health outcomes and poorer self-efficacy for pain management among those who used cannabis for pain relief compared to those who did not use the drug (Degenhardt et. al., 2015). Therefore, it is possible that cannabis use is related to lower levels of self-efficacy, which in turn predict increased pain intensity and affective symptoms.

In summary, the effects of cannabis use on aspects of self-efficacy and symptom management among MAT are currently unclear and require further exploration. Therefore, the purpose of this study is to: 1) characterize frequency of cannabis use in a population of adults receiving MAT for opioid use disorder; 2) examine relationships between frequency of cannabis use, pain intensity, depression, anxiety, and self-efficacy; 3) examine whether cannabis use moderates the relationships between pain intensity and depression as well as between pain intensity and anxiety; and 4) explore whether self-efficacy could help account for interactions between pain intensity and cannabis use. We hypothesized that cannabis use would be high in adults receiving MAT, that symptoms of pain, anxiety, depression, and cannabis use frequency would be positively correlated with one another, and that self-efficacy would be inversely correlated with symptoms and cannabis use. We further predicted that cannabis use would moderate the relationships between pain intensity and depression as well as pain intensity and anxiety and that differences in self-efficacy among cannabis users would account for these interactions.

## **2. Methods**

### *2.1 Participant selection and procedures*

A power analysis indicated that a sample size of approximately 150 would be required to have power of .80 to detect small-to-medium sized effects ( $R^2 = .05$ ) with alpha set at .05. Therefore, 150 adults undergoing MAT for opioid use disorder were recruited from two outpatient treatment facilities in Washington State, where medical and recreational cannabis use were legal at the time of recruitment. Participants were invited to learn more about the proposed study by research assistants who were stationed at the treatment clinics' central waiting areas.



Eligibility criteria included ability to read and write English,  $\geq 18$  years of age, and currently taking daily prescribed medication for opioid use disorder (methadone or buprenorphine). Of 153 available to participate, 153 asked to be screened and 3 were deemed ineligible due to not having opioid medication prescribed. No other data were collected on those who did not participate. The final sample of participants was between the ages of 19 and 65 ( $M = 38.82$  years [ $SD = 11.24$ ]; 55.1% female). All participants provided verbal informed consent before completing the pencil and paper survey. Participants were compensated in the form of a \$20 Wal-Mart gift card for their time and no participants were excluded from the data analyses. The study protocol and materials were approved by the Institutional Review Board at Washington State University.

## 2.2 Measures

### 2.2.1. Demographics and participant characteristics questionnaire

Demographic and participant characteristic information collected included gender, age, race/ethnicity, income, marital status, education, medical diagnoses, and employment status.

### 2.2.2. Cannabis use questionnaire

Self-reported cannabis use was collected by participants answering four questions related to use. Participants answered “yes” or “no” to “Have you ever used marijuana?” Those who reported “yes” were asked to continue answering questions about cannabis use. “Yes” and “no” responses were provided to the questions, “In the past 12 months have you used marijuana?” and “In the past 30 days have you used marijuana?” Participants were then asked about cannabis use frequency, “In the past 30 days how many days have you used marijuana?” by circling one response out of seven possible answers (i.e., never, 1-2 days, 3-5 days, 6-9 days, 10-19 days, 20-29 days, all 30 days). Participants were asked if in the past 12 months they used marijuana to manage aches or pains, if they were registered as a medical marijuana patient, and possible

reasons for using cannabis selected from the options of “recreation/social,” “pain,” “sleep,” “anxiety/stress,” and “withdrawal.” No valid and reliable cannabis use questionnaires were found at the time of data collection so items were modeled after national health surveys used to collect data on substance use.

### 2.2.3. Pain intensity questionnaire (*PROMIS Pain Intensity instrument*)

The three-item universal pain intensity short form from Patient-Reported Outcomes Measurement Information System (PROMIS) was used to measure how intense pain is on average, at its worst, and now. Participants use a 1 to 5 scale to make these ratings with 1 indicating no pain and 5 indicating very severe pain. A sum of the three items gives an overall intensity raw score that is converted to a T-score (a score of 50 is the average for U.S. general population with a standard deviation of 10). The short-form has internal reliability of greater than .80 and has good convergent validity with  $r = .83$  with Brief Pain Inventory severity (Cella et al., 2010).

### 2.2.4. Depressive symptom questionnaire (*Patient Health Questionnaire [PHQ-8]*)

The eight-item Patient Health Questionnaire depressive symptom scale (PHQ-8) was used to measure depression. Items require patients to rate how often they have been bothered by various symptoms of depression in the last two weeks and are rated as 0 = “not at all” to 3 = “nearly every day.” Overall a score of  $\geq 10$  is the cut-off for current major depression. The PHQ was shown to be more than 90% as accurate as use of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-V)* in detecting depressive symptoms in the general population, supporting the tool’s construct validity (Kroenke et al., 2009). Published internal reliability scores are .86 to .92 (Kroenke, Spitzer, Williams, & Löwe, 2010).

