The Effect of Medicinal Cannabis on Pain and Quality of Life Outcomes in Chronic Pain: a Prospective Open-label Study

Simon Haroutounian, PhD,a,b Yael Ratz, PharmD,a Yehuda Ginosar, MD,c Karina Furmanov, MSc,d Fayez Saifi, MD,a,c Ronit Meidan, RN,a Elyad Davidson, MD,a,c,*

a Pain Relief Unit, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

b Division of Clinical and Translational Research, Department of Anesthesiology, Washington University School of Medicine, Saint Louis, MO, USA

c Department of Anesthesia and Critical Care Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

d Hebrew University-Hadassah School of Dental Medicine, Jerusalem, Israel

* Corresponding author at: Pain Relief Unit, Department of Anesthesia and Critical Care Medicine, Hadassah-Hebrew University Medical Center, Jerusalem 91120, Israel. Tel: +972-2677-6911; fax: +972-2677-6524; email: edavidson@hadassah.org.il
ABSTRACT

Objectives: The objective this prospective, open-label study was to determine the long-term effect of medicinal cannabis treatment on pain and functional outcomes in subjects with treatment-resistant chronic pain.

Methods: The primary outcome was change in pain symptom score on the S-TOPS (Treatment Outcomes in Pain Survey – Short Form) questionnaire at 6 months follow-up in intent-to-treat (ITT) population. The secondary outcomes included change in S-TOPS physical, social and emotional disability scales, pain severity and pain interference on brief pain inventory (BPI), sleep problems, and change in opioid consumption.

Results: 274 subjects were approved for treatment; complete baseline data were available for 206 (ITT), and complete follow-up data for 176 subjects. At follow-up, pain symptom score improved from median 83.3 (95% CI 79.2-87.5) to 75.0 (95% CI 70.8-79.2), P<0.001. Pain severity score (7.50 [95% CI 6.75-7.75] to 6.25 [95% CI 5.75-6.75] and pain interference score (8.14 [95% CI 7.28-8.43] to 6.71 [95% CI 6.14-7.14]) improved (both P<0.001), together with most social and emotional disability scores. Opioid consumption at follow-up decreased by 44% (P<0.001). Serious adverse effects led to treatment discontinuation in two subjects.

Discussion: The treatment of chronic pain with medicinal cannabis in this open-label, prospective cohort resulted in improved pain and functional outcomes, and significant reduction in opioid use. The results suggest long-term benefit of cannabis treatment in this group of patients, but the study's non-controlled nature should be considered when extrapolating the results.

Key words: Chronic Pain, Cannabis, Quality of Life, Pain Outcomes
INTRODUCTION

Chronic pain is one of the leading causes of disability worldwide. With 15-30% prevalence in the general adult population\(^1,\)\(^2\) and annual costs in the US alone exceeding 500 billion dollars\(^3\), it has an enormous negative societal impact. Current pharmacotherapy of chronic pain is less than satisfactory\(^4,\)^\(^5\), and less than two thirds of patients with chronic pain obtain sufficient pain relief with the available drugs\(^6\). Even with the use of biopsychosocial approach to chronic pain, the long-term pain management outcomes are often suboptimal\(^7,\)\(^8\). Clearly, additional approaches are needed to improve treatment outcomes of patients suffering from chronic pain.

Cannabis has been used for centuries in medicine for various indications, but a substantial progress in the biomedical research of exogenous and endogenous cannabinoids did not begin before the discovery of the chemical structure of \(\Delta-9\) tetrahydrocannabinol (THC) and additional cannabinoids in the 1960’s\(^9\). The analgesic effect of cannabinoids has been demonstrated by extensive preclinical research\(^10\), but has been less consistent in human studies\(^11-17\). Since the publication of the initial systematic review and meta-analysis on the analgesic effect of cannabinoids\(^12\) and a call for more extensive cannabinoid pain research\(^13\), more clinical evidence has become available in the last decade\(^18,\)\(^19\).

