


A Preliminary Study of Stress, Mental Health, and Pain Related to the COVID-19 Pandemic and Odds of Persistent Prescription Opioid Use



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BACKGROUND: The COVID-19 pandemic has been associated with increased opioid prescribing. It is not known if perceived COVID-19 related stress is associated with increased odds of long-term opioid use.

OBJECTIVE: To determine if greater COVID-19-related stress and worsening pain attributed to the pandemic was associated with LTOT over a 6-month observation period.

DESIGN: Longitudinal cohort.

PARTICIPANTS: Patients ($n=477$) from two midwestern health care systems, with any acute or chronic non-cancer pain, starting a new period of 30–90-day prescription opioid use, were invited to participate in the Prescription Opioids and Depression Pathways Cohort Study, a longitudinal survey study of pain, opioid use, and mental health outcomes.

MAIN MEASURES: Baseline and 6-month follow-up assessments were used to measure the association between perceived COVID-19 stressors, the perception that pain was made worse by the pandemic and the odds of persistent opioid use, i.e., remaining a prescription opioid user at 6-month follow-up. Multivariate models controlled for demographics, opioid dose, and change in pain characteristics, mental health measures, and social support.

KEY RESULTS: Participants were, on average, 53.9 (± 11.4) years of age, 67.1% White race, and 70.9% female. The most frequently endorsed COVID-19 stressor was “worry about health of self/others” (85.7% endorsed) and the least endorsed was “worsened pain due to pandemic” (26.2%). After adjusting for all covariates, “worsened pain due to pandemic” (OR=2.88; 95%CI: 1.33–6.22), change in pain interference (OR=1.20; 95%CI: 1.04–1.38), and change in vital exhaustion (OR=0.90; 95%CI: 0.82–0.99) remained significantly associated with persistent opioid use.

CONCLUSIONS: Patients who attribute worsening pain to the COVID-19 pandemic are more likely to be persistent opioid users. Further research is warranted to identify mechanisms underlying this association. Clinicians may consider discussing pain in the context of the pandemic to identify patients at high risk for persistent opioid use.

KEY WORDS: pain; opioid; COVID-19; cohort; epidemiology.

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INTRODUCTION

The COVID-19 pandemic has been associated with adverse consequences for non-cancer pain patients. Pandemic-related stress and mood disruption have been linked to worse pain intensity and pain-related impaired functioning^{1–4} which in turn can contribute to increased opioid use and high-risk concomitant benzodiazepine use.⁵

Cross-sectional survey studies found respondents with chronic pain and post-surgical pain perceived worsening pain severity and worsening pain interference early in the COVID-19 pandemic.^{1,3} In some cases, this perception was correlated with worsening mood, sleep problems, worries about the future, and feelings of insecurity.^{2,3} In contrast, Mun and colleagues⁶ survey of chronic pain patients in the first year of the pandemic revealed little to no worsening in pain severity, pain interference, emotional distress, and opioid misuse.

The pandemic is associated with reduced access to, and utilization of, non-pharmacological pain therapies^{7,8} and postponed surgical interventions,⁹ all of which may contribute to worsening pain and increased opioid use.¹⁰ However, there is mixed evidence regarding changes in use of prescription opioids during the first year of COVID-19.^{8,11–13} Recent analyses

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of nationally distributed medical claims data observed that compared to the same time period prior to the pandemic, patients with pain were more likely to receive prescription opioids for longer duration and greater potency in the first year of the pandemic.¹⁴ In addition, patients were more likely to transition from non-pharmacological pain management to opioids during the first 9 months of the COVID-19 pandemic compared to the first 9 months of 2019.¹⁴

The long-term effects of the pandemic on prescription opioid use are not clear. We carried out the present research using data from the Prescription Opioids and Depression Pathways Cohort Study.¹⁵ This is an on-going, prospective cohort study of new 30–90-day prescription opioid users who complete baseline, 6-month, and 12-month follow-up assessments. Although enrollment is on-going and only 30% of the cohort has had the opportunity to complete the 12-month follow-up, we believe using data from participants who completed baseline and the 6-month follow-up is appropriate. There is an urgent need to communicate the potential for COVID-19-related stress to contribute to long-term opioid therapy (LTOT) as the pandemic waxes and wanes but remains a public health crisis.

Our first objective was to determine if any COVID-19-related stressor (e.g., concerns about health, concerns about social isolation, reporting pandemic worsened pain, etc.) was associated with persistent prescription opioid use over a 6-month period. Second, we determined if this association was independent of demographic factors, change in pain measures, mental well-being, and social support.

