ORIGINAL RESEARCH

Caffeine as an opioid analgesic adjuvant in fibromyalgia

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Background: Caffeine's properties as an analgesic adjuvant with nonsteroidal anti-inflammatory drugs/acetaminophen are well documented. However, little clinical research has explored caffeine's effects on opioid analgesia. This study assessed the effects of caffeine consumption on pain and other symptoms in opioid-using and nonusing chronic pain patients meeting the survey criteria for fibromyalgia.

Materials and methods: Patients presenting to a university-based pain clinic completed validated self-report questionnaires assessing symptoms. Patients (N=962) meeting the fibromyalgia survey criteria were stratified by opioid use and further split into groups based on caffeine amount consumed per day (no caffeine, or low, moderate, high caffeine). Analysis of covariance with Dunnett's post hoc testing compared pain and symptom severity between the no caffeine group and the caffeine consuming groups.

Results: In opioid users, caffeine consumption had modest but significant effects on pain, catastrophizing, and physical function. Lower levels of pain interference were associated with low and moderate caffeine use compared to no caffeine intake. Lower pain catastrophizing and higher physical function were observed in all caffeine dose groups, relative to the no caffeine group. Lower pain severity and depression were observed only in the moderate caffeine group. In opioid nonusers, low caffeine intake was associated with higher physical function; however, no other significant effects were observed.

Conclusion: Caffeine consumption was associated with decreased pain and symptom severity in opioid users, but not in opioid nonusers, indicating caffeine may act as an opioid adjuvant in fibromyalgia-like chronic pain patients. These data suggest that caffeine consumption concomitant with opioid analgesics could provide therapeutic benefits not seen with opioids or caffeine alone.

Keywords: caffeine, fibromyalgia, opioid analgesics, pain, analgesic adjuvant, chronic pain

Introduction

Caffeine intake is ubiquitous throughout the world and it is considered the most widely consumed psychoactive drug in the USA,[1] with 85% of American adults reporting consuming at least one caffeinated beverage per day.[2] Caffeine is a central nervous system (CNS) stimulant with lipophilic properties allowing it to easily cross the blood–brain barrier.[3] Consumption of caffeine is associated with many well-known psychologic and physiologic effects such as increased vigilance and attention,[4] elevated mood,[5] and cardiovascular effects.[6] Caffeine also acts as an analgesic adjuvant in the treatment of acute pain, with a relative potency of 1.1–1.4 for analgesics (aspirin, ibuprofen, acetaminophen) containing caffeine compared to the same analgesics administered alone.[7–9] Whereas the role of caffeine as an analgesic adjuvant is well documented,

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the direct and indirect intrinsic effects of caffeine on pain are complex and remain poorly understood, particularly in chronic pain populations.

Caffeine's mechanism of action occurs primarily through nonselective antagonism of adenosine receptors. Adenosine is known to be involved in pain processing and modulation, exhibiting both pronociceptive and antinociceptive effects[10] depending on the binding site, receptor subtype activated, duration of administration, and dose.[11–14] Adenosine A_1 receptors are concentrated in the dorsal horn of the spinal cord and their activation causes inhibition of adenylyl cyclase, the enzyme responsible for catalyzing the cyclization of adenosine triphosphate to cyclic adenosine monophosphate.[12] It is thought that increased K^+ conductance and neuronal hyperpolarization (presynaptic inhibition) of nociceptive dorsal horn neurons following activation of A_1 receptors is the underlying mechanism of adenosine's antinociceptive action in the CNS.[12,15] In the periphery, A_1 receptors are less densely distributed, but are located on the sensory afferent fibers, mainly C-fibers, and their activation exhibits antinociceptive effects as well.[16,17]

Preclinical studies have confirmed adenosine's antinociceptive properties and caffeine's antagonistic effect on those properties.[18] For instance, Goldman et al showed that adenosine was released during acupuncture in a mouse model of postsurgical pain, and that chronic pretreatment with caffeine attenuated the antinociceptive effect of acupuncture in a dose-dependent manner.[11] Sawynok and Reid demonstrated that caffeine binding to A_1 receptor inhibited the antinociceptive action of acetaminophen and increased or decreased pain behavior in the mouse formalin test depending on the dose administered.[19] These studies suggest that antagonism of adenosine A_1 receptors by caffeine can, depending on the dose, enhance antinociception or, conversely, interfere with analgesic treatments and/or increase pain.

