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Problematic Use of Prescription Opioids and Medicinal Cannabis Among Patients Suffering from Chronic Pain

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Abstract

Objective. To assess prevalence rates and correlates of problematic use of prescription opioids and medicinal cannabis (MC) among patients receiving treatment for chronic pain.

Design. Cross-sectional study.

Setting. Two leading pain clinics in Israel.

Subjects. Our sample included 888 individuals receiving treatment for chronic pain, of whom 99.4% received treatment with prescription opioids or MC.

Methods. Problematic use of prescription opioids and MC was assessed using DSM-IV criteria, Portenoy's Criteria (PC), and the Current Opioid Misuse Measure (COMM) questionnaire. Additional sociodemographic and clinical correlates of problematic use were also assessed.

Results. Among individuals treated with prescription opioids, prevalence of problematic use of opioids according to DSM-IV, PC, and COMM was 52.6%, 17.1%, and 28.7%, respectively. Among those treated with MC, prevalence of problematic use of cannabis according to DSM-IV and PC was 21.2% and 10.6%, respectively. Problematic use of opioids and cannabis was more common in individuals using medications for longer periods of time, reporting higher levels of depression and anxiety, and using alcohol or drugs. Problematic use of opioids was associated with higher self-reported levels of pain, and problematic use of cannabis was more common among individuals using larger amounts of MC.

Conclusions. Problematic use of opioids is common among chronic pain patients treated with prescription opioids and is more prevalent than problematic use of cannabis among those receiving MC. Pain patients should be screened for risk factors for problematic use before initiating long-term treatment for pain-control.

Key Words. Prescription Opioids; Medicinal Cannabis; Problematic Use; Chronic Pain; Portenoy's Criteria

Introduction

In recent decades, awareness to pain management has increased among health care professionals [1]. Prescription opioids are one of the most common modalities for pharmacological treatment of pain, and have proven useful for the treatment of acute pain [2,3], pain related to cancer [4], and have increasingly been used for the treatment of chronic noncancer pain [5]. Nevertheless, there is increasing concern regarding opioid use due to the alarming increase in emergency-room visits associated with adverse effects of opioid use, substance abuse-treatment admissions, and death from overdose [6,7]. Growing awareness of potential problematic use of opioids is one of the background factors associated with the search for alternative modalities to reduce pain. In the past two decades, medicinal cannabis (MC) has been used widely for pain control in the United States and in several countries worldwide [8,9]. Due to great variability in the legal status of MC in different countries and several methodological challenges (e.g., lack of standardized dose, variability in potency, etc.), research regarding prevalence of use and potential problematic use is lacking [10].

It has been repeatedly suggested that long-term treatment with opioids may be complicated by development of tolerance, addiction, and abnormal pain sensitivity [11]. In such cases, pain may not be adequately managed and may even be worsened [12]. There is evidence to suggest that risk factors for developing an addictive disorder in the context of pain treatment with opioids include a personal or family history of addiction, poly-substance use, poor support system, and co-occurring psychiatric disorders [13], though the contribution of several other sociodemographic and clinical factors are less clear [14]. Although approximately 10% of lifetime cannabis users develop cannabis addiction [15], risk factors associated with the progression from cannabis use to addiction have been studied in the general population and not among pain patients.

Several studies have explored the prevalence of opioid addiction and problematic use among pain patients, including reports on chronic noncancer pain patients [16,17]. In studies using DSM-based criteria [18], the prevalence rates varied from 1.9% to 37%. However, the use of DSM criteria for diagnosing dependence in chronic pain patients treated with opioids has been argued by several authors to be inappropriate as it emphasizes physical dependence, a predicted and physiologic response to chronic opioid ingestions [19,20]. Thus, alternative criteria have been offered incorporating behavioral aspects of addiction. A common alternative is Portenoy's Criteria (PC), which emphasizes specific behavioral aspects of prescription opioid addiction, such as unsanctioned dose escalation, acquisition of opioids from other medical sources or from non-medical sources, manipulation of medical system for the purpose of obtaining additional opioids, and drug hoarding or sales [21]. Studies based on such behavioral criteria have reported problematic use of opioids affecting between 0% to 50% of chronic noncancer pain patients [22,23]. Accordingly, it seems that studies based solely on DSM criteria or PC indicate a very broad range of prevalence rates, confounding understanding of these results [13]. To the best of our finding, to date there has been no published data on rates of problematic use of cannabis among those treated with MC.

