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The impact of chronic pain and depression on medication for opioid use disorder treatment: A mixed-methods analysis

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Summary

Background: Opioid use disorder (OUD) is associated with significant morbidity and mortality. Medication for opioid use disorder (MOUD) is a cost-effective treatment, but retention rates vary widely. **Aim:** Mixed methods studies are needed to better understand how depression and pain impact the experience of OUD and MOUD treatment experiences. **Methods:** Participants were recruited from an urban addiction treatment center in the United States. Along with demographic characteristics, current pain severity, pain interference, pain catastrophizing, and depression were assessed via self-report. Correlational analyses, multivariable logistic regression models, Fisher exact tests, and Wilcoxon signed rank tests were used to examine the impact of demographic characteristics, physical pain, and depression on multiple treatment outcomes: 90-day treatment engagement (total number of dispensed MOUD doses), retention (yes/no still in treatment at 90 days), and opioid use (positive/negative urinalysis for opioids at 90 days). Ten participants were interviewed about their history with physical pain, depression, opioid use, and OUD treatment experiences. Themes were identified using a rapid analysis, top-down approach. **Results:** Fifty participants enrolled in the study and received buprenorphine (12%) or methadone (88%). Older age was associated with 90-day treatment engagement. Higher depression scores were associated with a positive opioid urinalysis at 90-day follow-up. In interviews, participants reported experiencing chronic physical pain and depression before and during their OUD and an interest in addressing mental and physical health in addiction treatment. **Conclusions:** Addressing co-occurring physical and mental health concerns during MOUD treatment has the potential to improve the treatment experience and abstinence from opioids.

Key Words: Opioid use disorder; Medication for opioid use disorder; Depression; Chronic pain; Treatment engagement; Treatment retention

1. Introduction

Approximately 4% of adults in the United States have been diagnosed with an opioid use disorder (OUD) [2]. OUD is associated with increased morbidity [18], greater criminal justice involvement [9], and lower employment rates [24]. According to recent estimates, OUD-related reductions in quality of life, fatal overdoses, health care use, criminal justice involvement, and lost productivity cost the US economy $1.02 trillion in 2017 [11].

In medication for OUD (MOUD) outpatient treatment programs, as many as 80% of patients endorse physical pain [25] and 64% endorse severe chronic pain [18]. Compared to OUD patients without chronic pain, OUD patients with chronic pain report

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higher rates of psychiatric co-morbidities and significant physical and psychosocial impairments such as more severe psychiatric symptom severity and lower well-being [17, 25]. Additionally, a greater proportion of patients who presented to an outpatient pain clinic and used opioids also suffered from depression (43.6% vs. 26.8%; [16]).

OUD is highly comorbid with other mental health conditions. According to the 2020 National Survey on Drug Use and Health, individuals that endorsed any mental illness were more likely to have misused opioids in the past year than those who did not report a mental illness (11.6% vs. 2.3% respectively) [28]. Major depressive disorder has one of the highest co-occurrence rates with OUD, ranging from 40% to 52.7% [5, 17, 31]. OUD patients with co-occurring depression are nearly three times more likely to have co-occurring chronic pain, four times more likely to overdose, and eight times more likely to experience suicidal ideation or attempt suicide [31].

OUD, pain, and depression are highly comorbid [1]. However, the direction of these relationships remains unclear due to overlapping neurobiological profiles and symptom presentations [1]. Goesling and colleagues found that depressed chronic pain patients using opioids had higher levels of functioning than non-depressed patients, suggesting that opioids may relieve both physical and affective pain [16]. Thus, depression may complicate recovery for pain patients who are also using opioids. However, one study found that patients with greater pain interference were more likely to be retained in MOUD, suggesting that pain-related functional impairments may promote treatment engagement [6].

Engagement in evidence-based, cost-effective treatment is essential for reducing morbidity and mortality for patients with OUD and co-occurring psychiatric and medical needs. When patients remain engaged in MOUD treatment, we see reduced overall medical costs, criminal justice costs, morbidity, overdose, and mortality [4, 10, 26]. However, retention rates in outpatient MOUD programs vary widely (e.g., 19-94% for 3-month regimens, [30]. A recent systematic review suggests that median retention rates are low: approximately 57% at 12 months [23].

