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Research paper

Depression and anxiety among chronic pain patients receiving prescription opioids and medical marijuana

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ABSTRACT

Background: High rates of depression and anxiety have been consistently reported among patients suffering from chronic pain. Prescription opioids are one of the most common modalities for pharmacological treatment of pain, however in recent years medical marijuana(MM) has been increasingly used for pain control in the US and in several countries worldwide. The aim of this study was to compare levels of depression and anxiety among pain patients receiving prescription opioids and MM.

Methods: Participants were patients suffering from chronic pain treated with prescription opioids (OP,N = 474), MM (N = 329) or both (OPMM,N = 77). Depression and anxiety were assessed using the depression module of the Patient Health Questionnaire (PHQ-9) and the Generalized Anxiety Disorder scale (GAD-7).

Results: Prevalence of depression among patients in the OP, MM and OPMM groups was 57.1%, 22.3% and 51.4%, respectively and rates of anxiety were 48.4%, 21.5% and 38.7%, respectively. After controlling for confounders, patients in the OP group were significantly more likely to screen positive for depression (Adjusted Odds Ratio(AOR) = 6.18;95%CI = 4.12–9.338) and anxiety(AOR = 4.12;CI = 3.84–5.71)) compared to those in the MM group. Individuals in the OPMM group were more prone for depression (AOR for depression = 3.34;CI = 1.52–7.34)) compared to those in the MM group.

Limitations: Cross-sectional study, restricting inference of causality.

Conclusions: Levels of depression and anxiety are higher among chronic pain patients receiving prescription opioids compared to those receiving MM. Findings should be taken into consideration when deciding on the most appropriate treatment modality for chronic pain, particularly among those at risk for depression and anxiety.

1. Introduction

Chronic pain has been reported to affect at least 8% of the population in developed countries annually (Andrew et al., 2014). The total healthcare cost associated with pain in the US has been estimated at $261 to $300 billion per year (Gaskin and Richard, 2012), with average annual costs of pain patients estimated to be three times higher than of individuals without chronic pain (Berger et al., 2004). Chronic pain has been associated with a significant decrease in daily activities, occupational productivity and quality of life (Breivik et al., 2006; Patel et al., 2012; Smith et al., 2007). In addition, individuals suffering from chronic pain have high rates of comorbid psychiatric disorders which may further reduce activity and quality of life, including drug and alcohol use disorders, mood and anxiety disorders (Demyttenaere et al., 2007; Feingold et al., 2016a; Gerrits et al., 2014, 2012).

The association between chronic pain, depression and anxiety has gained particular attention due to high rates of co-morbidity (Dersh et al., 2002). Up to 54% of pain patients have been reported to suffer from co-morbid depression, and up to 50% have been reported to suffer from anxiety, with particularly high rates of Generalized Anxiety Disorder (Gadermann et al., 2012), specific phobia and panic disorder (Banks and Kerns, 1996; Dersh et al., 2002; Knaster et al., 2012; McWilliams et al., 2003). The causal association between depression and anxiety and chronic pain is yet unclear, with findings supporting both an antecedent and consequent association (Magni et al., 1994;

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Polatin et al., 1993).

Prescription opioids are one of the most common modalities for the pharmacological treatment of pain, and have proven useful for the treatment of acute pain (Moore and McQuay, 1997; Shang and Gan, 2003) and pain related to cancer (Carr et al., 2004). In addition, these medications have been increasingly used for the treatment of chronic nonmalignant pain (Compton and Volkow, 2006). However, in the past two decades there is gradual awareness of public health risks associated with the increase in prescriptions to opioids (such as risks of diversion, overdose and addiction (Volkow and McLellan, 2016)) warranting the search for alternatives means for treatment of chronic pain. Medical marijuana (MM) has been used widely for pain control in the US and in several countries worldwide, becoming increasingly popular as a potential alternative to prescription opioids for the treatment of chronic pain (Hill, 2015; Jensen et al., 2015). However, due to great variability in the legal status of MM in different countries, data pertaining to the sociodemographic and clinical characteristics of chronic pain patients receiving MM compared to those receiving prescription opioids is scarce (Hall and Weier, 2015). Specifically, there is a lack of data regarding rates of co-occurring depression and anxiety among individuals receiving these two treatments. This may be important as the use of opioids and marijuana may in itself differentially affect levels of depression, anxiety and perceived pain.

