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Medical cannabis treatment for chronic pain: Outcomes and prediction of response

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Abstract

Background: Although studied in a few randomized controlled trials, the efficacy of medical cannabis (MC) for chronic pain remains controversial. Using an alternative approach, this multicentre, questionnaire-based prospective cohort was aimed to assess the long-term effects of MC on chronic pain of various aetiologies and to identify predictors for MC treatment success.

Methods: Patients with chronic pain, licensed to use MC in Israel, reported weekly average pain intensity (primary outcome) and related symptoms before and at 1, 3, 6, 9 and 12 months following MC treatment initiation. A general linear model was used to assess outcomes and identify predictors for treatment success (≥30% reduction in pain intensity).

Results: A total of 1,045 patients completed the baseline questionnaires and initiated MC treatment, and 551 completed the 12-month follow-up. At 1 year, average pain intensity declined from baseline by 20% [−1.97 points (95%CI = −2.13 to −1.81;

$p < 0.001$)]. All other parameters improved by 10%–30% ($p < 0.001$). A significant decrease of 42% [reduction of 27 mg; (95%CI = −34.89 to 18.56, $p < 0.001$)] from baseline in morphine equivalent daily dosage of opioids was also observed. Reported adverse effects were common but mostly non-serious. Presence of normal to long sleep duration, lower body mass index and lower depression score predicted relatively higher treatment success, whereas presence of neuropathic pain predicted the opposite.

Conclusions: This prospective study provides further evidence for the effects of MC on chronic pain and related symptoms, demonstrating an overall mild-to-modest long-term improvement of the tested measures and identifying possible predictors for treatment success.

1 | INTRODUCTION

With almost no new drug approvals for chronic pain in nearly two decades, low efficacy and significant safety concerns regarding currently available pharmacological agents, there is a huge clinical challenge in providing effective chronic pain management (Busse et al., 2018; Fitzcharles & Eisenberg, 2018). Not surprisingly, medical cannabis (MC) is increasingly viewed as a legitimate therapy for chronic pain (Choo et al., 2016) and its medically approved use is growing substantially despite a clear lack of solid evidence for its effectiveness and safety (Hill & Palastro, 2017).

MC has been studied most extensively in the context of neuropathic pain (NP), and rarely in relation to other pain conditions. So far, over 20 randomized controlled trials (RCTs) have been conducted, some on cannabis-based medicines and others on herbal cannabis (Aviram & Samuelly-Leichtag, 2017). The inconsistent results of these studies have led to numerous meta-analyses (Andreae et al., 2015; Aviram & Samuelly-Leichtag, 2017; Iskedjian et al., 2007; Martín-Sánchez et al., 2009; Meng et al., 2017; Mücke et al., 2018; Nugent et al., 2017; Stockings et al., 2018; Whiting et al., 2015; Wong et al., 2020), altogether showing limited-to-modest analgesic effects at best with relatively frequent adverse effects. Hence, the effectiveness of MC for chronic pain remains questionable.

Hence, two major important questions related to MC and chronic pain should be addressed: First, has the focus on studying (and possibly on prescribing) MC mainly for NP been justified? In other words, is MC truly more effective for NP than for other pain conditions (e.g. inflammatory pain)? Indeed, a recent meta-regression that compared the efficacy of cannabinoids for NP to its efficacy for other chronic pain aetiologies found no significant difference between them (Wong et al., 2020). Second, can predictors for treatment success be identified? Typically, RCTs are not aimed at answering these questions, whereas well-conducted, large-scale cohort studies may be helpful. Indeed, several cohort studies on MC for chronic pain have been published in recent years (Abuhasira et al., 2018; Haroutounian et al., 2016; Hoggart et al., 2015; Ware et al., 2015; Yassin et al., 2016; Zaki et al., 2017) and point towards its potential effectiveness. However, none of these studies provided data on the relative effectiveness of MC for different chronic pain conditions nor identified measures, which can predict good treatment response. Furthermore, most of these cohort studies had significant methodological shortcomings such as a lack of multiple follow-up time points or a disregard for missing data.

The aims of the present study were to collect high-quality, large-scale, longitudinal and comprehensive data on (a) the effectiveness of MC for different chronic pain conditions and related symptoms, (b) MC safety features and (c) characteristics identifying patients who are prone to respond to MC treatment.

Significance

This "real world" paper shows that MC mildly to modestly attenuates chronic pain and related symptoms. MC treatment can also cause frequent, mostly non-serious adverse effects, although central nervous system (CNS)-related AEs that can impair the ability to drive vehicles are not uncommon. This study is novel in identifying possible predictors for treatment success, including normal to long sleep duration, lower BMI and lower depression scores. In contrast to current beliefs, the diagnosis of neuropathic pain predicts a less favourable outcome. These findings provide physicians with new data to support decision making on recommendations for MC treatment.

2 | METHODS

2.1 | Israeli MC regulations

The Israeli Ministry of Health (IMOH) regulations allow issuing an MC license to treat chronic non-cancer pain preferably of neuropathic origin only in patients who have been using conventional treatment options for at least a year, unsuccessfully, and have exhausted all other treatment options (Landshaft et al., 2017). In the case of chronic NP at least several types of first- and second-line medications should have been tried including anticonvulsants, antidepressants and opioids. Other chronic pain aetiologies (i.e. musculoskeletal, headache causing or visceral) are less frequently approved unless they exist concomitantly with NP. Applications for MC use are completed by the treating physicians and include the following: pain and background diagnoses, previous pain treatments, the recommended MC dose (grams per month), route of administration and requested cultivar/s (strain/s name/s), based on the physician's best judgment (as no formal national guidelines exist). Completed applications are sent to the IMOH, which either approve or decline the request. Subsequent renewal applications need to be made every 6–12 months. The approved initial monthly dose is 20 gr/month regardless of the route of administration or 0%–24% cannabidiol (CBD)/0%–20% (-)-Δ^9-*trans*-tetrahydrocannabinol (THC) concentrations (Landshaft et al., 2017), and with an incremental increase of 10 gr/month in license renewals. Two routes of MC consumption are approved: inflorescence (for smoking or inhaling) and/or oil extracts (for sublingual use). At the time this study was conducted, MC at any given dose had a fixed price of about $100 and was mostly non-reimbursable. The official contraindications for MC in Israel are pregnancy, lactation and family history of psychotic illness. Thus far, over 70,000 licenses for MC use have been issued by the IMOH.

2.2 | Study procedure

This multicentre, prospective, long-term study was conducted between December 2015 and October 2019. The Ethics Committee of the University of Haifa (# 278/15) approved the study for physicians practicing in private clinics. Institutional ethic committees (Rambam Medical Center, #0272-15-RMB; Chaim Sheba Medical Center, #3670-16-SHC) approved the study for physicians employed by these public hospitals. This was a pure observational study with no interventional component whatsoever, so similar to other observational studies (Abuhasira et al., 2018; Haroutounian et al., 2016; Hoggart et al., 2015; Ware et al., 2015; Yassin et al., 2016; Zaki et al., 2017), registration at the Clinical Trials Register was not required. Importantly, no recognizable information on participating patients is published in this article.