METHODS

Patient Recruitment

Participants were enrolled in the Prescription Opioids and Depression Pathways Cohort Study, henceforth termed the Pathways Study, which is designed to determine the mental health consequences of LTOT and risk factors for prescription opioid use disorder. The study protocol has been reported in detail.¹⁵ In brief, eligible patients were identified from the electronic health records of Saint Louis University's academic medical practice in St. Louis, MO, and Henry Ford Health in Detroit, MI. Patients were eligible to enroll in the study if they were starting a new period of prescription opioid use, defined as no opioid use in the prior 3 months, and were free of cancer. Opioid use and cancer status were identified in electronic health records and confirmed in screening questions. Patients who completed the baseline assessment were invited to complete 6- and 12-month follow-up surveys. The current 6-month retention rate is approximately 82%. The present study uses data from the first 477 patients who completed baseline, 6-month follow-up assessments, and answered questions about COVID-19 stressors. Baseline enrollment began in November 2019. Measures of COVID-19-related stress were added to the 6-month follow-up survey in September 2020. Prior to

incorporating the COVID-19 questions, 62 participants completed baseline. Therefore, the current study uses data from 477 participants who completed baseline and 6-month follow-up between September 2020 and January 2022.

All assessments were administered in REDCap and either completed by the subject on the internet or by a telephone interviewer entering answers into REDCap. Patients provided informed consent prior to participation. Patients were given a \$50 gift card for each survey completed. All procedures were approved by Saint Louis University and Henry Ford Health's Institutional Review Boards.

Variables

Outcome. Prescription opioid use at baseline and 6-month follow-up was based on self-report of the opioid type, frequency (daily vs. non-daily), and dose. Persistent opioid use was defined as using a prescription opioid at 6-month follow-up.

Primary Exposure. COVID-19-related stressors were derived from the Complementary and Integrative Research (CAIR) Pandemic Impact Questionnaire (C-PIQ).¹⁶ The C-PIQ measures experiences in the past 2 weeks and includes the following questions: (1) How much are you reading, watching, listening, talking or thinking about coronavirus/COVID-19? (2) How much do you worry about your health or the health of your friends or family? (3) How stressful have changes in social contacts, like family or friends, been for you? (4) How stressful have changes in your way of life, like changes in finances, education, living situation, childcare, etc. been for you? (5) How much has your mental/emotional health been worsened by the COVID-19 pandemic? We created a sixth question based on C-PIQ format which was as follows: (6) How much has your pain been worsened by the COVID-19 pandemic? For questions 1 and 2, binary (no/yes) variables were computed by combining response options never/rarely (no) vs. occasionally/often/most of the time (yes). Binary variables for questions 3 through 6 were created by combining response options not at all/ slightly (no) vs. moderately/very/extremely (yes).

Covariates

Demographic measures included age, race, gender, and marital status.

Pain Measures. The Brief Pain Inventory (BPI)^{17,18} measured pain site, severity, and pain interference. Participants reported whether they had pain in 17 different body locations (e.g., neck, lower back, upper back, legs etc.) which was used to define number of pain sites. Pain severity was measured via 4-items: worst in last 30 days, least in last 30 days, pain on average, and current pain. Pain severity was the average of these 4-items on a scale from "0=no pain" to "10=pain as bad as you can imagine." Seven pain interference questions assessed whether pain has interfered with general activity, mood, walking ability, normal work, relationships, sleep,

and enjoyment of life in the last 30 days. The pain interference score was the average of these 7-items on a scale of “0=does not interfere” to “10=completely interferes.”

Prescription Opioid Measures. We adjusted for baseline morphine equivalent dose (MME) and the baseline score on the Prescribed Opioids Difficulty scale (PODS).¹⁹ We used only the baseline MME and PODS because patients no longer using opioids at 6-month follow-up did not receive these assessments in follow-up surveys. The PODS measures psychosocial problems and concerns about opioid use. Higher scores indicate greater problems with opioids with scores ≥ 16 considered high.

Mental Health Measures. Mental health measures included generalized anxiety measured via the GAD-7, anhedonia measured via the Snaith-Hamilton Pleasure Scale (SHAPS) and vital exhaustion measured using the Maastricht Vital Exhaustion brief form. The GAD-7 measures general anxiety with higher scores indicating worse anxiety and a score ≥ 15 indicating severe anxiety.²⁰ The SHAPS measures anhedonia with higher scores indicating more severe anhedonia. A score ≥ 3 indicates high anhedonia.²¹ Vital exhaustion is a measure of “unusual fatigue, increased irritability and feelings of demoralization,” and higher scores indicate worse vital exhaustion. A score of ≥ 10 indicates high vital exhaustion.²²

Social Support and Date of Survey Completion. The PROMIS SF v2.0–Emotional Support 4a scale measured emotional support.²³ Higher scores indicate more social support. Using ≥ 60 as a cut-off, we dichotomized the measure into low and high social support. Last, because the pandemic has waxed and waned, we controlled for the following time periods when surveys were completed: 3/2/20–12/31/20, 1/1/21–11/1/21, 11/2/21–present, or unknown. Measures obtained from baseline and 6-month follow-up are shown in Fig. 1.

Analytic Approach

Change scores were computed for pain severity, pain interference, number of pain sites, generalized anxiety, anhedonia, vital exhaustion, and emotional support by subtracting baseline scores from 6-month scores. Therefore, a change score of

1-point represents an increase from baseline to 6-month follow-up. For all measures, except emotional support, decreasing scores represent improvement. All other covariates were measured at baseline only.