Initially, peripheral adenosine A_3 receptors were thought to contribute to the development of inflammatory pain through the release of serotonin and histamine from the mast cells.[20,21] However, recent findings suggest A_3 receptor activation to be antinociceptive.[22–25] Furthermore, activation of peripheral adenosine A_{2A} and A_{2B} receptors stimulates adenylyl cyclase and increases cyclic adenosine monophosphate levels in sensory afferent nerve terminals, resulting in increased nociception.[10,26] Antagonism of peripheral A_2 adenosine receptors is one proposed mechanism by which caffeine acts as an adjuvant to modulate the effect of other nonopioid analgesics.[10]

Fibromyalgia (FM) is a chronic pain condition affecting roughly 2%–8% of the adult population.[27] It is characterized by widespread pain, increased sensitivity to external stimuli, fatigue, and memory problems. Research related to this condition has grown significantly over the previous two decades, although the effects of caffeine in this population have not been addressed. In this study, we examined the effects of caffeine on pain and other symptoms in the presence and absence of concomitant opioid analgesics in chronic pain patients meeting the American College of Rheumatology 2011 Survey Criteria for FM. We hypothesized that caffeine would show an intrinsic analgesic effect as evidenced by reduced self-reported pain severity in caffeine consumers, and an analgesic adjuvant effect in patients taking opioids.

Materials and methods

New patients at a university-based tertiary pain clinic (Back and Pain Center, Department of Anesthesiology, University of Michigan Health System) presenting between November 2010 and February 2014 were evaluated. As part of an ongoing research initiative, the new patients completed an initial assessment consisting of a validated survey battery regarding the symptoms and routine sociodemographic and medication/substance use information. These data were collected primarily for clinical care and secondly for clinical research. Approval to collect these data was granted by the University of Michigan Medical School Institutional Review Board, and due to these data being used primarily in the context of clinical care, a waiver of informed consent was granted. In lieu of consent, patients were given written documentation explaining potential data use in research and given the opportunity to opt out of participation. Data were entered into the Assessment of Pain Outcomes Longitudinal electronic data capture system.[28–32] Only those patients meeting the 2011 FM survey criteria[33] were included in the present analysis. The FM survey criteria includes the Widespread Pain Index, where patients indicate the locations of their pain on 19 body areas, and additional questions regarding the severity of their FM symptoms. Scoring criteria for FM includes: widespreadness ≥7 and symptom severity ≥5 or widespreadness =3–6 and symptom severity ≥9.[33]

Consumption of caffeinated beverages was assessed using both a dichotomous item where patients indicated "yes or no" to daily consumption of caffeinated beverages, as well as a continuous variable where patients were asked to report the average number of cups consumed each day. Use of opioid analgesics of any type was assessed as part of a concomitant medications questionnaire. Smoking and alcohol drinking

statuses were also collected as a dichotomous yes/no question; those responding in the positive were asked to report the number of cigarettes and alcoholic drinks consumed per day. Lastly, information on use of pain medications known to be potentiated by caffeine, including aspirin, ibuprofen, and/or acetaminophen, was collected as a dichotomous yes/no question.

Patients were stratified into "opioid user" and "opioid nonuser" subgroups. To assess for dose-dependent caffeine effects within opioid user stratum and nonuser stratum, patients were further split into four groups of caffeine consumption (no caffeine, or low, moderate, or high caffeine intake) following a tertile split of number of caffeinated beverages consumed per day in those who reported caffeine consumption.