Although co-occurring depression is associated with poorer psychosocial outcomes for OUD patients, studies evaluating the impact of depression on treatment engagement have produced mixed findings. A recent review suggests that depression is not consistently associated with treatment engagement [15]. Zhu and colleagues found that depression predicted poorer psychosocial functioning, yet greater engagement in MOUD treatment [32]. Unlike depression, age has been a consistent predictor of treatment engagement, with older age associated with increased engagement [23, 27].

In sum, co-occurring physical and mental health interact and influence the clinical presentation, needs, and treatment outcomes of OUD patients. Our goal was to understand predictors of OUD treatment involvement and outcomes, as well as to support OUD treatment interventions that target depression and pain. We used a mixed-methods design to best understand the lived experiences of individuals with OUD and co-occurring physical pain or depression and identify ways to improving MOUD treatment involvement and outcomes.

2. Methods

This study was approved by the University of Maryland, Baltimore's Institutional Review Board (HP-98483). Participants were adults (≥ 18 years of age) attending MOUD treatment at an addiction treatment center in an urban Mid-Atlantic city. The treatment center provided methadone and buprenorphine, and participants receiving either MOUD were eligible for the study. At the start of the study, recruitment focused on individuals new to treatment, (i.e., within 30 days of initiating MOUD). To reach targeted enrollment, we expanded eligibility to include any individuals involved in the MOUD program. Participants were compensated $25 for completing quantitative study measures and $25 for completing qualitative interviews.

2.1. Quantitative data

The quantitative assessment included brief measures of demographic information, depression symptoms, and pain experiences. Predictors of interest were self-reported depression, pain catastrophizing, pain severity, and pain interference. The Patient Health Questionnaire (PHQ-9) assessed depression symptoms over the past 2 weeks (range = 0 "not at all" to 3 = "nearly every day") (α = .88). A score ≥ 10 is considered clinically significant [20]. The Pain Catastrophizing Scale (PCS) assessed level of pain rumination, magnification, and helplessness on a scale from 0 ("not at all") to 4 ("all the time") (α = .96) and a score ≥ 30 is considered clinically significant [29]. The first item of the Defense and Veterans Pain Rating Scale (DVPRS) measured current pain severity on a scale from 0 ("no pain") to 10 ("as bad as it could be") supplemental DVPRS items measured the impact of chronic pain on daily activities, sleep, mood, and stress (range = 0 "no impact/interference" to 10 "completely interferes"; [8]). Scores of ≥ 4 on each supplemental item suggest moderate-to-severe pain interference in that domain, with an overall average score of ≥ 4 suggesting moderate-to-severe overall interference [8].

Table 1. Interviewee Characteristics

Interviewee	Age	Gender	PHQ-9[1]	DVPRS current pain[2]	PCS[3]
Christian	40	Male	19	10	47
Elina	26	Female	15	7	31
Jacob	27	Male	11	6	36
Leonora	37	Female	17	6	20
Anton	52	Male	15	5	0
Mario	45	Male	9	4	14
Vivienne	53	Female	17	8	39
Isaiah	51	Male	13	6	27
Max	39	Male	8	3	36
Sonia	51	Female	23	7	42

[1]PHQ-9 = Patient Health Questionnaire-9; [2] DVPRS = Defense and Veterans Pain Rating Scale; [3]PCS = Pain Catastrophizing Scale.

Outcomes of interest were extracted from participant medical records, and focused on illicit opioid use, treatment engagement, and treatment retention 90 days after baseline. Opioid use was defined as a urinalysis test that was positive for opioids within two weeks of the 90-day date (yes/no); engagement was defined as consistency of care as measured by total MOUD doses received (more doses indicated more consistent engagement); and treatment retention was defined as documentation of medication dosing (yes/no) within two weeks of the 90-day date.

2.2. *Qualitative data*

A subsample of participants (n = 10) who reported moderate depression and pain symptoms completed one-on-one interviews about lived experiences with pain, depression, opioid use, and MOUD treatment with a member of the study team. Eligible participants needed to have both a score of ≥ 9 on the PHQ-9 and a score of ≥ 4 on DVPRS item 1 (current pain severity), or a score of ≥ 30 on the PCS. Interviews lasted approximately 1 hour and were audio recorded and transcribed.