The aim of the present study is to explore rates of depression and anxiety among individual receiving treatment for chronic pain, comparing individuals receiving prescription opioids and those receiving MM.

2. Materials and methods

2.1. Sample

Subjects for this study were recruited during a 6-month period in two large pain centers in Israel. Patients treated for chronic pain (i.e. pain lasting for more than three months (Elliott et al., 1999)) were approached for recruitment for the study. The response rate was 57%, encompassing a total of 890 participants. Patients participating in the study were not reimbursed for their participation and all subjects were required to sign an informed consent form prior to participation, 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 (Harrison, 1997)). This study was approved by the Institutional Review Board (IRB) committee at both medical centers.

3. Measures

3.1. Sociodemographic and clinical data

The following data was collected from each participant using self-administered questionnaires:

1. 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.
2. Medical history: participants were asked regarding lifetime diagnoses of common medical conditions including hypertension, liver disease, heart disease, ulcer or duodenum disease, migraine, herniated disc, arthritis and fibromyalgia.
3. History of substance use, including any twelve-month and lifetime use of the following substances: alcohol, cannabis, synthetic cannabinoids (‘Spice’, K2, etc.), MDMA, LSD, bath salts and heroin. This list was based on the most common substances used in Israel (Lev-Ran et al., 2014).
4. Pain indices – average level of pain (0–10) in the past month.

3.2. Psychiatric comorbidities

Co-occurring psychiatric disorders were screened for using the following tools:

1. The depression module of the Patient Health Questionnaire (PHQ-9): a nine items questionnaire based on DSM-IV criteria for major depressive disorder. 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-off points for mild, moderate, moderate-severe and severe depression, respectively. A score of 10 was used as a cut-off score indicating "positive" for screening of clinical depression (Kroenke et al., 2001). Sensitivity and specificity of the PHQ-9 have been reported to be 75% and 90%, respectively (Spitzer et al., 1999).
2. Generalized anxiety disorder scale (GAD-7): a 7-item measure based on DSM-IV criteria for GAD (Spitzer et al., 1999). Each item is rated on a 0–3 scale relating to the frequency of anxiety symptoms over the last two weeks (0 = ‘not at all’ to 3 = ‘nearly every day’ (Lowe et al., 2008)). 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" screening of GAD (Lowe et al., 2008). Sensitivity and specificity of the GAD-7 are 89% and 82%, respectively. Though GAD-7 was designed as a screening tool for Generalized Anxiety Disorder, it is regarded a reliable self-report measure of anxiety in the general population (Lowe et al., 2008).

3.3. Statistical analysis

In order to establish differences between levels of anxiety and depression among subjects receiving prescription opioids and those receiving MM, we categorized subjects into those receiving opioids exclusively (OP group), those receiving MM exclusively (MM group) and those receiving both (OPMM group). Multinomial regression analyses were used to compare prevalence rates of categorical variables, with individuals in the MM group set as the reference group. Independent-sample *t*-tests (two-tailed) were applied for comparison of continuous variables. In order to specifically compare the odds of depression or anxiety among groups, we used multiple logistic regression analyses in which MM was the reference group. In order to control for possible confounding effect of sociodemographic and clinical factors which may account for differences in level of misuse (Fillingim et al., 2009), each analysis was conducted in two progressive models: the first included an unadjusted analysis and the second controlled for the following confounders: sociodemographic variables, medical history, history of substance use, average level of pain and amount of time using pain medication. Analyses were performed using SPSS software, 21st version.