Self-report measures

Brief pain inventory

The brief pain inventory (BPI) includes two subscales, pain severity and pain interference. The pain severity scale is calculated as the mean of four items which assess worst, least, average, and current pain on a 0–10 scale. Pain interference is calculated as the mean of seven items which patients rate on a 0–10 scale, and is used to assess how much their pain interferes with areas of their life (general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life) over the previous week. Higher scores are indicative of increased pain severity and interference.[34]

PROMIS physical function

The 10-item self-reported physical function measures capability, including functioning of upper and lower extremities and central regions, as well as instrumental activities in daily living. The items are rated 0–4 and summed to generate a raw score. Raw scores are converted to standardized t-scores, with a mean of 50 and a standard deviation of 10. Higher scores indicate better physical function.[35]

Hospital anxiety and depression scale

This scale assesses anxiety and depression in nonpsychiatric populations. The survey has two seven-item subscales, with scores ranging from 0 to 21, with higher scores indicative of greater anxiety and depression. A score ≥11 on either subscale is considered a "case" of anxiety or depression.[36]

Coping strategies questionnaire – catastrophizing subscale

This assesses patients' catastrophizing caused by their symptoms. It is a six-item subscale from the original 27-item coping strategies questionnaire, which was used to evaluate negative thinking or catastrophizing as a reaction to pain. Scores range from 0 to 36 and higher scores are indicative of greater pain catastrophizing.[37]

Positive and negative affect schedule (PANAS)

This was used to assess mood and affect (positive and negative).[38] The PANAS includes two 10-item subscales with 5-point Likert scales, with the subscale scores ranging from 10 to 50. The 10-item subscales are summed to provide the PANAS negative and positive affect scores, where a higher score on the negative affect subscale is indicative of higher negative affect or the extent to which an individual feels aversive mood states and general distress and a higher score on the positive affect subscale is indicative of higher positive affect or the extent to which an individual feels enthusiastic, active, and alert.

Statistical analysis

Normality of all data was assessed by histogram and q–q plots. Missing data were handled as per each measure's instructions. Univariate analyses were conducted to determine significant covariates on caffeine consumption within each opioid stratum; Chi-square tests (χ^2) and independent sample t-tests were used for categorical and continuous variables, respectively. Unadjusted differences in independent measures were assessed between opioid strata using independent samples t-tests. Levine's test was used to assess for equality of variances in t-tests. Analysis of covariance was used to assess significant differences in independent measures between caffeine quartiles within the opioid strata. Dunnett's post hoc test was used to assess significant pairwise differences in estimated marginal means between the caffeine consuming groups (low, moderate, high intake) and a no caffeine control group. Categorical variables are reported as frequency (%), whereas unadjusted and adjusted continuous measures are reported as mean ± standard deviation (SD) and mean ± standard error, respectively. All analyses were two-tailed with significance set at $p<0.05$. Statistical analysis was conducted using JMP 10 (SAS Institute Inc., Cary, NC, USA).

Results

One thousand one hundred and seventy-seven FM patients completed the initial survey battery; 674 (57%) of the patients were on current opioid therapy and 503 (43%) were not on opioid therapy. Also, 215 patients were excluded due to missing caffeine data. Nine hundred and sixty-two FM patients (67% female) with a mean age of 47.6±13.5 years were included in the study. Of them, 568 (59%) patients were on

daily or as needed opioid therapy (66% female) and had a mean age 47.6±12.9 years and 394 (41%) were not on opioid therapy (68% female) and had a mean age 47.7±14.2 years (Tables 1 and 2). The proportion of opioid users (81%) and nonusers (80%) that reported consuming caffeine did not differ significantly between opioid user and nonuser strata (p=0.572). Racial distribution differed significantly between opioid strata (χ^2=15.8, p=0.015), with the nonuser stratum having a greater proportion of non-White patients. Gender proportions were similar between opioid strata and between caffeine intake levels within each stratum. All other demographic characteristics were similar between opioid strata.

