

# Depression and Anxiety Among Patients on Chronic Opioid Therapy

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## Abstract

**Background:** Chronic noncancer pain (CNCP) and chronic opioid therapy (COT) commonly coexist with comorbid depression and anxiety. We investigated the prevalence of depression and anxiety and their correlates at the time of controlled substance agreement (CSA) enrollment among patients with CNCP and a history of depression or anxiety on COT.

**Methods:** Retrospective analysis of 1066 patients in a Midwest primary care practice enrolled in CSAs for COT between May 9, 2013, and August 15, 2016. Patients with self-reported symptoms or a clinical history of depression or anxiety were screened at CSA enrollment using the Patient Health Questionnaire–9 item scale and the Generalized Anxiety Disorder–7 item scale.

**Results:** The percentage of patients screening positive for depression and anxiety at CSA enrollment was 15.4% and 14.4%, respectively. Patients screening positive for depression or anxiety were more likely to be younger, unmarried, unemployed, and live alone compared to patients not screening positive. Patients screening positive for depression or anxiety were more likely to smoke cigarettes and report concern from friends or relatives regarding alcohol consumption. Compared to patients screening negative, patients screening positive for depression had higher odds of receiving opioid doses of  $\geq 50$  morphine milligram equivalents per day (adjusted odds ratio: 1.62; 95% confidence interval: 1.01-2.58).

**Conclusion:** Anxiety and depression are prevalent at enrollment in CSAs among patients receiving COT. Future research is needed to determine whether recognition of anxiety and depression leads to improved management and outcomes for this population.

## Keywords

chronic opioid therapy, controlled substance agreement, major depressive disorder, anxiety, chronic noncancer pain

## Introduction

Chronic noncancer pain (CNCP) is a prevalent and complex clinical problem.<sup>1</sup> Over 25 million patients experience daily CNCP,<sup>2</sup> and pain represents one of the most common indications for which patients visit their doctors annually.<sup>3</sup> Chronic opioid therapy (COT), defined as opioid use greater than 90 days<sup>4</sup> has increasingly been utilized to manage CNCP, but evidence for long-term efficacy is limited.<sup>5</sup> Chronic opioid therapy is associated with health risks including abuse and overdose.<sup>6</sup> The increasing availability of opioids and associated risks necessitate understanding the characteristics of patients receiving COT for CNCP.<sup>7</sup>

Mental health conditions such as major depressive disorder (MDD) and anxiety are prevalent among patients with CNCP.<sup>1,6-11</sup> Among patients with CNCP, the historical prevalence of depression has been reported to range from 5.9% to

46% in primary care clinics.<sup>12</sup> Both MDD and CNCP are closely related such that increasing severity of one commonly correlates with increasing severity of the other.<sup>13</sup> Patients with CNCP and concomitant MDD have a greater likelihood of using opioids at higher doses and for longer durations with

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an increased risk of abuse.<sup>6</sup> An estimated 35% of patients with chronic pain have an anxiety disorder.<sup>14</sup> Patients with anxiety disorder report greater interference from pain<sup>15</sup> and worse scores in health-related quality of life.<sup>16</sup> Management of patients with CNCP and concomitant mental health disorders can be challenging, especially if the underlying mental health condition is underrecognized.<sup>13</sup>

Controlled substance agreements (CSAs) are a guideline-recommended, risk mitigation tool outlining the treatment parameters for COT and facilitating early identification of risks.<sup>17,18</sup> Presence of a mood or anxiety disorder should be assessed in patients prescribed COT.<sup>19</sup> Although lifetime prevalence of MDD or anxiety among patients on COT has been reported,<sup>1,8</sup> the prevalence and clinical correlates of concurrent depression or anxiety among patients on COT at the time of CSA enrollment are unknown.

We conducted a retrospective study of patients in a Midwest multispecialty primary care practice enrolled in CSAs for COT. Among patients self-reporting a history of depression or anxiety, we assessed presence of depression and anxiety, demographic characteristics, opioid dosing, and efficacy of pain management.

## Methods

### Study Setting

Mayo Clinic Midwest (MCM) is a medical center in South-eastern Minnesota. Employee and Community Health is a multisite, primary care practice of MCM located in Olmsted County, Minnesota. Employee and Community Health provides care to approximately 152 000 patients by clinicians in pediatrics, family medicine, and internal medicine. The institutional review board of Mayo Clinic reviewed and approved this research. Informed consent was not required.