The earlier studies demonstrated cannabinoid efficacy in pain and spasticity associated with multiple sclerosis (MS)\(^15,\)\(^17\), but two recent trials of oromucosal tetrahydrocannabinol/cannabidiol (THC/CBD) failed to show improved analgesia over placebo in neuropathic pain in MS and diabetic polyneuropathy\(^14,\)\(^16\). A few placebo-controlled studies have demonstrated the effectiveness of smoked cannabis in pain associated with HIV neuropathy\(^20,\)\(^21\) and peripheral nerve injury\(^22\), but these were of very short, 5-14 days, duration. Long-term (beyond 15 weeks) effectiveness data on oral and smoked cannabinoids in chronic pain are available only from small case series\(^11,\)\(^23,\)\(^24\).
Overall, the available evidence indicates that smoked cannabis may be effective for chronic pain treatment, but there is a lack of long-term prospective data in a sufficiently large patient sample. Medicinal cannabis is not FDA-approved, but was recently approved by the Israeli Ministry of Health, including for the treatment of chronic pain. Given the lack of longitudinal data on the analgesic efficacy of cannabis, the objective of the current study was to prospectively assess the long-term effect of cannabis on pain and functional outcomes in patients with chronic pain.

PATIENTS AND METHODS

This was a prospective, open-label, single-arm longitudinal study carried out at the ambulatory pain clinic of the Pain Relief Unit, Hadassah-Hebrew University Medical Center in Jerusalem. The study was conducted and is reported in concordance with STROBE statement.

Between June 1, 2010 and January 1, 2013, the study enrolled all consecutive patients that met the following inclusion criteria: 1) age > 18 years old, 2) chronic pain with duration of 3 months or longer, and 3) lack of satisfactory analgesic response or intolerable adverse effects with at least two analgesics from two different drug classes at full dose.

Subjects were excluded if they 1) were unable to read and understand the intervention risks and benefits form, 2) had history of drug abuse or dependence, 3) had psychiatric comorbidity (or history) of schizophrenia or acute psychosis, or family history of schizophrenia, 4) had high risk of drug abuse (determined by the study psychologist) or non-adherence to pharmacotherapy (determined by the study clinical pharmacist), 5) did not have a proper trial with two first/second line analgesic drugs for the underlying painful condition (i.e. - the dosage was increased to the maximum recommended dose, or dose-limiting side effects appeared), or 6) were pregnant or breastfeeding.
For subjects who fulfilled the above criteria – an individual application for cannabis treatment was sent for approval by the Ministry of Health. The application was submitted by a pain management physician so that an individual patient would receive a license to use medicinal cannabis for the treatment of chronic pain. In addition to confirmation that the patient was treated in the pain clinic, it included the patient's pain medical history, diagnosis, and a statement that the patient had exhausted conventional analgesic modalities for the relevant pain diagnosis as stipulated by the Ministry of Health. Only after such individual approval, a temporary license to use medicinal cannabis was issued, with a requirement for license renewal every 6-12 months. All the subjects read and signed the consent form on the potential risks and benefits of the intervention at the time of application to the Ministry of Health. Questionnaire use for data collection in this study was separately approved by the Institutional Review Board of Hadassah Medical Organization.

Upon receipt of the cannabis license, subjects were educated on proper cannabis use and received a prescription for the study medication, which was dispensed at pre-approved distribution points by a certified provider. The initial recommended cannabis dose was 20 grams/month, which could be obtained as smoked cannabis (patients could either roll the cigarette themselves or obtain pre-filled 1 gram cannabis cigarettes) or the same monthly amount dispensed in baked cookies, or as an olive oil extract (drops).

The patients were instructed to titrate cannabis dose starting with one cigarette puff (or 1 drop of the cannabis oil) a day, and increase by increments of 1 puff/drop per dose, to frequency of up to 3 times a day until satisfactory pain relief was achieved, or side effects appeared. Cannabis was to be consumed at the home address only. The subjects were instructed to refrain from driving for at least 6 hours after consuming cannabis or longer if they felt disoriented or drowsy.
If no adequate pain relief was achieved, and the patient did not report adverse effects with the monthly dose of 20 grams, the dose could be further increased based on physician’s judgment and subsequent approval by the Ministry of Health.