The mean caffeine amount consumed per day did not differ between opioid users and nonusers (2.2 vs 2.0 cups/day, p=0.236). The range of caffeine intake within each tertile was the same in both opioid strata: low (≤1 cups/day), moderate (1.5–2.5 cups/day), and high (≥3–12 cups/day). Mean caffeine consumed within each tertile was also similar between opioid users and nonusers, respectively: low (1.1 vs 1.0 cups/day), moderate (2.1 vs 2.1 cups/day), and high (4.5 vs 4.6 cups/day), all p>0.727. In the opioid user stratum, 158 (28%) patients reported ibuprofen use, 119 (21%) reported

using acetaminophen, and 71 (13%) reported using aspirin. Patients in the nonuser stratum reported similar proportions, with 130 (33%) patients reporting ibuprofen use, 101 (26%) reporting acetaminophen use, and 37 (9%) reporting aspirin use. The proportion of patients taking aspirin, ibuprofen, and/or acetaminophen (49% and 51% for users and nonusers, respectively), which act as analgesic adjuvants, did not differ between caffeine intake levels within opioid users (p=0.446) or nonusers (p=0.615). Compared to nonusers, opioid users had significantly increased pain interference (degrees of freedom [DF]=936, t=3.87, p=0.001), catastrophizing (t=2.24, p=0.025), depression (DF=961, t=2.12, p=0.034), and negative affect (DF=868, t=2.06, p=0.004) and decreased physical function (DF=883, t=5.42, p=0.001) and positive affect (t=2.78, p=0.005).

Effect of caffeine intake on patient-reported outcomes in opioid users

Univariate analysis indicated that caffeine intake in the opioid user stratum differed significantly by gender (χ^2=20.00, p<0.001), with a higher proportion of males in the high intake group, and by current smoking status (χ^2=47.03, p<0.001;

Table 1 Opioid user stratum sociodemographic characteristics and substance use split by caffeine intake

Variable	Total	No caffeine	Low	Moderate	High	χ^2	p-value
n (% strata)	568	107 (19)	141 (25)	144 (25)	176 (31)		
Gender (female)	374 (66)	72 (67)	112 (79)	92 (64)	98 (56)	20.00	**<0.001**
Race (Caucasian/White)	497 (89)	86 (82)	120 (85)	134 (93)	157 (92)	27.32	0.073
Ethnicity (non-Hispanic/Latino)	85 (88)	10 (77)	25 (93)	28 (90)	22 (85)	2.41	0.491
Income							
<$22,500	212 (41)	46 (50)	43 (33)	51 (40)	72 (45)	10.88	0.284
$22,051–$45,000	124 (24)	16 (17)	37 (28)	36 (28)	35 (22)		
$45,001–$100,000	135 (26)	24 (26)	39 (30)	29 (23)	43 (27)		
>$100,000	44 (9)	7 (8)	13 (10)	13 (10)	11 (7)		
Education							
Graduate school	54 (10)	5 (5)	17 (12)	12 (9)	20 (12)	24.39	0.059
College graduate	110 (20)	17 (17)	32 (23)	34 (24)	27 (16)		
College not graduate	196 (35)	35 (34)	48 (34)	57 (40)	56 (33)		
Vocational school	22 (4)	6 (6)	8 (6)	1 (1)	7 (4)		
High school graduate	125 (22)	26 (25)	30 (21)	25 (18)	44 (26)		
High school not graduate	50 (9)	14 (14)	6 (4)	12 (9)	18 (11)		
Living situation							
Live alone	76 (14)	17 (16)	19 (14)	26 (18)	14 (8)	27.65	0.068
Live with spouse	289 (52)	46 (44)	71 (51)	71 (50)	101 (58)		
Live with young children	72 (13)	10 (10)	17 (12)	16 (11)	29 (17)		
Live with adult children	30 (5)	6 (6)	8 (6)	10 (7)	6 (3)		
Live with parents	38 (7)	15 (14)	7 (5)	8 (6)	8 (5)		
Live with significant other	33 (6)	6 (6)	9 (7)	9 (6)	9 (5)		
Live with roommate	22 (4)	4 (4)	7 (5)	3 (2)	8 (5)		
Current smoker	193 (35)	25 (25)	30 (22)	44 (32)	94 (56)	47.03	**<0.001**
Alcohol use	67 (15)	9 (10)	18 (17)	21 (18)	19 (14)	3.09	0.378
Acute analgesic use[a]	270 (48)	47 (44)	68 (55)	76 (64)	79 (52)	2.67	0.446

Notes: The currency is US$. Data presented as frequency (%); Chi-square (χ^2) test of proportions. Bold p-value indicates significance, p<0.05. [a]Aspirin, ibuprofen and/or acetaminophen.