Analyses were performed with SAS v9.4 (SAS Institute, Cary, NC) at an alpha level of 0.05. A repeated measures difference-in-difference analysis, using a 2 (baseline, 6-month) \times 2 (persist, stop) factorial repeated measures ANOVA for each pain, mental health, and social support variable, was conducted to assess whether change in these variables from baseline to 6-month follow-up is different based on whether patients persisted or stopped opioid use (see e-Table 1).

Bivariate Analyses. Chi-square tests estimated the bivariate association of each COVID-19 item and persistent opioid use at 6-month follow-up. Separate, bivariate logistic regression analyses estimated the association between COVID-19 stressors, demographics, change in pain measures, baseline MME and baseline PODS and change in mental health measures and persistent opioid use using odds ratios and 95% confidence intervals.

Multivariate Analyses. Multivariate logistic regression models estimated the association between COVID-19 stressors and odds of persistent opioid use. Subsequent models first adjusted for demographic variables, then change in pain variables, followed by adjustment for baseline MME and baseline PODS and change in mental health and social support measures. A fully adjusted model included all covariates. The associations between COVID-19 items, covariates, and persistent opioid use were expressed as odds ratios with 95% confidence intervals. Collinearity was evaluated by computing the variance inflation factor (VIF) and tolerance, both of which revealed no evidence of collinearity.

Sensitivity Analyses. Persistent opioid use may include a mix of intermittent and daily opioid users. To determine if COVID-19-related stressors were more strongly associated with persistent daily vs. persistent non-daily opioid use, we computed a fully adjusted multivariate, multinomial model. The primary outcome was no opioid use, non-daily opioid use, and daily opioid use at 6-month follow-up.

Baseline:

- demographics
- prescription opioid use
- brief pain inventory
- Prescription opioid difficulties scale
- GAD-7 (generalized anxiety)
- SHAPS (anhedonia)
- vital exhaustion
- emotional support

6-month follow-up:

- COVID-19 questions
- prescription opioid use
- brief pain inventory
- GAD-7 (generalized anxiety)
- SHAPS (anhedonia)
- vital exhaustion
- emotional support

Figure 1 Timing of assessments used in present study.

RESULTS

Sample characteristics at baseline and 6-month follow-up are shown in Table 1. Participants' average age was 53.9 (± 11.4), 67.1% were White race, and 27.4% Black race. The majority were women (70.9%) and nearly half were married (48.8%). The most frequently endorsed COVID-19 item was worry about health (85.7%) and the least often endorsed item was worsening pain due to COVID-19. Among all participants, 65.8% became persistent opioid users. The average baseline pain severity score was 5.9 \pm 1.8, average baseline pain

Table 1 Sample Characteristics (n=477) Who Completed all COVID-19 Stress Questions

	Baseline n (%)	6-month follow-up n (%)
<i>Demographics</i>		
Age (mean, sd)	53.9 (11.4)	
Race		
White	314 (67.1%)	
Black	128 (27.4%)	
Other	26 (5.6%)	
Gender		
Man	139 (29.1%)	
Woman	338 (70.9%)	
Marital status		
Married/live with partner	232 (48.8%)	
Never married	82 (17.3%)	
Widow/Div/Sep	161 (22.9%)	
<i>COVID-19 stress</i>		
Reading/watching/thinking about COVID-19		372 (78.0%)
Worry about health of self/others		409 (85.7%)
Stressful change in social/family contacts		278 (58.3%)
Stressful change in way of life		265 (55.6%)
Worsened mental/emotional health		223 (46.8%)
Worsened pain due to pandemic		125 (26.2%)
<i>Prescription opioid and pain measures</i>		
Persistent opioid use at 6-month follow-up		314 (65.8%)
MME ^a (median, IQR)	15.0 (10.0–33.8)	7.5 (0.0–15.0) ⁱ
PODS ^b (mean, sd)	8.1 (9.7)	6.4 (9.8) ⁱ
Pain severity ^c (mean, sd)	5.9 (1.8)	5.2 (2.2)
Pain interference ^d (mean, sd)	6.7 (2.3)	5.0 (2.8)
# pain sites (mean, sd)	6.0 (3.8)	5.5 (3.8)
<i>Mental health and emotional support</i>		
GAD-7 ^e (mean, sd)	5.7 (5.8)	5.2 (5.7)
Anhedonia ^f (mean, sd)	2.3 (3.2)	2.2 (3.1)
Vital exhaustion ^g (mean, sd)	5.8 (4.3)	5.6 (4.4)
Emotional support ^h (mean, sd)	54.6 (9.1)	53.7 (9.7)

^aMorphine milligram equivalent dose

^bPrescribed Opioids Difficulty Scale. Ranges from 0 to 60 (cut-point 16 or more is high)

^cBPI Pain Severity ranges from 0 to 10; ^dBPI Pain Interference ranges from 0 to 10

^eGeneralized anxiety ranges from 0 to 21 (cut-point of 10 or more is at least moderate)

^fAnhedonia (SHAPS) ranges from 0 to 14 (cut-point of 3 or more is high)

^gVital exhaustion ranges from 0 to 17 (cut-point of 10 or more is high)

^hPROMIS-ES SF4: raw scores range from 0 to 20. Per scoring protocols, raw scores are converted to standardized T-scores. A standardized T-score of 60 or more (1 SD or more above mean) is high

ⁱOnly among participants who were persistent opioid users at 6-month follow-up

interference score was 6.7 \pm 2.3, and mean number of pain sites at baseline was 6.0 \pm 3.8. Baseline MME dose was 27.9 \pm 31.4. The prevalence of specific pain sites is shown in the appendix, e-table 1. The most prevalent site was low back pain.