Hebrew-speaking patients aged ≥18 years applying for a first time MC license for treating any form of chronic non-cancer–related pain were eligible for participating in the study. After explaining the study procedures, participating physicians (pain specialists, rheumatologists or orthopaedic surgeons) who regularly complete applications for MC licensure, obtained written informed consents from eligible patients. Copies of the consent forms along with the patients' pain diagnoses and contact information were sent to the study coordination centre. To avoid any possible influence of collected data on physicians' decisions regarding clinical management of their patients, prescribing physicians had no access to data collected on individual patients.

Patients were instructed to complete the study questionnaires at baseline, before MC treatment initiation (T_0), and at five follow-up times, one (T_1), three (T_3), six (T_6), nine (T_9) and twelve (T_{12}) months following treatment initiation. The questionnaire consisted of 188 questions at baseline and a variable number of about 150 follow-up questions, which were presented in a dynamic format customized to individual responses where responses on a particular question determined the subsequent questions asked. In order to further reduce study burden, patients were also given the choice to skip questions. Hence, each patient completed a unique set of questions and each question received a different number of responses. No financial compensation was offered to participating patients. The STROBE statement checklist for cohort studies is presented in Methods S1.

2.3 | Online survey

Data were collected online by the secured survey technology Qualtrics® (Provo, Utah, version 12018) (Qualtrics, 2015). Whenever patients had difficulties with the use of the web platform, the questionnaires could be completed by phone, with the assistance of the study coordinators.

2.4 | Study questionnaires

Physicians reported data on pain aetiology using the ICD-9 code. Baseline patient questionnaires included information on age, gender, BMI, marital status, formal education level, tobacco and alcohol consumption, duration of pain, previous cannabis use including the reason for that use (self-treatment or recreational) and co-morbidities. The following data were collected at baseline and at the five follow-up time points: (a) average (determined a priori as the study's primary outcome measure), worst and least

weekly pain intensity (0–10, NPS); (b) analgesics consumption and (c) MC treatment characteristics (administration route/s, monthly dose and MC cultivar name/s) and seven validated Hebrew versions of the following questionnaires were used in the study: short-form McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987); Pain Disability Index (PDI) (Pollard, 1984); Quality of life, EuroQol (EQ5) (Brooks & Group, 1996); Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989); Beck Depression Inventory II (BDI-II) (Beck et al., 1996); General Anxiety Disorder (GAD-7) (Spitzer et al., 2006) and Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995). Using a predetermined list (Aviram & Samuelly-Leichtag, 2017), patients were requested to report adverse effects (AEs) at each follow-up time point and whether or not they could attribute each AE directly to MC use. AEs were later classified as serious or non-serious, according to the FDA definition (Moore et al., 2007). Notably, data on diversion and misuse/dependence were not collected.

2.5 | Statistical analysis

R software (V.1.1.463) with lme4 (Bates et al., 2014) and tidyverse (Wickham, 2019) packages were used to analyse changes in outcome measures by generalized linear and logistic mixed-effect regression models (Gewandter et al., 2014). Stepwise forward model selection was used for assessing the relationship between MC treatment response and various predictors. Due to the prospective, longitudinal data collection design, each of the time points had a different sample size, which was analysed with the corresponding baseline information. Therefore, Chi-square or Kruskal–Wallis rank tests were conducted to establish similarity of demographic data between the five follow-ups. The Shapiro–Wilk test of normality demonstrated non-normal distribution for all measures. Thus, data are presented as median ± IQR (Q1-Q3, i.e. quartiles 25 and 75) or standard error of mean (*SEM*) when noted. Differences were considered significant at the $p < 0.05$ level, after Bonferroni corrections. Incidences are presented as numbers and percentages of patients. Minimum required sample size was calculated for the primary outcome)change in average weekly pain intensity(prior to the initiation of the study, by G*Power statistical analysis (Faul et al., 2007), while taking into account the following: six time point repeated measures analysis, within- and between-group interactions, medium effect size (0.25), $\alpha \leq 0.05$, power of 0.80 and 47 observables (all measured parameters). Based on these, a sample size of 217 patients was determined as appropriate. For a linear multiple regression, fixed model, R^2 deviation from zero, with a medium effect size (0.25), $\alpha \leq 0.05$, power of 0.80 and 47 observables, the required sample size was 153 patients. Notably, due to the exploratory nature of the study and many potential subgroup analyses, no maximum sample size objective was determined. Importantly, since most demographics of the sample did not change significantly between time points, T_1 demographic characteristics are presented in the text. For calculating predictors for clinical response to MC treatment, we defined treatment success as ≥30% reduction in average weekly pain intensity from baseline for each patient individually.

3 | STATISTICAL ANALYSES RATIONALE

Due to the large number of questionnaires, we expected substantial missing data at all five follow-up time points. In an attempt to diminish missing data, the recommendations of the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities and Networks (ACTTION) group (who are partnered with the United States FDA) were employed (Gewandter et al., 2014). Hence, we chose to construct a mixed-effect model (Begg et al., 1996; Little, et al., 2012; Little, et al., 2012). This model uses data from complete and incomplete cases, which makes it possible to analyse data by an intention-to-treat (ITT) approach. The assumption is that missing data are random, and that the mechanism is dependent on observed outcomes but independent of unobserved outcomes (Gewandter et al., 2014).

4 | RESULTS

4.1 | Sample

Although 1,661 patients completed the baseline (T_0) questionnaires, 616 (37%) were not eligible for the statistical analyses mainly, but not solely, due to disapproval of their MC applications by the IMOH (Figure 1, CONSORT flow diagram). Of the remaining 1,045 patients with MC license approval and initiation of MC treatment, follow-up questionnaires were completed by 829 (at T_1), 788 (T_3,), 656 (T_6), 595 (T_9) and 551 (T_{12}) participants. The following reasons led to the decline in the number of participants over time: lost to follow-up [376 patients (35%)], ceased MC treatment due to ineffectiveness [50 patients (4%)] and due to AEs [26 patients (2%)], regulatory problems [e.g. failure of license renewal, 33 patients (3%)] and declined further participation [8 patients (0.8%)]. Notably, two patients (0.1%) passed away during the follow-up period, both from complications of pneumonia. Thus, data regarding the primary outcome measure at baseline and at least at one additional time point were provided by 851 patients, who were included in the statistical analyses, yielding altogether 3,072 observations. About 80% of the patients provided data online and the rest by telephone calls.