Table 2 Opioid nonuser stratum sociodemographic characteristics and substance use split by caffeine intake

Variable	Total	No caffeine	Low	Moderate	High	χ^2	p-value
n (% stratum)	394	80 (20)	118 (30)	88 (22)	108 (28)		
Gender (female)	266 (68)	54 (68)	84 (71)	63 (72)	65 (50)	4.04	0.257
Race (Caucasian/White)	310 (81)	59 (75)	87 (76)	70 (84)	94 (90)	35.32	**0.002**
Ethnicity (non-Hispanic/Latino)	70 (85)	11 (85)	20 (87)	19 (79)	20 (91)	1.33	0.722
Income							
<$22,500	142 (40)	32 (49)	36 (32)	26 (32)	48 (49)	14.49	0.106
$22,051–$45,000	84 (24)	13 (20)	26 (23)	20 (25)	25 (26)		
$45,001–$100,000	92 (26)	14 (22)	36 (32)	24 (30)	18 (19)		
>$100,000	36 (10)	6 (9)	13 (12)	11 (14)	6 (6)		
Education							
Graduate school	45 (12)	13 (16)	14 (12)	10 (12)	8 (8)	23.43	0.075
College graduate	81 (21)	13 (16)	29 (25)	34 (29)	15 (14)		
Some college	134 (35)	22 (28)	42 (36)	29 (35)	41 (39)		
Vocational school	15 (4)	4 (5)	3 (3)	0 (0)	8 (8)		
High school graduate	86 (22)	21 (26)	25 (21)	16 (19)	24 (2)		
Some high school	26 (7)	7 (9)	4 (3)	5 (6)	10 (9)		
Living situation							
Live alone	64 (17)	17 (23)	17 (15)	11 (13)	19 (18)	16.49	0.742
Live with spouse	180 (47)	31 (42)	60 (52)	38 (45)	51 (48)		
Live with young children	38 (7)	5 (7)	11 (10)	10 (12)	12 (11)		
Live with adult children	28 (7)	7 (9)	8 (7)	7 (8)	6 (6)		
Live with parents	25 (7)	8 (11)	8 (7)	4 (5)	7 (7)		
Live with significant other	17 (5)	2 (3)	6 (5)	9 (11)	8 (7)		
Live with roommate	2 (1)	3 (4)	4 (3)	6 (7)	4 (4)		
Current smoker	115 (31)	13 (17)	28 (25)	22 (26)	52 (51)	28.98	**<0.001**
Alcohol use	76 (24)	15 (21)	26 (30)	14 (21)	21 (25)	2.14	0.545
Acute analgesic use[a]	199 (51)	36 (45)	64 (54)	43 (49)	56 (52)	1.80	0.615

Notes: The currency is US$. Data presented as frequency (%); Chi-square (χ^2) test of proportions. Bold p-value indicates significance, $p<0.05$. [a]Aspirin, ibuprofen, and/or acetaminophen.

Table 1). After controlling for gender and smoking status, caffeine was found to have a significant main effect on pain interference ($F=2.77$, $p=0.041$), pain catastrophizing ($F=4.16$, $p=0.006$), and physical function ($F=4.97$, $p=0.002$; Table 3). Post hoc analysis revealed that compared to the no caffeine group, the low caffeine group had significantly lower pain interference ($p=0.028$), pain catastrophizing ($p=0.022$), and higher physical function ($p=0.003$). The moderate caffeine group had significantly less pain severity ($p=0.041$), pain interference ($p=0.033$), pain catastrophizing ($p=0.048$) and depression ($p=0.024$), and higher physical function ($p=0.001$). The high caffeine intake group reported significantly lower pain catastrophizing ($p=0.002$) and higher physical function ($p=0.015$).

