Psychiatry Research 313 (2022) 114573

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Medical cannabis use in Canada and its impact on anxiety and depression: A retrospective study

Faraz Sachedina *, Carole Chan, Rahim S. Damji, Olga J. de Sanctis

Harvest Medicine, Two Executive Place1824 Crowchild Tr. NW, Unit 101Calgary, ABT2M 3Y7

ARTICLE INFO

Keywords:
GAD-7
PHQ-9
Mental health
Anxiety treatment
Depression treatment

ABSTRACT

This was a retrospective study of patients utilizing medical cannabis who received their medical cannabis documentation and allotment from a Harvest Medicine clinic in Canada to determine the impact of medical cannabis on anxiety and depression outcomes. Patients included in the study were at least 18 years of age with completed validated questionnaires for anxiety (GAD-7) and depression (PHQ-9) at their initial evaluation and at least one follow-up visit. There were 7,362 patients included in the sample, of which the average age was 49.8 years, and 53.1% were female. There were statistically significant improvements between baseline and follow-up scores for both the GAD-7 and PHQ-9, with larger improvements seen for patients who were actively seeking medical cannabis to treat anxiety or depression. From 12 months on, those reporting anxiety had an average decrease in GAD-7 scores that was greater than the minimum clinically important difference of 4, and the same was seen for patients reporting depression from 18 months on, with the average decrease in PHQ-9 scores more than the MCID minimum clinically important difference of 5. This study provides some evidence to support the effectiveness of medical cannabis as a treatment for anxiety and depression.

1. Introduction

Medical cannabis first became legal in Canada in 2001 when the Marijuana Medical Access Regulations program was implemented (Fischer et al., 2015). This program was later replaced in 2013 when the Marijuana for Medical Purposes Regulations were implemented, allowing for licensed producers to cultivate cannabis for medical purposes, as opposed to patients accessing medical cannabis from the government, or growing it themselves (Ko et al., 2016). To access medical cannabis from a licensed producer, patients in Canada must consult with a medical doctor or qualified nurse practitioner, who will provide them with a medical document that indicates their daily allotment in grams and the length of time for their qualification, which cannot exceed one year (Ko et al., 2016).

Medical cannabis is used by patients for symptom management for an incredibly diverse range of conditions for which there are varying levels of clinical evidence of efficacy (Boehnke et al., 2019; Bonn-Miller et al., 2014; Eurich et al., 2019; Hazekamp et al., 2013; Mahabir et al., 2020; Reinarman et al., 2011; Sexton et al., 2016). In North America, chronic pain is consistently the most cited reason for seeking medical cannabis, often followed closely by mental health conditions such as anxiety, depression and post-traumatic stress disorder (Boehnke et al., 2019; Eurich et al., 2019; Lucas and Walsh, 2017; Mahabir et al., 2020; Sexton et al., 2016). Unfortunately the evidence surrounding the use of medical cannabis to treat mental health conditions is lagging far behind what is available for chronic pain.

Not only is there a paucity of evidence to support the use of medical cannabis to treat conditions such as anxiety and depression, the available data are conflicting, with some data that support its use, and other data to suggest that it may deteriorate or worsen an individual's anxiety or depression, which has led to circumstances that are challenging for patients, physicians and policymakers to navigate (Black et al., 2019; Crippa et al., 2009; Danielsson et al., 2016a; Feingold et al., 2017; Lev-Ran et al., 2014a; Mammen et al., 2018; Turna et al., 2017). However, despite the lack of clinical evidence, when surveyed, the majority of patients using medical cannabis for anxiety or depression report an improvement in their symptoms and a positive impact on their quality of life (Sexton et al., 2016; Turna et al., 2019).

As it is estimated that approximately 10% of Canadians are estimated to suffer from anxiety (McRae et al., 2016) and 11.3% from depression, ("Mental and substance use disorders in Canada," n.d.) this is an important population to be focusing research efforts on. Results of a

* Corresponding author.
E-mail address: faraz.sachedina@gmail.com (F. Sachedina).

https://doi.org/10.1016/j.psychres.2022.114573
Received 23 April 2021; Received in revised form 20 April 2022; Accepted 21 April 2022
Available online 25 April 2022

survey of 2032 Canadian medical cannabis patients from 2017 found that over 20% of respondents were using medical cannabis as a substitute for anti-depressant or anti-anxiety medications (Lucas and Walsh, 2017).

Real-world data are a powerful resource that may be used to advance knowledge and provide insight surrounding the practical application of a variety of treatments in use today (FDA, 2018). Data collected from medical cannabis clinics in Canada provide the opportunity to explore the use and outcomes of patients using medical cannabis in a real-world setting. To contribute to the available literature and medical understanding of the impact that cannabis has on anxiety and depression outcomes, we conducted a retrospective database study of Canadian medical cannabis patients.

2. Methods

This was a retrospective study of patients utilizing medical cannabis who received their medical cannabis documentation and allotment from a Harvest Medicine clinic in Canada. Harvest Medicine is an industry-leading network of specialty medical cannabis clinics that provides its patients in-person services from four clinic locations as well as through its secure telemedicine platform. The Harvest Medicine clinics provide qualified patients with the required medical documentation to in turn submit to their licensed producer of choice. Harvest Medicine's licensed producer referral practices are impartial, referring patients to a range of licensed producers based on the requirements of each patient.