The available research to date suffers from several methodological drawbacks, particularly small sample sizes and use of questionnaires that do not appropriately distinguish physical tolerance and addictive behaviors [13]. The goals of this study were: 1) to explore the prevalence of problematic use of prescription opioids and MC among individuals experiencing chronic pain and treated in specialized pain centers, using various diagnostic tools; and 2) to explore the factors associated with problematic use among individuals receiving long-term treatment for pain.

Methods

Sample

The study sample included chronic pain patients (N = 888) treated in the two largest pain centers in Israel: Sheba Medical Center and Sourasky Medical Center. Each patient treated at these two centers for chronic pain (i.e., pain lasting for more than 3 months [24]) was approached for recruitment for the study during a 6-month period (November 2014 to April 2015). The response rate was 57%. Patients were excluded from the sample if they had language barriers not allowing for understanding of the questionnaires or had a cognitive or motor dysfunction that prevented them from filling out the questionnaires. Prior to participation in this study, every patient was required to sign an informed consent form, which was then immediately detached from the questionnaire upon completion and indexed (in order to allow anonymous data collection and increase reliability of respondents' replies) [25]. This study was approved by the IRB committee at both medical centers.

Measures

Given that terminology regarding Substance Use Disorders (SUDs) is dynamic and inconsistent across time and regions, and given the variability in outcome measures obtained using the different questionnaires included in the study, we collectively use the term "problematic use" for those who qualify for a positive diagnosis using DSM-IV, PC, or COMM-based criteria.

Problematic Use of Opioids

Problematic use of prescription opioids was assessed using the following tools:

Opioid dependence criteria from the Alcohol Use Disorder and Associated Disabilities Interview Schedule–Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (AUDADIS-IV), a fully structured diagnostic interview designed to assess alcohol, drug, and mental disorders according to DSM-IV diagnostic criteria in both clinical and general populations. It has been reported to have high reliability for SUDs and other psychiatric disorders [26,27]. In the current study, we used the AUDADIS-IV items based on DSM-IV criteria for opioid dependence: three out of seven criteria are required in order to rank positive for dependence, each criteria comprises one or more dichotomous items; for example, dose escalation criteria were represented by the question "Did you often use a medicine or drug in larger amounts or for a much longer period than you meant to?", whereas the DSM-IV criterion, which refers to side effects caused or exacerbated by the drug, is represented by two separate questions: "(Did you) continue to use a medicine or drug even though it was making you feel depressed, uninterested in things, or suspicious or distrustful of other people?" and "Did you continue to use a medicine or drug even though you knew it was causing you a health problem or making a health problem worse?" Moderate reliability for AUDADIS diagnosis of lifetime nonmedical opioid dependence in the general population has been reported (kappa = 0.59 [28]). Diagnosis according to DSM criteria was used due to its utility in clinical psychiatric settings as it has been previously used in similar studies [29], allowing for comparison of findings. Though the AUDADIS is originally intended to be used by a lay interviewer, in order to reduce response bias in participants' replies (particularly common in substance use-related questions and questionnaires [30]), we included it as a self-reported questionnaire. Participants were instructed to turn to the trained research assistant on site for any questions.

Portenoy's Criteria: a 10-item self-report questionnaire designed by Portenoy [21] that has been reported to show high inter-rater agreement (reliability of 0.93), high sensitivity (0.85), and specificity (0.96) [31]. Portenoy suggests the following criteria for diagnosing problematic use in the context of patients taking opioids for chronic pain: a positive response to items A (an intense desire for the drug and B (an overwhelming concern about the drug's availability) as well as at least one additional positive reply to any of the following items: unsanctioned dose escalation; continued dosing despite significant side effects; use of drug to treat symptoms not targeted by therapy; unapproved use during periods of no symptoms; manipulation of the treating physician or medical system for the purpose of obtaining additional drugs; acquisition of drugs from other medical sources or from nonmedical sources and drug hoarding.

Current Opioid Misuse Measure [32]: a 17-item self-report questionnaire that tracks current aberrant medication-related behaviors during opioid treatment. All items are rated from 0 = never to 4 = very often (e.g., In the past 30 days, how often have you needed to take pain medications belonging to someone else?). The questionnaire has been shown to have good validity (positively correlating with urine toxicology results [$P < 0.05$]) and reliability (0.86) [33]. In this study, 40% of the respondents received a total score of 0 in the COMM questionnaire (median = 3; interquartile range = 7). In order to prevent an artificial inflation in the proportion of positive COMM scores, these respondents were considered "true negative" rather than excluded from analysis.

Problematic Use of Cannabis

Problematic use of cannabis was assessed using the following tools:

Cannabis dependence criteria from the Alcohol Use Disorder and Associated Disabilities Interview Schedule–Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (AUDADIS-IV).