4. Results

Among participants, 474 (59%) were treated with prescription opioids exclusively, 329 (41%) were treated with MM exclusively and 77 (8.6%) received both. The remaining 10 subjects, receiving neither prescription opioids nor MM were excluded from analyses in this study. The proportion of women was significantly higher in the OP group compared to the MM group ($p < 0.01$) group, as was the proportion of patients receiving a disability allowance ($p < 0.01$) (Table 1). Patients in the OP group were more likely to report lifetime use of alcohol and drugs compared to those in the MM group ($p < 0.0.5$ for both). The most common substances concurrently used (past 12 months) among patients in the OP group were alcohol (31.6%), cannabis (18.2%) and LSD (1.1%), whereas the most common among those in the MM group were alcohol (37.2%), MDMA (0.6%) and LSD (0.3%) (naturally all MM patients were cannabis users). No significant differences were found in rates of common medical conditions between the two groups. Patients

Table 1
Socio-demographic and medical data among chronic pain patients, comparing individuals receiving medical marijuana (MM) to those receiving prescription opioids (OP) and both (OPMM) using multinomial regression.

	MM (N = 329)		OP (N = 474)		OPMM (N = 77)		MM Vs. OP	MM Vs. OPMM
	N	%			N	%	Odds Ratio/p-value	Odds Ratio/p-value
Sex								
Female	118	35.9	230	48.5	40	51.9	1	1
Male	211	64.1	244	51.4	37	48.1	0.59/ < 0.0001	0.52/0.01
Place of birth								
Israel	229	69.8	328	69.2	53	68.8	1	1
Other	99	30.2	146	30.8	24	31.2	1.03/0.853	1.05/0.866
Years of education								
1–9	30	9.1	34	7.2	2	2.6	1	1
10–12	151	45.9	214	45.2	29	38.2	1.25/0.411	2.88/0.163
+13	148	45	225	47.6	45	59.2	1.34 < 0.28	4.56/0.043
Employment status								
Currently Working	114	34.9	187	39.8	24	31.2	1	1
Currently Not Working	213	65.1	283	60.2	53	68.8	0.81/0.159	1.828/0.539
Receiving disability allowance								
No	199	60.9	261	55.5	21	27.3	1	1
Yes	128	39.1	209	44.5	56	72.7	0.51/ < 0.0001	1.71/0.054
Marital status								
With partner	212	64.6	332	70.2	51	66.2	1	1
Without partner	116	35.4	141	29.8	26	33.8	0.78/0.098	0.93/0.971
Number of children								
0	33	12.1	57	12.8	10	14.9	1	1
1–3	186	62	230	51.6	39	58.2	0.72/0.164	0.69/0.539
4+	81	27	159	35.7	18	26.9	1.14/0.62	0.73/0.486
Age categories								
18–29	25	8	46	10	6	8.2	1	1
30–44	76	24.2	137	29.7	23	31.5	0.98/0.943	1.26/0.651
45–64	133	44.3	167	36.1	31	42.5	0.68/0.164	0.97/0.953
65+	80	25.5	112	24.2	13	17.8	0.76/0.343	0.68/0.474
Type of residence								
Urban	275	83.6	399	84.2	67	88.2	1	1
Rural	54	16.4	75	15.8	9	11.8	0.96/0.823	0.68/0.324
Ever diagnosed with hypertension?								
No	225	68.8	344	72.6	50	65.8	1	1
Yes	102	31.2	130	27.4	26	34.2	0.83/0.248	1.15/0.611
Ever diagnosed with a liver disease?								
	313	95.7	458	96.6	72	94.7	1	1
Yes	14	4.3	16	3.4	4	5.3	0.78/0.508	1.24/0.709
Ever diagnosed with a heart disease?								
No	284	86.9	421	88.8	65	85.5	1	1
Yes	43	13.1	53	11.2	11	14.5	0.83/0.4	1.12/0.76
Ever diagnosed with an ulcer or duodenum disease?								
No	269	82.3	387	81.8	71	93.4	1	1
Yes	58	17.7	86	18.2	5	6.6	1.03/0.872	0.32/0.021
Ever diagnosed with a migraine?								
No	248	75.8	347	73.2	54	71.1	1	1
Yes	79	24.2	127	26.8	22	28.9	1.15/0.402	1.28/0.386
Ever diagnosed with a herniated disc?								
No	135	41.3	173	36.5	26	34.2	1	1
Yes	192	58.7	301	63.5	50	65.8	1.22/0.171	1.35/0.258
Ever diagnosed with arthritis?								
No	249	76.6	359	75.7	64	84.2	1	1
Yes	76	23.4	115	24.3	12	15.8	1.05/0.775	0.61/0.153
Ever diagnosed with fibromyalgia?								
No	261	79.8	339	84.2	54	72	1	1
Yes	66	20.2	75	15.8	21	28	0.74/0.112	1.54/0.14

in the OP group were significantly more prone to report pain levels of 9–10 out of 10compared to patients in the MM group ($p < 0.01$). (Table 2). The OPMM group had a significantly higher proportion of women compared to the MM group ($p < 0.05$). Patients in the OPMM group were significantly more likely to have 13 or more years of education and report lifetime history of ulcer or duodenum disease ($p < 0.05$ for both) compared to patients in the MM group.