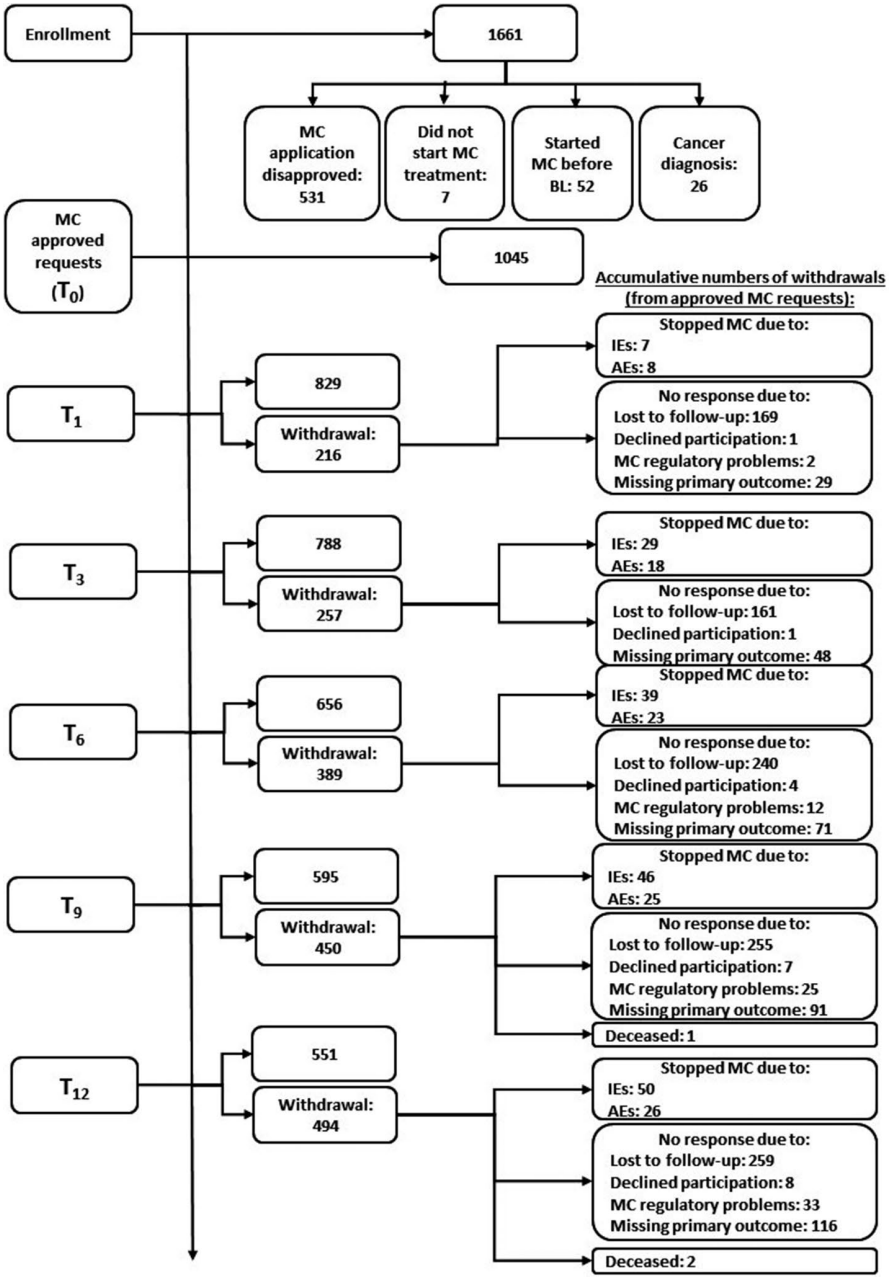

FIGURE 1 CONSORT 2010 flow diagram (numbers of patients). Reasons for patients' withdrawal at each time point; MC, medical cannabis; AEs, adverse effects; IEs, ineffectiveness. T_1, One-month Follow-Up; T_3, Three-month Follow-Up; T_6, Six-month Follow-Up; T_9, Nine-month Follow-Up; T_{12}, Twelve-month Follow-Up

4.2 | Baseline demographic and pain characteristics

Baseline demographic characteristics did not differ between eligible (n = 1,045) and non-eligible (n = 616) patients for age, gender, comorbidities or overall analgesics consumption. Nonetheless, eligible patients were significantly more likely to have chronic NP, and less likely to have musculoskeletal pain or other pain aetiologies (Table 1). Although, as mentioned, there was no difference between eligible and non-eligible patients in overall analgesics consumption ($\chi^2_{(1)} = 0.19$, $p = 0.67$), eligible patients consumed more NSAIDs and anticonvulsants at baseline ($\chi^2_{(1)} = 9.9, p < 0.01$ and $\chi^2_{(1)} = 5.9, p < 0.05$, respectively; Table S1).

Eligible participants were aged 47 ± 37–60 years and 57% (n = 469) were men. Previous exposure to cannabis was reported by 59% (n = 480) for self-treatment (n = 420) rather than for recreational purposes (n = 58) (Table 2). Chi-square (χ^2) test revealed that at T_1, patients with previous exposure to cannabis in comparison to naïve patients were significantly younger [42 (34–54) and 54 (44–66) years, respectively; $\chi^2_{(1)} = 0.31$, $p < 0.001$]; consumed MC as an inflorescence at higher rates (92% and 63%, respectively; $\chi^2_{(1)} = 114.0$, $p < 0.001$); and reported less MC-related AEs (33% and 47%, respectively; $\chi^2_{(1)} = 17.0, p < 0.001$). Pain duration was 6 ± 3–12 years with a median average weekly baseline pain intensity (primary outcome) of 8 ± 7–9 (0–10 NPS), and was similar at baseline for all follow-up time points ($\chi^2_{(4)} = 0.68$, $p = 0.95$ and $\chi^2_{(4)} = 1.20, p = 0.87$ respectively). Forty six per

TABLE 1 Characteristics of eligible versus non-eligible participants

Group	Eligible		Non-eligible	*p*	(χ^2)[a]/Kruskal-Wallis rank[b]
Observations		No of patients			
	1,045		616		
Median ± IQR					
Age at BL	47 ± 37–60		48 ± 35–61	0.84	0.03[b]
Missing	20 (2)		209 (34)		
No of patients (%)					
Gender at BL					
Male	567 (57)		325 (53)	0.99	0.0[b]
Female	427 (43)		289 (47)		
Missing	51 (4)		2 (<1)		
Pain aetiologies at BL[c]					
Neuropathic	322 (31)		159 (26)	<0.001	21.0[b]
Musculoskeletal	112 (11)		109 (18)		
Other	46 (4)		42 (7)		
Visceral	26 (2)		21 (3)		
Headache	23 (2)		21 (3)		
Combinations	516 (49)		264 (43)		
Comorbidities at BL					
Yes	569 (54)		267 (43)	0.94	0.006[b]
No	412 (39)		195 (31)		
Missing	64 (6)		154 (25)		
Overall analgesics consumption at BL					
Yes	793 (76)		363 (59)	0.67	0.19[b]
No	186 (18)		79 (13)		
Missing	66 (6)		174 (28)		

Abbreviations: BL, Baseline; IQR, Inter quartile range; *N*, Number of patients.

[a]Pearson's Chi-squared test.

[b]Kruskal-Wallis rank sum test.

[c]Pain aetiologies refer to patients with chronic pain ethology only from one origin, combinations refer to patients with more than one chronic pain ethology

cent of the patients ($n = 385$) were diagnosed with a single pain aetiology and the remainder had multiple pain aetiologies. Notably, based on the ICD-9/10 codes, NP was the most common concurrent diagnosis in the analysed cohort (72%, $n = 595$ at T_1) (Table S2).

4.3 | Treatment characteristics

Inflorescence of MC was the most common route of administration, increasing significantly from 81% ($n = 665$) at T_1 to 86% ($n = 456$) at T_{12} ($\chi^2_{(4)} = 40.24$, $p < 0.001$), mostly through cigarette smoking, mainly without any tobacco additive. In contrast, consumption of oil extracts, mostly sublingually, decreased over time (Table S3). Overall reported monthly MC dose increased from 20 ± 20–20 g at T_1 to 30 ± 20–30 at T_{12} ($\chi^2_{(4)} = 1{,}250.32$, $p < 0.001$). Based on the publicly available cultivators declarations of Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) content in their cultivars, patients in this cohort consumed mostly THC dominant cultivar/s ($n = 133$, 74%), followed by THC/CBD balanced cultivar/s ($n = 44$, 24%), and only a small fraction consumed only CBD dominant cultivar/s ($n = 4$, 2%).