Modified Portenoy's Criteria: Due to the lack of specific diagnostic tools for measuring problematic use of cannabis in the context of chronic pain, we additionally used a modified version of the PC questionnaire, substituting "opioid" with "Medicinal Cannabis".

Psychiatric Comorbidities

We screened for co-occurring psychiatric disorders using the following tools:

The depression module of the Patient Health Questionnaire (PHQ-9): The PHQ-9 has nine items based on DSM-IV criteria. Each item scored on a three-point scale (0 = not at all to 3 = nearly every day), with total scores of 5, 10, 15, and 20 representing cut-points for mild, moderate, moderately severe, and severe depression, respectively. We used a score of 10 as the cut-off score indicating "positive" for depression [34]. Sensitivity and specificity of the PHQ-9 have been reported to be 75% and 90%, respectively [35].

Generalized anxiety disorder scale (GAD-7): GAD-7 is a seven-item measure based on DSM-IV criteria [35]. Each item is rated on a 0–3 scale relating to the frequency of anxiety symptoms over the last 2 weeks (0 = not at all to 3 = nearly every day). Total scores of 5, 10, and 15 represent mild, moderate, and severe levels of anxiety. We used a score of 10 as the cut-off score indicating "positive" for GAD [36]. Sensitivity and specificity of the GAD-7 are 89% and 82%, respectively.

All questionnaires were translated into Hebrew by back-translation and the Hebrew version was validated separately for each questionnaire.

Sociodemographic and Clinical Data

The following data were additionally collected from each participant:

Socio-demographic data, including sex, age, country of birth, type of residence (urban/rural), years of education, employment status, eligibility for disability allowance, marital status, and number of children.

Medical history: self-reported lifetime diagnosis of a list of common medical conditions, including hypertension, liver disease, heart disease, ulcer or duodenum disease, migraine, herniated disc, arthritis, fibromyalgia, and depression.

History of substance use, including past-year lifetime use, as well as self-reported lifetime addiction to the following substances (based on the most common substances used in Israel [37]): alcohol, cannabis, synthetic cannabinoids ("Spice", K2, etc.), cocaine, bath salts, and heroin.

Prescription opioid and MC use questionnaire, including measures of average and maximal levels of pain in the past month, as well as method of administration of opioids (oral or transdermal), and MC (smoking or drops), duration of treatment with opioids or MC, and average amount of MC used (number of drops per day, monthly dose in grams, and number of joints per day). Due to great variability in standards of equianalgesic conversion tables [38], doses of prescription opioids were not included in the analysis.

Statistical Analysis

Prevalence rates of problematic use of opioids and cannabis were calculated as the percentage of individuals who qualified for such diagnoses among those who were currently treated with each substance. For each substance separately, chi-square and logistic regression analyses were used for comparison of categorical variables, and independent-sample t-tests were applied for comparison of continuous variables. For all further analyses exploring factors associated with problematic use, we defined "problematic use" as meeting Portenoy's Criteria, as it does not include physical criteria and may therefore be considered more specific (i.e., reducing false-positive errors). Analyses were performed using SPSS software [39].

Results

Prevalence and Sociodemographic Characteristics of Problematic Use of Opioids and Cannabis

Among respondents, 471 (53.4%) were treated with prescription opioids without being concurrently treated with MC, 329 (37.3%) were treated with MC without being treated with prescription opioids, 77 (8.7%) were treated concurrently with prescription opioids and MC, and 5 (0.6%) were treated with neither prescription opioids nor MC. Among individuals who were currently treated with opioids (with or without current use of MC [N = 551]), the prevalence of problematic use of opioids was 52.6%, 17.1%, and 28.7% according to DSM-IV criteria, PC, and the COMM questionnaire, respectively. Among individuals who were currently treated with MC (with or without use of prescription opioids [N = 406]), prevalence of problematic use of cannabis was 21.2% when diagnosed according to DSM-IV criteria and 10.6% when using the modified PC (Figure 1). No significant differences were found in rates of problematic use of opioids and cannabis between the two medical centers. Among individuals treated with prescription opioids, those with and without a diagnosis of problematic use according to PC differed significantly ($P < 0.05$) in age, employment status, marital status, and type of residence. Among individuals treated with MC, those diagnosed with problematic use according to PC differed significantly from those without such diagnosis in employment status ($P < 0.01$) and marital status ($P < 0.05$) (Table 1).