### 2.2.5. Generalized anxiety questionnaire (*General Anxiety Disorder Scale [GAD-7]*)

The seven-item General Anxiety Disorder scale (GAD-7) was used to measure anxiety. This scale requires participants to rate how much they have been bothered by various symptoms of anxiety over the past two weeks using a scale ranging from 0 (not at all) to 3 (nearly every day). Overall a score of  $\geq 10$  is the cut-off for current GAD (Spitzer, Kroenke, Williams, & Lowe, 2006). Published internal reliability scores are .86 to .92, and convergent validity has been shown with  $r = .72$  with the Beck Anxiety Inventory (Kroenke et al., 2010).

#### *2.2.6. Self-efficacy questionnaires*

The Patient-Reported Outcomes Measurement Information System (PROMIS) Self-Efficacy for Managing Emotions is a four-item assessment of one's confidence to manage various emotions such as "I can handle negative feelings" and "I can bounce back from disappointment." The PROMIS Self-Efficacy for Managing Symptoms is a four-item assessment of one's confidence to manage symptoms in different settings such as "I can manage my symptoms during my daily activities" and "I can work with my doctor to manage my symptoms" (Hong et al., 2016). Responses range from 1 "I am not at all confident" to 5 "I am very confident" and are summed to provide a total self-efficacy score. Acceptable internal consistency ( $>.70$ ) has been demonstrated and convergent validity shown with Self-efficacy for Managing Chronic Disease ( $r = .56-.75$ ) (Gruber-Baldini, Velozo, Romero, & Sherman, 2017).

#### *2.3 Data analysis*

Data were analyzed using IBM Statistical Package for the Social Sciences (SPSS) Version 24. Frequency distributions and descriptive statistics were used to characterize the sample. Bivariate correlations were tabulated between cannabis frequency, pain intensity, anxiety, depression, and self-efficacy in order to examine relationships among these variables. Moderation analyses were conducted using Hayes' PROCESS macro for SPSS, to examine

whether cannabis frequency moderated the relationships between pain intensity and anxiety as well as pain intensity and depression. More specifically, one moderation analysis was conducted with pain intensity as the predictor variable, cannabis use frequency as the moderator variable, and depression as the outcome variable. A second moderation analysis was then conducted with anxiety as the outcome variable. Two follow-up moderation analyses were subsequently conducted in which the two components of self-efficacy (managing symptoms, managing emotions) were added as covariates in order to explore whether self-efficacy could help account for the presence of significant pain intensity x cannabis frequency interactions. Alpha was set at .05.

### **3. Results**

#### *3.1. Descriptive statistics*

The sample shows high frequency of cannabis use: 92.7% have used cannabis at some point in their life, 66.7% have used in the past year, and 52.7% have used in the past month. Additionally, 27.5% of all respondents reported using cannabis twenty or more days of the past month and can be classified as “heavy users.” Heavy cannabis use has been defined as a pattern of use that meets DSM-5 criteria for moderate to severe cannabis use disorder, which can manifest in individuals who use cannabis three to five times a week or more (American Psychiatric Association, 2013; Cermak, 2016). Half of all participants reported using marijuana in the past 12 months to manage aches or pains, but only 5.3% reported that they were registered as a “medical marijuana” patient. Of the 100 participants who provided a reason for ever using cannabis, the most common response was for “recreation” or “social” reasons (80%), followed by pain (60%), sleep (53%), anxiety/stress (49%), and withdrawal (34%).

The sample exhibits high levels of depression, anxiety, and pain: 59.7% were at or above the cut off for major depression (with 12.2% exhibiting severe major depression), over 63.4% were at or above the cut off for moderate generalized anxiety (with 33.8% exhibiting severe anxiety), and 58.1% had received a chronic pain diagnosis (with 13.8% of the sample scoring one standard deviation or above the U.S. mean in pain intensity).

Participants were dichotomized into whether or not they had used cannabis in the past 30 days. Recent cannabis users showed comparable levels of depression,  $t(134) = 1.17, p = .25, d = .20$ , anxiety  $t(137) = 0.85, p = .40, d = .14$ , and pain intensity,  $t(140) = 1.71, p = .09, d = .29$ , as individuals who had not used cannabis in the past month. More than half (55.6%) of the sample reported having received a mental health diagnosis; most frequently reported were major depression (36.7%), bipolar disease (20.0%), and generalized anxiety disorder (17.3%).

Demographic characteristics of the participants are provided in Table 1.