Difference-in-difference analysis for all continuous measures assessed at baseline and 6-month follow-up by persistent opioid use status is shown in supplementary appendix, e-table 2. Pain severity ($p=0.0009$) and pain interference ($p=0.0085$) decreased significantly less among persistent opioid users compared to those who stopped opioid use by 6-month follow-up. Generalized anxiety severity decreased significantly ($p=0.0027$) among persistent opioid users but remained the same among those who stopped. Change in anhedonia scores ($p=0.006$) and change in vital exhaustion ($p=0.0081$) significantly differed by persistent opioid use status. Those who stopped opioids had a significant increase in anhedonia while those who persisted had no change. Conversely, those who stopped opioids had no change in vital exhaustion but those with persistent opioid use had a significant decrease. Change in emotional support differed between those who stopped opioid use vs. those who had persistent opioid use ($p=0.0240$). Emotional support significantly decreased among those who stopped opioid use but there was no change among persistent opioid users. There was no significant difference in number of pain sites between baseline and follow-up among patients who stopped vs. remained on opioids.

As shown in Figure 2, patients who endorsed COVID-19 related “stressful changes in social/family contacts” were significantly ($p=0.019$) more likely to be persistent opioid users compared to those who did not endorse this item (70.1% vs. 59.8%). Those who reported “worsened pain due to pandemic” were significantly ($p=0.005$) more likely to be persistent opioid users compared to those who did not report worsened pain (76.0% vs. 62.2%). Other COVID-19-related stressors were not significantly associated with persistent opioid use.

The bivariate associations between each COVID-19 stressor and odds of persistent opioid use are shown in Table 2. Participants who did vs. did not report experiencing “stressful change in social/family contacts” were 58% more likely to be persistent opioid users (OR=1.58; 95%CI: 1.08–2.32). Participants who did vs. did not report “worsened pain due to pandemic” were 92% more likely to be persistent opioid users (OR=1.92; 95%CI: 1.21–3.06). There were no significant bivariate associations between other COVID-19 stressors and persistent opioid use.

Changes in pain severity and pain interference were significantly associated with persistent opioid use (OR=1.21; 95%CI: 1.08–1.36 and OR=1.12; 95%CI: 1.03–1.22, respectively). Changes in generalized anxiety, anhedonia, and vital exhaustion and emotional support were significantly associated with small decreases in odds of persistent opioid use. Change in emotional support was associated with a minimal increase in odds of persistent opioid use.

Multivariate models estimating the association between COVID-19 stressors at 6-month follow-up and persistent

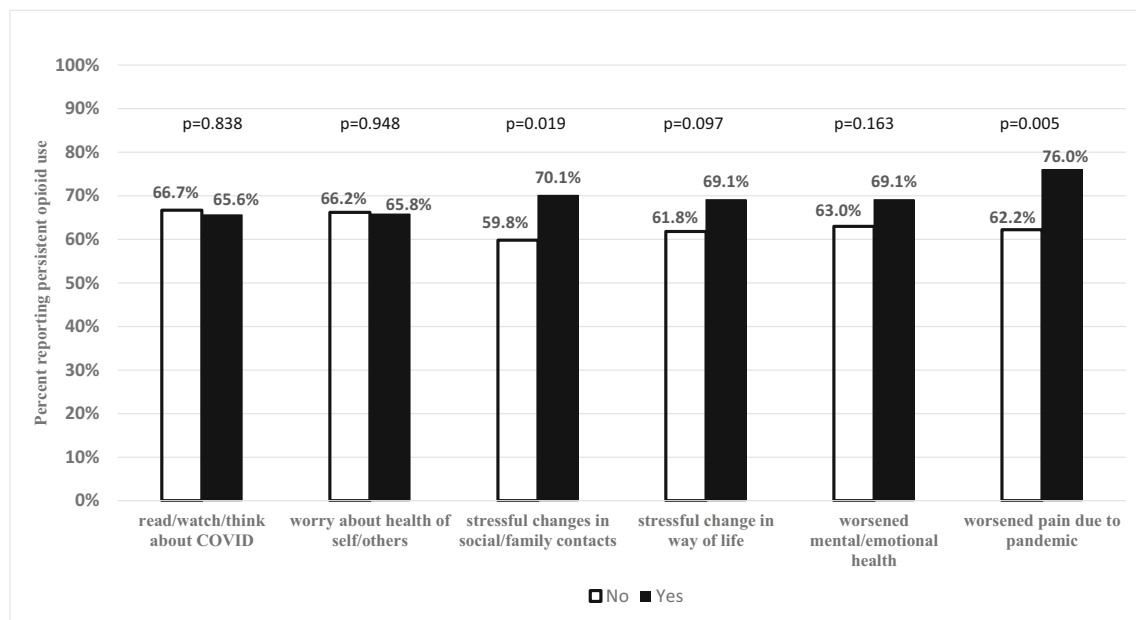


Figure 2 Persistent opioid use at 6-month follow-up by COVID-19-related stressors.