2.3. *Data Analysis Plan*

First, we calculated descriptive statistics for demographic, predictor, and outcome variables. Second, we conducted Pearson correlational analyses to identify significant relationships and inform regression models. Due to the collinearity between pain and depression assessments and small sample size, we decided against exploring whether these variables interacted to predict treatment involvement and outcomes. Third, we conducted a linear regression to evaluate predictors of treatment engagement and a logistic regression to evaluate predictors of treatment retention for participants with available data. Because of the small number of participants who completed a 90-day urinalysis, we used Fisher's exact tests and Wilcoxon signed rank tests to evaluate the relationship between predictors and 90-day opioid use. Alpha levels less than 0.05 were considered significant for all analyses.

Qualitative interviews were analyzed using a rapid analysis, top-down approach to identify themes related to pain, depression, and their relationship to opioid use and treatment **[3, 12]**. Each transcript was reviewed by two research staff and quotes related to key themes were entered into a matrix with rows representing each participant and columns representing key themes. Themes and illustrative quotes were discussed during team meetings to address any discrepancies and summarize key ideas. Pseudonyms and participant characteristics are presented in **Table 1**.

3. Results

3.1. *Sample characteristics*

Fifty MOUD patients participated in the study. The sample was predominantly Black (60%) males (64%) over the age of 45 (M = 47.78, range = 25 – 81). Most participants had at least a high school education or GED (72%) and were unemployed (64%). Participants, on average, had 4.76 (range = 1 – 15, SD = 3.24) prior treatment episodes for heroin, fentanyl, or other OUD. Black participants tended to be older than white and other race participants ($r = .39$, $p < .01$). Participant demographic characteristics are presented in **Table 2**. Of the 50 participants, 29 (58%) were enrolled within 30 days and 21 (42%) were enrolled after 30 days. Of these 21 individuals, seven were involved for longer than one year and two were involved for three or more years (range = 35 days – 4.9 years). A majority (88%) of participants were prescribed methadone (n = 44), and the remainder were prescribed buprenorphine (n = 6).

Table 2. Descriptive Statistics of Sample Demographics

Demographic	N (%)
Race	
Black	30 (60)
White	16 (30)
Other	4 (8)
Age	
18-49	23 (46)
50+	26 (52)
Male Gender	32 (64)
Level of Education	
Less than high school	14 (28)
High school/GED	24 (48)
Some college	10 (20)
Associate's degree	1 (2)
Bachelor's degree	1 (2)
Employment Status[a]	
Employed full-time	6 (12)
Employed part-time	3 (6)
A student	1 (2)
Retired/disabled	16 (32)
Unemployed	32 (64)
In jail/prison	2 (4)
Most Recent Route of Use	
Insufflation	38 (76)
Intravenous	10 (20)
Oral	1 (2)
Smoke	1 (2)
Discharged Before 90 Days	15 (30)
Reason for Discharge	Patients (n= 15)
Lost to Follow-Up	11 (73%)
Transfer	4 (27%)

n = 50; aCheck all that apply

Depression scores were normally distributed. Half of the sample scored in the minimal (0 – 4) or mild (range 5 – 9) range and half scored between the moderate (range 10 – 14) and severe (>19) range (M = 9.86, SD = 6.67). Approximately one third (32%) of participants reported clinically significant (≥ 30) pain catastrophizing (PCS M = 19.76, SD = 15.53). On average, participants reported pain severity as low-to-moderate (DVPRS item 1 M = 3.28, SD = 2.94) and reported moderate (≥ 4) pain interference (M = 3.98, SD = 3.25).

3.2. *Quantitative findings*

The number of days between treatment initiation and study enrollment was calculated to determine if the inclusion criteria expansion impacted outcomes. There was a negative relationship between days in treatment before study enrollment and pain severity (DVPRS, r = -.33, p =.02). In other words, the longer a participant was involved in treatment, the less severe they rated their current pain.

Male gender and depression were negatively related, such that males reported lower depression symptoms compared to females (r = -.41, p < .01). Higher depression scores were associated with higher ratings of pain interference (r = .69), current pain (r = .50), and pain catastrophizing (r = .67, ps < .001). Pain catastrophizing was significantly correlated with pain interference (r = .80) and current pain (r = .55, ps < .001). Additionally, pain interference and current pain were positively correlated (r = .79, p < .001). Greater pain interference was also associated with a greater number of prior treatment episodes (r = .28, p < .05). Correlation results appear in **Table 3**.