**Table 1.** *Participants' characteristics (N=150)*

<b>Gender</b>	<b>N</b>	<b>%</b>	<b>Missing</b>
Female	81	55.1%	3
Male	66	44.9%	
<b>Household Income</b>			
<\$20,000	92	64.8%	27
\$20-39,000	14	9.9%	
\$40-99,000	12	9.8%	
\$100,000+	5	3.5%	
<b>Highest level of Education</b>			
< High School	19	13.3%	7
High School/GED Diploma	56	39.2%	
Some College	43	30.1%	
Associate or Technical Certificate	18	12.6%	
Bachelors Degree	4	2.8%	
Graduate Degree	3	2.1%	
<b>Marital Status</b>			
Married or Widowed	35	24.8%	9
Divorced or Separated	38	27.0%	
Living with Partner	19	13.5%	
Never Married/Other	49	34.7%	

<b>Employment Status</b>			
Full time	27	18.9%	7
Part time	16	11.2%	
Unemployed	19	13.3%	
Disabled	42	29.4%	
Retired	3	2.1%	
Student	3	2.1%	
Homemaker	21	14.7%	
Other	12	8.4%	
<b>Race</b>			
White	123	86.0%	7
American Indian/Alaska Native	8	5.6%	
Black	2	1.4%	
Asian America	1	0.7%	
Multiracial	5	3.5%	
Other	4	2.8%	
<b>Ethnicity</b>			
Non-Hispanic	127	92.7%	13
Hispanic/Latino	10	7.3%	

### 3.2. Correlations

As predicted, the results of the bivariate correlation analyses revealed significant positive correlations between pain intensity and depression, pain intensity and anxiety, as well as between depression and anxiety (see Table 2). Significant negative correlations were detected between self-efficacy for managing symptoms and both depression and anxiety, as well as between self-efficacy for managing emotions and both depression and anxiety. Cannabis frequency was only significantly negatively correlated with self-efficacy for managing emotions.

**Table 2.** Bivariate correlations among selected variables for the full sample ( $N=150$ )

Variable	1	2	3	4	5
1. Pain Intensity	--				
2. Depression	.30**	--			
3. Anxiety	.38**	.69**	--		
4. Cannabis	-.04	-.01	-.05	--	

Frequency					
5. Self-Efficacy for Managing Symptoms	-.16	-.49**	-.34**	-.07	--
6. Self-Efficacy for Managing Emotions	-.07	-.43**	-.35**	-.20*	-.75**

Note. \*  $p < .01$ ; \*\*  $p < .001$ .

### 3.3. Moderation Analyses

#### 3.3.1. Pain intensity and depression.

As shown in Table 3 (Model 1), cannabis frequency moderated the positive relationship between pain intensity and depression. Further probing of the interaction revealed that for those in the lower 10<sup>th</sup> and 25<sup>th</sup> percentile of cannabis use (i.e., individuals who reported never using cannabis in the past 30 days) there was no significant relationship between pain intensity and depression,  $b = .10$ ,  $p = .20$  (95% CI =  $-.05$  to  $.24$ ). In contrast, there were significant positive relationships between pain intensity and depression for those in the 50<sup>th</sup> percentile of cannabis frequency (i.e., individuals who reported using 1-2 days in the past month)  $b = .16$ ,  $p = .01$  (95% CI =  $.04$  to  $.28$ ), the 75<sup>th</sup> percentile (individuals who reported using 20-29 days in the past month),  $b = .42$ ,  $p < .001$  (95% CI =  $.24$  to  $.60$ ), and the 90<sup>th</sup> percentiles (i.e., individuals who reported using cannabis all 30 days of the past month) of cannabis frequency,  $b = .48$ ,  $p < .001$  (95% CI =  $.26$  to  $.70$ ).

As shown in Table 3 (Model 2), an additional moderation analysis with the two components of self-efficacy entered as covariates revealed that the interaction between pain intensity and cannabis frequency was no longer statistically significant ( $p = .07$ ). Nevertheless, further probing revealed a significant positive relationship existed between pain intensity and depression only for those in the top 50<sup>th</sup> percentile,  $b = .14$ ,  $p = .01$  (95% CI =  $.03$  to  $.24$ ) 75<sup>th</sup>

percentile,  $b = .29, p < .001$  (95% CI = .13 to .46) and 90<sup>th</sup> percentile,  $b = .33, p = .001$  (95% CI = .13 to .53) of cannabis frequency.

*3.3.2. Pain intensity and anxiety.* Similarly, as shown in Table 3 (Model 3) cannabis frequency was also found to moderate the relationship between pain intensity and anxiety. Probing of this interaction revealed significant positive relationships between pain intensity and anxiety for individuals in the 10<sup>th</sup> and 25<sup>th</sup> percentiles,  $b = .17, p = .02$  (95% CI = .02 to .31), 50<sup>th</sup> percentile,  $b = .23, p = .003$  (95% CI = .11 to .35), 75<sup>th</sup> percentile,  $b = .47, p < .001$  (95% CI = .28 to .66), and 90<sup>th</sup> percentile  $b = .53, p < .001$  (95% CI = .29 to .76), in cannabis frequency. Once again, the relationships between pain intensity and anxiety become significantly stronger as cannabis frequency increases.