Effect of caffeine intake on patient-reported outcomes in opioid nonusers

In the opioid nonuser stratum, caffeine intake was found to differ significantly in univariate analysis by race ($\chi^2=35.32$, $p=0.002$) and current smoking status ($\chi^2=28.98$, $p<0.001$; Table 2). After controlling for covariates, caffeine was found to have a significant main effect on physical function ($F=3.23$,

$p=0.023$; Table 4). Post hoc assessment of adjusted scores revealed low caffeine consumers had significantly higher physical function ($p=0.016$) compared to the no caffeine group.

Discussion

To our knowledge, this is the first study assessing the effects of caffeine consumption on pain and symptoms in patients with FM-like chronic pain. The results of this study show that patients using opioids who also consume caffeine reported less pain severity, pain-related interference in daily life, pain catastrophizing, and depression, as well as higher physical function, compared to those patients taking opioids but not consuming caffeine. Furthermore, these results suggest a dose-dependent effect of caffeine on opioid analgesia: low to moderate amounts of caffeine consumption improve symptoms, whereas higher amounts of caffeine typically do not. Patients not on opioid therapy who consume caffeine exhibited no differences in pain and symptoms compared to those not consuming caffeine, except for improved levels of physical function in the caffeine consumers, suggesting that caffeine's antinociceptive action is limited to concurrent use with opioid analgesics.

Table 3 Analysis of covariance showing the effects of caffeine intake on patient-reported outcomes in opioid users

Patient-reported outcome	No caffeine	Low	Moderate	High	Main effects		Pairwise comparison with no caffeine[a]		
					F	p-value	Low	Moderate	High
Pain severity	7.25±0.14	6.93±0.12	6.79±0.12	7.03±0.11	2.09	0.101	0.202	**0.041**	0.473
Pain interference	8.35±0.15	7.85±0.13	7.87±0.12	7.94±0.12	2.77	**0.041**	**0.028**	**0.033**	0.072
Physical function	30.64±0.59	33.18±0.52	33.34±0.50	32.78±0.48	4.97	**0.002**	**0.003**	**0.001**	**0.015**
Catastrophizing	23.66±1.05	19.98±0.92	20.47±0.86	19.00±0.83	4.16	**0.006**	**0.022**	**0.048**	**0.002**
Depression	11.83±0.40	10.97±0.35	10.47±0.34	11.04±0.32	2.31	0.076	0.223	**0.024**	0.274
Anxiety	10.86±0.45	10.63±0.40	9.94±0.39	10.76±0.37	1.11	0.346	0.958	0.274	0.997
Positive affect	22.55±0.88	23.59±0.76	23.83±0.73	24.00±0.70	0.60	0.618	0.670	0.518	0.427
Negative affect	28.61±0.95	26.31±0.82	27.38±0.80	27.95±0.75	1.29	0.276	0.150	0.605	0.898

Notes: Adjusted marginal mean ± standard error; adjusted for gender and current smoking status; [a]Dunnett's post hoc test assessed pairwise differences between the no caffeine group and the caffeine groups (low, moderate, high). Bold p-value indicates significance, p<0.05.

Table 4 Analysis of covariance showing the effect of caffeine intake on patient-reported outcomes in opioid nonusers