Among individuals diagnosed with problematic use of opioids using DSM-IV criteria, the most common specific criteria included withdrawal (98.3%), persistent desire or repeated unsuccessful attempt to quit (94.8%), and significant time consumed by use or recovery from use (64.1%); the most common criteria among those diagnosed according to PC were an intense desire for the drug (100%), overwhelming concern about the drug's availability (100%), and dose escalation (94.7%), and the items that received the highest rates of positive answers (i.e., any reply besides "never" when asked about frequency of possible problems) among those diagnosed with problematic use of opioids according to the COMM questionnaire were trouble with thinking clearly or memory problems (46.5%), getting angry with people (37.9%), and having people complain about not
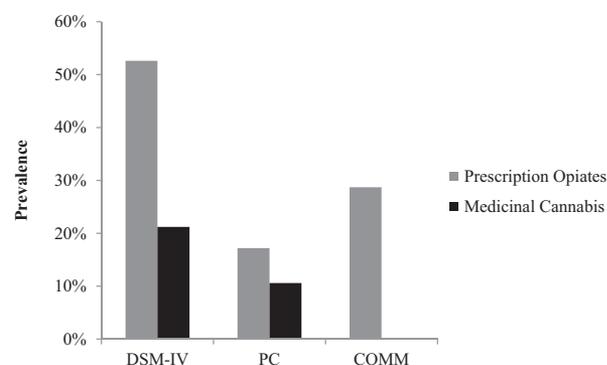

Figure 1 Prevalence of problematic use of prescription opioids and medicinal cannabis among pain patients, according to Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV), Portenoy's Criteria (PC), and Current Opioid Misuse Measure (COMM).

Table 1 Socio-demographic data and prevalence of problematic use of prescription opioids and medicinal cannabis among individuals suffering from chronic pain, as diagnosed according to Portenoy's Criteria

	Pain Patients (N = 888)							
	Total		Opioids Misuse			Cannabis Misuse		
	N	%	N	%	P value	N	%	P value
Sex								
Male	498	56.1	55	19.6		31	12.5	
Female	390	43.9	39	14.4	0.62	12	7.6	0.06
Place of birth								
Israel	615	69.3	72	18.9		36	12.8	
Former Soviet Union	42	4.7	8	25		1	5.3	
Americas	15	1.7	0	0		0	0	
Europe	58	6.5	2	5.4		2	7.7	
Asia	154	17.4	12	3.3		4	5.8	
South Africa	3	0.3	0	0	0.06	0	0	0.4
Years of education								
1–6	7	8	1	25		0	0	
7–9	59	6.7	5	15.6		5	17.2	
10–12	401	45.3	52	21.4		24	13.3	
13–15	299	33.7	26	13.6		11	8	
16+	120	13.5	8	10.1	0.2	2	3.6	0.12
Employment status								
Unemployed	406	45.9	60	23.5		28	14.7	
Part-time employee	109	12.3	14	21.5		2	3.8	
Full-time employee	200	22.6	14	10.5		7	9.2	
Pensioner	147	16.6	4	4.9		4	5.3	
Independently employed	20	2.3	1	7.7	0.001	1	11.1	0.000
Receiving disability allowance								
No	413	46.7	39	13.8		14	9.4	
Yes- Social security	411	46.5	47	19.9		25	13	
Yes- Military	60	6.8	7	22.6	0.88	4	11.8	0.6
Marital status								
Married/living with partner	599	67.6	64	16.7		22	19.5	
Single	118	13.3	7	9.6		8	14	
Divorced/separated	111	12.5	19	33.3		11	17.7	
Widowed	58	6.5	3	8.1	0.02	2	8.7	0.03
Number of children								
0	101	12.3	8	11.9		5	11.6	
1–3	460	56	51	19		23	10.2	
4+	260	31.7	26	14.7	0.62	10	10.1	0.77
Age categories								
18–29	78	9.1	10	19.2		5	16.2	
30–44	238	27.8	32	20		9	9.1	
45–64	335	39.1	39	19.7		19	11.6	
65+	206	24	11	8.8	0.03	7	7.5	0.48
Type of residence								
Urban	745	84	87	18.7		39	11.1	
Rural	142	16	7	8.4	0.02	5	8.6	0.39

completing necessary tasks (28.3%). Among individuals diagnosed with problematic use of cannabis using DSM-IV criteria, the most common specific positive criteria were withdrawal (91.9%), significant time consumed by use or recovery from use (68.6%), and using the substance in a larger amount and for a longer period than intended (50%); the most common criteria among those diagnosed according to PC were an

intense desire for the drug (100%), overwhelming concern about the drug's availability (100%), and dose escalation (93%).