Table 2 Unadjusted Association Between Individual COVID-19 Stressors, Covariates, and Persistent Opioid Use

	OR (95% CI)
Reading/watching/thinking about COVID-19	0.95 (0.60–1.51)
Worry about health of self/others	0.98 (0.57–1.69)
Stressful change in social/family contacts	1.58 (1.08–2.32)
Stressful change in way of life	1.38 (0.94–2.02)
Worsened mental/emotional health	1.31 (0.90–1.92)
Worsened pain due to pandemic	1.92 (1.21–3.06)
Age (continuous)	0.99 (0.97–1.00) ⁱ
Race	
White	ref
Black	1.03 (0.66–1.59)
Other	0.59 (0.74–1.71)
Male gender	1.12 (0.74–1.71)
Marital status	
Married	ref
Never married	1.25 (0.73–2.14)
Widow/Div/Sep	1.03 (0.67–1.56)
Change in Pain severity ^a	1.21 (1.08–1.36)
Change in Pain interference ^b	1.12 (1.03–1.22)
Change in # pain sites	0.96 (0.90–1.03)
Baseline MME ^c	1.00 (0.99–1.00) ⁱ
Baseline PODS ^d	1.01 (0.99–1.03)
Change in GAD-7 ^e	0.94 (0.91–0.98)
Change in anhedonia ^f	0.91 (0.86–0.98)
Change in vital exhaustion ^g	0.93 (0.88–0.98)
Change in emotional support ^h	1.03 (1.00–1.05)

^aBPI Pain Severity ranges from 0 to 10; ^bBPI Pain Interference ranges from 0 to 10

^cMorphine milligram equivalent dose

^dPrescribed Opioids Difficulty Scale. Ranges from 0 to 60 (cut-point 16 or more is high)

^eGeneralized anxiety ranges from 0 to 21 (cut-point of 10 or more is at least moderate)

^fAnhedonia (SHAPS) ranges from 0 to 14 (cut-point of 3 or more is high)

^gVital exhaustion ranges from 0 to 17 (cut-point of 10 or more is high)

^hPROMIS-ES SF4: raw scores range from 0 to 20. Per scoring protocols, raw scores are converted to standardized T-scores. A standardized T-score of 60 or more (1 SD or more above mean) is high

ⁱNot statistically significant

opioid use at 6-month follow-up before and after adjusting for covariates are reported in Table 3. After simultaneous adjustment for all COVID-19 stressors (model 1), only “worsened pain due to pandemic” remained significantly associated with persistent opioid use (OR=1.83; 95%CI: 1.09–3.04). This association remained largely unchanged after adjusting for baseline demographics (model 2). The association between “worsened pain due to pandemic” and persistent opioid use at 6-month follow-up was attenuated and no longer statistically significant after adjusting for change in pain severity, pain interference, and number of pain sites in model 3. As shown in model 4, after adjusting for baseline MME, baseline PODS, and change in generalized anxiety, anhedonia, vital exhaustion, and emotional support, the association was of greater magnitude and statistically significant (OR=3.52; 95%CI: 1.72–7.20). In the fully adjusted model (model 5), “worsened pain due to pandemic” remained significantly associated with persistent opioid use (OR=2.88; 95%CI: 1.33–6.22). In the full model, a 1-point larger increase in change in pain interference was associated with greater odds of persistent opioid use at 6-month follow-up (OR=1.20; 95%CI: 1.04–1.38). Conversely, a 1-point larger increase in change in vital exhaustion was associated with lower odds of persistent use (OR=0.90; 95%CI: 0.82–0.99). Other covariates were not significantly associated with persistent opioid use.

Multinomial model results are shown in e-table 3. “Worsened pain due to pandemic” was significantly associated with persistent daily opioid use at 6-month follow-up (OR=3.82; 95%CI: 1.61–9.08) but was not significantly associated with non-daily opioid use at 6-month follow-up (OR=2.09; 95%CI: 0.86–5.10).