Among all participants in the study, rates of depression were 42.2% and rates of anxiety were 37%. Prevalence of depression among patients in the OP, MM and OPMM groups was 57.1%, 22.3% and 51.4%, respectively. Prevalence of anxiety was 48.4% among patients in the OP group, 21.5% among those in the MM group and 38.7% in the

Table 2
Clinical characteristics among chronic pain patients, comparing individuals receiving medical marijuana (MM) to those receiving prescription opioids (OP) and both (OPMM) using multinomial regression.

	MM (N = 329)		OP (N = 474)		OPMM (N = 77)		MM Vs. OP	MM Vs. OPMM
	N	%			N	%	Odds Ratio/p-value	Odds Ratio/p-value
Time using medications								
0–1 years	50	15.5	78	17.4			1	
1–2 years	113	35	75	16.8			0.42/ < 0.0001	
3+ years	160	49.5	294	64.8			1.18/0.427	
Average level of pain								
1–2	6	1.8	2	0.4	2	2.6	1	1
3–4	25	7.6	15	3.2	1	1.3	1.08/0.504	0.12/0.105
5–6	76	23.2	80	16.9	9	11.7	3.16/0.167	0.35/0.245
7–8	114	34.8	150	31.6	34	44.2	3.95/0.096	0.89/0.895
9–10	107	29.3	227	62.2	31	40.3	6.36/0.025	0.87/0.868
Alcohol use: past-year								
No	206	62.8	323	68.4	49	63.6	1	1
Yes	122	37.2	149	31.6	28	36.4	0.78/0.098	0.96/0.892
Any drug use: past-year								
No	326	99.4	462	97.9	75	97.4	1	1
Yes	2	0.6	10	2.1	2	2.6	3.53/0.105	4.35/0.145
Alcohol use: lifetime								
No	151	46.2	254	53.8	36	46.8	1	1
Yes	176	63.8	218	46.2	41	53.2	0.74/0.034	0.98/0.927
Drug use: lifetime								
No	298	91.1	448	94.9	72	93.5	1	1
Yes	29	8.9	24	5.1	5	6.5	0.55/0.037	0.71/0.501

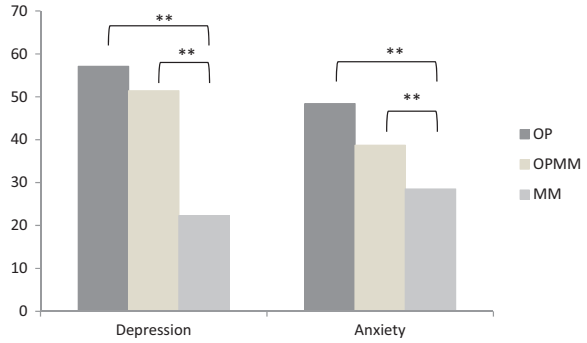

Fig. 1. Prevalence of depression and anxiety as diagnosed according to the Patient Health Questionnaire (PHQ-9) and the General Anxiety Disorder (GAD-7) scale, among patients with chronic pain receiving prescription opioids (OP), medical marijuana MM or both (OPMM). **p < 0.01.

OPMM group (Fig. 1 and Supplementary Fig. 1).