4.4 | Pain measures

Improved pain measures from T_0 were observed to all time points (Figure 2). Worthwhile noting are the following significant changes between T_0 and T_{12}: average weekly pain intensity reduced by 20% from 8 ± 7–9 to 6 ± 5–8 (OR −1.97; 95%CI = −2.13 to −1.81; $p < 0.001$); least pain intensity declined by 33% from 6 ± 4–8 to 3 ± 2–6 (OR −1.88; 95%CI = –2.08 to –1.67; $p < 0.001$) and worst pain intensity

TABLE 2 Demographic characteristics of eligible patients

	Follow-up time points					
	T_1 ($n = 829$)	T_3 ($n = 788$)	T_6 ($n = 656$)	T_9 ($n = 595$)	T_{12} ($n = 551$)	$(\chi^2)^a$/Kruskal-Wallis rank[b] (p value)
Median ± IQR (no. of patients)						
Age	47 ± 37–60 (818)	46 ± 36–58 (778)	45 ± 36–58 (649)	45 ± 36–57 (588)	46 ± 37–57 (545)	3.71[ab] (0.44)
Missing	11 (1)	10 (1)	7 (1)	7 (1)	6 (1)	
BMI	25 ± 22–29	25 ± 22–29	25 ± 22–29	25 ± 22–29	25 ± 22–29	3.66[b] (0.45)
Missing	137 (17)	144 (18)	107 (16)	88 (15)	71 (13)	
No. of patients (%)						
Gender						
Male	469 (57)	446 (57)	376 (58)	342 (58)	317 (58)	0.26[a] (0.99)
Missing	4 (<1)	3 (<1)	3 (<1)	3 (<1)	2 (<1)	
Comorbidities						
Yes	474 (58)	447 (57)	341 (53)	303 (51)	284 (52)	9.95[a] (0.04)
Missing	8 (<1)	3 (<1)	13 (2)	5 (<1)	2 (<1)	
Tobacco smoking						
Yes	411 (50)	402 (49)	322 (49)	297 (50)	271 (49)	0.75[a] (0.94)
Missing	4 (<1)	3 (<1)	1 (<1)	3 (<1)	2 (1)	
Alcohol consumption						
Yes	417 (51)	391 (50)	335 (51)	314 (53)	275 (50)	13.31[a] (0.34)
Missing	6 (<1)	7 (<1)	4 (<1)	0	3 (<1)	
Previous cannabis experience						
Yes	480 (59)	477 (62)	409 (63)	369 (63)	348 (64)	5.26[a] (0.26)
Missing	12 (1)	14 (2)	9 (1)	10 (2)	7 (1)	
Reason for previous cannabis experience						
Self-treatment	420 (88)	413 (87)	354 (87)	317 (86)	301 (87)	0.76[a] (0.94)
Recreational	58 (12)	62 (13)	53 (13)	52 (14)	47 (14)	
Missing	2 (<1)	2 (<1)	2 (<1)	0	0	

Abbreviations: #, comorbidities do not add up to 100% due to concomitant disorders; BMI, Body mass index; IQR, Interquartile range; *N*, Number of patients; Percentages are rounded and without decimal points; T_1, One-month Follow-Up; T_{12}, Twelve-month Follow-Up; T_3, Three-month Follow-Up; T_6, Six-month Follow-Up; T_9, Nine-month Follow-Up; Yes means number of subjects (%) who responded positively to the question.

[a]Pearson's chi-squared test.

[b]Kruskal–Wallis rank sum test.

by 21% from 9 ± 8–10 to 8 ± 6–9 (OR –1.36; 95%CI = –1.52 to –1.21; $p < 0.001$). The total SF-MPQ score dropped by 23% from 28 ± 22–35 to 20 ± 12–28 (OR –8.27; 95%CI = −9.03 to −7.52; $p < 0.001$). Within the SF-MPQ, the affective pain components showed a reduction of 33% from 7 ± 5–9 to 4 ± 2–6 (OR − 2.56; 95% CI = −2.80 to −2.32; $p < 0.001$) and the sensory pain components by 21% from 21 ± 17–27 to 15 ± 10–22 (OR − 5.77; 95%CI = −6.35 to −5.19; $p < 0.001$).

4.5 | Analgesics consumption

At T_{12}, 43% of the patients ($n = 191$) who had been using analgesic medications prior to MC treatment initiation were no longer using them ($\chi^2_{(5)} = 253.2$; $p < 0.001$). This was true for all classes of analgesic drugs including over the counter analgesics, non-steroidal anti-inflammatory drugs, anticonvulsants and antidepressants. As for opioid use, 24% and 20% of the participants who had been using weak or strong opioids, respectively, at baseline stopped using them by the time they reached the 12-month follow-up ($\chi^2_{(5)} = 27.3$, $p < 0.001$; $\chi^2_{(5)} = 21.9$; $p < 0.001$, respectively; Table 3). Additionally, the number of concomitant medications was reduced at all follow-up time points (Table S4). When translated into morphine equivalent dose, a significant, 42%, decrease from baseline use of 20.5 ± 0–60 mg of morphine equivalent to 0 ± 0–20 mg at T_{12} was found (OR − 26.72; 95% CI = −34.89 to − 18.56; p <0 .001).

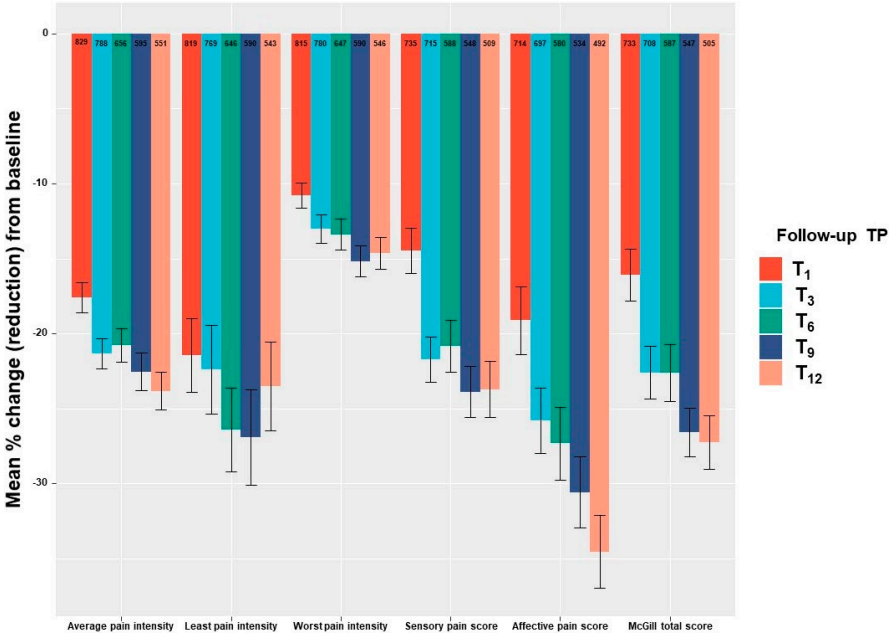

FIGURE 2 Percentage change from baseline pain measures. Each colour represents a specific follow-up time point; TP, Time point; T_1, One-month Follow-Up; T_3, Three-month Follow-Up; T_6, Six-month Follow-Up; T_9, Nine-month Follow-Up; T_{12}, Twelve-month Follow-Up; Error bar values are standard error. Numbers in the bars represent the number of patients who provided data on each measure at a particular time point