After 90 days post-baseline assessment, the average number of methadone and buprenorphine doses per participant was 64 (range = 4-90), with 75% having 50-90 doses at 90 days. At 90-day follow-up, 35 (70%) participants remained in treatment. Thirty of the 35 (86%) participants who were retained completed a 90-day drug screen. Twenty-four of the 30 (80%) participants who completed a 90-day drug screen tested positive for opioids.

Age significantly predicted treatment engagement after controlling for depression, pain, and demographic characteristics (p = .05, **Table 4**). We did not identify significant predictors of retention. Baseline depression scores significantly predicted opioid use at 90-day follow-up such that those who tested positive had higher baseline depression scores (11.2 vs. 3.2, p = 0.03, **Table 5**).

3.3. *Qualitative findings*

Of the 10 participants invited to complete qualitative interviews, half (50%) identified as Black and half identified as white or other race. The average age of interviewed participants was 42.1 years (range = 26 – 53) and 60% had at least a high school education or GED equivalent. Interviewed participants, on average, had 5.1 (range = 1 – 15, SD = 4.43) prior treatment episodes for heroin, fentanyl, or other OUD. In terms of depression symptoms, two scored in the mild range (5 – 9), two scored in the moderate range (10 – 14), and 6 scored in the severe range (>19) (M = 14.7, SD = 4.62). Sixty percent of participants interviewed reported clinically significant pain catastrophizing (≥ 30) and 90% scored ≥ 4 on the DVPRS (range = 3 – 10). **Table 1** summarizes demographic and clinical characteristics of interviewed participants.

Table 3. Correlation Matrix of MOUD Predictors and Outcomes

	Days	Engagement	Retention	Opioid Use	Age	Male[d]	Black	Education	Treatment History	DVPRS Pain Inter.	DVPR Pain Severity	PCS	PHQ-9
Days[a]	1.00												
Engagement	0.19	1.00											
Retention[b]	-0.01	0.88***	1.00										
Opioid Use[c]	0.23	-0.09	-0.09	1.00									
Age	0.19	0.34*	0.18	0.05	1.00								
Male[d]	-0.03	0.01	-0.03	-0.41*	0.09	1.00							
Black[e]	0.22	0.07	0.00	0.03	0.39**	0.07	1.00						
Education	-0.12	-0.05	-0.04	-0.11	0.05	-0.16	-0.27	1.00					
Treatment History	-0.01	0.11	0.18	0.08	-0.01	0.27	-0.15	-0.13	1.00				
DVPRS Pain Interference	-0.26	-0.11	-0.04	0.13	-0.12	-0.19	0.09	0.06	0.28*	1.00			
DVPRS Pain Severity	-0.33*	-0.18	-0.13	0.11	-0.16	-0.13	-0.10	0.11	0.13	0.79***	1.00		
PCS	-0.20	-0.00	0.04	0.08	0.05	-0.11	0.21	0.02	0.27	0.80***	0.55***	1.00	
PHQ-9	-0.17	-0.04	0.07	0.45*	0.00	-0.41**	0.10	-0.01	0.01	0.69***	0.50***	0.67***	1.00

n = 50 (n= 49 for treatment history); [a] Days between treatment start and study enrollment; [b] 0 = not retained at 90 days; 1 = retained at 90 day. [c]0 = negative urinalysis at 90 days; 1 = positive urinalysis at 90 days. n = 30. [d]Male = 1, female = 0; [e]Black = 1, White and other = 0; education = less than HS = 1, HS/GED = 2, College + = 3. DVPRS = Defense and Veterans Pain Rating Scale; PCS = Pain Catastrophising Scale; PHQ-9 = Patient Health Questionnaire-9,
*p < .05, ** p < .01, *** p < .001

3.4. Opioid use and chronic pain.

Participants commonly described physical pain preceding onset of opioid addiction. Pain was described as resulting from congenital conditions (e.g., being born with a curved spine), surgery, acute injuries (e.g., motor vehicle accident), or manual labor. For many, prescription opioids were a gateway to illicit opioids (fentanyl, heroin) to reduce pain intensity.