Harvest Medicine uses the electronic medical record (EMR) system Input Health to collect data and manage patients' records. At their initial visit with their healthcare provider (HCP), the EMR includes fields to record date of birth, gender, education, income, employment status, martial and living status, health history and social behaviours; however, not all of these fields are mandatory to complete in the EMR. Additionally, patients of Harvest Medicine complete the General Anxiety Disorder-7 (GAD-7) and Patient Health Questionnaire-9 (PHQ-9) at their initial visit. The GAD-7 is one of the most frequently used, validated, self-reported questionnaires that is used to screen for, diagnose, and assess the severity of generalized anxiety disorder in clinical practice and research (Jordan et al., 2017; Spitzer et al., 2006). The PHQ-9 is a reliable and valid measure of depression severity and is comprised of a 9-item self-rated instrument that has been validated in general populations, medical populations and psychiatric samples (Kroenke et al., 2001; Rancans et al., 2018). Patients are also asked to complete the GAD-7 and PHQ-9 at follow-up, although during the data collection period from 2017 to 2020 it was not mandatory, and therefore not all patients have these scores available at follow-up.

In order to utilize the extensive amount of data in the Harvest Medicine EMR, a retrospective study protocol was written and reviewed by the Health Research Ethics Board of Alberta to ensure proper handling of the study data (Protocol # HREBA.CHC-20–0076). Data were exported and reviewed for 31,194 patients seen at a Harvest Medicine clinic between August 2017 and December 2020, and the following eligibility criteria were applied: 1) Patients 18 years of age or older, 2) Initial GAD-7 and PHQ-9 completed, 3) At least one follow-up GAD-7 or PHQ-9 completed. In total, 7362 patients met the eligibility criteria with an average of 2.5 (SD=0.85) score completions and were included in the analysis.

Patient data were analyzed using R Studio (Boston, MA). All information was summarized using descriptive statistics expressed as a mean (standard deviation (SD)) for continuous variables, and number (percent) for categorical variables. Follow-up GAD-7 and PHQ-9 scores were summarized by date into seven follow-up windows: 1 month, 3 months, 6 months, 12 months, 18 months, 24 months and greater than 24 months, and paired t-tests were conducted to compare the change in GAD-7 and PHQ-9 scores between baseline and each follow-up visit. This was done in two subgroups: patients who reported seeking medical cannabis to treat anxiety (for the GAD-7 analysis) or depression (for the PHQ-9 analysis) at baseline, and those who did not. Further, regression analyses were completed to determine if reporting anxiety or depression, age, gender or baseline GAD-7 or PHQ-9 score were significant predictors of the change in score from baseline to follow-up for GAD-7 and PHQ-9 scores. These analyses were conducted for three different timepoints: 3–6 months, 12–18 months, and 24 months or greater. For patients who had multiple follow-up scores reported within a window, the average of the scores was taken prior to calculating the difference between baseline and follow-up. All tests were completed with a significance level of 0.05. P-values less than 0.001 are expressed as $p<0.001$, and 95% confidence intervals (CI) are provided where appropriate.

3. Results

3.1. Demographics

The average age of the sample was 49.8 years (SD = 15.5), and 53.1% were female (Table 1). The most common level of education was college (38.9%) followed by high school (28.3%). Approximately one fifth of the sample was unemployed or disabled, and 45.8% were employed full-time. More than half of the sample (63.9%) earned $50,000 or more per year. The majority of patients were married or living common-law and living with their partner or partner and children. Two-thirds of the sample identified as current drinkers based on self-assessment, and 17.1% as current smokers. Among this sample, 43.9% of patients reported anxiety as a reason for seeking medical cannabis, and 25.9% reported depression.

3.2. GAD-7 scores

The mean baseline GAD-7 score among individuals reporting anxiety as a reason for seeking medical cannabis was 11.1 (SD=5.5), compared to 5.5 (SD=5.3) among those not seeking medical cannabis for anxiety (Table 2). Paired t-tests were conducted to compare the difference between follow-up and baseline scores at all timepoints. Among those reporting anxiety as a reason for seeking medical cannabis treatment, GAD-7 scores decreased over time (Fig. 2), and at all timepoints the difference between the original baseline scores and the follow-up scores were statistically significant, with the largest mean difference seen for scores recorded more than two years following the baseline score (mean difference = 5.2, $p<0.001$). The largest decrease in scores was seen between 1 and 3 months, after which the average scores leveled off slightly, but did not increase. GAD-7 scores also decreased among those not reporting anxiety as a reason for seeking treatment, although not as much as in patients reporting anxiety. The lowest average score was reported at three months after which the scores increased, although they did not return to the same level as baseline. Paired t-tests demonstrated statistically significant differences in scores at all time points when comparing baseline to follow-up.

Regression analyses determined that at all time points (3–6 months, 12–18 months, and 24+ months), a higher baseline score was predictive of a greater decrease in follow-up scores (Supplemental Table 1). Further, at 12–18 months and 24+ months, being older and being male were predictive of greater decreases in GAD-7 scores. The changes in scores are plotted in Supplemental Figs. 1–3 and demonstrate a relationship between baseline GAD-7 score and subsequent change.

Overall, more than three-quarters of patients reported no change or a decrease in GAD-7 scores from baseline to follow-up, and at two years, almost half of patients reported a decrease of 4 points or more, representing the minimum clinically important difference (MCID) (Table 4). The proportion of patients who saw their score increase from baseline to follow-up decreased over time, with 24.0% at 3–6 months down to 19.3% at 24+ months.

Table 1
Demographic characteristics for 7362 patients included in the retrospective study of medical cannabis patients.