4.6 | Related symptoms, functioning and quality of life

A significant decrease was found in the scores of disability (19% reduction) from 6.7 ± 5.3–7.9 to 4.7 ± 3.1–6.6 (OR −1.72; 95% CI = −1.86 to −1.57; $p < 0.001$) and quality of life (25% reduction) from 5 ± 4–6 to 3 ± 2–5 (OR −1.29; 95%CI = −1.41 to −1.18; $p < 0.001$), indicating improvement in these measures. Anxiety levels decreased by 40% from 10 ± 5–16 at T_0 to 5 ± 2–9 at T_{12} (OR −3.69; 95%CI = −4.12 to −3.25; $p < 0.001$), depression severity also dropped by 32% from 18 ± 12–27 at T_0 to 11 ± 6–19 at T_{12} (OR −6.20; 95%CI = −6.84 to −5.56; $p < 0.001$) and pain catastrophizing scores reduced by 17%, from 39 ± 31–46 at T_0 to 26 ± 12–37 at T_{12} (OR −12.13; 95%CI = −13.11 to −11.16; $p < 0.001$). Finally, sleep disturbance decreased by 33% from 13 ± 10–16 at T_0 to 8 ± 5–11 at T_{12} (OR − 4.53; 95%CI = −4.87 to −4.19; $p < 0.001$) and sleep duration increased between T_0 and T_{12} by 14% from 5 ± 4–6 to 6 ± 5–7 hr (OR 0.88; 95%CI = 0.76 to 0.99; $p < 0.001$; (Figure 3).

4.7 | Safety

Overall, 30%–40% of patients reported AEs. Reported AEs were mostly non-serious according to the FDA definition (Moore et al., 2007) and their overall incidence significantly decreased over time ($\chi^2_{(4)} = 23.4$; $p < 0.001$). The most frequently reported AEs in declining order were related to the central nervous system, gastrointestinal system and psychological events (i.e. sweet craving, anxiety; Table 4). All specific AEs are reported in Table S5. Ceasing MC use due to AEs during the 1-year follow-up was noted by 26 (2%) patients who provided data on AEs (Figure 1). Nonetheless, we assume that an additional unknown number of patients who were lost to follow-up might have discontinued MC use due to AEs.

Comparison between patients who reported MC-related AEs at T_1 ($n = 320$) and those who did not ($n = 489$), showed that the former were significantly older [48 (36–63) versus 46 (37–57) years; $\chi^2_{(1)} = 0.12$, $p < 0.01$] and were less likely to use MC by inflorescence (71% versus 87%, respectively; $\chi^2_{(1)} = 32.0$, $p < 0.001$). Additional comparisons between the two groups at all subsequent time points yielded similar results (data not shown). When referring to the association between MC dose and AEs, patients at T_{12} were categorized according to one of the three following groups: (a) low dose—those consuming 20 gr per month (27%); (b) medium dose—30 gr per month (52%) and (iii) high dose—40 gr or more per month (19%). Comparison between the low- and high-dose groups showed higher rates of AEs among the low-dose group (43% versus 25%; $\chi^2 = 20.0$, $p < 0.001$).

Data on AEs in patients who dropped out from the study is mostly lacking, with the exception of 35 patients for whom the most frequently reported AEs were dizziness, fatigue, bad taste and apathy.

A few serious AEs were reported during the follow-up period but due to lack of precise medical information their relation to MC use is unclear. They included two deaths due to complications of pneumonia and 26 hospitalizations due to surgeries (14 orthopaedic surgeries, 4 abdominal, 3 unreported types, 2 urological, and oncology related, cardiac and plastic surgeries (1 each). An additional 30 hospitalizations were reported, due to uncontrolled pain

TABLE 3 Analgesics consumption—Overall and by type

	Follow-up time points				
	T_1 ($n = 829$)	T_3 ($n = 788$)	T_6 ($n = 656$)	T_9 ($n = 595$)	T_{12} ($n = 551$)
	No. of patients (%)				
Overall analgesics consumption					
Consumed at BL	657 (79)	630 (80)	522 (80)	472 (79)	444 (81)
Ceased all analgesics at FU[a]	216 (33)	216 (34)	216 (41)	193 (41)	191 (43)
No analgesics at BL	161 (19)	149 (19)	125 (19)	117 (20)	105 (19)
Started any analgesics at FU[b]	40 (25)	26 (17)	20 (16)	19 (16)	22 (21)
Missing	11 (1)	9 (1)	9 (1)	6 (1)	2 (<1)
OTCs					
Consumed OTCs at BL	133 (16)	125 (16)	102 (16)	89 (15)	74 (13)
Ceased OTCs at FU[a]	47 (35)	48 (38)	38 (37)	31 (34)	22 (30)
No OTCs at BL	308 (37)	289 (37)	204 (31)	190 (32)	179 (32)
Started OTCs at FU[b]	19 (6)	25 (9)	29 (14)	25 (13)	26 (15)
NSAIDs					
Consumed NSAIDs at BL	113 (14)	103 (13)	70 (11)	72 (12)	71 (13)
Ceased NSAIDs at FU[a]	35 (31)	45 (44)	27 (39)	27 (38)	18 (25)
No NSAIDs at BL	328 (39)	311 (39)	236 (36)	207 (35)	182 (33)
Started NSAIDs at FU[b]	19 (6)	19 (6)	21 (9)	17 (8)	19 (10)
Weak opioids (WO)					
Consumed WO at BL	162 (20)	163 (21)	111 (17)	107 (18)	87 (16)
Ceased WO at FU[a]	56 (35)	66 (40)	39 (35)	29 (27)	21 (24)
No WO at BL	279 (34)	251 (32)	195 (30)	172 (29)	166 (30)
Started WO at FU[b]	17 (6)	23 (9)	16 (8)	17 (10)	26 (16)
Strong opioids (SO)					
Consumed SO at BL	277 (33)	262 (33)	188 (29)	179 (30)	151 (27)
Ceased SO at FU[a]	65 (23)	54 (21)	40 (21)	36 (20)	30 (20)
No SO at BL	164 (20)	152 (19)	118 (18)	100 (17)	102 (19)
Started SO at FU[b]	15 (9)	13 (9)	11 (9)	11 (11)	14 (14)
Anticonvulsants					
Consumed anticonvulsants at BL	195 (24)	187 (24)	148 (23)	138 (23)	121 (22)
Ceased anticonvulsants at FU[a]	58 (30)	62 (33)	51 (34)	44 (32)	30 (25)
No anticonvulsants at BL	246 (30)	227 (29)	158 (24)	141 (24)	132 (24)
Started anticonvulsants at FU[b]	8 (3)	16 (7)	13 (8)	13 (9)	8 (6)
Antidepressants					
Consumed antidepressants at BL	181 (22)	165 (21)	128 (20)	124 (21)	108 (20)
Ceased antidepressants at FU[a]	51 (28)	50 (30)	35 (27)	41 (33)	24 (22)
No antidepressants at BL	260 (31)	249 (32)	178 (27)	155 (26)	145 (26)
Started antidepressants at FU[b]	9 (3)	12 (5)	14 (8)	12 (8)	9 (6)

Abbreviations: BL, Baseline; NSAIDs, Non-steroid anti-inflammatory drugs; OTC, Over the counter; T_1, One-month Follow-Up; T_{12}, Twelve-month Follow-Up; T_3, Three-month Follow-Up; T_6, Six-month Follow-Up; T_9, Nine-month Follow-Up.