### Study Population

Patients with CNCP on COT were eligible for study inclusion if they previously provided authorization to access their medical record and completed depression and/or anxiety screening at CSA enrollment between May 9, 2013, and August 15, 2016. Patients self-reporting any symptoms or clinical diagnosis of depression and/or anxiety completed the Patient Health Questionnaire–9-item scale (PHQ-9) to screen for depression<sup>20</sup> and the Generalized Anxiety Disorder–7-item scale (GAD-7) to screen for anxiety disorders, respectively.<sup>21</sup> Patients were considered depression “screen-positive” if their PHQ-9 score was  $\geq 10$ . Patients were considered anxiety “screen-positive” if their GAD-7 score was  $\geq 10$ . Patients who did not pick up their first prescription following CSA enrollment were excluded.

### Controlled Substance Agreement Enrollment

Controlled substance agreement enrollment is recommended by institutional guidelines if patients are expected to be on a

Drug Enforcement Agency (DEA) schedule II, III, or IV medication for  $\geq 3$  months. Patients enrolled in hospice, nursing homes, palliative care, or group homes are exempt. Provider discretion is allowed for patients receiving  $< 10$  pills per month. Upon CSA enrollment, nursing staff review CSA treatment parameters. The CSA specifies receipt of prescriptions from a single provider, restrictions on dose changes without approval, urine drug screening, and prescription renewal process. The Minnesota Prescription Drug Monitoring Program is queried to review prescribed DEA schedule medications.

### Data Collection

**Controlled substance agreement.** Data collected at CSA enrollment were entered into a separate, secure clinical database and included patient demographics, primary indication for COT, and PHQ-9 and GAD-7 results.

**Administrative data.** Data were obtained from patient-provided information and billing data obtained annually and include race, educational status, employment status, relationship status, alcohol use, and tobacco use. Age-weighted Charlson Comorbidity Index<sup>22-24</sup> (CCI) scores served as a measure of comorbidity burden. The CCI was calculated using an institutional protocol and administrative billing data 1 year prior to the date of CSA enrollment.

**Electronic Health Record (EHR) data.** Opioid prescription data were converted into morphine milligram equivalents per day (MME/day). Total opioid dose per day was calculated by multiplying the maximum prescribed doses per day by the amount of opioid per dose. Estimated MME/day was calculated by multiplying total opioid dose per day by a morphine equivalent conversion factor.<sup>4,25</sup>

### Statistical Analyses

Distribution of patient demographic characteristics, opioid therapy indication, comorbidities, opioids, and pain scores was compared between patients with depression and anxiety. Frequencies and proportions were calculated for categorical variables, and associations were assessed with  $\chi^2$  test for independence. If  $\chi^2$  test assumptions were violated (cell sizes  $< 5$ ), the Fisher exact test was used. Mean and standard deviation, median and interquartile range, and mode were calculated for continuous variables. Each continuous variable was assessed for normality using histogram plots, measures of skewedness and kurtosis, and the Shapiro-Wilk test for normality. Associations were assessed by comparing variable means using the 2-sample  $t$  test when the continuous variable was normally distributed. Pooled  $t$  statistics are provided where the folded F equality of variance estimates were equal ( $P > .05$ ) and Satterthwaite  $t$  statistics where variances were unequal ( $P \leq .05$ ). Wilcoxon 2-sample tests were employed for non-normally distributed variables. All data management and statistical analyses were performed using Statistical Analysis