When comparing individual items in the PHQ-9 questionnaire, patients in the OP group invariably replied "almost every day" more commonly than those in the MM group (for example "how often did you suffer from poor appetite or overeating?"). Patients in the MM group replied "not at all" to all specific PHQ-9 items more commonly than those in the OP group. The same was true for individual items in the GAD-7 (for example, patients in the OP group replied "almost every day" when asked how often they felt "so restless that it is hard to sit still" more often than those in the MM group). Patients in the OPMM group replied "almost every day" significantly ($p < 0.05$) more commonly than those in the MM group in each of the PHQ-9 and GAD-7 items. Few differences were found when comparing specific depressive and anxiety items between the OPMM and OP group: those in the OPMM group replied “almost every day” significantly ($p < 0.01$) more commonly in PHQ-9 item “trouble falling or staying asleep, or sleeping too much” and in GAD-7 item “being so restless that it is hard to sit still”.

Among patients in the OP group, logistic regression analysis revealed no significant differences in the odds to screen positive for either depression or anxiety among those who reported past-year use of (non-prescribed) cannabis compared to those who did not use cannabis. Patients in the OP group were at increased odds for depression and anxiety compared to those in the MM group. This was maintained after controlling for potential confounders; patients in the OP group were significantly more likely to screen positive for depression (Adjusted Odds Ratio (AOR) = 6.18; 95% Confidence Interval (CI) = 4.12–9.33) and anxiety (AOR = 3.84; CI = 2.59–5.7) compared to those in the MM group. This was maintained when conducting separate comparisons by levels of depression and anxiety: mild, moderate, moderate-severe and severe (Table 3). Individuals in the OPMM group were at a significantly increased odds for depression (AOR = 3.12; CI = 1.56–6.24), as well as moderate (AOR = 4.79; CI = 1.54–14.91) and moderate-severe (AOR = 3.54; CI = 1.17–10.732) depression compared to individuals in the MM group. Individuals in the OPMM group were at significantly smaller odds for depression (AOR = 0.4 CI = 0.2–0.83) and anxiety (AOR = 0.38; CI = 0.19–0.78) as well as moderate (AOR = 0.2; CI = 0.05–0.76) depression and severe anxiety (AOR = 0.26; CI = 0.08–0.83) compared to individuals in the OP group.

5. Discussion

In this study we explored rates of depression and anxiety among patients receiving treatment for chronic pain, comparing patients receiving prescription opioids and those receiving MM. Though no differences were found in rates of common medical conditions associated with pain and in rates of co-occurring substance use, patients in the OP group had higher rates of depression and anxiety compared to those in the MM group. After controlling for potentially confounding factors, patients in the OP group had significantly greater odds to screen positive for depression and anxiety, as well as report higher rates of each individual depression and anxiety symptom explored, compared to those in the MM group. Individuals in the OPMM group were at significantly increased odds for depression as well as reported higher rates of each individual depression and anxiety symptom explored compared to those in the MM group, and reported lower levels of depression and anxiety compared to those in the OP group.

Rates of depression and anxiety in our study were within the range

Table 3
Prevalence of depression and anxiety as diagnosed according to the Patient Health Questionnaire (PHQ-9) and the General Anxiety Disorder (GAD-7) scale, comparing pain patients receiving prescription opioids (OP) and medical marijuana (MM) exclusively.

	Medical Marijuana		Prescription Opioids				
	N	(%)	N	(%)	Odds Ratio (CI[a])	Adjusted Odds Ratio[b] (CI)	P-Value[c]
Depression							
Less than mild	167	51.1	73	15.7	1	1	
Mild	87	26.6	127	27.3	3.34 (2.27–4.92)	3.85 (2.39–6.21)	< 0.0001
Moderate	24	7.3	90	19.3	8.58 (5.06–14.54)	18.02 (8.46–38.35)	< 0.0001
Moderate-severe	26	8	95	20.4	8.36 (5–13.97)	12.04 (5.86–24.73)	< 0.0001
Severe	23	7	81	17.4	8.06 (4.7–13.81)	12.73 (5.56–29.13)	< 0.0001
Anxiety							
Less than mild	205	63.1	139	29.6	1	1	
Mild	50	15.4	103	22	3.04 (2.03–4.53)	3.1 (1.95–4.94)	< 0.0001
Moderate	35	10.8	89	19	3.75 (2.4–5.86)	3.83 (2.23–6.57)	< 0.0001
Severe	35	10.8	138	29.4	5.81 (3.79–8.93)	7.7.3 (4.3–13.9)	< 0.0001

[a] CI = Confidence Interval.
[b] Controlling for sociodemographic and clinical variables.
[c] For adjusted model.