	N (%) or Mean (SD)
Age (n = 7362)	49.8 (15.5)
Gender (n = 7362)	
Female	3912 (53.1%)
Male	3442 (46.8%)
Other	8 (0.1%)
Education (n = 6814)	
College	2652 (38.9%)
High school	1927 (28.3%)
Undergraduate degree	1255 (18.4%)
Postgraduate degree	558 (8.2%)
Professional degree	238 (3.5%)
Grade school	154 (2.3%)
Postdoctoral degree	30 (0.4%)
Employment (n = 6998)	
Full-time	3206 (45.8%)
Part-time	772 (11.0%)
Unemployed	642 (9.2%)
Disabled	660 (9.4%)
Homemaker	244 (3.5%)
On leave	182 (2.6%)
Other	1292 (18.5%)
Income (n = 6127)	
Under $20,000	577 (9.4%)
$20,000-$35,000	725 (11.8%)
$35,000-$50,000	908 (14.8%)
$50,000-$75,000	1147 (18.7%)
$75,000-$100,000	1116 (18.2%)
$100,000-$150,000	952 (15.5%)
Over $150,000	702 (11.5%)
Marital status (n = 7069)	
Married	3758 (53.2%)
Single	1686 (23.9%)
Common law	740 (10.5%)
Divorced	446 (6.3%)
Separated	247 (3.5%)
Widowed	192 (2.7%)
Living situation (n = 6050)	
Lives with partner/spouse	2531 (41.8%)
Lives with partner/spouse and children	1546 (25.6%)
Lives alone	1002 (16.6%)
Lives with housemate(s)	605 (10.0%)
Lives with children	366 (6.0%)
Alcohol history (n = 6606)	
Current drinker	4410 (66.8%)
Former drinker	1078 (16.3%)
Never drinker	1118 (16.9%)
Smoking history (n = 6561)	
Never smoker	2884 (44.0%)
Former smoker	2559 (39.0%)
Current everyday smoker	852 (13.0%)
Current someday smoker	266 (4.0%)
Conditions reported (n = 7362)	
Anxiety	3230 (43.9%)
Depression	1905 (25.9%)
Any other	6998 (91.1%)

Table 1 summarizes the baseline demographic characteristics for the patients included in the retrospective study. The number of patients with the characteristic reported is specified in brackets for each row. SD = standard deviation.

3.3. PHQ-9 scores

The mean baseline PHQ-9 score among individuals reporting depression as a reason for seeking medical cannabis was 13.7 (SD=6.0), compared to 7.4 (SD=5.6) among those not seeking medical cannabis for depression (Table 3). Paired t-tests were conducted to compare the differences between follow-up and baseline scores. Among those reporting depression, PHQ-9 scores decreased over time (Fig. 2), and at all timepoints the difference between the follow-up and baseline score was statistically significant. The most noticeable decrease in scores was between baseline and three months, after which average scores continued to decrease, but not as drastically. PHQ-9 scores also decreased from baseline to follow-up for those not reporting depression, and although the differences were not as large, they were significantly different statistically. For these patients, the average scores leveled-off following three months.

Table 2
GAD-7 scores over time.

	Treatment for Anxiety(n = 3230)	Treatment for Other Condition(n = 4132)
Baseline	11.1 (5.5)	5.5 (5.3)
1 month	(n = 75)	(n = 92)
Mean (SD)	11.1 (4.7)	5.2 (4.7)
Mean	1.9	1.0
Difference	0.8–3.0	0.1–1.8
95% CI	<0.001	0.03
p-value		
3 months	(n = 524)	(n = 789)
Mean (SD)	7.6 (5.4)	3.4 (4.3)
Mean	3.7	1.2
Difference	3.2–4.2	0.9–1.5
95% CI	<0.001	<0.001
p-value		
6 months	(n = 511)	(n = 663)
Mean (SD)	7.4 (5.4)	3.8 (4.5)
Mean	3.7	1.7
Difference	3.2–4.2	1.3–2.0
95% CI	<0.001	<0.001
p-value		
12 months	(n = 1363)	(n = 1782)
Mean (SD)	6.9 (5.2)	3.7 (4.3)
Mean	4.1	1.5
Difference	3.8–4.4	1.3–1.7
95% CI	<0.001	<0.001
p-value		
18 months	(n = 762)	(n = 815)
Mean (SD)	6.6 (5.1)	3.8 (4.6)
Mean	4.3	2.3
Difference	3.9–4.7	2.0–2.7
95% CI	<0.001	<0.001
p-value		
24 months	(n = 425)	(n = 396)
Mean (SD)	6.1 (5.0)	3.9 (4.3)
Mean	4.6	2.9
Difference	4.0–5.1	2.4–3.4
95% CI	<0.001	<0.001
p-value		
>24 months	(n = 766)	(n = 661)
Mean (SD)	6.0 (5.0)	4.3 (4.7)
Mean	5.2	2.8
Difference	4.8–5.6	2.3–3.2
95% CI	<0.001	<0.001
p-value		

Table 2 summarizes the GAD-7 scores for patients included in the study over time, separated by those who reported seeking medical cannabis to treat anxiety and those who did not. The number of patients with a follow-up score is reported for each time period. Paired t-tests were conducted to determine if the difference between the follow-up score and baseline score for the group of patients was statistically significant. SD = standard deviation; CI = confidence interval.

Regression analysis determined that at all time points (3–6 months, 12–18 months, and 24+ months), a higher baseline score and being male were predictive of a greater decrease in follow-up scores (Supplemental Table 1). The changes in scores are plotted in Supplemental Figs. 4–6 and demonstrate the relationship between baseline PHQ-9 score and subsequent change.