Patient-reported outcome	No caffeine	Low	Moderate	High	Main effects		Pairwise comparison with no caffeine[a]		
					F	p-value	Low	Moderate	High
Pain severity	7.11±0.19	6.60±0.16	6.76±0.18	6.81±0.17	1.53	0.207	0.084	0.400	0.450
Pain interference	7.81±0.22	7.17±0.18	7.54±0.21	7.33±0.20	1.85	0.138	0.111	0.798	0.251
Physical function	33.35±0.77	36.19±0.64	34.51±0.51	35.76±0.68	3.23	**0.023**	**0.016**	0.700	0.102
Catastrophizing	19.56±1.31	18.38±1.09	18.50±1.20	18.12±1.21	0.25	0.864	0.760	0.956	0.858
Depression	11.29±0.53	9.88±0.43	10.59±0.50	9.80±0.46	1.97	0.118	0.163	0.648	0.088
Anxiety	10.11±0.52	10.04±0.43	10.14±0.50	10.30±0.46	0.06	0.981	1.000	0.998	0.942
Positive affect	23.93±1.08	25.14±0.87	25.00±0.99	25.23±0.89	0.36	0.781	0.449	0.720	0.771
Negative affect	26.05±1.17	25.14±0.93	25.90±1.05	25.46±0.98	0.16	0.922	0.883	1.000	0.973

Notes: Adjusted marginal mean ± standard error; adjusted for race and current smoking status; [a]Dunnett's post hoc test assessed pairwise differences between the no caffeine group and the caffeine groups (low, moderate, high). Bold p-value indicates significance, p<0.05.

Few clinical studies have examined the relationship between caffeine consumption and chronic pain and the aggregate data remain inconclusive. For instance, chronic low back pain (LBP) patients reported consuming twice the amount of caffeine per day compared to patients without chronic LBP (392.4 vs 149.8 mg/day).[39] However, in another study, no differences in pain severity were seen in low, moderate, and high caffeine consuming chronic LBP patients.[40] More recently, there has been interest regarding use of caffeine as an adjuvant in cancer pain treatment. One study found that caffeine infusion produced a weak but nonsignificant reduction in pain intensity in cancer patients receiving morphine,[41] while another found caffeine infusion significantly reduced pain and drowsiness in cancer patients on opioid therapy, but this effect was not considered clinically relevant compared to controls that did not receive caffeine.[42]

We hypothesized that caffeine intake would have a significant dose-dependent effect on FM pain severity, regardless of opioid status. Counter to this hypothesis, we did not observe significant intrinsic effects of caffeine on pain severity in the opioid nonuser subgroup. However, exploratory analyses (not shown) not controlling for multiple comparisons showed significant effects of caffeine in opioid nonusers: moderate caffeine users had significantly lower pain severity and pain-related interference than the patients not consuming caffeine. Thus, caffeine may exhibit weak intrinsic analgesic effects in some chronic pain patients, but additional work in this area is warranted before definitive conclusions can be drawn.

Our second hypothesis, that caffeine would augment opioid analgesia was derived from preclinical findings in animal pain models. Preclinical studies have shown that caffeine combined with an opioid analgesic significantly improved the opioid's antinociceptive effects compared to opioid administration alone,[43–45] with one study reporting a decrease in morphine ED_{50} by 22%–53% with the addition of caffeine.[46] Some studies have shown that caffeine's adjuvancy is dose dependent, wherein high caffeine doses potentiate and lower doses can have no effect[45] or even inhibit[44] the analgesic effect of opioids.[43,45] The findings of this study confirmed our secondary hypothesis that caffeine would augment opioid analgesia, in that patients on opioid therapy who consumed caffeine had lower pain than the patients on opioid therapy

who do not consume caffeine. In addition, a dose-dependent effect was observed in that moderate amounts of caffeine consumption that were associated with the lowest level of pain severity. It should be noted that although this analysis failed to detect a significant main effect of caffeine on pain severity in opioid users, an unadjusted analysis (not controlling for covariates) did show a significant overall effect of caffeine (data not shown). Thus, washout of the main effect of caffeine on pain severity in the covariate analysis could be attributed to smoking's antinociceptive effects[47] or possible gender differences.