of those previously reported among chronic pain patients (Cheatle and Gallagher, 2006; Knaster et al., 2012). A previous study using similar assessment methods (i.e. PHQ-9 and GAD-7 score ≥ 10) reported similar rates of depression and slightly lower rates of anxiety among patients with Musculoskeletal pain (Bair et al., 2008). In line with previous research, reported rates of depression and anxiety among pain patients in this study were markedly higher compared to reported rates within the general population using similar assessment tools (Neria et al., 2010). For example, estimated rates of current positive screening for depression and anxiety (i.e. scoring ≥ 10 in the PHQ-9 and GAD-7 questionnaires) in the general population in Germany (resembling a 10 total score in the PHQ-9 and GAD-7) were 5.6% and 5.1%, respectively (Kocalevent et al., 2013; Lowe et al., 2008).

Among individuals receiving prescription opioids exclusively, 57.1% screened positive for depression. This is in line with previous studies which have focused on pain patients receiving opioids (Campbell et al., 2015; Dersh et al., 2002). The inhibitory effect of opioids on the brain have been documented and longitudinal studies in the general population have linked recurrent use of opioids with an increased risk for developing depression (Martins et al., 2012). Though opioids in themselves have been repeatedly found to attenuate anxiety (see for example the review by Colasanti et al. (2011)), almost one half of the pain patients receiving prescription opioids in our sample screened positive for anxiety. This may be partially due to ongoing withdrawal symptoms among individuals receiving prescription opioids daily, which can results in well-characterized autonomic and somatic symptoms, which are classically accompanied by symptoms such as restlessness, irritability, anxiety and dysphoria (Haertzen et al., 1970; Koob and Le Moal, 2005; Schulteis and Koob, 1996).

Among pain patients receiving only MM, rates of depression and anxiety were approximately 22% and 21%, respectively. To the best of our knowledge these are novel findings regarding rates of these disorders among chronic pain patients receiving MM. It has been previously reported that among applicants presenting to a MM specialty practice in the US, 9.3% and 18.7% screened positive for depression and anxiety, respectively, yet these were not necessarily chronic pain patients (Nunberg et al., 2011). Our results are generally in line with reported 26% and 27% rates of DSM-IV based depression and anxiety, respectively, among daily cannabis users in the general population (Feingold et al., 2016b; Patton et al., 2002). Though frequency of use was not specifically examined in our study, previous reports indicate that more than two-thirds of MM users use marijuana daily (Reinarman et al., 2011), indicating that rates of depression and anxiety among individuals suffering from chronic pain in the MM group in our sample were similar to those of daily cannabis users in the general population. Accordingly, given repeated reports of higher levels of anxiety and depression among chronic pain patients in general, it is possible that MM partially attenuates these symptoms. This is in line with our findings that individuals in the OPMM group reported slightly lower levels of depression and anxiety compared to those in the OP group, though this may also be partially explained by lower reported levels of severe pain, and was not explored specifically in our study.

The nature of the association between cannabis use, depression and anxiety is not yet clear. Despite repeating evidence pointing that cannabis use and depression tend to co-occur and several longitudinal studies linking cannabis use with increased risk for developing depression (Lev-Ran et al., 2013; Swift et al., 2001), it has been recently suggested that this association may be in fact attributed to clinical confounders rather than to the direct effect of cannabis use (Feingold et al., 2015; WHO, 2016). In addition, it has actually been suggested that action at cannabinoid receptors is linked to a reduction in depressive behaviors (Degenhardt et al., 2000). Furthermore, research indicates a link between use of rimonabant, a cannabinoid CB1 receptor antagonist, and depression (Hill and Gorzalka, 2009; Horder et al., 2010), possibly implying that antagonistic (and not agonistic) activity on the CB1 receptor may induce depression.

Though cannabis has been shown to induce transient anxiety-like symptoms (D'Souza et al., 2004), a recent meta-analysis has questioned this finding (Twomey, 2017) and there is lack of data indicating increased incidence of anxiety disorders following cannabis use (Feingold et al., 2016b; WHO, 2016; Zvolensky et al., 2006). Furthermore, specific cannabinoids, particularly cannabidiol (CBD) has been reported to reduce anxiety (see for example Zuardi et al., 1982), indicating that specific cannabis strains including different ratios of cannabinoids may differentially affect anxiety.