The Israeli Ministry of Health has standard regulations on approved strains and cultivating procedures for the licensed cannabis dispensaries. At the time of the study there were no GMP (Good Manufacturing Practices) in place for medicinal cannabis; however, Ministry of Health performs occasional measurements of quality and THC/CBD levels to ascertain the products meet minimum and maximum THC/CBD concentrations. The THC concentration in smoked product is 6-14% (11-19% in oral formulations e.g. cookies), and the CBD concentration is 0.2-3.8%, (0.5-5.5% in oral formulation) (data source - Israeli Ministry of Health).

Cannabis treatment was added to the existing analgesic regimen. The study did not include a formal requirement to discontinue other analgesics; however all subjects were encouraged to attempt gradual dose reduction and possible discontinuation of other analgesics, particularly chronic opioids, due to potential long-term concerns of endocrinopathy and cognitive dysfunction.

The efficacy of cannabis on pain and pain-related quality of life (QoL) was assessed by administering the S-TOPS (Treatment Outcomes in Pain Survey – Short Form) questionnaire, sleep problem index (SPI) subscale of MOS sleep measure, and the Brief Pain Inventory (BPI), before the treatment, and approximately at 6 months clinic follow-up.

The primary outcome was pain reduction (change from baseline) after 6 months assessed by the Pain Symptom scale of the S-TOPS instrument in the intent to treat (ITT) population. The secondary outcomes included change from baseline in the following: 1) in physical disability, family and social disability, role-emotional disability, and patient satisfaction with outcomes scales
of the S-TOPS; 2) sleep problem index; 3) pain severity and pain interference scales of the BPI; 4) opioid consumption. Outcomes analyses were performed for per protocol (PP) population as well.

Patient-reported side effects were collected at each clinic visit and at the time of follow-up questionnaire completion. Side effects were considered serious if they were life-threatening, resulted in hospitalization or emergency department visit, or required medical intervention for resolution.

**Statistical analyses**

Change from baseline of primary and secondary outcomes was assessed by paired t-test for normally distributed data and by Wilcoxon signed rank test for non-normally distributed data. The normality of data distribution was assessed by Shapiro-Wilk test. Baseline observation carried forward (BOCF) imputation method was used for ITT analysis for both primary and secondary outcomes; PP analysis was performed for completers to assess the robustness of the findings. These methods were also used for subgroup analyses. Although BOCF and PP have their limitations, our study design prevented us from constructing a more comprehensive imputation algorithm such as a mixed-effect regression model, as the lack of multiple follow-ups did not allow to reliably determine patterns of data missingness. Linear regression analysis was performed to test the possible association between improved pain and deterioration in physical function. A priori sample size calculation was not performed, as we had no prior data on what might be the expected effect size of cannabis treatment on our primary outcome measure. The goal was to enroll a sample larger than 150 subjects to enable the robust assessment of effect.

Differences were considered significant at P<0.05 level. Normally distributed data are presented as mean, categorical data are presented as median, with either standard deviation (SD) or 95%
Confidence Interval (CI) as appropriate. Statistical analyses were performed with SigmaPlot 12.5 (Systat Software, Inc).