**Table 1.** Demographic Characteristics of Patients Completing a PHQ-9 or GAD-7 at CSA Enrollment.

Characteristic	Screen-Positive for Depression			Screen-Positive for Anxiety		
	No	Yes	P Value	No	Yes	P Value
n (%)	664 (84.6)	121 (15.4)	–	495 (85.6)	83 (14.4)	–
Age			.0255			.0124
Mean (SD)	62.4 (14.6)	59.5 (14.8)		61.1 (14.5)	56.9 (14.2)	
Median (IQR)	62.6 (52.6-73.2)	58.8 (49.6-66.3)		60.9 (51.1-71.0)	56.5 (47.0-66.0)	
Range	24.8-100.1	30.3-94.1		24.8-97.9	31.1-91.2	
Gender, n (%)			.6300			.2115
Female	435 (65.5)	82 (67.8)		336 (67.9)	62 (74.7)	
Male	229 (34.5)	39 (32.2)		159 (32.1)	21 (25.3)	
Race, n (%)			.3205			.0742
Other/unknown	39 (5.9)	10 (8.3)		28 (5.7)	9 (10.8)	
White	625 (94.1)	111 (91.7)		467 (94.3)	74 (89.2)	
Marital status, n (%)			<.0001			.0019
Divorced	93 (14.0)	33 (27.3)		79 (16.0)	22 (26.5)	
Married	393 (59.2)	48 (39.7)		284 (57.4)	32 (38.6)	
Single	88 (13.3)	29 (24.0)		71 (14.3)	21 (25.3)	
Widowed	90 (13.6)	11 (9.1)		61 (12.3)	8 (9.6)	
Education level, n (%)			.6622			.9401
Missing	116	31		84	23	
4-year college graduate or more	152 (27.7)	25 (27.8)		121 (29.4)	19 (31.7)	
High school or less	164 (29.9)	23 (25.6)		111 (27.0)	16 (26.7)	
Some college or 2-year degree	232 (42.3)	42 (46.7)		179 (43.6)	25 (41.7)	
Employment status, n (%)			<.0001			.0001
Missing	74	16		57	12	
Employed	192 (32.5)	21 (20.0)		154 (35.2)	11 (15.5)	
Other	38 (6.4)	15 (14.3)		36 (8.2)	10 (14.1)	
Retired	249 (42.2)	31 (29.5)		162 (37.0)	20 (28.2)	
Unemployed	27 (4.6)	7 (6.7)		19 (4.3)	7 (9.9)	
Work disabled	84 (14.2)	31 (29.5)		67 (15.3)	23 (32.4)	
Living arrangement, n (%)			.0001			.0434
Missing	103	20		83	13	
Live alone	126 (22.5)	41 (40.6)		100 (24.3)	25 (35.7)	
Does not live alone	435 (77.5)	60 (59.4)		312 (75.7)	45 (64.3)	
Depression PHQ-9 score			–			–
Mean (SD)	3.0 (2.7)	14.6 (4.3)				
Anxiety GAD-7 score						–
Mean (SD)				2.4 (2.7)	15.0 (3.2)	

Abbreviations: CSA, controlled substance agreement; GAD-7, Generalized Anxiety Disorder–7-item scale; IQR, interquartile range; PHQ-9, Patient Health Questionnaire–9-item scale; SD, standard deviation.

Software version 9.3 (Cary, North Carolina), and significance was assumed when  $P \leq .05$ .

We evaluated the association between positive screening for anxiety and for depression independently by deploying unadjusted and adjusted logistic regression models against the outcome of receiving an opioid dose of  $\geq 50$  MME/day. We included factors in the adjusted model which proved to be significant when independently modeled against the outcome. We reported odds ratios (ORs) and associated 95% confidence intervals (CIs).

## Results

We identified 1066 eligible patients. Among these, 785 (73.6%) patients completed a PHQ-9 and 578 (54.2%)

completed a GAD-7 upon enrollment (Table 1). Compared to screen-negative patients, patients who screened positive for depression or anxiety were younger, unmarried, not employed, and more likely to live alone.

Patients screening positive for depression were more likely to report a need to cut down on alcohol consumption (Table 2). Patients screening positive for depression and anxiety were more likely to report that relatives or friends expressed worry or complain about their alcohol intake and more likely to report cigarette smoking.

Patients screening positive for anxiety received higher mean MME/day (Table 3). Although patients screening positive for depression were more likely to report difficulty with pain, the scores for current pain, average pain over the past week, and worst pain over the past week were all