Table 3 Association Between Type of COVID-19 Stress and Worsening Pain, Mental Health, and Persistent Opioid Use (Outcome Is Opioid Use at 6-Month Follow-up (Yes/No))

	Model 1 COVID-19 stress	Model 2 ^d Model + 1 demographics	Model 3 Model 1+ pain variables	Model 4 Model 1+ mental health/social support	Model 5 Full model ⁱ
Reading/watching/thinking about COVID-19	0.85 (0.51–1.40)	0.86 (0.51–1.45)	0.89 (0.53–1.48)	1.39 (0.75–2.57)	1.29 (0.66–2.53)
Worry about health of self/others	0.82 (0.44–1.52)	0.88 (0.46–1.67)	0.86 (0.46–1.61)	0.62 (0.29–1.34)	0.77 (0.34–1.75)
Stressful change in social/family contacts	1.48 (0.94–2.31)	1.71 (1.07–2.73)	1.44 (0.91–2.28)	1.67 (0.95–2.95)	1.52 (0.82–2.82)
Stressful change in way of life	1.13 (0.72–1.79)	1.14 (0.71–1.83)	1.04 (0.65–1.66)	1.35 (0.75–2.44)	1.14 (0.60–2.15)
Worsened mental/emotional health	0.90 (0.55–1.46)	0.81 (0.49–1.34)	0.88 (0.53–1.45)	0.79 (0.42–1.50)	0.77 (0.39–1.53)
Worsened pain due to pandemic	1.83 (1.09–3.04)	2.04 (1.19–3.50)	1.63 (0.96–2.76)	3.52 (1.72–7.20)	2.88 (1.33–6.22)
Age (continuous)		0.99 (0.97–1.00) ⁱ			0.98 (0.95–1.00) ⁱ
Race					
White		ref			ref
Black		0.91 (0.57–1.47)			1.35 (0.71–2.58)
Other		0.48 (0.20–1.14)			0.61 (0.19–1.88)
Male gender		1.55 (0.97–2.48)			1.64 (0.89–3.00)
Marital status					
Married		ref			ref
Never married		1.14 (0.62–2.08)			1.55 (0.69–3.49)
Widow/Div/Sep		1.12 (0.71–1.78)			0.99 (0.54–1.81)
Change in Pain severity ^a			1.17 (1.02–1.35)		1.16 (0.96–1.40)
Change in Pain interference ^b			1.04 (0.94–1.15)		1.20 (1.04–1.38)
Change in # pain sites			0.94 (0.88–1.01)		0.92 (0.83–1.02)
Baseline MME ^c				0.99 (0.99–1.00) ⁱ	1.00 (0.99–1.01)
Baseline PODS ^d				1.00 (0.97–1.03)	1.00 (0.97–1.04)
Change in GAD ^e				0.98 (0.92–1.04)	0.97 (0.91–1.04)
Change in anhedonia ^f				0.94 (0.87–1.02)	0.93 (0.85–1.01)
Change in vital exhaustion ^g				0.92 (0.85–1.00) ⁱ	0.90 (0.82–0.99)
Change in emotional support ^h				1.03 (1.00–1.07) ⁱ	1.03 (1.00–1.07) ⁱ

^aBPI Pain Severity ranges from 0 to 10; ^bBPI Pain Interference ranges from 0 to 10

^cMorphine milligram equivalent dose

^dPrescribed Opioids Difficulty Scale. Ranges from 0 to 60 (cut-point 16 or more is high)

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^hPROMIS-ES SF4: raw scores range from 0 to 20. Per scoring protocols, raw scores are converted to standardized T-scores. A standardized T-score of 60 or more (1 SD or more above mean) is high

ⁱNot statistically significant

^jAdjusted for varying intensity of pandemic in the USA: 3/2/20–12/31/20, 1/1/21–11/1/21, 11/2/21–present, unknown

DISCUSSION

Among a cohort of persons with non-cancer pain and a new period of 30–90-day prescription opioid use at baseline, we observed that after multivariate adjustment, patients who perceived the COVID-19 pandemic worsened their pain were nearly 3 times more likely to remain on opioids at 6-month follow-up. Change in pain interference and vital exhaustion remained significant in multivariate models. Pain interference

declined less among persistent opioid users compared to opioid quitters which is consistent with our observation that for each unit increase in change in pain interference there was 20% greater odds of persistent opioid use. Vital exhaustion scores did not change in those who stopped opioids and decreased in persistent users which is consistent with evidence that each unit increase in change in vital exhaustion was associated with 10% lower odds of persistent opioid use.

There was some evidence that perceiving the pandemic worsened pain had a greater association with daily vs. non-daily persistent opioid use at 6-month follow-up. It is possible that those who attribute greater pain to the pandemic were more likely to be daily opioid users. However, the multinomial model led to smaller cell sizes and large confidence intervals which prohibit strong conclusions regarding these associations.

This study advances current understanding of the numerous COVID-19 pandemic-related stressors thought to be associated with prescription opioid use. In bivariate models, only stressful change in social/family contacts was significantly associated with persistent opioid use. However, this association did not remain after accounting for the perception that the pandemic worsened pain and other covariates. Clinicians screening for LTOT risk factors related to the COVID-19 pandemic may consider focusing on asking patients if they attribute increasing pain to the pandemic.