RESULTS

Participant flow and baseline characteristics

Overall, 308 patients have been considered for cannabis treatment (patient disposition CONSORT chart in Figure 1). The treatment for 34 patients was not approved by the Ministry of Health (diagnoses - low back pain n=9, fibromyalgia n=8, radicular low back pain n=5, widespread myofascial pain n=5, peripheral neuropathic pain n=2, central neuropathic pain n=1, persistent postsurgical pain n=1, post-amputation pain n=1, widespread pain after traumatic brain injury n=1, and complex regional pain syndrome n=1). Forty-nine subjects had either missing baseline S-TOPS data, or completed the first questionnaire after beginning the cannabis treatment and were excluded from analysis. Nineteen terminal cancer patients (11 of which had metastatic cancer pain) died before or soon after treatment initiation; none of the deaths was judged to be related to the study drug. Eleven subjects discontinued the treatment early because of side effects, and 4 subjects discontinued due to ineffectiveness. Fifteen subjects were lost to follow-up or have been self-discharged to a different pain clinic, therefore had no follow-up data available. ITT analysis was performed on all 206 subjects who provided baseline data. A total of 176 subjects have completed the study and were included in PP analysis.

In ITT population, the average subject age was 51.2 (15.4) years, 62.0% of the subjects were male (127 male, 79 female), and the most frequent diagnoses were musculoskeletal widespread pain (n=62, 30.1%), peripheral neuropathic pain (n=49, 23.8%), and radicular low back pain (n=39, 18.9%). The majority of subjects (n=192, 93.2%) suffered from chronic noncancer pain, while 14 (6.8%) subjects had cancer pain. The additional baseline pain characteristics are presented in Table
1, and distribution of pain conditions in Table 2. The mean (SD) follow-up to completion of outcomes assessment (S-TOPS and BPI) was 210 (96.6) days. Patient disposition in PP population was not significantly different. At the follow-up, 136 subjects received cannabis cigarettes, 8 subjects received a combination of cigarettes and drops, 17 subjects received only drops, 9 subjects received only cookies, and 6 received a combination of cookies and drops. The mean (SD) monthly prescribed amount of cannabis at follow-up (in any route of administration) was 43.2 (17.9) grams. Before cannabis treatment, 73 of the 176 subjects in PP population received analgesic treatment with strong opioids (morphine, oxycodone, fentanyl, hydromorphone, buprenorphine, and methadone). Additional 10 subjects received tramadol and 5 subjects both tramadol and a strong opioid. The detailed use of strong opioids is presented in Table 3. The median daily dose among opioid users (in daily oral morphine sulfate (MO) equivalents) was 60.0 mg (95% CI 45.0-90.0). The conversion rates from daily MO dose (mg) were as following: 30 to 20 mg/day oral oxycodone; 30 to 10 mcg/h for transdermal fentanyl; 30 to 15 mg/patch for transdermal buprenorphine; 30 to 300 mg/day for oral tramadol; 150 to 1 mg/day for intrathecal morphine; and 750 to 1 mg/day for intrathecal hydromorphone \textsuperscript{32,33}. The conversion from methadone was dose-dependent \textsuperscript{34,35}.

**Primary Outcome**

S-TOPS pain symptom score improved from 83.3 (95% CI 79.2-87.5) to 75.0 (95% CI 70.8-79.2), P<0.001. Overall, the pain symptom score was improved in 65.9% of subjects, did not change from baseline in 8.0%, and deteriorated in 26.1% of subjects. In PP analysis, the improvement in pain symptom score was similar – from 83.3 (95% CI, 79.2-87.5) to 75.0 (95% CI, 70.8-79.2), P < 0.001.
Secondary Outcomes

S-TOPS family-social disability, role-emotional disability, satisfaction with outcomes, and sleep problem index all improved from baseline, P<0.001 (Figure 2). BPI subscales of pain severity and pain interference were also significantly improved from baseline, all P<0.01 (Figure 3). The change in physical disability-lower body was not significant in ITT population, but significant in PP population: from 75.0 (95% CI 75.0-83.3) to 75.0 (95% CI 66.7-75.0), P<0.001. Physical disability-upper body scale of S-TOPS did not change from baseline to follow-up (P=0.48).

Of 73 subjects on opioid therapy at baseline, 32 have discontinued opioid treatment at follow-up. This is a 44% reduction from baseline in the percentage of subjects receiving opioid treatment (41 versus 73, P<0.001). Two subjects continued receiving tramadol, and none received both tramadol and strong opioids at follow-up. The median oral morphine equivalent dose among the subjects still receiving opioids at follow up decreased from 60.0mg (95% CI 45.0-90.0) to 45mg (95% CI 30.0-90.0), however, this reduction did not reach statistical significance (P=0.19, Mann-Whitney test).