An additional moderation analysis with the two components of self-efficacy entered as covariates revealed that the interaction between pain intensity and cannabis frequency was no longer statistically significant (see Table 3, Model 4). Again, further probing revealed significant relationships between pain intensity and anxiety at each level of cannabis frequency and these relationships increase in strength as the frequency of cannabis use increases.

**Table 3.** Results of moderation analyses examining the interaction between pain intensity and cannabis frequency in predicting depression and anxiety



	B	95% CI	
		Lower	Upper
Model 1: Pain Intensity x Cannabis Frequency → Depression			
Model $R^2 = .16^{**}$			
Interaction $\Delta R^2 = .05^*$			
Pain Intensity	0.10	-0.05	0.24
Cannabis Frequency	-3.44*	-6.04	-0.83
Pain Intensity x Cannabis Frequency	0.06*	0.02	0.11
Model 2: Pain Intensity x Cannabis Frequency → Depression (with Self-Efficacy Covariates)			
Model $R^2 = .37^{**}$			
Interaction $\Delta R^2 = .02$			
Pain Intensity	0.10	-0.03	0.23
Cannabis Frequency	-2.30	-4.64	0.04
Self-Efficacy for Managing Symptoms	-0.23*	-0.39	-0.07
Self-Efficacy for Managing Emotions	-0.13	-0.27	0.02
Pain Intensity x Cannabis Frequency	0.04	-0.004	0.08
Model 3: Pain Intensity x Cannabis Frequency → Anxiety			
Model $R^2 = .20^{**}$			
Interaction $\Delta R^2 = .04^*$			
Pain Intensity	0.17*	0.02	0.31
Cannabis Frequency	-3.20*	-5.86	-0.54
Pain Intensity x Cannabis Frequency	0.06*	0.01	0.11
Model 4: Pain Intensity x Cannabis Frequency → Anxiety (with Self-Efficacy Covariate)			
Model $R^2 = .33^{**}$			
Interaction $\Delta R^2 = .01$			
Pain Intensity	0.18*	0.05	0.32
Cannabis Frequency	-2.17	-4.66	0.33
Self-Efficacy for Managing Symptoms	-0.08	-0.25	-0.09
Self-Efficacy for Managing Emotions	-0.18*	-0.34	-.03
Pain Intensity x Cannabis Frequency	0.03	-0.01	0.08

Note. b = unstandardized regression coefficient; 95% CI = 95% confidence interval;  $R^2$  = proportion of variance accounted for in the model; Interaction  $\Delta R^2$  = proportion of variance accounted for by the interaction term; \*  $p < .05$ , \*\*  $p < .001$ .

#### 4. Discussion

As expected, symptoms of pain, depression, and anxiety were high in the sample of MAT patients and these symptoms were positively correlated with one another. Contrary to expectations, these symptoms were unrelated to cannabis use. Nevertheless, our results indicate that frequency of cannabis use moderates the relationships between pain and anxiety and pain

and depression. For those who use cannabis most frequently, the positive relationship between symptoms of pain and negative affect grows stronger, suggesting cannabis potentiates the connection of these symptoms. Indeed, only those individuals who reported no use of cannabis in the past 30 days demonstrate no significant relationship between pain intensity and depression. Current biopsychosocial models of pain control recognize that one can experience pain without necessarily experiencing high depression or anxiety (Buhrman et al., 2015; Dear et al., 2015). Results from the current study may indicate that cannabis use interferes with ones' ability to "unbundle" a set of co-existing symptoms. Clinically relevant interventions, therefore, could be aimed towards building coping skills (such as cognitive behavioral therapy and self-management techniques) that reduce reliance on cannabis and assist in the management of mood symptoms across a broad range of pain levels and pain-related syndromes (Ehde, Dillworth, & Turner, 2014).

Generally, as self-efficacy in managing chronic health problems increases, symptoms can be relieved (Lorig et al., 2008). Frequently, pain and self-efficacy are inversely related because as one builds confidence in managing pain, one can reduce pain intensity (Jackson et al., 2014; Wilson et al., 2015). The lack of the expected significant inverse relationship between self-efficacy and pain in our sample could be due to using a general self-efficacy scale versus an instrument specific to pain self-efficacy, or to unique characteristics of our MAT sample, and should be investigated further. Notably, we did find significant relationships between the two components of self-efficacy and affective symptoms. As hypothesized, poorer confidence in the ability to manage symptoms and emotions were associated with increased negative affect. Further, our results indicate that cannabis frequency is negatively correlated with self-efficacy for managing emotions. This suggests that cannabis use may decrease confidence for managing

emotions or that diminished confidence in the ability to manage emotions may increase the frequency of cannabis use. Moreover, our results showed that after statistically controlling for self-efficacy, cannabis frequency was no longer a significant moderator of the relationships between pain and negative affect. This overall pattern of results suggests that the decreased levels of self-efficacy associated with more frequent cannabis use may be driving these interactions. In other words, the results indicate that more frequent cannabis use increases the strength of the relationship between pain intensity and negative affect because it is associated with decreased self-efficacy for managing these symptoms.