There are several potential explanations for the strong association between perceiving pain was made worse by the pandemic and persistent opioid use. Barriers to non-pharmacological pain treatments have occurred during the pandemic^{7,8} and patients may attribute worsening pain due to COVID-19 if access to pain management was restricted. A byproduct of the pandemic is chronic stress which is a risk factor for chronic pain and long-term opioid use.^{24,25} Another explanation for our results could be that those who reported pain was worsened by the pandemic also perceived such pain as an injustice (e.g., belief that the pandemic was mismanaged). Persons who perceive pain is unjust are less likely to accept pain in their lives, exhibit more expressive pain, and are more likely to be prescribed opioids.^{26,27} Last, patients may attribute worsening pain due to the pandemic because they became infected with COVID-19; in severe cases, this can lead to posttraumatic stress disorder and depression,²⁸ both conditions associated with worse pain outcomes and greater risk for LTOT.

Our results are largely consistent with an exploratory study of change in pain experiences before, during, and after the first COVID-19 wave²⁹ which revealed chronic pain was linked to cognitive overload and impaired ability to cope with pandemic related stress.²⁹ However, the same patients had little change in pain severity and experienced improvement in pain interference.²⁹ A longitudinal study of 1500 persons with chronic pain revealed no significant decline in pain severity and pain interference during the first year of the pandemic.⁶ The limited variation in pain severity and pain interference is consistent with our results.

Although changes in pain interference and vital exhaustion were significantly associated with persistent opioid use, examination of mean scores for both measures reveals very small differences between those who stopped vs. continued opioid use at follow-up. Thus, it is not clear that clinically meaningful change occurred or that clinically meaningful differences exist between those who quit vs. those who persisted.

Strengths and Limitations

It is possible that non-response biased our study. However, the current 6-month retention rate is about 82% which reduces concerns about non-response bias. The Pathways Study is primarily designed to determine if long-term prescription opioid use leads to incident depression. We did not include depression in the current study because it is measured using a diagnostic interview at baseline and 12-month follow-up and thus with only 6-month follow-up data we would not be able to model change in depression.

The cohort was recruited from two large metropolitan areas in the middle of the USA and may not generalize to other locations. Results could differ in regions, such as the eastern U.S. where excess mortality was greatest during the early phase of the pandemic.³⁰ However, the cohort's racial diversity improves generalizability. Self-reported opioid use could be biased; however, research on the validity of self-reported medications that could be stigmatizing, such as antidepressants and benzodiazepines, indicates excellent agreement between self-report and pharmacy records and medical claims.^{31,32} We are unable to draw conclusions about the temporal direction of COVID-19 stress and persistent opioid use because both were measured at the 6-month follow-up survey, and our change scores in this observational cohort study do not estimate causal effects.³³

Conclusions

Patients who attributed worsening pain to the COVID-19 pandemic were more likely to remain prescription opioid users over a 6-month observation period and may be more likely to be persistent daily as compared to non-daily opioid users. Worsening pain interference, but not pain severity, was a risk factor for persistent opioid use. Further quantitative and qualitative research is needed to identify patient experiences with the COVID-19 pandemic that explain these associations. Clinicians who prescribe opioids may consider discussing pain in the context of the pandemic to identify patients at risk for long-term opioid use. Further research is warranted to determine if pandemic-related stress mediates or moderates the relationships between mental illness and risk for opioid use disorder and between long-term prescription opioid use and worsening mood and depression.