Sociodemographic Differences Among Individuals with Problematic Use of Opioids and Cannabis

Problematic use of opioids according to PC was inversely associated with age ($P < 0.05$), indicating that individuals 65 years of age and older had significantly lower odds of receiving a diagnosis of problematic use compared with individuals whose age was between 18 and 64. Additionally, individuals residing in rural areas had significantly ($P < 0.05$) lower odds of receiving a diagnosis of problematic use compared with those residing urban areas. Individuals who reported a lifetime diagnosis of depression had significantly ($P < 0.001$) higher odds of receiving a diagnosis of problematic use compared with those without such diagnosis. Increased prevalence of problematic use of cannabis according to PC was significantly ($P < 0.05$) associated with country of birth, indicating that individuals born outside Israel had lower odds of receiving a diagnosis of problematic use compared with individuals born in Israel. Concerning marital status, results indicated that individuals with a partner or spouse had significantly ($P < 0.05$) greater odds of receiving a diagnosis of problematic use compared with individuals without a partner. Finally, individuals who reported a lifetime diagnosis of depression had significantly ($P < 0.05$) greater odds of receiving a diagnosis of problematic use compared with those without depression (Table 2).

Clinical Characteristics of Individuals with Problematic Use of Opioids and Cannabis

Individuals with problematic use of prescription opioids reported significantly higher average ($\bar{x} = 4.49$, t $= 3.23$, $P < 0.01$) and maximum ($\bar{x} = 4.78$, t $= 2.38$, $P < 0.05$) levels of pain compared with those without problematic use. Use of MC for 5 years or more was associated with higher rates of problematic use of cannabis ($\chi^2 = 12.66$, $P < 0.05$). Individuals smoking MC and suffering from problematic use of cannabis were treated with significantly higher monthly average doses in grams ($\chi^2 = 9.83$, $P < 0.05$) and smoked a higher number of daily joints (t $= 2.48$, $P < 0.05$). Among those diagnosed with problematic use of cannabis, the majority received less than 60 grams per month with 5.1% receiving 80 grams or more per month. Apart from MC, the most commonly used substances among individuals treated with prescription opioids were alcohol (32%), non-prescribed cannabis (19%), LSD (1.1%) and synthetic cannabinoids (0.7%); the most commonly used substances among those treated with MC, apart from prescription opioids, were alcohol (36.9%), Ecstasy (1.1%), and LSD (0.5%). Heroin was used by 0.5% of those receiving MC. As specific questions pertaining to use of (non-prescribed) opioids among MC users were not included in the substance use questionnaire, these data

are not available. Among individuals who were treated with prescription opioids but not with MC, past-year prevalence of non-medicinal cannabis use was 18.9%. Prevalence of past-year and lifetime use of alcohol and drugs was significantly higher among individuals with problematic use of prescription opioids or cannabis or both compared with those without such problematic use. Self-reported alcohol use disorders, but not drug use disorders, were significantly higher among those with problematic use of prescription opioids or cannabis or both compared with those without such problematic use (Table 3).

Our findings revealed that 88% of individuals with problematic use of opioids and 46.5% of those with problematic use of cannabis also qualified for positive screening for depression, whereas positive screening for GAD was prevalent among 74.5% of individuals with problematic use of opioids and 41.9% of those with problematic use of cannabis. Logistic regression analyses revealed that any diagnosis of depression, particularly moderate-severe and severe depression, was significantly associated with problematic use of opioids and cannabis, and that a diagnosis of GAD, particularly severe anxiety, was associated with problematic use of both opioids and cannabis (Table 4).

Discussion

In this study, we explored rates of problematic use of prescription opioids and MC among individuals receiving treatment for chronic pain. Using different measuring tools, problematic use of opioids and MC was found to be common among pain patients. Problematic use of prescription opioids or MC or both was found to be associated with more severe pain, concurrent use of alcohol and drugs, and higher levels of depression and anxiety.

In line with previous findings, prevalence of problematic use of prescription opioids varied substantially when using different measuring tools [17,40]. This is in line with findings on prevalence rates of other substance use and psychiatric disorders, which vary when using different measuring tools [41,42]. This reported variation may be attributed to differences between the measuring tools in the time frames they refer to, the extent to which questions are detailed, and differences in the examples and specific wording used in the questions within each questionnaire [43]. It should be acknowledged that these three tools measure different, though partially overlapping, phenomena. The DSM-IV is a diagnostic checklist used as a reference, but not specifically appropriate for this patient population; PC delineates criteria that indicate problematic use in chronic pain patients on long-term opioid therapy; and COMM measures specific aberrant medication-related behaviors during opioid treatment.