In subgroup analysis, there were no differences in the primary outcome between neuropathic (peripheral or central neuropathic pain, n=59) versus non-neuropathic (all nociceptive and mixed pain diagnoses, n=147) pain, or between male (n=127) and female (n=79) patients.

We also tested the association between the change in S-TOPS pain symptom score and change in S-TOPS physical disability scale, to confirm that improved pain did not come at the expense of increased functional impairment. Linear regression analysis showed that improvement in pain was significantly associated with improvement in physical function (r=0.35, p<0.001).

Adverse Effects

Nine subjects discontinued treatment due to mild to moderate adverse effects (AEs) - primarily sedation, heaviness, nervousness and difficulty to concentrate. Two additional subjects discontinued
treatment due to serious side effects: one subject because of elevated liver transaminases, and one elderly subject was admitted to the emergency room in a confusional state, and was discharged after four days of hospitalization. Both subjects were receiving cannabis drops at the time the AEs were recorded.

DISCUSSION

In this prospective open label study with mean follow-up of 7 months, patients with chronic pain showed improvement from baseline in pain and pain-related QoL outcomes following treatment with medicinal cannabis. The results in this mixed group of nociceptive and neuropathic pain patients are consistent with previous smaller, short-term studies, and a recent large long-term study, demonstrating effectiveness of smoked cannabis in chronic pain.

A significant percentage of subjects discontinued opioid therapy during the study. This type of reduction in opioid requirements with cannabinoid therapy is consistent with previous reports, and supported by preclinical findings on synergistic analgesic efficacy of opioids and cannabinoids. Opioid use for chronic pain increases the risk of endocrinopathy, bowel dysfunction, cognitive decline, hospitalization and death from overdose, and is also associated with increased costs and comorbidities. With a recent study reporting that introducing medicinal cannabis laws resulted in decreased state-level opioid overdose mortality rates, this is an important area for further research.

The short-lasting AEs of acute cannabis exposure or cannabis toxicity are well-documented; these affect a variety of systems and include nausea, dizziness, headache, increased heart rate, reduced auditory/verbal and visual/spatial memory recall and recognition, as well as poorer attention and reaction times. The long-term effects of cannabis, however, especially in the setting of chronic pain management, are less documented. A systematic review of cannabis treatment in a variety of
conditions (e.g. pain, glaucoma, multiple sclerosis, nausea) reported no difference in serious side effects or death between cannabis and controlled groups, but increased risk of non-serious side effects, especially respiratory, neurological, gastrointestinal, psychiatric, and eye disorders \(^{51}\).

The rate of cannabis discontinuation due to side effects in our study was low, (11 of 206 subjects, 5.3\%), and almost identical to the recent prospective COMPASS study (10 of 215 subjects discontinued due to side effects) \(^{41}\). Numerous studies have reported an association between illegal use of cannabis and cardiovascular and cerebrovascular risks by detecting cannabinoids in blood or urine screens after myocardial infarction or stroke, but it is very challenging to establish causality, as many of these subjects have had numerous risk factors for these conditions including comorbidities and use of tobacco, alcohol and other illicit drugs \(^{52}\). In addition, some but not all studies suggest that acute consumption of cannabinoids has been also linked with increased likelihood of being involved in motor vehicle accidents \(^{53}\); however, clear guidance regarding abstinence from driving while under cannabinoid treatment has not been established, especially in the case of lawfully prescribed, chronic treatment \(^{54}\). Based on some experimental data, the suggestion is not to drive for at least 3-4 hours after cannabis consumption \(^{55},^{56}\). Our recommendation to abstain from driving for 6 hours, although more conservative, is based on the large inter-patient variability in THC pharmacokinetics \(^{57}\). Due to the increasing use of medicinal cannabis in many countries worldwide, recommendations have been published recently \(^{58},^{59}\), with regard to patient selection, monitoring, dosing regimen selection, and driving; however, these should be regarded as preliminary guidelines until more consistent data are available.