A similar proportion of patients improved or stayed the same with respect to their PHQ-9 scores as with GAD-7 scores, ranging from 74.4% to 82.2% of patients seeing an improvement or no change between baseline and follow-up. The largest proportion of patients who improved by the 5-point MCID for the PHQ-9, was at 24+ months, similar to the GAD-7. Between one-quarter to one-fifth of patients reported worsening PHQ-9 scores at follow-up.

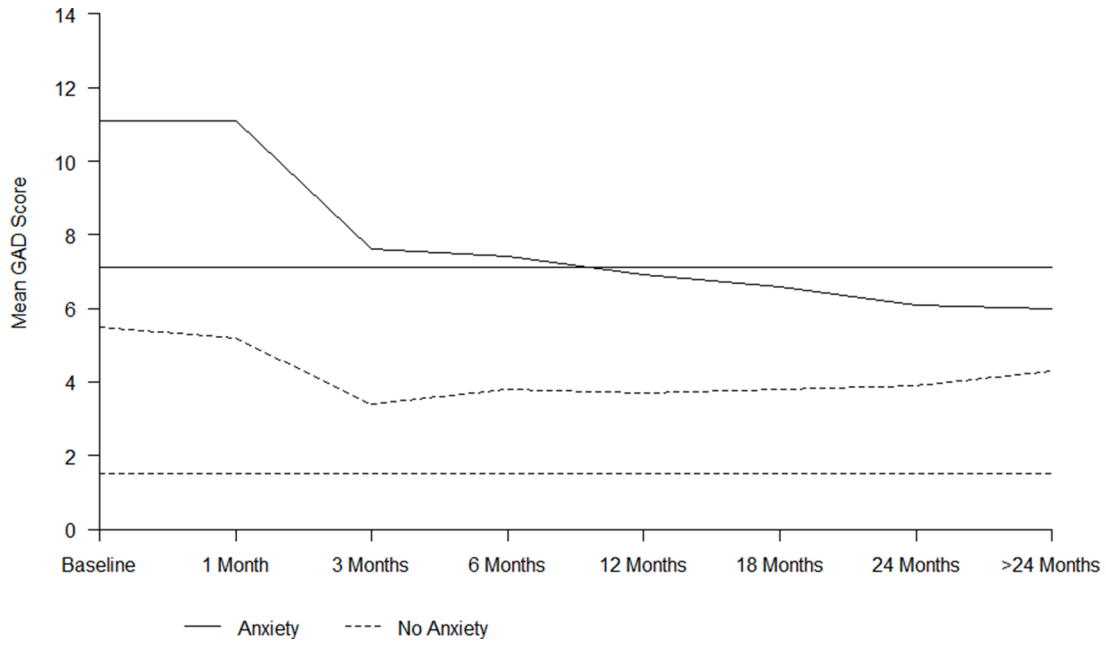

Fig. 1. Mean GAD-7 scores over time, by individuals reporting anxiety compared to those who did not. The horizontal lines represent the minimal clinically important difference from baseline for each group.

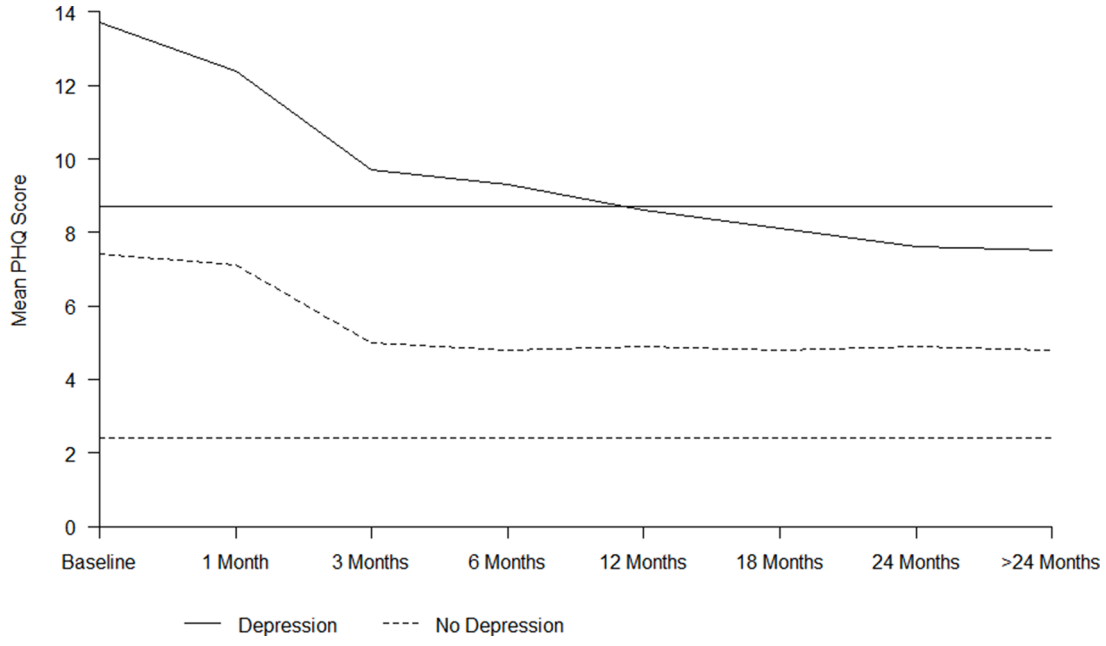

Fig. 2. Mean PHQ-9 scores over time, by individuals reporting depression compared to those who did not. The horizontal lines represent the minimal clinically important difference from baseline for each group.