Given that prevalence rates in this study are based on the same clinical sample, our findings indicate that rates

Table 2 Odds ratio of problematic use of prescription opioids and medicinal cannabis, as diagnosed according to Portenoy's Criteria, according to sociodemographic and clinical variables

	Pain Patients (N = 888)			
	Opioid Misuse Odds Ratio, 95% CI	*P* value	Cannabis Misuse Odds Ratio, 95% CI	*P* value
Sex				
Female	1		1	
Male	1.44 (0.92–2.59)	0.11	1.74 (0.87–3.49)	0.12
Place of birth				
Israel	1		1	
Other	1.57 (0.94–2.26)	0.09	0.41 (0.18–0.95)	0.039
Years of education				
10+	1		1	
1–9	0.93 (0.41–2.46)	0.99	1.68 (0.61–4.63)	0.31
Employment status				
Currently working	1		1	
Currently not working	1.49 (0.92–2.4)	0.1	1.75 (0.83–3.68)	0.14
Receiving disability allowance				
Yes	1			
No	0.68 (0.42–1.09)	0.12	0.81 (0.41–1.58)	0.53
Marital status				
With partner	1		1	
Without partner	0.95 (0.59–1.55)	0.85	1.9 (1.01–3.59)	0.048
Number of children				
0	1		1	
1+	0.65 (0.3–1.41)	0.28	0.86 (0.32–2.34)	0.77
Age				
18–64	1		1	
65+	0.39 (0.20–0.76)	0.006	0.64 (0.27–1.51)	0.31
Type of residence				
Urban	1		1	
Rural	0.4 (0.18–0.9)	0.02	0.69 (0.26–1.82)	0.45
Ever diagnosed with hypertension?				
Yes	1		1	
No	0.73 (0.44–1.23)	0.24	0.74 (0.36–1.52)	0.41
Ever diagnosed with a liver disease?				
No	1		1	
Yes	1.65 (0.58–4.66)	0.34	1.08 (0.24–4.86)	0.92
Ever diagnosed with a heart disease?				
No	1		1	
Yes	0.66 (0.31–1.44)	0.3	1.09 (0.43–2.71)	0.86
Ever diagnosed with an ulcer or duodenum disease?				
No	1		1	
Yes	1.46 (0.84–2.55)	0.18	1.55 (0.7–3.42)	0.28
Ever diagnosed with a migraine?				
No	1		1	
Yes	1.33 (0.82–2.15)	0.25	1.22 (0.6–2.49)	0.58
Ever Diagnosed with a herniated disc?				
No	1		1	
Yes	1. (0.63–1.59)	0.99	0.78 (0.41–1.49)	0.46
Ever diagnosed with arthritis?				
No	1		1	
Yes	1.34 (0.81–2.22)	0.25	1.3 (0.62–2.7)	0.48
Ever diagnosed with fibromyalgia?				
No	1		1	
Yes	1.69 (0.99–2.89)	0.05	1.73 (0.89–3.5)	0.12
Ever diagnosed with depression?				
No	1		1	
Yes	3.73 (2.34–5.95)	0.000	2.66 (1.39–5.09)	0.003

Table 3 Clinical characteristics among individuals with and without problematic use of prescription opioid and medicinal cannabis, as diagnosed according to Portenoy's Criteria

| | Pain Patients (N = 888) | | | | | |
| | Opioid Misuse | | *P* value | Cannabis Misuse | | *P* value |
	Yes $\bar{x}$ (S.D)	No $\bar{x}$ (S.D)		Yes $\bar{x}$ (S.D)	No $\bar{x}$ (S.D)	
Average level of pain in past month	4.49 (0.76)	4.17 (0.88)	0.001	4.07 (1.14)	3.93 (0.97)	0.38
Maximum level of pain in past month	4.78 (0.59)	4.61 (0.63)	0.017	4.65 (0.69)	4.53 (0.75)	0.30
Oral administration	78.7%	85.8%				
Patch administration	21.3%	14.2%	0.085			
Using more than one year: years of use						
1	12%	7.8%		10.3%	16.3%	
2	8.4%	12%		12.8%	28%	
3	9.6%	16.4%		15.4%	22.7%	
4	10.8%	17.3%		25.6%	12.3%	
5+	59%	46.5%	0.088	35.9%	25.7%	0.013
Using less than one year: months of use						
0–2	44.4%	29.5%		66.7%	14.5%	
3–4	11.1%	17.9%		0%	27.4%	
5–7	33.3%	24.4%		0%	35.5%	
8–10	11.1%	21.8%		33.3%	21%	
11–12	0%	6.4%	0.72	0%	1.6%	0.15
Liquid cannabis: number of drops per day				13.33 (3.05)	11.8 (9.7)	0.78
Cannabis smoking: grams per month						
10–20				15.4%	30.7%	
21–40				33.3%	41%	
41–60				38.5%	23.1%	
61–80				7.7%	3.6%	
80+				5.1%	1.6%	0.043
Cannabis smoking: number of joints per day in past month				3.03 (0.96)	2.52 (1.17)	0.014
Alcohol use : past year						
Yes	43.6%	29.9%		53.5%	35.1%	
No	56.4%	70.1%	0.01	46.5%	64.9%	0.018
Drug Use : past year						
Yes	5.3%	1.5%		4.7%	0.6%	
No	94.7%	98.5%	0.022	95.3%	99.4%	0.01
Alcohol use : lifetime						
Yes	62.8%	44%		79.1%	50.7%	
No	37.2%	56%	0.001	20.9%	49.3%	0.000
Drug use : lifetime						
Yes	10.6%	4.2%		23.3%	6.6%	
No	89.4%	95.8%	0.011	76.7%	93.4%	0.000
Alcohol addiction: lifetime						
Yes	12.8%	1.8%		11.6%	1.9%	
No	87.2%	98.2%	0.000	88.4%	98.1%	0.000
Drug addiction: lifetime						
Yes	2.1%	0.7%		4.7%	1.4%	
No	97.9%	99.3%	0.172	95.3%	98.6%	0.12