[a]For these variables, the presented percentages represent the change between number of patients consuming analgesics at BL to patients stopping analgesics at the specific time point.

[b]For these variables, the presented percentages represent the change between the number of patients who did not consume analgesics at BL to patients and started consuming analgesics at the specific follow-up time point.

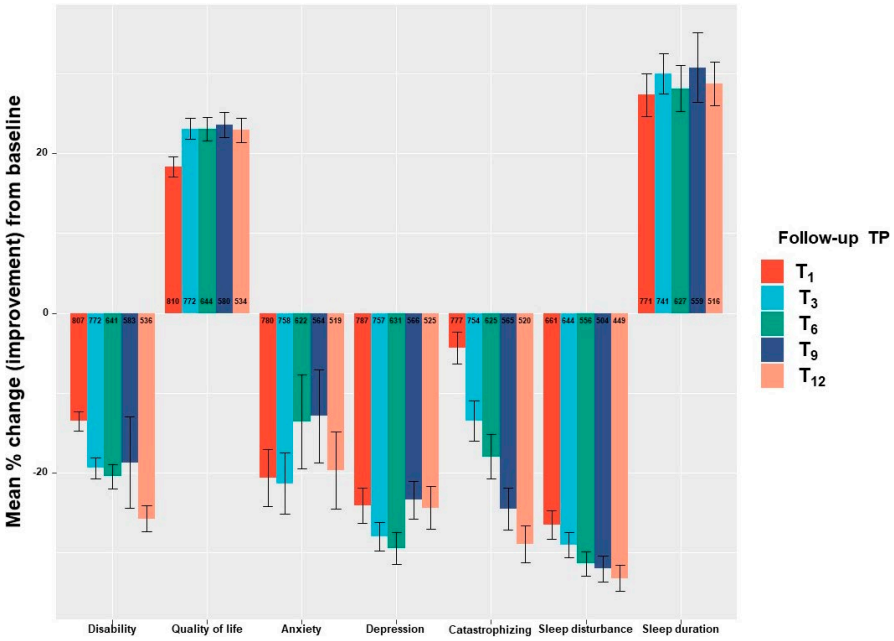

FIGURE 3 Percentage change from baseline-related symptoms. For quality of life and sleep duration, percentages were normalized so that positive values represent improvement. In all other measures, negative values indicate an improvement. Each colour represents a specific follow-up time point. TP, Time point; T_1, One-month Follow-Up; T_3, Three-month Follow-Up; T_6, Six-month Follow-Up; T_9, Nine-month Follow-Up; T_{12}, Twelve-month Follow-Up. Numbers on the bars represent the number of patients who provided data on each measure at a particular time point. Error bar values are standard error

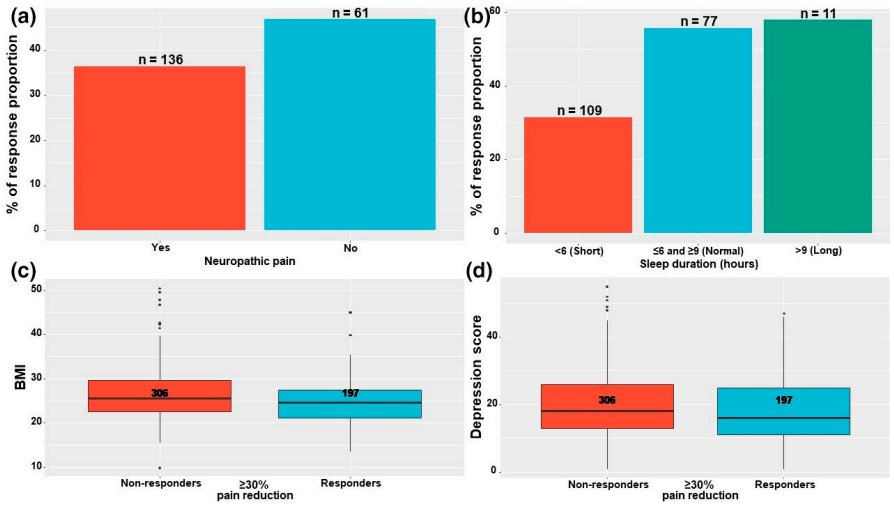

FIGURE 4 Prediction of treatment success. BMI, Body mass index; Measures found to significantly estimate treatment success at T_{12} (defined as ≥30% reduction in weekly average pain intensity). A and B: *Y* axis represents the % of responders within the dichotomous and categorical parameters categories respectively. C and D: *Y* axis represents the linear BMI and depression scores

(9 patients), cardiovascular events (7), infections (7), falls (2) and injury, dialysis, dehydration and allergy (1 each). Additionally, some central nervous system (CNS)-related AEs that may be associated with impaired driving (e.g. confusion, disorientation, impaired attention, dizziness, impaired psychomotor functions and vertigo) can potentially be regarded as serious AEs. At least one such AE was reported by 28%-39% of patients throughout the follow-up period.

4.8 | Prediction of response

In order to identify predictors for treatment success which are not influenced by the higher response rate at the short-term follow-up (e.g. 1 month), we ran a general logistic mixed model on the 551 patients who provided data on the primary outcome at the 12-month time point. Thirty-nine per cent of them ($n = 213$) achieved the threshold of treatment success (i.e. ≥30% decrease from baseline in average weekly pain intensity) and were regarded as 'responders'.

We fitted the general linear model (estimated using ML optimizer) to predict treatment success following assessment of all measures compatible for producing a significant effect on the model. Six baseline stand-alone measures emerged with a significant effect: presence of NP, BMI, sleep duration, depression, disability and opioid consumption (measured by morphine equivalent dose). Next, we used a stepwise method with four variables (presence of NP, sleep duration, BMI and depression score) to provide a best outcome model, without collinearity between variables. Effect sizes were labelled following Chen's (2010) recommendations. The model's

TABLE 4 Reported MC-related adverse events

Follow-up time points						
	T_1 ($n = 829$)	T_3 ($n = 788$)	T_6 ($n = 656$)	T_9 ($n = 595$)	T_{12} ($n = 551$)	*p* value
No. of patients (%)						
General (any)	320 (40)	271 (35)	203 (32)	185 (32)	162 (30)	<0.001
CNS	166 (21)	145 (19)	93 (15)	87 (15)	89 (17)	<0.01
GI	125 (16)	109 (14)	83 (13)	84 (15)	77 (14)	0.74
Psychological	89 (11)	83 (11)	66 (10)	64 (11)	47 (9)	0.65
Musculoskeletal	46 (6)	46 (6)	35 (6)	33 (6)	34 (6)	0.97
Cardiovascular	43 (5)	31 (4)	28 (4)	21 (4)	26 (5)	0.56
Visual	43 (5)	44 (6)	40 (6)	40 (7)	49 (9)	0.07
Auditory	22 (3)	21 (3)	20 (3)	14 (2)	18 (3)	0.89
Number of concurrent AEs						
0	489 (59)	500 (63)	438 (67)	395 (66)	378 (67)	0.40
1–3	95 (11)	93 (12)	62 (10)	56 (9)	41 (7)	
4–6	57 (7)	41 (5)	32 (5)	26 (4)	27 (5)	
7–10	35 (4)	27 (3)	31 (5)	20 (3)	19 (3)	
>10 (11–58 range)	68 (8)	57 (7)	43 (7)	51 (9)	48 (9)	

Abbreviations: AEs, adverse events; CNS, central nervous system; GI, gastrointestinal; *P* value based on Pearson's chi-squared test;T_1, One-month Follow-Up; T_{12}, Twelve-month Follow-Up; T_3, Three-month Follow-Up; T_6, Six-month Follow-Up; T_9, Nine-month Follow-Up.

power was Tjur's $R^2 = 0.091$ and its intercept was OR 1.73; 95%CI = 0.54-5.60; $p = 0.39$.