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REFERENCES

- Hruschak V, Flowers KM, Azizoddin DR, Jamison RN, Edwards RR, Schreiber KL. Cross-sectional study of psychosocial and pain-related variables among patients with chronic pain during a time of social distancing imposed by the coronavirus disease 2019 pandemic. *Pain* 2021;162(2):619-629.
- Nieto R, Pardo R, Sora B, Feliu-Soler A, Luciano JV. Impact of COVID-19 lockdown measures on Spanish people with chronic pain: an online study survey. *J Clin Med*. 2020;9(11).
- Mun CJ, Campbell CM, McGill LS, Aaron RV. The early impact of COVID-19 on chronic pain: a cross-sectional investigation of a large online sample of individuals with chronic pain in the United States, April to May, 2020. *Pain Med*. 2021;22(2):470-480.
- Scherrer JF, Miller-Matero LR, Salas J, et al. Characteristics of patients with non-cancer pain and perceived severity of COVID-19 related stress. *Mo Med*. 2022;119:229-236.
- Charron E, Okifuji A, Bryan MA, et al. Pain severity and interference and substance use among community pharmacy patients prescribed opioids: a secondary analysis of the PHARMSCREEN Study. *J Pain*. 2022.
- Mun CJ, Campbell CM, McGill LS, Wegener ST, Aaron RV. Trajectories and individual differences in pain, emotional distress, and prescription opioid misuse during the COVID-19 pandemic: a one-year longitudinal study. *J Pain*. 2022.
- Licciardone JC. Demographic characteristics associated with utilization of noninvasive treatments for chronic low back pain and related clinical outcomes during the COVID-19 pandemic in the United States. *J Am Board Fam Med*. 2021;34(Suppl):S77-S84.
- Manchikanti L, Singh VM, Staats PS, et al. Fourth wave of opioid (illicit drug) overdose deaths and diminishing access to prescription opioids and interventional techniques: cause and effect. *Pain Physician*. 2022;25(2):97-124.
- Cisternas AF, Ramachandran R, Yaksh TL, Nahama A. Unintended consequences of COVID-19 safety measures on patients with chronic knee pain forced to defer joint replacement surgery. *Pain Rep*. 2020;5(6):e855.
- Farrow L, Gardner WT, Tang CC, Low R, Forget P, Ashcroft GP. Impact of COVID-19 on opioid use in those awaiting hip and knee arthroplasty: a retrospective cohort study. *BMJ Qual Saf*. 2021.
- Pesce A, Sudyhanata R, Ritz D, Thomas R, Ackerman G, Bollman K. Effects of a pandemic and isolation on alcohol and psychoactive medication use in a population of rehabilitation and pain patients. *Ann Clin Lab Sci*. 2021;51(5):694-697.
- Licciardone JC. Impact of COVID-19 on utilization of nonpharmacological and pharmacological treatments for chronic low back pain and clinical outcomes. *J Osteopath Med*. 2021;121(7):625-633.
- Rikin S, Perez HR, Zhang C, et al. Changes in outpatient opioid prescribing during the COVID-19 pandemic: an interrupted time series analysis. *J Prim Care Community Health*. 2022;13:21501319221076926.
- Lee B, Yang KC, Kaminski P, et al. Substitution of nonpharmacologic therapy with opioid prescribing for pain during the COVID-19 pandemic. *JAMA network open*. 2021;4(12):e2138453.
- Salas J, Scherrer JF, Tuerk P, et al. Large posttraumatic stress disorder improvement and antidepressant medication adherence. *J Affect Disord*. 2020;260:119-123.
- Lang AJ. Complementary and Integrative Research (CAIR) Lab. https://www.phenxtoolkit.org/toolkit_content/PDF/CAIR_PIQ.pdf. 2008.
- Cleeland CS. The Brief Pain Inventory User Guide. In. Houston, TX: University of Texas M.D. Anderson Cancer Center; 1991.
- Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain* 2004;20(5):309-318.
- Banta-Green CJ, Von Korff M, Sullivan MD, Merrill JO, Doyle SR, Saunders K. The prescribed opioids difficulties scale: a patient-centered assessment of problems and concerns. *Clin J Pain*. 2010;26(6):489-497.
- Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166:1092-1097.
- Nakonezny PA, Carmody TJ, Morris DW, Kurian BT, Trivedi MH. Psychometric evaluation of the Snaith-Hamilton pleasure scale in adult outpatients with major depressive disorder. *Int Clin Psychopharmacol* 2010;25:328-333.
- Meesters C, Appels A. An interview to measure vital exhaustion II. reliability and validity of the interview and correlations of vital exhaustion with personality characteristics. *Psychol Health* 1996;11:573-581.
- Sinita E, Coghill D. The use of stimulant medications for non-core aspects of ADHD and in other disorders. *Neuropharmacology* 2014;87:161-172.
- Sullivan MD. Depression effects on long-term prescription opioid use, abuse, and addiction. *Clin J Pain* 2018;34(9):878-884.
- Lindell M, Grimby-Ekman A. Stress, non-restorative sleep, and physical inactivity as risk factors for chronic pain in young adults: A cohort study. *PLoS One* 2022;17(1):e0262601.
- Karos K, McParland JL, Bunzli S, et al. The social threats of COVID-19 for people with chronic pain. *Pain* 2020;161(10):2229-2235.
- Carriere JS, Martel MO, Kao MC, Sullivan MJ, Darnall BD. Pain behavior mediates the relationship between perceived injustice and opioid prescription for chronic pain: a Collaborative Health Outcomes Information Registry study. *J Pain Res*. 2017;10:557-566.
- Clauw DJ, Hauser W, Cohen SP, Fitzcharles MA. Considering the potential for an increase in chronic pain after the COVID-19 pandemic. *Pain*. 2020;161(8):1694-1697.
- Page MG, Dassieu L, Develay E, et al. Stress and pain before, during and after the first wave of the COVID-19 pandemic: an exploratory longitudinal mixed methods study. *Front Pain Res (Lausanne)*. 2021;2:725893.
- Polyakova M, Kocks G, Udalova V, Finkelstein A. Initial economic damage from the COVID-19 pandemic in the United States is more widespread across ages and geographies than initial mortality impacts. *Proc Natl Acad Sci U S A*. 2020;117(45):27934-27939.
- Boudreau DM, Doescher MP, Saver BG, Jackson JE, Fishman PA. Reliability of Group Health Cooperative automated pharmacy data by drug benefit status. *Pharmacoepidemiology and Drug Safety*. 2005;14:877-884.
- Pit SW, Byles JE, Cockburn J. Accuracy of telephone self-report of drug use in older people and agreement with pharmaceutical claims data. *Drugs and Aging*. 2008;26(1):71-80.
- Tennant PWG, Arnold KF, Ellison GTH, Gilthorpe MS. Analyses of 'change scores' do not estimate causal effects in observational data. *Int J Epidemiol*. 2021.

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