4. Discussion

The real-world data available for this current study provide much needed insight into the use of medical cannabis to treat anxiety and depression. The patients included in this study sought medical cannabis treatment at their own discretion and were provided with their medical documentation at the judgement of their HCP, representing a substantial amount of real-world data. Patients included in these analyses were able to choose their medical cannabis products, including the method of administration and concentration of THC and CBD.

4.1. Demographics

Comparing the population of patients included in the current study to the general Canadian population, there were many similarities. With respect to education, a greater prevalence of our patients reported a college education compared to results from the 2016 Canadian census; 38.9% compared to 33.2% ("Education Highlight Tables, 2016 Census - Highest level of educational attainment (general) by selected age groups 25 to 64, both sexes,% distribution 2016, Canada, provinces and territories, 2016 Census – 25% Sample data," n.d.). The proportion of our patients with a bachelor's degree or higher was very similar to the Canadian population, 30.1% compared to 28.5%. Overall, the patient

Table 3
PHQ-9 scores over time.

	Treatment for Depression(n = 1905)	Treatment for other Condition (n = 5457)
Baseline	13.7 (6.0)	7.4 (5.6)
1 month	(n = 50)	(n = 117)
Mean (SD)	12.4 (5.3)	7.1 (5.6)
Mean Difference	3.6	0.6
95% CI	2.0–5.2	−0.2–1.3
p-value	<0.001	0.15
3 months	(n = 322)	(n = 978)
Mean (SD)	9.7 (6.3)	5.0 (4.7)
Mean Difference	4.8	1.6
95% CI	4.1–5.5	1.3–1.9
p-value	<0.001	<0.001
6 months	(n = 326)	(n = 845)
Mean (SD)	9.3 (6.6)	4.8 (4.7)
Mean Difference	4.4	2.0
95% CI	3.7–5.1	1.7–2.3
p-value	<0.001	<0.001
12 months	(n = 865)	(n = 2240)
Mean (SD)	8.6 (5.8)	4.9 (4.7)
Mean Difference	4.8	2.4
95% CI	4.4–5.3	2.2–2.6
p-value	<0.001	<0.001
18 months	(n = 406)	(n = 1158)
Mean (SD)	8.1 (5.7)	4.8 (4.6)
Mean Difference	5.7	3.0
95% CI	5.1–6.3	2.7–3.3
p-value	<0.001	<0.001
24 months	(n = 193)	(n = 611)
Mean (SD)	7.6 (5.8)	4.9 (4.9)
Mean Difference	6.1	3.7
95% CI	5.1–7.0	3.2–4.1
p-value	<0.001	<0.001
>24 months	(n = 344)	(n = 1099)
Mean (SD)	7.5 (5.7)	4.8 (4.6)
Mean Difference	6.4	3.8
95% CI	5.7–7.1	3.5–4.2
p-value	<0.001	<0.001

Table 3 summarizes the PHQ-9 scores for patients included in the study over time, separated by those who reported seeking medical cannabis to treat depression and those who did not. The number of patients with a follow-up score is reported for each time period. Paired t-tests were conducted to determine if the difference between the follow-up score and baseline score for the group of patients was statistically significant. SD = standard deviation; CI = confidence interval.

Table 4
Increases and decreases in GAD-7 and PHQ-9 scores.

	3–6 months	12–18 months	24+ months
GAD-7	n = 2210	n = 4210	n = 1876
Decrease or No Change	1680 (76.0%)	3240 (77.0%)	1514 (80.7%)
Overall	946 (42.8%)	1631 (38.7%)	593 (31.6%)
3 points or less	734 (33.2%)	1609 (38.2%)	921 (49.1%)
4 points or more Increase	530 (24.0%)	970 (23.0%)	362 (19.3%)
PHQ-9	n = 2198	n = 4172	n = 1886
Decrease or No Change	1636 (74.4%)	3294 (79.0%)	1550 (82.2%)
Overall	1019 (46.4%)	1813 (43.5%)	725 (38.4%)
4 points or less	617 (28.1%)	1481 (35.5%)	825 (43.7%)
5 points or more Increase	563 (25.6%)	878 (21.0%)	336 (17.8%)

Table 4 summarizes the average changes in GAD-7 and PHQ-9 scores by follow-up timepoint. The number of patients with a follow-up score is reported for each timepoint. The minimum clinically important difference for the GAD-7 is 4, and for the PHQ-9 is 5.

sample had an education level very comparable, or slightly higher than the general Canadian population. From the 2016 Canadian census, 37.4% of individuals aged 25 and older reported working full-time in the previous year, compared to 45.8% of patients from the current study ("Labour Highlight Tables, 2016 Census). However, a much smaller proportion of our patients reported part-time work than compared to the Canadian population, 11.0% compared to 30.5%. With respect to those who did not work in the previous year, this was reported by 32.1% of the Canadian population compared to 24.7% of our patients. On a high level, our patient population differed by about 6% with respect to marital status compared to the general Canadian population. Of the patient population, 63.7% were partnered, compared to 57.5% of the Canadian population, and 36.3% were not partnered compared to 42.5% of the Canadian population ("Families, Households and Marital Status Highlight Tables,").