I played baseball my whole childhood… then I hurt my knee real bad…(then) I started doing construction work…and just never felt right…So, then I started experimenting with pills and stuff like that to overcome the pain and stuff to keep working… (Mario)

Additionally, while pain interfered with functioning, particularly employment, opioid use was credited with supporting functioning despite intense pain:

(Referring to heroin) *I guess that's how I was able to work for so long…. I could do anything I needed to do. (Isaiah).*

Although the reason for initiating opioids was to reduce pain, the reason for continued use was two-fold: to reduce pain and experience euphoric effects (i.e., get high). *It's just the opiates is the main source of helping my pain. And it's an alternate drug for me. You know, a result that…I want (Sonia).* An exception to this theme was noted by Anton, who described only experiencing pain during withdrawal, *(The pain of withdrawal is) four times as bad as a flu.*

3.5. Opioid use and depression

Depression and opioid use were inextricably related. *Drinking, drugs, depression, it just all goes hand-in-hand (Leonora).* Some participants described a combination of depression and chronic pain as preceding the onset of opioid addiction. For example, Max observed:

I think chronic pain and depression are pretty much the only two reasons people get high really, you know what I mean?… If people address those things, that's going to stop a lot of addiction, maybe not stop it, but slow it down…. What other reason would you do drugs? Me destroying my body because I'm happy, no.

Many participants described using opioids to "suppress" and "numb" not only physical pain, but also emotional pain:

The reason we get high is we don't like to feel our feelings (Max); (Heroin) make(s) you forget all the bad, all the messed-up stuff in life… you're suppressing the pain and the depression (Sonia); … I was using, you know, for

Table 4. Predictors of 90-Day Treatment Engagement

Parameter	Estimate	Standard error	t Value	p-value
Intercept	34.81	23.07	1.51	0.14
Age	0.83	0.41	2.02	0.05
Male [a]	-2.12	11.65	-0.18	0.86
Race [b]	-6.42	12.35	-0.52	0.61
College or more vs less than HS	-4.63	14.29	-0.32	0.75
HS/GED vs less than HS	-9.08	12.33	-0.74	0.47
Treatment history	0.49	1.93	0.26	0.80
DVPRS pain severity	-1.54	2.74	-0.56	0.58
DVPRS pain interference	0.16	3.71	0.04	0.97
PCS	0.21	0.54	0.40	0.69
PHQ-9	-0.28	1.17	-0.24	0.81
Days [c]	0.01	0.01	0.52	0.61

[a] Male = 1, female = 0; [b] Black = 1; White and other = 0; [c] Days between treatment start and study enrollment; PNRS = Pain Numeric Rating Scale; DVPRS = Defense and Veterans Pain Rating Scale; PCS = Pain Catastrophizing Scale; PHQ-9 = Patient Health Questionnaire-9

the physical pain and… the mental pain as well…because it kind of numbs you (Jacob).

Participants acknowledged that the numbing effects of opioid intoxication were temporary and that the depression they were avoiding would return or worsen during withdrawal, which drove the cycle of addiction:

I mean, pretty much you just want to be numb. You get high, you forget about it. That's pretty much how it works, and then it comes back, and you get high again. (Leonora)

(Heroin) helps then because it's suppressing and… numbing your feelings…but it don't help. It makes it worse because you're on a roller coaster again of trying to get yourself clean…It help for that moment, but it's going to come back. So, I feel that it don't really help. (Sonia)

For Elina and Isaiah, the isolation caused by addiction contributed to depression:

I used to get my nails done, my toes done. Stuff like that I stopped doing for myself because of me be-

Table 5. Predictors of 90-Day Opioid Use

	Total (N=30)	Negative (N=6)	Positive (N=24)	Test statistic	p
Male sex	18(60.0%)	6(100.0%)	12(50.0%)		0.06*
Race					1.00*
Black	16(53.3%)	3(50.0%)	13(54.2%)		
White/Other	14(46.7%)	3(50.0%)	11(45.8%)		
Education					0.86*
College +	9(30.0%)	2(33.3%)	7(29.2%)		
HS/GED	12(40.0%)	3(50.0%)	9(37.5%)		
Less than HS	9(30.0%)	1(16.7%)	8(33.3%)		
Age	48.6 ± 12.3	47.3 ± 11.6	48.9 ± 12.7	-0.18§	0.86
Treatment history	5.0 ± 3.4	4.4 ± 3.8	5.1 ± 3.4	-0.44§	0.66
DVPRS pain severity	3.3 ± 2.8	2.7 ± 2.3	3.4 ± 2.9	-0.66§	0.51
DVPRS pain interference	3.9 ± 3.2	3.1 ± 2.7	4.1 ± 3.3	-0.63§	0.53
PCS	18.8 ± 14.8	16.3 ± 15.1	19.4 ± 15.0	-0.42§	0.68
PHQ-9	9.6 ± 7.3	3.2 ± 4.9	11.2 ± 6.9	-2.19§	0.03
Days [a]	181.6 ± 336.6	32.2 ± 40.9	218.9 ± 367.7	-0.73§	0.47