**Table 2.** Indication for Chronic Opioid Therapy, Charlson Comorbidity Index, and Substance Use Assessment.

Characteristic	Screen-Positive for Depression			Screen-Positive for Anxiety		
	No	Yes	P Value	No	Yes	P Value
Indication, n (%)			.7891			.3258
Musculoskeletal pain	430 (64.8)	74 (61.2)		312 (63.0)	44 (53.0)	
Chronic pain syndrome	104 (15.7)	24 (19.8)		82 (16.6)	18 (21.7)	
Neuropathy	63 (9.3)	11 (9.2)		46 (9.3)	7 (8.4)	
Migraine/headache	27 (3.9)	6 (4.9)		24 (4.8)	5 (6.0)	
Other	40 (6.3)	6 (4.9)		31 (6.3)	9 (22.9)	
Age-weighted Charlson Comorbidity Index			.4677			.1516
Mean (SD)	3.9 (3.2)	3.8 (3.1)		3.6 (3.1)	3.2 (3.0)	
Median (IQR)	3.0 (1.0-6.0)	3.0 (1.0-6.0)		3.0 (1.0-5.0)	2.0 (1.0-4.0)	
Range	0.0-18.0	0.0-13.0		0.0-18.0	0.0-15.0	
Felt the need to cut down on alcohol, n (%)			.0008			.0509
Missing	80	17		63	11	
No	559 (95.7)	90 (86.5)		411 (95.1)	64 (88.9)	
Yes	25 (4.3)	14 (13.5)		21 (4.9)	8 (11.1)	
Relatives/friends worry/complain about alcohol intake, n (%)			.0009			.0483
Missing	75	20		57	15	
No	580 (98.5)	94 (93.1)		429 (97.9)	64 (94.1)	
Yes	9 (1.5)	7 (6.9)		9 (2.1)	4 (5.9)	
Smoking status, n (%)			<.0001			.0320
Missing	90	21		67	15	
No	473 (82.4)	63 (63.0)		345 (80.6)	46 (67.6)	
Yes	101 (17.6)	37 (37.0)		83 (19.4)	22 (32.4)	

Abbreviations: IQR, interquartile range; SD, standard deviation.

higher for patients with positive depression or anxiety screens.

In the uncontrolled models, patients who were screen-positive for anxiety and depression had increased odds of having an opioid prescription  $\geq 50$  MME/day (OR: 1.85; 95% CI: 1.13-3.05; OR: 1.80; 95% CI: 1.18 to 2.71, respectively). Within the anxiety model when controlling for marital status, smoking status, and age, this observed effect disappeared. However, patients who were screen-positive for depression had higher odds of receiving opioids  $\geq 50$  MME/day after controlling for marital status, smoking status, and age (adjusted OR: 1.62; 95% CI: 1.01-2.58).

## Discussion

Among patients completing a PHQ-9 or GAD-7 at CSA enrollment, we observed rates of 15.4% and 14.4% for screen-positive depression and anxiety, respectively. This is consistent with previous literature which has observed rates of major depression ranging from 5.9% to 46% among patients with chronic pain in primary care.<sup>12</sup> Previous studies have suggested that an estimated 35% of patients with chronic pain have an anxiety disorder,<sup>14</sup> but this estimate was based upon a past year diagnosis. In contrast, we assessed the point prevalence of anxiety at CSA enrollment.

We observed that patients screening positive for depression or anxiety at CSA enrollment were less likely to be married. Our data are consistent with previous research regarding the

interrelation of chronic pain, mental health conditions, and marital status.<sup>26-29</sup> Although we did not collect information on the quality of marital relationships in our cohort, such data may be helpful to assess the potential relationships between the quality of the relationships and the use of opioids for the management of chronic pain.

Tobacco or alcohol abuse is frequently comorbid among patients with depression and anxiety.<sup>30-32</sup> The relationship between depression and smoking in patients with chronic pain receiving opioids is complex.<sup>33</sup> We observed that patients who were screen-positive for depression or anxiety were more likely to smoke. Alcohol is the most common concomitant drug involved in opioid overdose,<sup>34</sup> and alcohol use among patients on COT can increase the risk of opioid misuse.<sup>18,35</sup> Our findings suggest a possible risk of concurrent alcohol misuse among patients screening positive for depression or anxiety.