Current alcohol consumption was lower among the patient population than the general Canadian population; however, the measures of alcohol history may not be directly comparable. Of the patient population, 66.8% reported being current drinkers. Per Health Canada, 78% of Canadians reported consuming an alcoholic beverage in the last year ("Canadian Tobacco Alcohol and Drugs (CTADS) Survey: 2017 summary - Canada.ca,"). Tobacco smoking was slightly higher among the patient population than the general population; 17.1% compared to 15.0% ("Canadian Tobacco Alcohol and Drugs (CTADS) Survey: 2017 summary - Canada.ca,"). Overall, demographics of the patient population were comparable to the general Canadian population, demonstrating that at least among our sample, the average Canadian medical cannabis user does not differ substantially from the average Canadian.

Compared to other studies of medical cannabis patients, more demographic information was available in the EMR for our study patients than what is typically reported. Employment rates were similar between our patient population and a population of 1746 Californian medical cannabis patients, but our patient sample reported higher education (Reinarman et al., 2011). Employment and education were similar to the patient population who completed a survey by Sexton et al., which included medical cannabis patients from 18 countries (Sexton et al., 2016). Females however, were disproportionately represented in the current patient sample compared to most medical cannabis population studies, but this may be explained by the fact that 50.0% of the current patient population reported anxiety and/or depression, and these two conditions are more commonly reported among female medical cannabis patients than male (Mahabir et al., 2020). The average age was slightly younger than a comparable Canadian population of medical cannabis patients, 51.2 years compared to 49.8 years (Eurich et al., 2019).

Among patients reporting anxiety or depression as a reason for seeking medical cannabis treatment at baseline, there was a clinically significant difference in their scores reported at later follow-ups. From 12 months on, those reporting anxiety had an average decrease in GAD-7 scores that was greater than the MCID of 4 (Toussaint et al., 2020). The same was seen for those reporting depression from 18 months on, with the average decrease in PHQ-9 scores more than the MCID of 5 (Löwe et al., 2004; Round et al., 2020). For both outcome measures, the most notable change in scores occurred at the 3-month mark, after which scores continued to trend down but at a more gradual pace. We hypothesize that this occurred as a result of patients using the first three months to find the product(s) that benefitted them most and maintained a level of success following this. Given the retrospective nature of the study and the absence of an inactive comparator, it is possible that some of the benefit patients derived from their treatment could have been due to a placebo effect; however, as average scores did not increase again after their initial descent it shows promise that there was some true and lasting benefit to treatment. Among those reporting anxiety and depression, average baseline scores correlated to moderate anxiety and depression, which by 3 months dropped to mild severity (Kroenke et al., 2001; Levis et al., 2019; Manea et al., 2015; Spitzer et al., 2006).

Treatment with medical cannabis also on average benefited patients who did not seek treatment for anxiety or depression specifically. Although following the 3-month mark average GAD-7 scores rose slightly, and PHQ-9 scores leveled-off, they did not return to the baseline level. The average baseline scores for both measures corresponded to mild severity of anxiety and depression, and while the categorization for depression did not change, the average GAD-7 score among this patient group dropped below 4, representing minimal anxiety following their initiation of cannabis treatment.

An interesting trend emerged among the change in GAD-7 and PHQ-9 scores when plotted against baseline scores and when input into regression analyses; patients who began their treatment with cannabis with lower baseline scores were significantly more likely to report worse outcome scores at follow-up. This trend may provide some insight into the conflicting evidence in the literature as it relates to the impact that cannabis has on anxiety and depression (Black et al., 2019; Crippa et al., 2009; Danielsson et al., 2016a; Feingold et al., 2017; Lev-Ran et al., 2014a; Mammen et al., 2018; Turna et al., 2017). Based on our findings, we propose the explanation that patients who actively seek treatment with medical cannabis for anxiety and depression are more likely to benefit as they are selecting products and using cannabis mindfully with this specific intention, whereas patients who are using cannabis for other indications may instead find their anxiety and/or depression symptoms slightly worsened as these indications are not being considered as part of their treatment goals. We can however assume that this is not the case for all individuals who do not actively seek treatment for anxiety or depression, as average scores still decreased over time for this group.

The results of this study are largely encouraging for the use of cannabis to manage symptoms of anxiety and depression, which may be surprising to some based on the inconclusiveness of many prior studies. The most recently published systematic review and meta-analysis reviewing the use of medicinal cannabinoids to treat various mental disorders found minimal evidence to indicate that medical cannabis can improve anxiety or depression (Black et al., 2019). A major limitation of included studies was that the studies were not examining anxiety or depression as a primary condition, but rather as a secondary outcome alongside another medical condition, most frequently pain or multiple sclerosis. Further to that, the majority of these trials had small sample sizes and short intervention periods. Other literature examining the relationship between cannabis use, anxiety and depression has largely focused on temporal causality and defining if cannabis use leads to the development of anxiety or depression, or if anxiety or depression leads individuals to cannabis use (Danielsson et al., 2016b; Grunberg et al., 2015; Lev-Ran et al., 2014b; Mammen et al., 2018).

This study uses a patient population and methodology not otherwise available in the literature for direct comparison. The large sample size and use of validated questionnaires are significant strengths of the current study in addition to the use of a sample of patients who were certified medical cannabis users. However, the retrospective nature limited aspects of the study, including missing demographic data and the use of a convenience sample. Further, pharmaceutical medication use, psychiatric therapy use, psychotic symptoms, and diagnostic information outside of the GAD-7 and PHQ-9 were not available. Limitations with EMR data collection were also identified including the absence of data regarding product selection and use. This has since been addressed within the Harvest Medicine EMR so that data collection moving forward will include this additional information in sufficient detail for future analysis. Further, the sample of patients cannot be assumed to be representative of all medical cannabis patients, as all patients came from a single clinical network within Canada. Areas of future research for Harvest Medicine will include more in-depth analyses into patients' medical characteristics, pharmaceutical and cannabis treatment selections to further explore the impact of medical cannabis treatment on individual conditions.