A clear message from our data and others (Stein et al., 2015) is that symptoms of pain, anxiety, and depression are high in people in active MAT and that these symptoms come together. Respondents in our study reported using cannabis to assist in relief of their heavy symptom burden, most notably pain, sleep, and anxiety/stress. Yet, our data suggest that recent cannabis users have comparable levels of pain, anxiety, and depression, as non-users. Nevertheless, frequent use of cannabis may be interfering with patients' ability to disentangle symptoms of pain and emotional distress. This underscores an important discrepancy between patients' positive beliefs about the role of cannabis in symptom management and the more complicated detrimental influence cannabis may have on symptom entanglement. As has been noted in research on adults with obsessive-compulsive disorder, use of cannabis to cope with a cluster of symptoms may function more as a "Band-Aid" versus addressing the underlying root of discomfort (Spradlin, Mauzay, & Cuttler, 2017). The effectiveness of cannabis for relieving distressing symptoms remains mixed and requires further research, particularly for those in MAT. Some studies indicate that cannabis decreases psychological distress for those with chronic pain (Bonn-Miller, Boden, Bucossi, & Babson, 2014; Hazekamp, Ware, Muller-Vahl,

Abrams, & Grotenhermen, 2013), while other studies suggest that a reduction in cannabis use may lead to improvements in depression, anxiety, and sleep (Hser et al., 2017; Moitra, Anderson, & Stein, 2016). Our sample did not show a relationship between cannabis use and pain, so future studies should examine causal relationships with high quality randomized controlled designs and determine whether different populations are more or less likely to benefit from cannabis for pain relief.

Given this overall pattern of results, important next steps include understanding how self-efficacy can be improved through targeted interventions for specific symptom self-management, especially in cannabis users. It would also be worthwhile exploring whether improving self-efficacy reduces reliance on cannabis to cope with symptom burden and helps to disentangle the relationships between pain and negative affect. More generally, it may be important to examine the myriad of symptoms and learn more about how they interact and respond to therapies. Extending symptom assessment beyond unidimensional measurements and providing holistic, comprehensive measurements has been suggested as an important development needed to improve clinical practice, research, and health outcomes, particularly with people experiencing pain (Dworkin et al., 2005; Wilson, 2014).

*4.1. Limitations.* The self-report and cross-sectional nature of the collected data presents a limitation to our study that precludes the ability to make causal conclusions. Potential issues of recall exist as well as social desirability in completing the survey questions. We believe that the use of well-validated instruments to collect data on symptoms is a strength, however, the cannabis use data collection tools we used were less rigorous and cannot quantify cannabis use precisely. This may have reduced our ability to detect the predicted correlations between cannabis use and symptoms of pain, depression, and anxiety. Additionally, we recognize that

ours is a treatment-based convenience sample, and the results may not represent those who use opioids “recreationally.” Yet, few declined to participate, therefore, the findings are likely representative of the larger population of MAT patients. Finally, while our sample size afforded sufficient power to detect the interactions under investigation, some subsets of the sample (e.g., “heavy” cannabis users) were relatively modest in size. Future studies should therefore aim to recruit a larger sample, extend data collection beyond a single point in time, and strive to collect objective clinical data that can supplement self-reports and strengthen confidence in the findings.

#### *4.2. Conclusion*

The present sample of MAT patients reported using cannabis to mitigate symptom burdens, including to manage pain, sleep, anxiety, and withdrawal symptoms. For those with more frequent cannabis use, there were stronger associations between symptoms of pain, depression and anxiety. However, cannabis frequency was no longer a significant moderator of these relationships after controlling for self-efficacy, suggesting that cannabis use may be undermining self-efficacy and thereby potentiating the links between these symptoms. An important next step is understanding whether self-efficacy can be improved through targeted interventions for specific symptom self-management, and whether this helps reduce and disentangle the burden of symptoms for people in MAT. Helping people understand that mood can be treated independently of pain, and that a diagnosis of chronic pain does not necessitate high levels of depression and anxiety can be a first step in unraveling this cluster of symptoms. Our findings emphasize the need for future research that can confirm or invalidate perceptions from individuals that cannabis is helpful. Such information is critical in assisting clinicians in guiding and advising people in MAT on the use of cannabis.