Explicitly, the presence of NP predicted lower rates of treatment success (OR 1.63; 95% CI = 1.05–2.54; $p < 0.05$). Normal (6–9 hr) and long (>9 hr) sleep duration predicted higher rates of treatment success as compared to short (<6 hr) sleep duration (OR 2.53; 95%CI = 1.67-3.85; $p < 0.001$ and OR 3.62; 95%CI = 1.38–9.94; $p < 0.005$). Lower BMI scores predicted higher rates of treatment success (OR 0.93; 95%CI = 0.90–0.97; $p < 0.001$). Lower depression scores showed a trend of predicting higher rates of treatment success (OR 0.98; 95%CI = 0.96–1.00; $p = 0.07$) (Figure 4). Notably, age and gender were also controlled in the model but were not found to be significant (for full model results, see Table S6). Although the stand-alone variables, disability score and morphine equivalent dose consumption measures did not fit the model, lower (6.4 ± 5–7.9) disability scores were reported by responders as compared to non-responders (6.7 ± 5.6–7.7; OR 0.14; 95%CI = −0.037–0.31; $p = 0.06$). Similarly, morphine equivalent dose consumption was lower (15 ± 0–35) for the responders than for the non-responders (24 ± 0–60) (OR 0.07; 95%CI = −0.14 to 0.28; $p < 0.05$).

Due to the uncontrolled nature of this study and the amount of missing data, supplementary analysis was conducted, with the same general logistic mixed model but with a more conservative treatment success definition of ≥50% decrease from baseline in average weekly pain intensity. Accordingly, 119 patients were regarded as responders at T_{12}. Specifically, the model's power was Tjur's $R^2 = 0.089$ and its intercept was OR 0.23 95%CI = −0.08 to 0.64; $p = 0.005$. Ultimately, normal and long of sleep duration at baseline predicted a higher rate of treatment success as compared to short sleep duration (OR 2.81 95% CI = 1.74–4.55; $p < 0.001$ and OR 4.23 95% CI = 1.47–11.42; $p = 0.005$). Also, longer chronic pain duration and better quality-of-life score at baseline were established as predictors for higher rate of treatment success (OR 1.04 95% CI = 1.01–1.06; $p = 0.001$ and OR 0.87 95%CI = 0.76–1.00; $p = 0.04$ respectively; Table S7) (Figure 4.

5 | DISCUSSION

The first finding of this study was an overall improvement in all pain measures in response to MC treatment that was preserved along the 1-year follow-up. This finding is congruent with reports of several other similar studies (Abuhasira et al., 2018; Haroutounian et al., 2016; Hoggart et al., 2015; Yassin et al., 2016; Zaki et al., 2017). However, a common methodological shortcoming of cohort studies in general, including the previously cited cohorts on MC, is the lack of properly handling missing data, which can be as high as 67% of the patients (Abuhasira et al., 2018). In the present cohort, unlike previous ones, we have employed generalized linear and logistic mixed-effect regression models, which are regarded as the 'state of the art' statistical methods for handling missing data and reducing associated biases (Gewandter et al., 2014). This leads to augmented reliability

of the current findings despite losing a considerable number of patients during follow-up.

The reported reduction in pain in the present cohort was statistically significant, but mostly did not exceed 15%–25%. This leads to the conclusion that, overall, MC provides a modest effect on chronic pain intensity. Nonetheless, given the complexity of the patients who all had long-lasting resistant pain often of multiple aetiologies and frequent comorbidities, the reported magnitude of improvement can also be regarded as clinically significant. Debate exists in the literature on how to define a clinically significant analgesic effect. Suggested thresholds are ≥30% (Moore et al., 2010; Whiting et al., 2015) or ≥2 points (Farrar et al., 2000) reduction in pain intensity. The primary outcome measure in the present study has not met these requirements (−1.97 points or 20% reduction from baseline at the 1-year time point). Notably, more lenient criteria have also been used is previous analgesic cohort studies: Yassin et al. (2016), for example, have set 10% reduction in total pain score following 1-year of MC treatment as "a minimal clinically important change" and Bestard and Toth (2011) reported that gabapentin, a first-line treatment for NP, produced "a clinically significant" 1.2 point reduction in pain at the end of a prospective 6-month cohort study (Bestard & Toth, 2011).

In addition to its effect on pain intensity, this study showed that MC has a beneficial effect on multiple related symptoms. Similar effects of cannabinoids have been reported by others including on sleep (Ferguson & Ware, 2015; Russo et al., 2007; Sznitman et al., 2020; Whiting et al., 2015), depression (Feingold et al., 2017) and quality of life (Ellis et al., 2009; Haroutounian et al., 2016; Lahat et al., 2012; Yassin et al., 2016). A possible advantage of the present study is that it allows to compare the magnitude of improvement between the different measures, repeatedly, over 1-year. Indeed, the effect on most measures seems similar in magnitude and stable over time. It is even comparable to the effects of distinct medical treatments for specific symptoms, such as brotizolam for sleep (Roehrs et al., 1983) and selective serotonin reuptake inhibitors for depression (Taylor et al., 2006). Yet, some of our findings do not agree with those found in other cohorts. For example, in contrast to our study, previous work has suggested that MC consumption does not change pain catastrophizing (Shah et al., 2017) or even aggravates anxiety (Martin-Santos et al., 2012).

Of interest is our findings regarding the reduction in consuming all types of analgesic medications, which further supports earlier reports of analgesics sparing effect of MC treatment (Bradford et al., 2018; Haroutounian et al., 2016; McCarty, 2018; Stith et al., 2017; Yassin et al., 2016). In light of the 'opioid epidemic' (Fitzcharles & Eisenberg, 2018), reduction in opioids consumption and even cessation of their use is an important goal. Although the total daily dose of opioids at baseline was not very high in the current study, the oral morphine equivalence calculation showed a steep reduction in the consumed opioid dose. Despite the encouraging nature of this observation, two reservations should be noted. First, there are no data on opioid reducing effects of MC in patients consuming higher opioid doses, so generalization of these findings is not recommended. Second, the reduction in opioid consumption, which accompanies MC use, can be attributed to patients simply replacing scheduled prescription drugs with scheduled cannabis (Stith et al., 2017), especially since most of our patients used THC-dominant rather than high CBD-dominant cannabis cultivars. However, even if true, this substitution seems to lead to positive outcomes such as improvement in pain, associated symptoms, functioning and quality of life.