To our knowledge, this study is the largest completed to date examining the impact of medical cannabis use on anxiety and depression outcomes utilizing longitudinal data and validated questionnaires. It provides evidence on the effectiveness of medical cannabis as a treatment for anxiety and depression that otherwise is not currently available, demonstrating that patients who seek treatment with medical cannabis for anxiety and depression can experience clinically significant improvements. This study offers reasonable justification for the completion of large clinical trials to further the understanding of medical cannabis as a treatment for anxiety and depression.

CRediT authorship contribution statement

Faraz Sachedina: Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration. **Carole Chan:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration. **Rahim S. Damji:** Writing – review & editing, Supervision. **Olga J. de Sanctis:** Conceptualization, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

Dr. Sachedina and Ms. Chan are employees of Harvest Medicine and were compensated for their work on this manuscript as per their employee agreement.

Dr. de Sanctis is an independent physician consultant for Harvest Medicine and was not compensated with regard to this study.

Dr. Damji is an independent physician consultant for Harvest Medicine and was not compensated with regard to this study.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This work was supported as part of an internal project at Harvest Medicine. Authors were compensated according to their employment agreement.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2022.114573.

References

Black, N., Stockings, E., Campbell, G., Tran, L.T., Zagic, D., Hall, W.D., Farrell, M., Degenhardt, L., 2019. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. Lancet Psychiatry. https://doi.org/10.1016/S2215-0366(19)30401-8.

Boehnke, K.F., Gangopadhyay, S., Clauw, D.J., Haffajee, R.L., 2019. Qualifying conditions of medical cannabis license holders in the United States. Health Aff. 38, 295–302. https://doi.org/10.1377/hlthaff.2018.05266.

Bonn-Miller, M.O., Boden, M.T., Bucossi, M.M., Babson, K.A., 2014. Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. Am. J. Drug Alcohol Abuse 40, 23–30. https://doi.org/10.3109/00952990.2013.821477.

Crippa, J.A., Zuardi, A.W., Martín-Santos, R., Bhattacharyya, S., Atakan, Z., McGuire, P., Fusar-Poli, P., 2009. Cannabis and anxiety: a critical review of the evidence. Hum. Psychopharmacol. https://doi.org/10.1002/hup.1048.

Danielsson, A.K., Lundin, A., Agardh, E., Allebeck, P., Forsell, Y., 2016a. Cannabis use, depression and anxiety: a 3-year prospective population-based study. J. Affect. Disord. 193, 103–108. https://doi.org/10.1016/j.jad.2015.12.045.

Danielsson, A.K., Lundin, A., Agardh, E., Allebeck, P., Forsell, Y., 2016b. Cannabis use, depression and anxiety: a 3-year prospective population-based study. J. Affect. Disord. 193, 103–108. https://doi.org/10.1016/j.jad.2015.12.045.

Education Highlight Tables, 2016 Census - Highest level of educational attainment (general) by selected age groups 25 to 64, both sexes,% distribution 2016, Canada, provinces and territories, 2016 Census –25% Sample data [WWW Document], n.d. URL https://www12.statcan.gc.ca/census-recensement/2016/dp-pd/hlt-fst/edu-sco/Table.cfm?Lang=E&T=11&Geo=00&View=2&Age=2 (accessed 12.3.20).

Eurich, D.T., Hanlon, J.G., Boisvenue, J.J., Meng, H., Dyck, J.R.B., 2019. A description of the medical cannabis use in Ontario, Canada. Cannabis Cannabinoid Res. 4, 131–135. https://doi.org/10.1089/can.2018.0036.

FDA, 2018. Framework For FDA's Real-World Evidence Program. FDA Framew.

Feingold, D., Brill, S., Goor-Aryeh, I., Delayahu, Y., Lev-Ran, S., 2017. Depression and anxiety among chronic pain patients receiving prescription opioids and medical marijuana. J. Affect. Disord. 218, 1–7. https://doi.org/10.1016/j.jad.2017.04.026.

Fischer, B., Kuganesan, S., Room, R., 2015. Medical marijuana programs: implications for cannabis control policy - observations from Canada. Int. J. Drug Policy. https://doi.org/10.1016/j.drugpo.2014.09.007.

Grunberg, V.A., Cordova, K.A., Bidwell, L.C., Ito, T.A., 2015. Can marijuana make it better? Prospective effects of marijuana and temperament on risk for anxiety and depression. Psychol. Addict. Behav. 29, 590–602. https://doi.org/10.1037/adb0000109.

Hazekamp, A., Ware, M.A., Muller-Vahl, K.R., Abrams, D., Grotenhermen, F., 2013. The medicinal use of cannabis and cannabinoids-an international cross-sectional survey on administration forms. J. Psychoact. Drugs 45, 199–210. https://doi.org/10.1080/02791072.2013.805976.

Jordan, P., Shedden-Mora, M.C., Löwe, B., 2017. Psychometric analysis of the Generalized Anxiety Disorder scale (GAD-7) in primary care using modern item response theory. PLoS ONE 12, 1–14. https://doi.org/10.1371/journal.pone.0182162.