Hepatic impairment is rarely associated with cannabis use, but abnormal liver transaminase levels have been reported \(^{60}\), and it is plausible to assume that increase in liver transaminase levels in one of study subjects was treatment-related. Although psychiatric AEs such as acute psychosis have been reported with cannabis use, no such effects occurred in our study. One elderly patient (83
years old) was hospitalized in a confusional state, and this was considered by the caregivers to be associated with the cannabis treatment. We did not have an upper age limitation for inclusion in our study, but perhaps the use of cannabis in the elderly population warrants a greater caution. Both serious AEs that caused treatment discontinuation occurred while the subjects took cannabis olive oil extract at the monthly dose of 20mg. Large variability in the rate and extent of absorption with oral cannabinoids has been reported \(^{61,62}\), but we do not know whether the mode of administration has played a critical role in these subjects.

One of the possible reasons for the infrequency of psychiatric AEs in our study could be the rigorous patient selection process and comprehensive patient education. We set strict criteria and excluded participants with background or family history of schizophrenia, psychosis and similar psychiatric disorders. In addition, the subjects underwent detailed assessment of potential for drug abuse and treatment non-compliance by a psychologist and a clinical pharmacist, respectively.

The main limitations to the clinical use of cannabis for chronic pain have been the lack of long-term prospective studies on effectiveness, the concern of cognitive and psychiatric AEs \(^{63}\), and the legal issues associated with cannabis use. Brief interventions in crossover controlled studies, or long-term follow-ups in small groups of patients are typically not sufficient to address these limitations. Our study addresses the changes in pain and pain-related QoL outcomes over 7 months of treatment, and demonstrates relative low incidence of adverse effects in a carefully selected group of subjects.

Overall, the rate of serious AEs and discontinuation due to AEs was low in or study, and this is consistent with findings in a systematic review of literature on cannabinoid treatment of chronic pain – where among 18 studies involving 766 subjects no serious AEs were reported, and most of the reported AEs were tolerable and did not lead to treatment discontinuation \(^{18}\).

The dosing of cannabinoids for pain has been another important matter of debate; there is a wide variability in various reported and recommended doses for medicinal cannabis for pain, ranging
from 12 to 48 grams/month \textsuperscript{59, 64}. This perhaps reflects the wide inter-individual variability in pharmacological response to cannabis and the lack of clear dose-response relationship \textsuperscript{50}, necessitating individually-adjusted dose titration. The variability in active cannabinoid concentration in the final product may further contribute to inconsistency in different recommendations. Although the cultivation process is standardized by the Israeli Ministry of Health, including periodic measurement of THC and CBD concentrations, it is not a pharmaceutical grade product, and the up to 3-fold variability in THC concentration among the various dosage forms (6\% minimal concentration in the smoked, and 19\% maximum concentration in the oral dosage forms) could have affected our results.

The physical disability-upper body and physical disability-lower body subscales of the S-TOPS questionnaire did not change significantly from baseline in our study. This result on upper body disability is not unexpected, given the low disability scores at baseline, but together these data may suggest that cannabis treatment preferentially affects the perception of pain and its emotional and social implications, rather than objectively determined physical disability.

**Strengths and Limitations of the Study**

The main limitation of this study is the lack of a control group. In treating pain, the placebo effect can be substantial \textsuperscript{65}; therefore our ability to draw conclusions about true pharmacological efficacy of cannabis in this study is limited. An additional limitation of this type of cohort study is lack of frequent periodic assessment of all AEs, which resulted in capturing primarily serious AEs and those that led to treatment discontinuation. In addition, we have systematically assessed baseline pharmacotherapy and subsequent dose changes with opioids only, but our methodology neither allowed determining causality between cannabis treatment and opioid consumption, nor testing the association between cannabis treatment and changes in consumption of non-opioid analgesics. In this cohort, 63\% of the study population was male, which may misrepresent the general chronic
pain population. Typically, chronic pain prevalence is 20-30% higher in women, while painful conditions such as fibromyalgia may be 2-13 times more prevalent in women, depending on the diagnostic criteria. However, the outcomes were not different for males and females, when analyzed separately.