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**Contributors**

Authors Marian Wilson, Celestina Barbosa-Leiker, Oladunni Oluwoye, Teresa Bigand, and Mary Lee Roberts designed the study and wrote the protocol. Authors Teresa Bigand and Mary Lee Roberts assisted with literature searches and developing the introduction and discussion sections. Authors Hannah Gogulski and Carrie Cuttler planned and performed the data analysis and wrote the methods and results section with direction and feedback from Marian Wilson and Celestina Barbosa-Leiker. Marian Wilson wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## References

- Alford, D. P., German, J. S., Samet, J. H., Cheng, D. M., Lloyd-Travaglini, C. A., & Saitz, R. (2016). Primary care patients with drug use report chronic pain and self-medicate with alcohol and other drugs. *Journal of General Internal Medicine*, 31(5), 486–491. <http://doi.org/10.1007/s11606-016-3586-5>
- American Psychiatric Association. (2013). Opioid use disorder Diagnostic and Statistical Manual of Mental Disorders (5 ed.). Arlington, VA: American Psychiatric Publishing.
- Bachhuber, M. A., Saloner, B., Cunningham, C. O., Barry, C. L. (2014). Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med*, 174(10), 1668–1673. doi:10.1001/jamainternmed.2014.4005
- Batki, S. L., Canfield, K. M., & Ploutz-Snyder, R. (2011). Psychiatric and substance use disorders among methadone maintenance patients with chronic hepatitis C infection: Effects on eligibility for hepatitis C treatment. *Am J Addict*, 20(4), 312–318. doi:10.1111/j.1521-0391.2011.00139.x
- Bawor, M., Dennis, B. B., Varenbut, M., Daiter, J., Marsh, D. C., Plater, C.,...Samaan, Z. (2015). Sex differences in substance use, health, and social functioning among opioid users receiving methadone treatment: a multicenter cohort study. *Biology of Sex Differences*, 6, 21. <http://doi.org/10.1186/s13293-015-0038-6>
- Bonn-Miller, M., Boden, M., Bucossi, M., Babson, K. (2014). Self-reported cannabis use characteristics, patterns, and helpfulness among medical cannabis users. *The American Journal of Drug and Alcohol Abuse*, 40(1). <http://dx.doi.org/10.3109/00952990.2013.821477>
- Bradford, A. C., & Bradford, W. D. (2016). Medical marijuana laws reduce prescription

- medication use in Medicare Part D. *Health Affairs*, 35(7), 1230-1236. doi: 10.1377/hlthaff.2015.1661
- Buhrman, M., Syk, M., Burvall, O., Hartig, T., Gordh, T., & Andersson, G. (2015). Individualized guided Internet-delivered cognitive behavior therapy for chronic pain patients with comorbid depression and anxiety: a randomized controlled trial. *Clin J Pain*, 31(6), 504-16. doi: 10.1097/AJP.0000000000000176
- Cella, D. J, Riley, W., Stone, A., Rothrock, N., Reeve, B., Yount, S., Amtmann, D.,...Hays, R. (2010). Initial adult health item banks and first wave testing of the Patient-Reported Outcomes Measurement Information System (PROMIS™) Network: 2005–2008. *Clin Epidemiol*, 63(11), 179–1194. doi:10.1016/j.jclinepi.2010.04.011
- Cermak, T. L. (2016). Clinical approach to the heavy cannabis user in the age of medical marijuana. *Journal of Psychoactive Drugs*, 48(1), 31-40. doi:10.1080/02791072.2015.1130279
- Centers for Disease Control and Prevention (CDC). 2017. Opioid Overdose. Retrieved August 13, 2017 from <https://www.cdc.gov/drugoverdose/data/overdose.html>
- Cornish, R., Macleod, J., Strang, J., Vickerman, P., & Hickman, M. (2010). Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. *BMJ*, 341, c5475. doi: <https://doi.org/10.1136/bmj.c5475>
- Corroon, J. M., Mischley, L. K., & Sexton, M. (2017). Cannabis as a substitute for prescription drugs – a cross-sectional study. *Journal of Pain Research*, 10, 989–998. <http://doi.org/10.2147/JPR.S134330>