Mean ± SD reported for total group and subgroups by urinalysis results for Wilcoxon tests. DVPRS = Defense and Veterans Pain Rating Scale; PCS = Pain Catastrophizing Scale; PHQ-9 = Patient Health Questionnaire-9.
[a] Days between treatment start and study enrollment. * Fischer's exact test. § Wilcoxon test

ing depressed and sitting up here going through withdrawals with the opiates. (Elina)

It's possible heroin can affect (depression) because I guess if I wasn't using, I would find something to do with my time. But me using…You're spending most of the day just sitting around or trying to find a way to get it. That makes you depressed. (Isaiah)

Acknowledging the relationship between opioid use and depression motivated Christian to seek treatment:

Just like when I came to (addiction treatment center), the day before that I was going through (withdrawal)…I got me some drugs-But then I was just like, I'm tired of keep doing this to myself… I could die…. Like depression is when I can't get off the floor to even take my own stuff. Like, that's crazy. Like a drug should not make a person feel that way.

3.6. MOUD treatment experience

Many participants reported feeling relieved when addiction treatment providers took their pain seriously. Jacob reported withholding his pain from addiction treatment providers due a history of being denied medications because of his substance use history, *It's like you're not allowed to be in pain if you're an addict, you know?*

Generally, participants reported that non-opioid pain medication (e.g., gabapentin) and exercise could effectively reduce their pain. While some participants found that MOUD helps reduce pain severity *((Methadone) definitely is a life saver with the pain* (Max)), some exceptions to this were noted.

For example, Anton shared this belief, *They say that methadone is a pain management drug. I don't believe it…my wife was put on it for pain management and it don't help.*

Additionally, some participants, like Leonora, described ongoing opioid use during MOUD treatment due to her belief that methadone, alone, would not be a sufficient panacea:

I didn't get on the methadone for (pain)…if I don't have the opiates…then it's like a hundred times worse pain...That's what scares me…

Finally, participants hoped that addressing pain and mental health during addiction treatment through medication and talk therapy would support their recovery. *This is the first time I'm trying to introduce the mental health…You can't just say 'Okay, I'm going to get help for my addiction, but not the mental health' and I think that's what I was missing the whole time. (Anton)*

4. Discussion

In a sample of predominantly Black, middle-aged males receiving MOUD with mild depression symptoms and moderate chronic pain, older age predicted 90-day treatment engagement. Additionally, depression, but not chronic pain, predicted 90-day opioid use. Our qualitative and quantitative findings shed light on the complex, bidirectional relationships between mental and physical health in a sample of patients with OUD. For example, multiple measures of pain experience were related to depression. Notably, many participants described using opioids to improve physical or mental functioning. Greater pain interference was associated with a greater number of prior treatment episodes, which suggests that functional impairment likely persists during ongoing opioid use and may motivate ongoing treatment. In addition, participants described opioid intoxication as numbing mental and physical pain at some times but worsening both at others. Symptoms of depression (e.g., sadness, anhedonia, lethargy) overlap with symptoms of opioid intoxication and, for some patients, symptoms of physical pain overlap with symptoms of opioid withdrawal. Overall, our findings highlight the importance of using a comprehensive treatment approach to address physical and emotional distress that frequently precedes and co-occurs with opioid addiction.

Our findings are consistent with existing literature that older age is associated with greater OUD treatment engagement **[23, 27]**. Additionally, our findings support existing theories that patient characteristics, such as co-occurring mental health concerns and coping dispositions, may be less predictive of retention than environmental factors such as criminal justice involvement and psychosocial problems, or treatment-specific factors such as staff problem-solving abilities **[21]**. Overemphasizing patient characteristics and underemphasizing environmental factors may explain why behavioral interventions do not consistently improve treatment retention among opiate-dependent patients **[30]**.