Despite those limitations, performing a randomized, controlled trial of a similar size and duration, considering the unconventional route of cannabis delivery, is associated with immense challenges. Our results demonstrate not only a symptomatic long-term improvement in pain scores, but rather robust functional improvement on various QoL domains including sleep, and substantial improvement in satisfaction with treatment outcomes. The significant decrease in the percentage of patients treated with opioids suggests an objective improvement following cannabis treatment.

In summary, this long-term prospective cohort suggests that cannabis treatment in a mixed group of patients with treatment-resistant chronic pain may result in improved pain, sleep and QoL outcomes, as well as reduced opioid use. There are limitations to this open-label study that should be carefully considered before extrapolating the study results to the general population: these are primarily its uncontrolled design and careful patient selection for low drug abuse, psychiatric illness and non-adherence risks.

ACKNOWLEDGEMENTS:

We would like to acknowledge Dr. Yacov Ezra and Ram Livay for important clinical involvement in this study, and to Prof. Ian Gilron for valuable comments on the manuscript.

The study did not have external funding, and was performed only with internal support from Hadassah-Hebrew University Pain Relief Unit.

The authors declare no conflicts of interest to declare.
REFERENCES


**Figure 1.** CONSORT chart – patient disposition.

ITT, intent to treat; PP, per protocol.

**Figure 2.** Changes in S-TOPS outcomes and sleep problem index, from baseline to follow-up, ITT population.

Changes from baseline (gray) to 7-month follow-up (dotted white) on S-TOPS and SPI scales (median, 95% CI).

S-TOPS, treatment outcomes in pain survey – short form. Higher S-TOPS scores indicate higher disability, except SatOut, which has an inverted scale: 0=no satisfaction; 100= maximum satisfaction

*** P<0.001

Pain Symptom: 83.3 (95% CI 79.2-87.5) to 75.0 (95% CI 70.8-79.2) P<0.001.

PD-LB (physical disability – lower body): 75.0 (95% CI 66.7-83.3) to 75.0 (95% CI 66.7-75.0) P=0.17.

PD-UB (physical disability – upper body): 16.7 (95% CI 16.7-25.0) to 16.7 (95% CI 16.7-25.0) P=0.48.

Fam-Soc Disab (family-social disability): 75.0 (95% CI 68.7-75.0) to 56.2 (95% CI 50.0-62.5) P<0.001.

Role-Emot Disab (role-emotional disability): 70.0 (95% CI 60.0-80.0) to 40.0 (95% CI 50.0-62.5) P<0.001.

SPI (sleep problem index): 66.8 (95% CI 62.2-71.1) to 51.1 (95% CI 47.2-54.4) P<0.001.

SatOut (satisfaction with outcomes): 20.0 (95% CI 10.0-30.0) to 70 (95% CI 60.0-80.0) P<0.001.

**Figure 3.** Changes in BPI pain severity and pain interference from baseline (gray) to follow-up (dotted white), ITT population.

Brief Pain Inventory (BPI) pain severity score changed from median 7.50 (95% CI 6.75-7.75) to 6.25 (95% CI 5.75-6.75), and pain interference score from median 8.14 (95% CI 7.28-8.43) to 6.71 (95% CI 6.14-7.14).