Perhaps the most novel finding of this study is the identification of four measures which contribute to the prediction of long-term treatment success, judges by ≥30% decrease in average pain intensity in response to MC treatment. They include normal to long sleep duration (in both the primary and supplementary analyses), lower BMI, lower depression scores and, unexpectedly, a diagnosis other than NP. Although we do not have clear explanations for these findings, we raise some hypotheses regarding each of the identified predictors. *Short sleep duration* has been shown to be associated with altered pain sensitivity, possibly due to deteriorated central pain-modulatory circuits. Limited recovery sleep did not completely resolve these alterations in pain-modulatory processes, indicating that extensive recovery sleep is required (Simpson et al., 2018). Although our cohort showed increased sleep duration following MC treatment, we hypothesize that in patients with short sleep duration at baseline, sleep recovery was not sufficient to allow treatment success leaving them vulnerable to chronic pain over time. As for *lower BMI*, we are unaware of any previous studies on possible associations between BMI and response to analgesic treatment. However, being highly lipophilic, THC tends to accumulate in adipose tissue, a fact that may have pharmacokinetic consequences (Ashton, 2001; Kumar et al., 2008). We raise the possibility that in patients with higher BMI, MC constituents are rapidly absorbed in adipose tissue, resulting in lower plasma concentrations of active substances and less favourable outcomes. The opposite may occur in patients with low BMI. Further studies are required to explore this suggestion. *Depression* and chronic pain are known to be profoundly associated (Arnow et al., 2006; Lindsay & Wyckoff, 1981). Patients with higher levels of depression are frequently less likely to respond to analgesic treatments (Wasan et al., 2005), so this finding may be an indicator for treatment success in general rather than with MC specifically. Lastly, *Neuropathic pain* has traditionally been the focus of MC studies (Andreae et al., 2015; Häuser et al., 2018). Unexpectedly, this focus is not justified by the results of our study, which found that NP diagnosis failed to predict treatment success relative to

other pain conditions. Even when considering the more conservative supplementary analysis of ≥50% decrease in pain intensity, NP still did not predict treatment response. On second thought, this finding may not be surprising since NP has been broadly described as treatment resistant (Michels et al., 2011). Studies on MC in patients suffering from other forms of chronic pain should, therefore, needs to be encouraged. Notably, longer duration of chronic pain and higher QOL at baseline predicted treatment success in the supplementary analysis of ≥50% pain relief. These finding could also be taken into consideration, while shaping the "profile of the responding patient".

Our cohort demonstrates a variety of AEs, which affected about 40% of the patients at 1 month and declined in incidence over time to about 30% at 12 months. This decline suggests that adaptation and perhaps even tolerance occurs over time. On the other hand, the relatively high rates of AEs among patients consuming low MC dose (20 gr/month) at T_{12} may suggest that in at least some patients such tolerance may not occur. Overall, 2% of our sample ceased MC treatment due to AEs but conceivably, additional patients who were lost to follow-up may stopped using MC due to more troublesome or even serious AEs. A few serious AEs were reported during the follow-up period, including two deaths. Although the relationship between most of these serious AEs and cannabis treatment is unclear, causative relationships cannot be ruled out. Importantly, although data on motor vehicle accidents were not collected in the current study, associations between cannabis consumption and impaired driving are well documented (Hartman & Huestis, 2013). Hence, reported CNS-related AEs that may compromise driving cannot be ignored and should probably be regarded as serious AEs due to their potential life-threatening consequences. Moreover, while patients were requested to report "MC-related AEs", many of them were taking concomitantly psychotropic drugs and opioids (or even weaning from opioids), a fact that might have jeopardized their ability to identify specific "MC-related AEs". It should be mentioned that most of the sample in our study smoked MC, and only a minority utilized vaporizers; an effect that raises another safety concern regarding undesirable smoking-related diseases caused by noxious pyrolytic by-products (O'Connor & Hurley, 2008). However, half of our sample were already long-term tobacco smokers and only a minority (25%) smoked a mixture of tobacco and MC. Hence, the smoking hazard in our cohort is not necessarily related merely to MC smoking. Nonetheless, we wish to emphasize that smoking is not a desirable delivery system for MC treatment and should be discouraged for two reasons. Firstly, to reduce smoking hazards, and secondly, to reduce possible confusion between recreational use and medical treatment. This study has several limitations. First, self-report bias may have occurred. To diminish this bias, only validated questionnaires were utilized and patient responses were kept anonymous from their physician. Second, although the most advanced statistical approaches for missing data imputation were used, they do not completely protect the results from this shortcoming (Gewandter et al., 2014). Third, the fact that only 50% of the patients who completed the baseline questionnaires were included in the long-term analyses may affect generalization of findings and the determination of responder profile. However, a high unaccounted dropout rate is an inherent shortcoming of all such cohort studies (Abuhasira et al., 2018; Haroutounian et al., 2016; Yassin et al., 2016; Zaki et al., 2017). Forth, higher baseline pain intensities than typically seen in other studies (Portenoy et al., 2007) were reported by our patients (i.e. 8 versus 6–7). This may be attributed to the Israeli MOH regulations at the time this study was conducted, which approved MC licensure primarily to patients with otherwise intractable chronic NP. Fifth, due to the study design, it is hard to isolate a placebo from a 'true' drug effect. The consistent improvements in all examined parameters over a relatively long duration of time reduces but does not exclude the likelihood that this is merely a placebo effect. Sixth, although previous experience with cannabis could be a potential bias, the fact that no difference was found in the treatment response between patients reporting previous cannabis use and those reporting no previous use reduces the likelihood of such bias. Moreover, in contrast to RCTs in which homogeneous, "clean" populations of patients are mandatory, cohort studies, aimed to represent "real life" situations, are expected to include a wide range of populations (i.e. both previous MC users and naïve patients in our study and in at least one additional cohort study from Canada; Zaki et al., 2017). Lastly, a high rate of patients in our sample consumed THC-dominant cultivars, pointing to a potential recreational purpose of use (Morean & Lederman, 2019). While this might be true for some patients, at least one study showed that cultivars with higher THC content provided better analgesic response than low THC cultivars (Borgelt et al., 2013). Additionally, a much higher selection of high THC cultivars than high CBD cultivars (in fact only one per cultivator) were available in Israel at the time the study was conducted, consequently leading to the extended use of the former. In conclusion, this prospective, comprehensive and large-scale cohort demonstrated an overall mild-to-modest long-term improvement of all investigated measures, including pain, associated symptoms and importantly, reduction in opioid (and other analgesics) use. It seems likely that MC treatment can be safe for most patients, although study limitations make it difficult to draw firm conclusions. Lastly, normal to long sleep duration, lower BMI, lower depression scores and diagnosis other than NP predict clinical response to MC treatment.

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DISCLOSURES

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Joshua Aviram, Dorit Pud, David Meiri and Elon Eisenberg had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the analysis. Tamar Gershoni, Bareket Schiff-Keren, Miriam Ogintz, Simon Vulfsons, Tamar Yashar, Haim-Moshe Adahan, Silviu Brill, Howard Amital, Itay Goor-Aryeh, Dror Robinson, Leslie Green, Refael Segal, Yacov Fogelman, Oren Tsvieli, Ofir Morag, Vadim Tashlykov, Roee Sheinfeld and Ruth Goor contributed to the study by locating the compatible patients and carrying out the written informed consent procedure in their institutions. Ben Yellin, and Yelena Vysotsky assisted in statistical analysis. All authors participated in data collection, discussed the results and commented on the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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