Regarding specific symptoms of anxiety and depression, individuals in the OP group invariably reported these symptoms at higher frequency (nearly every day) compared to those in the MM group. The same was true for those in the OPMM group. This is important as higher frequency of symptoms may imply a more significant effect on the daily quality of life of patients receiving prescription opioids, though this could not be directly concluded from our study.

The present study has several limitations that should be taken in consideration. First, the response rate is lower than the recommended 70% (Bowling, 1996). This could be attributed to the fact that patients may be more reluctant to reply to questionnaires focusing on the use of analgesics and related substance use (Del Boca and Noll, 2000), particularly in a service where the substance itself is prescribed. It may well be that patients who refused to participate in the study differed from those who participated in levels of depression and

anxiety, thus limiting the generalizability of our findings. Second, as mentioned above the cross-sectional nature of the study does not allow for inference of directionality or possible causality of the association between treatment type and developing depression or anxiety. Even though lower levels of depression and anxiety among MM users were maintained after controlling for sociodemographic and clinical confounders, additional preliminary differences between the groups were unaccounted for and eventually influenced rates of depression and anxiety. In addition, though the PHQ-9 and GAD-7 questionnaires have consistently shown excellent validity in assessing depression and anxiety they could not be considered full clinical diagnosis thus limiting the generalizability of our results. Furthermore, this study did not take into consideration additional psychiatric co-morbidities (e.g. substance use disorders, psychotic disorders) or the use of psychiatric medications including antidepressants and anxiolytic medications which may be present among pain patients receiving opioids and MM and affect results. Finally this study included self-reported use of MM without access to the prescribed compounds themselves, therefore data regarding the cannabis composition (e.g. THC vs CBD ratios) which may differentially affect mood and anxiety (Micale et al., 2013; Zuardi et al., 1982) were lacking in this study.

As regulations and practices of medical marijuana differ substantially among countries, the local context must also be considered. In past decades, significant research on cannabis has emerged from Israel, including the isolation of Tetrahydrocannabinol (THC) by Prof. Raphael Mechoulam in the 1960s. Developments in the manufacturing of MM in Israel and its use for medical purposes have been substantial (Mechoulam, 2016; Sohn, 2015). Currently, formal indications for its use according to the Israeli Ministry of Health include the following areas: Cancer, Inflammatory Bowel Disease, Acquired Immunodeficiency Syndrome (AIDS), Multiple Sclerosis, Parkinson's Disease, Tourette's Syndrome, Pain, Terminal stages of life and Post-traumatic Stress Disorder. However, in general all formal indications for prescribing MM in Israel currently require exhaustion of common-practice medications. In the case of pain, this usually includes initial trials using prescription opioids. Despite the lack of systematic and updated data pertaining to severe opioid-related adverse effects, the incline in opioid use in Israel in recent years requires careful consideration practices of prescribing prescription opioids and the place of MM in the treatment of chronic pain.

The drastic incline in prescription opioids use in the US and other countries during recent years has raised concern due to an alarming increase in emergency room visits associated with adverse effects of opioid use, substance abuse-treatment admissions, and death from overdose (Jones et al., 2013; Volkow et al., 2014b). Growing awareness of the potential social and medical harms associated with opioid use is one of the background factors associated with the search for alternative modalities for pain reduction, such as MM. Our findings indicate that patients suffering from chronic pain receiving MM have lower rates of depression and anxiety compared to those receiving prescription opioids. While this cross-sectional data does not imply causality, as levels of depression and anxiety may further affect functionality and pain itself, these differences may prove important when deciding on the most appropriate treatment modality for chronic pain. Additional potential psychiatric outcomes of chronic cannabis use (such as increased risk for the incidence of psychotic disorders among those with predisposition), as well as physical effects of long term use (such as chronic bronchitis) should be carefully weighed against any potential benefits (Volkow et al., 2014a). Future longitudinal research, particularly studies focusing on differential effects of various cannabinoids (e.g. THC, CBD, etc.) on levels of depression and anxiety among chronic pain patients are required.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2017.04.026.

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