of problematic use of opioids were *at least* 17% of those treated with opioids, indicating that comorbidity of chronic pain and problematic use of prescription opioids may be substantially higher than previously assumed according to some reports [44,45]. This may actually be even higher when taking into account potential self-report bias, common in questionnaires focusing on substance use and misuse [43], particularly in a service

Table 4 Odds ratio of problematic use of prescription opioid and medicinal cannabis as diagnosed according to Portenoy's Criteria, based on levels of concurrent depression and anxiety

	Pain Patients (N = 888)			
	Opioid Misuse		Cannabis Misuse	
	Odds Ratio (95% CI)	*P* value	Odds Ratio (95% CI)	*P* value
Depression				
No	1		1	
Yes	4.66 (2.64–8.24)	0.000	2.55 (1.34–4.86)	0.004
No	1		1	
Mild	0.82 (0.3–2.3)	0.71	1.74 (0.74–4.1)	0.2
Moderate	2.29 (0.89–5.83)	0.084	1.82 (0.55–6.01)	0.32
Moderate-severe	3.11 (1.26–7.65)	0.014	3.65 (1.38–9.62)	0.009
Severe	8.87 (3.7–21.25)	0.000	4.32 (1.62–11.54)	0.003
GAD				
No	1		1	
Yes	4.14 (2.51–6.83)	0.000	2.45 (1.27–4.72)	0.007
No	1		1	
Mild	1.49 (0.64–3.44)	0.35	1.81 (0.74–4.4)	0.19
Moderate	3.05 (1.41–6.59)	0.005	1.53 (0.54–4.38)	0.42
Severe	6.46 (3.28–12.69)	0.000	4.29 (1.93–9.54)	0.000

providing the substance itself (e.g., prescription opioids prescribed in a pain clinic). Notably, as this is a cross-sectional study, directionality cannot be inferred and, while it is possible that individuals with problematic use of opioids are more prone to suffer from chronic pain [46], rates of problematic use of prescription opioids in this sample are much higher than those reported in the general population [47] and highlight the importance of awareness to problematic use of prescription opioids in pain clinics.

This study presents novel findings regarding prevalence of a problematic use of MC among patients suffering from chronic pain. Notably, almost one half of individuals who participated in this study were treated with MC. Previous studies have pointed out pain as the leading indication for treatment with MC [48,49], yet up-to-date, specific data pertaining to prevalence rates of problematic use of MC have not been published. Our findings suggest that among pain patients treated with MC at least 10.6% suffer from problematic use of cannabis. This is substantially lower than the prevalence of cannabis dependence reported among daily users within the general population [15]. Although frequency of use was not specifically addressed in our study, the average amount of MC used within the study population is in line with previous reports among MC patients [48]. Daily relief from pain is very common among chronic pain patients, thus assumed in our clinical sample as well [50,51]. The relatively low rates of problematic use of MC may be attributed to other differences between MC users and recreational cannabis users, including age and cultural background [15,52]. In addition, unlike recreational daily cannabis users, individuals using MC in Israel receive specific instructions concerning desired

dose, frequency, and time of MC use, as well as regulated doses requiring specific prescriptions [53], which may lower their chance for developing problematic use [54].