Some participants described chronic pain and depression as preceding to the onset of OUD. Others reported experiencing pain or depression exclusively during withdrawal or the period of active addiction, which drove the cycle of addiction. The biopsychosocial model suggests that chronic pain is maintained through a combination of physical (e.g., pain intensity), cognitive (e.g., thinking "I need opioids to manage pain"), behavioral (e.g., opioid addiction), and affective (e.g., depression) components **[13]**. Theoretically, addressing all biopsychosocial components are likely to promote abstinence in addiction treatment centers. A large portion (80%) of those with urinalysis data continued to test positive for opioids, with at least one interview participant continuing to misuse opioids for pain management while receiving MOUD; this could mean that persistent pain may compromise opioid abstinence. However, quantitative findings did not support a relationship between

chronic pain and 90-day treatment engagement, retention, or drug use. At the same time, the longer a participant was involved in treatment before study enrollment, the less severe they rated their pain. These findings could suggest that, although depression and pain may coincide with the onset of OUD, other factors, such as age, may play larger roles in treatment involvement and ongoing use.

There is considerable overlap between the signs and symptoms of depression and opioid use. Therefore, it can be challenging to distinguish between co-occurring depression with OUD and opioid-induced depression based on self-report measures alone. Many participants did not identify depression as preceding their opioid addiction or did not experience depression until they experienced opioid withdrawal and struggled with addiction. Our results showed that higher baseline depression scores predicted 90-day opioid use; thus, increasing our understanding of how depression varies over the course of recovery from OUD can help clinicians target depression symptoms at the most clinically-relevant time to prevent a return to opioid use.

Notably, our mixed methods design helped to shed light on the overlap between pain, depression, opioid use, and MOUD treatment experiences. During qualitative interviews, participants emphasized how attempts to numb both pain and depression perpetuated the cycle of opioid addiction. Many also shared the viewpoint that addressing mental and physical health concerns during addiction treatment would be beneficial for their physical pain and OUD recovery. Providers should inquire about chronic pain and depression when providing MOUD to individualize patient care. Incorporating evidence-based, non-pharmacological pain and depression interventions such as Cognitive Behavioral Therapy for Chronic Pain **[7]** or Depression **[14, 19]** may improve outcomes by addressing common experiences before and during OUD.

Limitations. While 90 days is a generally accepted follow-up timepoint for MOUD, OUD is a chronic condition that usually requires extended treatment lengths to support prolonged abstinence **[22]**. Our relatively small sample size may also limit the generalizability of our findings. Additionally, 42% of our sample had been retained in treatment for at least 30 days before study enrollment after expansion of the eligibility criteria. This expansion increased sample heterogeneity. Although length of time between treatment initiation and study enrollment was not related to 90-day treatment outcomes, it still may have affected our findings given that those who were in treatment longer experienced less pain severity. There are also many environmental characteristics and personal strengths that may influence treatment retention. For example, motivation, job skills, college education, help-seeking, community engagement, and social support are all associated with treatment retention **[21]**. Since we did not evaluate these factors, our results cannot determine whether depression or pain influences each of these circumstances. Finally, although some participants described chronic pain or depression as preceding their OUD, we cannot draw causal inferences from our qualitative or quantitative data due to the observational design of our study.

5. Conclusions

Overall, our findings provide further context for the ways that depression and chronic pain impact individuals in MOUD treatment. Understanding the impact of pain, depression, and other health factors on OUD development and treatment is important to consider when developing effective treatment plans for these individuals. Given high rates of pain and mental health concerns in OUD treatment-seeking populations, integrative care for these comorbid conditions is warranted.

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Contributors

M.B., A.B., H.F., A.G., designed the study and wrote the protocol. C.K., H.S., M.K., W.H., managed the literature searches and analyses. C.K., H.S., L.L., undertook the statistical analysis, and all the authors discussed the results. C.K., H.S., L.T., wrote the first draft of the manuscript. All

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Conflict of interest

All authors do not have any financial relationships with commercial interests to report.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. All patients gave their informed consent to the use and reporting of their de-identified data for this research study.

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