The mechanism by which caffeine potentiates opioid analgesics is complex and still unclear. Rats pretreated with caffeine showed significant potentiation of morphine antinociception and this effect was reversed by administration of naloxone, indicating the involvement of opioid receptor in caffeine's adjuvant effect.[45] Furthermore, in the same study, the ratio of morphine metabolite concentration to unchanged drug in the liver did not differ between caffeine-treated and control rats, suggesting caffeine did not influence morphine metabolism.[45] Nonetheless, caffeine-treated rats had significantly higher levels of morphine in the brain and plasma. This suggests that pharmacokinetic factors play some role in the effect of caffeine on morphine. Caffeine's ability to stimulate β-endorphin release in blood[48] and its ability to increase central noradrenaline turnover[49,50] suggest caffeine's mechanism of augmentation of opioid analgesia could also occur through enhanced endogenous opioid release and engagement of noradrenergic and adrenergic systems, which are involved in morphine's antinociceptive effects.

In addition to differences in pain severity, opioid users consuming low and moderate amounts of caffeine reported lower pain-related interference in activities, compared to opioid users who do not consume caffeine. Furthermore, opioid users consuming caffeine, regardless of the amount, had significantly improved physical function compared to opioid users not consuming caffeine. Interestingly, opioid nonusers consuming low amounts of caffeine also had significantly improved physical function compared to those not consuming caffeine.

Mood disturbances are a major component of FM and our results suggest caffeine use had a significant or marginally significant positive impact on depression in both opioid strata. Patients with FM and related centralized pain conditions (e.g., irritable bowel syndrome, interstitial cystitis, temporomandibular disorder) are believed to suffer from augmented CNS sensory processing[27] and are often recommended to avoid caffeine due to its stimulant properties. However, caffeine did not have an effect on anxiety in this study, regardless of opioid use. Interestingly, pain catastrophizing was significantly lower in caffeine consumers compared to nonconsumers in the opioid user stratum. Catastrophizing is often thought to overlap with anxiety; thus, we did not expect to see lower catastrophizing levels in patients consuming caffeine compared to those not consuming caffeine.

CNS adverse effects associated with opioid analgesics include sedative effects (e.g., consciousness and drowsiness), cognitive impairments (e.g., psychomotor impairment, slowed thinking process, and delirium), and toxic effects (e.g., opioid-induced hyperalgesia).[51] In contrast, caffeine is associated with reduced levels of fatigue,[52] improved physical performance,[53] increased attention and cognitive processing speed,[54] and elevated mood.[5] It is, therefore, possible that the positive effects of caffeine on pain interference, mood, and physical function in opioid users observed in this study could be the result of counteracting or diminishing the sedative and/or cognitive impairment effects of opioids. While our main objective was exploring the effect of caffeine consumption on pain in the presence and absence of opioid analgesics, these results show potential therapeutic benefits of caffeine in countering opioid adverse effects.

This study has several limitations. First, the cross-sectional design of this study does not allow for assessment of causation. Second, the self-reported nature of data collection has potential for bias and patients may have underreported medication and substance use due to perceived social stigma. Third, measurement of caffeine consumption and opioid use was limited. The type of opioid analgesic and the dose taken were not collected, and therefore, we were unable to assess opioid class-specific effects, as preclinical studies have suggested differences in caffeine's action with different opioid analgesics. Caffeine intake was reported as the number of cups consumed per day; the type and volume of beverage were not collected, preventing caffeine dose determination. Future studies examining the effects of caffeine and its interaction with opioids should incorporate highly precise measures of substance intake.

FM patients on opioid therapy who also use caffeine reported significantly lower symptoms compared to patients who do not consume caffeine. Moreover, a dose-dependent relationship was observed, where benefits were more consistently observed in low and moderate caffeine consumers and less frequently in high-dose consumers. The absence of effects of caffeine in opioid nonusers suggests that caffeine exhibits a weak but significant opioid analgesic adjuvant effect in chronic pain patients. However, further exploration of caffeine's intrinsic properties in chronic pain is warranted. Caffeine's effects on the measures of psychologic

and physical function in opioid users suggest that consumption of caffeine in conjunction with opioid analgesics could provide therapeutic benefits not seen with opioids or caffeine alone. These results were obtained in a large chronic pain sample; however, due to inconsistency in previous research on caffeine's intrinsic properties on pain and the novelty of opioid adjuvancy, further clinical research is necessary to confirm these findings.

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