- Dear, B. F., Gandy, M., Karin, E., Staples, L. G., Johnston, L., Fogliati, V. J., ... Titov, N. (2015). The Pain Course: a randomised controlled trial examining an internet-delivered pain management program when provided with different levels of clinician support. *Pain*, 156(10), 1920–1935. <http://doi.org/10.1097/j.pain.0000000000000251>
- Davoli, M., Bargagli, A. M., Perucci, C. A., Schifano, P., Belleudi, V., Hickman, ... Faggiano, F. (2007). Risk of fatal overdose during and after specialist drug treatment: The VEdeTTE study, a national multi-site prospective cohort study. *Addiction*, 102(12), 1954–1959. doi:10.1111/j.1360-0443.2007.02025.x
- Degenhardt, L., Lintzeris, N., Campbell, G., Bruno, R., Cohen, M., Farrell, M., & Hall, W. D. (2015). Experience of adjunctive cannabis use for chronic non-cancer pain: Findings from the Pain and Opioids IN Treatment (POINT) study. *Drug and Alcohol Dependence*, 147, 144–150. doi: 10.1016/j.drugalcdep.2014.11.031
- Dunn, K. E., Brooner, R. K., & Clark, M. R. (2014). Severity and interference of chronic pain in methadone-maintained outpatients. *Pain Medicine*, 15(9), 1540–1548. doi: 10.1111/pme.12430
- Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., ... Witter, J. (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*, 113, 9–19. doi:10.1016/j.pain.2004.09.012
- Ehde, D. M., Dillworth, T. M., & Turner, J. A. (2014). Cognitive-behavioral therapy for individuals with chronic pain: Efficacy, innovations, and directions for research. *American Psychologist*, 69(2), 153–166. <http://dx.doi.org/10.1037/a0035747>
- Grenald, S. A., Young, M. A., Wang, Y., Ossipov, M. H., Ibrahim, M. M., Largent-Milnes, T. M., & Vanderah, T. W. (2017). Synergistic attenuation of chronic pain using mu opioid

- and cannabinoid receptor 2 agonists. *Neuropharmacology*, 116, 59-70.  
<https://doi.org/10.1016/j.neuropharm.2016.12.008>
- Gruber-Baldini, A. L., Velozo, C., Romero, S., & Shulman, L. M. (2017). Validation of the PROMIS® measures of self-efficacy for managing chronic conditions. *Quality Life Research*, 26(7), 1915-1924. doi: 10.1007/s11136-017-1527-3
- Haj-Dahmane, S., & Shen, R.-Y. (2014). Chronic stress impairs  $\alpha_1$ -adrenoceptor-induced endocannabinoid-dependent synaptic plasticity in the dorsal raphe nucleus. *The Journal of Neuroscience*, 34(44), 14560–14570. <http://doi.org/10.1523/JNEUROSCI.1310-14.2014>
- Hall, W., & Weier, M. (2015). Assessing the public health impacts of legalizing recreational cannabis use in the USA. *Clinical Pharmacology & Therapeutics*, 97(6), 607-615. doi:10.1002/cpt.110.
- Hazekamp, A., Ware, M. A., Muller-Vahl, K. R., Abrams, D., & Grotenhermen, F. (2013). The medicinal use of cannabis and cannabinoids—an international cross-sectional survey on administration forms. *J Psychoactive Drugs*, 45(3), 199-210.
- Hong, I., Velozo, C. A., Li, C. Y., Romero, S., Gruber-Baldini, A. L., & Shulman, L. M. (2016). Assessment of the psychometrics of a PROMIS item bank: Self-efficacy for managing daily activities. *Quality of Life Research*, 25(9), 2221-2232. doi: 10.1007/s11136-016-1270-1
- Hser, Y.-I., Mooney, L. J., Huang, D., Zhu, Y., Tomko, R. L., McClure, E., Chou, C.-P., & Gray, K. M. (2017). Reductions in cannabis use are associated with improvements in anxiety, depression, and sleep quality, but not quality of life. *Journal of Substance Abuse Treatment*, 81(53), 53-58. doi: <http://dx.doi.org/10.1016/j.jsat.2017.07.012>

- Jackson, T., Wang, Y., Wang, Y., & Fan, H. (2014). Self-efficacy and chronic pain outcomes: A meta-analytic review. *Journal of Pain*, 15(8), 800-14. doi: 10.1016/j.jpain.2014.05.002
- Kadden, R. M., & Litt, M. D. (2011). The role of self-efficacy in the treatment of substance use disorders. *Addictive Behaviors*, 36(12), 1120–1126. <http://doi.org/10.1016/j.addbeh.2011.07.032>
- Kroenke, K., Spitzer, R., Williams, J., & Löwe, B. (2010). The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: A systematic review. *General Hospital Psychiatry*, 32(4), 345-359. <http://dx.doi.org/10.1016/j.genhosppsych.2010.03.006>
- Kroenke, K., Strine, T. W., Spitzer, R. L., Williams, J. B., Berry, J. T., & Mokdad, A. H. (2009). The PHQ-8 as a measure of current depression in the general population. *Journal of Affective Disorders*, 114(1), 163-173. doi: 10.1016/j.jad.2008.06.026
- Lorig, K. R., Ritter, P. L., Laurent, D. D., & Plant, K. (2008). The internet- based arthritis self-management program: A one- year randomized trial for patients with arthritis or fibromyalgia. *Arthritis Care & Research*, 59(7), 1009-1017.
- Miller, G. (2016). Pot and pain. *Science*, 354(6312), 566-568. doi: 10.1126/science.354.6312.566
- Moitra, E., Anderson, B. J., & Stein, M. D. (2016). Reductions in cannabis use are associated with mood improvements in female emerging adults. *Depress Anxiety*, 33, 332–338. doi:10.1002/da.22460
- National Academies of Sciences, Engineering, and Medicine. (2017). The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press. doi: 10.17226/24625