Patients who screened positive for anxiety received greater mean MME/day than screen-negative patients. However, both cohorts consistently reported higher mean pain scores compared to screen-negative patients. This is consistent with published literature reporting that patients with current or past mental health disorders are more likely to receive opioids at higher doses and for longer durations.<sup>7,10</sup> Emerging evidence also suggests that COT may be a risk factor for precipitating incident or recurrent depression in CNCP patients.<sup>6,10</sup> The effect of anxiety, through catastrophizing a maladaptive cognitive style exaggerating threat of pain, increases the risk of

**Table 3.** Prescribed Opioids and Pain Assessment.

Characteristic	Screen-Positive for Depression			Screen-Positive for Anxiety		
	No	Yes	P Value	No	Yes	P Value
MME/day			.0509			.0239
Mean (SD)	42.6 (64.5)	46.4 (43.3)		40.5 (46.9)	50.3 (48.6)	
Median (IQR)	30 (15.0-45.0)	30 (20.0-60.0)		30 (15.0-45.0)	30 (20.0-60.0)	
Range	3.8-723.0	5.0-240.0		3.8-640.0	10.0-270.0	
Report of difficulty with pain, n (%)			.0073			.1300
Missing	119	24		85	16	
No	128 (23.5%)	10 (10.3%)		91 (22.2%)	8 (11.9%)	
Unknown	8 (1.5%)	1 (1.0%)		6 (1.5%)	1 (1.5%)	
Yes	409 (75.0%)	86 (88.7%)		313 (76.3%)	58 (86.6%)	
Pain scores, n (%)	528 (67.3%)	105 (13.3%)		387 (67.0%)	74 (12.8%)	
Current pain			<.0001			<.0001
Mean (SD)	3.9 (2.4)	5.9 (2.5)		4.2 (2.5)	5.6 (2.6)	
Median (IQR)	4.0 (2.0-5.5)	6.0 (4.0-8.0)		4.0 (2.0-6.0)	6.0 (4.0-7.0)	
Range	0.0-10.0	0.0-10.0		0.0-10.0	0.0-10.0	
Average pain over the past week			<.0001			.0086
Mean (SD)	5.2 (1.9)	6.7 (2.0)		5.3 (2.0)	6.1 (2.2)	
Median (IQR)	5.0 (4.0-6.0)	7.0 (5.0-8.0)		5.0 (4.0-7.0)	6.0 (4.0-8.0)	
Range	0.0-10.0	2.0-10.0		0.0-10.0	2.0-10.0	
Worst pain over the past week			<.0001			.0012
Mean (SD)	7.4 (2.1)	8.6 (1.6)		7.6 (2.1)	8.4 (1.9)	
Median (IQR)	8.0 (6.0-9.0)	9.0 (8.0-10.0)		8.0 (6.0-9.0)	9.0 (7.0-10.0)	
Range	0.0-15.0	3.0-12.0		0.0-10.0	2.0-12.0	

Abbreviations: IQR, interquartile range; MME, morphine milligram equivalents; SD, standard deviation.

opioid misuse independent of depression and may be a coping strategy among CNCP patients.<sup>9</sup> Given mortality risks associated with opioid use  $\geq 50$  MME/day and our observation that patients with depression are more likely to receive doses in this range, our findings support mental health screening in patients on COT to identify individuals at heightened risk for opioid adverse events.

Strengths of this study include analysis of a large cohort of patients with a history of depression or anxiety on CSAs for COT in a large, primary care practice. Our study also provides insight on the prevalence of patients screen-positive for anxiety and depression at the time of CSA enrollment. Patients in our sample were screened for depression or anxiety with validated clinical instruments.

Limitations of this study include generalizability to other communities, given the low percentage of minority patients. Inferences regarding the prevalence of positive screens for depression or anxiety in this population are limited as data were obtained only from patients who completed a PHQ-9 or GAD-7 at CSA enrollment. Additionally, no data were collected regarding antidepressant use or other treatments for depression or anxiety, which can affect opioid use, dosing, and perceptions of pain.<sup>13</sup> We observed a positive GAD-7 to be 14.4% in our population, which we agree is lower than what has been reported.<sup>14</sup> However, our ascertainment of anxiety was a point prevalence estimate upon CSA enrollment, while previous studies have reported higher rates based upon a 12-month history of anxiety.

Primary care providers manage chronic pain and are most often the prescribers of COT.<sup>36-38</sup> Controlled substance agreements are intended to mitigate risk associated with COT and are increasingly recommended as part of a comprehensive management strategy in CNCP patients.<sup>17,18</sup> Our findings suggest that in patients with a history of depression or anxiety, screening positive for depression or anxiety at CSA enrollment is associated with sociodemographic characteristics and behavioral factors that may further increase risk. Further research is needed to determine whether recognition of depression, anxiety, or other factors associated with COT risks at the time of CSA enrollment leads to improved management and outcomes for this population.


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