*** P <0.001.
### Table 1. Demographic characteristic of the study participants (ITT population)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51.2 (15.4)</td>
<td>Years - mean (SD)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>127/79</td>
<td></td>
</tr>
<tr>
<td>Major Depressive Disorder (MDD) diagnosis</td>
<td>12 (5.8%)</td>
<td>Number (%) of subjects</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder (GAD) diagnosis</td>
<td>2 (1.0%)</td>
<td>Number (%) of subjects</td>
</tr>
<tr>
<td>MDD and GAD diagnosis</td>
<td>4 (1.9%)</td>
<td>Number (%) of subjects</td>
</tr>
<tr>
<td>Post-Traumatic Stress Disorder (PTSD) diagnosis</td>
<td>9 (4.4%)</td>
<td>Number (%) of subjects</td>
</tr>
<tr>
<td>MDD and PTSD diagnosis</td>
<td>2 (1.0%)</td>
<td>Number (%) of subjects</td>
</tr>
<tr>
<td>Follow-up time</td>
<td>7.0 (3.17)</td>
<td>Months – mean (SD)</td>
</tr>
<tr>
<td>Pain severity on S-TOPS</td>
<td>83.3 (79.2-87.5)</td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td>Physical Disability – LB on S-TOPS</td>
<td>75.0 (66.7-83.3)</td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td>Physical Disability – UB on S-TOPS</td>
<td>16.7 (16.7-25.0)</td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td>Family and social disability on S-TOPS</td>
<td>75.0 (68.7-75.0)</td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td>Role-emotional disability on S-TOPS</td>
<td>70.0 (60.0-80.0)</td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td>Patient satisfaction with outcomes on S-TOPS</td>
<td>20.0 (10.0-30.0)</td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td>Sleep Problem Index</td>
<td>66.8 (62.2-71.1)</td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td>Pain severity on BPI</td>
<td>7.50 (6.75-7.75)</td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td>Pain interference on BPI</td>
<td>8.14 (7.28-8.43)</td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td>Daily opioid use among opioid users (n=73)</td>
<td>60.0 (45.0-90.0)</td>
<td>Median (95% CI) oral MO equivalents</td>
</tr>
</tbody>
</table>

MDD, major depressive disorder; GAD, generalized anxiety disorder; PTSD, post-traumatic stress disorder. LB, lower body; UB, upper body; BPI, brief pain inventory; MO, oral morphine sulfate.

* satisfaction scale is inverted (0=no satisfaction; 100= maximum satisfaction);
Table 3. Baseline opioid use among study subjects

<table>
<thead>
<tr>
<th>Opioid</th>
<th>No. of subjects (total n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral oxycodone-paracetamol combination</td>
<td>33</td>
</tr>
<tr>
<td>Oral oxycodone, controlled release (with or without naloxone)</td>
<td>31</td>
</tr>
<tr>
<td>Transdermal fentanyl</td>
<td>12</td>
</tr>
<tr>
<td>Oral morphine, controlled or immediate release</td>
<td>8</td>
</tr>
<tr>
<td>Transdermal buprenorphine</td>
<td>7</td>
</tr>
<tr>
<td>Oral methadone</td>
<td>2</td>
</tr>
<tr>
<td>Oral transmucosal fentanyl</td>
<td>1</td>
</tr>
<tr>
<td>Intrathecal opioid by implanted pump</td>
<td>2*</td>
</tr>
</tbody>
</table>

Some subjects received a combination of more than 1 opioid.

* One subject received morphine, and one subject hydromorphone.
308 considered for treatment

- 34 not approved by MOH

274 approved for cannabis treatment

- 49 excluded (missing baseline data or baseline data obtained after treatment initiation)
- 19 terminal cancer patients (<3 months life expectancy)

206 patients (ITT analysis)

- 11 discontinued due to adverse effects
- 4 discontinued due to inefficacy
- 15 lost to follow-up or moved to a different clinic

176 completed the study (PP analysis)
Figure 3

The figure shows a bar graph comparing baseline and follow-up BPI scores for pain severity and pain interference.

- **Pain Severity**
  - Baseline: **7**
  - Follow-up: **6**

- **Pain Interference**
  - Baseline: **9**
  - Follow-up: **8**

Significant differences are indicated by ***.