Ko, G.D., Bober, S.L., Mindra, S., Moreau, J.M., 2016. Medical cannabis – the Canadian perspective. J. Pain Res. https://doi.org/10.2147/JPR.S98182.

Kroenke, K., Spitzer, R.L., Williams, J.B.W., 2001. The PHQ-9: validity of a brief depression severity measure. J. Gen. Intern. Med. 16, 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x.

Labour Highlight Tables, 2016 Census - Work activity during the reference year by selected age groups (65 years and over), both sexes, total – highest certificate, diploma or degree, 2015 counts, Canada, provinces and territories, 2016 Census –25% Sample data [WWW Document], n.d. URL https://www12.statcan.gc.ca/census-recensement/2016/dp-pd/hlt-fst/lab-tra/Table.cfm?Lang=E&T=11&Geo=00&SP=1&view=1&age=5&sex=1&education=1 (accessed 12.3.20).

Lev-Ran, S., Roerecke, M., Le Foll, B., George, T.P., McKenzie, K., Rehm, J., 2014a. The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. Psychol. Med. 44, 797–810. https://doi.org/10.1017/S0033291713001438.

Lev-Ran, S., Roerecke, M., Le Foll, B., George, T.P., McKenzie, K., Rehm, J., 2014b. The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. Psychol. Med. 44, 797–810. https://doi.org/10.1017/S0033291713001438.

Levis, B., Benedetti, A., Thombs, B.D., 2019. Accuracy of patient health questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. BMJ 365. https://doi.org/10.1136/bmj.l1476.

Löwe, B., Unützer, J., Callahan, C.M., Perkins, A.J., Kroenke, K., 2004. Monitoring depression treatment outcomes with the patient health questionnaire-9.

Lucas, P., Walsh, Z., 2017. Medical cannabis access, use, and substitution for prescription opioids and other substances: a survey of authorized medical cannabis patients. Int. J. Drug Policy 42, 30–35. https://doi.org/10.1016/j.drugpo.2017.01.011.

Mahabir, V.K., Merchant, J.J., Smith, C., Garibaldi, A., 2020. Medical cannabis use in the United States: a retrospective database study. J. Cannabis Res. 2, 32. https://doi.org/10.1186/s42238-020-00038-w.

Mammen, G., Rueda, S., Roerecke, M., Bonato, S., Lev-Ran, S., Rehm, J., 2018. Association of cannabis with long-term clinical symptoms in anxiety and mood disorders: a systematic review of prospective studies. J. Clin. Psychiatry. https://doi.org/10.4088/JCP.17r11839.

Manea, L., Gilbody, S., McMillan, D., 2015. A diagnostic meta-analysis of the patient health questionnaire-9 (PHQ-9) algorithm scoring method as a screen for depression. Gen. Hosp. Psychiatry 37, 67–75. https://doi.org/10.1016/j.genhosppsych.2014.09.009.

McRae, L., O'Donnell, S., Loukine, L., Rancourt, N., Pelletier, C., 2016. Mood and anxiety disorders in Canada, 2016. Healt Promot. Chronic Dis. Prev. Can. https://doi.org/10.24095/hpcdp.36.12.05.

Rancans, E., Trapencieris, M., Ivanovs, R., Vrublevska, J., 2018. Validity of the PHQ-9 and PHQ-2 to screen for depression in nationwide primary care population in Latvia. Ann. Gen. Psychiatry 17, 1–8. https://doi.org/10.1186/s12991-018-0203-5.

Reinarman, C., Nunberg, H., Lanthier, F., Heddleston, T., 2011. Who are medical marijuana patients? Population characteristics from nine California assessment clinics. J. Psychoact. Drugs 43, 128–135. https://doi.org/10.1080/02791072.2011.587700.

Round, J.M., Lee, C., Hanlon, J.G., Hyshka, E., Dyck, J.R.B., Eurich, D.T., 2020. Changes in patient health questionnaire (PHQ-9) scores in adults with medical authorization for cannabis. BMC Public Health 20, 987. https://doi.org/10.1186/s12889-020-09089-3.

Sexton, M., Cuttler, C., Finnell, J.S., Mischley, L.K., 2016. A cross-sectional survey of medical cannabis users: patterns of use and perceived efficacy. Cannabis Cannabinoid Res. 1, 131–138. https://doi.org/10.1089/can.2016.0007.

Spitzer, R.L., Kroenke, K., Williams, J.B.W., Löwe, B., 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch. Intern. Med. 166, 1092–1097. https://doi.org/10.1001/archinte.166.10.1092.

Toussaint, A., Hüsing, P., Gumz, A., Wingenfeld, K., Härter, M., Schramm, E., Löwe, B., 2020. Sensitivity to change and minimal clinically important difference of the 7-item generalized anxiety disorder questionnaire (GAD-7). J. Affect. Disord. 265, 395–401. https://doi.org/10.1016/j.jad.2020.01.032.

Turna, J., Patterson, B., Van Ameringen, M., 2017. Is cannabis treatment for anxiety, mood, and related disorders ready for prime time? Depress. Anxiety. https://doi.org/10.1002/da.22664.

Turna, J., Simpson, W., Patterson, B., Lucas, P., Van Ameringen, M., 2019. Cannabis use behaviors and prevalence of anxiety and depressive symptoms in a cohort of Canadian medicinal cannabis users. J. Psychiatr. Res. 111, 134–139. https://doi.org/10.1016/j.jpsychires.2019.01.024.