- National Institute on Drug Abuse. (2015). 2016–2020 NIDA Strategic plan: Advancing addiction science. National Institutes of Health: U.S. Department of Health and Human Services.
- Raby, W. N., Carpenter, K. M., Rothenberg, J., Brooks, A. C., Jiang, H., Sullivan, M., ... Nunes, E. V. (2009). Intermittent marijuana use is associated with improved retention in naltrexone treatment for opiate-dependence. *The American Journal on Addictions / American Academy of Psychiatrists in Alcoholism and Addictions*, 18(4), 301–308. doi:10.1080/10550490902927785
- Reiman, A., Welty, M., & Solomon, P. (2017). Cannabis as a substitute for opioid-based pain medication: Patient self-report. *Cannabis and Cannabinoid Research*, 2(1), 160–166. doi:[10.1089/can.2017.0012](https://doi.org/10.1089/can.2017.0012)
- Savant, J. D., Barry, D. T., Cutter, C. J., Joy, M. T., Dinh, A., Schottenfeld, R. S., & Fiellin, D. A. (2013). Prevalence of mood and substance use disorders among patients seeking primary care office-based buprenorphine/naloxone treatment. *Drug Alcohol Depend*, 127(1-3), 243-247. doi:<https://doi.org/10.1016/j.drugalcdep.2012.06.020>
- Schnoll, R. A., Martinez, E., Tatum, K. L., Glass, M., Bernath, A., Ferris, D., & Reynolds, P. (2011). Increased self-efficacy to quit and perceived control over withdrawal symptoms predict smoking cessation following nicotine dependence treatment. *Addictive Behaviors*, 36(1-2), 144-147. doi:10.1016/j.addbeh.2010.08.024
- Sexton, M., Cuttler, C., Finnell, J. S., & Mischley, L. K. (2016). A cross-sectional survey of medical cannabis users: Patterns of use and perceived efficacy. *Cannabis and Cannabinoid Research*, 1(1), 131-138. <https://doi.org/10.1089/can.2016.0007>

Spitzer, R. L., Kroenke, K., Williams, J. B., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of Internal Medicine*, 166(10), 1092-1097.

Spradlin, A., Mauzay, D., & Cuttler, C. (2017). Symptoms of obsessive-compulsive disorder predict cannabis misuse. *Addictive Behaviors*, 72, 159-164.  
doi:10.1016/j.addbeh.2017.03.023

Stein, M. D., Herman, D. S., Bailey, G. L., Straus, J., Anderson, B. J., Uebelacker, L. A., & Weisberg, R. B. (2015). Chronic pain and depression among primary care patients treated with buprenorphine. *Journal of General Internal Medicine*, 30(7), 935–941.  
<http://doi.org/10.1007/s11606-015-3212-y>

Substance Abuse and Mental Health Services Administration (SAMHSA). (2015). Substance use disorders. Retrieved 7/23/17 from <https://www.samhsa.gov/disorders/substance-use#opioid-use-disorder>

Termorshuizen, F., Krol, A., Prins, M., Geskus, R., van den Brink, W., van Ameijden, E. J. C. (2005). Prediction of relapse to frequent heroin use and the role of methadone prescription: An analysis of the Amsterdam Cohort Study among drug users. *Drug and Alcohol Dependence*, 79(2), 231-240. <http://dx.doi.org/10.1016/j.drugalcdep.2005.01.013>

Tkacz, J., Severt, J., Cacciola, J., Ruetsch, C. (2012). Compliance with buprenorphine medication-assisted treatment and relapse to opioid use. *The American Journal on Addictions*, 21(1), 55-62. doi:10.1111/j.1521-0391.2011.00186.x

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., Schmidtkofer, S., Westwood, M., &

- Kleijnen, J. (2015). Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA*, *313*(24), 2456–2473. doi:10.1001/jama.2015.6358
- Wilson, M. (2014). Integrating the concept of pain interference into pain management. *Pain Management Nursing*, *15*(2), 499-505. doi: 10.1016/j.pmn. 2011.06.004
- Wilson, M., Roll, J., Corbett, C., & Barbosa-Leiker, C. (2015). Empowering patients with persistent pain using an Internet-based self-management program. *Pain Management Nursing*, *16*(4), 503-514. <http://dx.doi.org/10.1016/j.pmn.2014.09.009>

**Highlights**

- Positive relationships between pain and mood are strengthened as cannabis use increases.
- Self-efficacy in symptom self-management may untangle complex co-existing symptoms.