Generally, rates of problematic use of MC among MC users seem lower than rates of problematic use of opioids among those prescribed opioids, yet this could not be directly concluded from our findings. As 8.7% of individuals received both prescription opioids as well as MC, these were not exclusive groups, limiting possible comparisons. Furthermore, formal indications for prescribing MC in Israel require exhaustion of common-practice medications, which usually include opioids for the management of chronic pain. Accordingly, it may be assumed that the majority of subjects receiving MC had been previously prescribed opioids, further limiting direct comparisons. Non-smokable cannabis preparations are currently available in some countries in buccal spray form (Sativex® or Nabixmols) that have been shown to be effective in spasticity related to multiple sclerosis indicating low levels of tolerance and adverse effects [55]. Accordingly, it is possible that non-smokable cannabis may be beneficial in reducing rates of problematic use of cannabis though this must be specifically explored. Alongside potentially reduced risks associated with use of cannabis as buccal spray, its effectiveness in chronic pain must be further explored. Current literature indicates possible benefit in cancer-pain refractory to opioids [56] and in neuropathic pain [57] but findings regarding non-cancer pain do not suffice.

Exploring sociodemographic factors associated with problematic use, we found that younger pain patients, those residing in urban areas, and those with a lifetime

diagnosis of depression were significantly more likely to suffer from problematic use of opioids. Individuals living without a partner and those who previously suffered from depression were significantly more likely to report problematic use of cannabis. None of the explored comorbid medical conditions were associated with significantly higher prevalence of problematic use of opioids or MC, suggesting that chronic pain itself, rather than any specific medical condition, is a factor highly associated with problematic use. Higher average and maximum levels of pain were observed among individuals with problematic use of opioids compared with those without such problematic use. This may imply that higher levels of pain may be highly associated with problematic use, perhaps by causing individuals to use opioids excessively; however, it should also be considered that individuals with chronic opioid use may suffer from opioid-induced hyperalgesia [58], actually contributing to increased levels of perceived pain. Problematic use of cannabis was associated with greater amounts of cannabis used and more frequent intake of smoked MC, but not with higher dosage of cannabis oil, thus suggesting a potentially higher safety profile, in terms of problematic use, of the latter.

Past-year and lifetime use of drugs and alcohol, as well as self-reported lifetime alcohol use disorders, were associated with increased prevalence of problematic use of prescription opioids and MC. This is in line with previous research that indicated high comorbidity of SUDs and problematic use of prescription opioids [54]. Notably, nearly 19% of individuals treated solely with prescription opioids had also used non-medicinal cannabis in the past year, indicating high rates of parallel substance use among pain patients. Positive screening for depression and GAD was detected among 43% and 37% of pain patients, respectively; these rates are substantially higher than the prevalence rates of depression and anxiety found within the general population when using similar diagnostic tools [36,59]. Co-occurring depression among pain patients has been previously associated with poorer quality of life [60] and higher rates of suicide ideation and attempts [61]. Our results suggest that depression and anxiety are associated with increased prevalence of problematic use of prescription opioids and MC, suggesting that pain treatment should also include screening and concurrent treatment for moderate and above depression and anxiety.

Several limitations should be considered when examining our results. First, the response rate is lower than the recommended 70% [62]. Nevertheless, this may actually indicate that the actual prevalence of problematic use in this population is even higher than that found here, as those individuals may be more reluctant to reply to questionnaires focusing on substance use and problematic use of substances [43], particularly in a service where the substance itself is prescribed. Second a formal diagnosis of opioid dependence according to DSM-IV could not be attributed in this study, as it requires a face-to-face interview as well as a preliminary indication of a maladaptive pattern of substance use leading to clinically significant impairment or distress and an indication that opioids are "being used in doses that are greatly in the excess of legitimate medical purpose..." and in the textual description "compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose" [18]. Therefore caution should be taken when interpreting DSM-based findings in this study. Third, as this is a cross-sectional study, directionality of the association between chronic pain and problematic use was not explored and causality could not be inferred. Fourth, data collected in this study relied on self-report, thus results may be biased due to potential lack of information or social desirability. Furthermore, we used a modified version of PC, and it is possible that specific MC-based tools should include different cannabis-related items, and may yield different results, though these are currently lacking. In addition, as this study included self-reported use of MC without access to the smoked compounds themselves, data regarding the cannabis composition (e.g., THC vs CBD ratios) were also lacking in this study. Finally, psychiatric comorbidity among individuals with problematic use of opioids or MC was explored using screening instruments rather than assessment tools that allow for a complete diagnosis.

Conclusion

This study indicates that even when using conservative measures, problematic use of opioids among chronic pain patients is highly prevalent. To the best of our knowledge, this is the first study to present data on problematic use of cannabis among chronic pain patients using MC. Careful screening for factors associated with problematic use using standardized tools should be implemented in pain clinics. Additionally, given the increasing popularity of MC use, more accurate tools for assessing problematic use of cannabis among pain patients are required.

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