Efficacy of different varieties of medical cannabis in relieving symptoms

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Abstract

Traditionally, cultivars of *Cannabis sativa* L. have been divided into sub-species based on their morphological properties, metabolic profile, and geographical origin. Interbreeding subspecies renders hybrids characterised by varying *sativa* and *indica* profiles, and unique cannabinoid ratios. As cannabinoid compounds like tetrahydrocannabinol (THC) and cannabidiol (CBD) are thought to be primarily responsible for the physiological effects of cannabis, unique strain profiles may provide different therapeutic benefits suitable for managing different symptoms and conditions. This study aims to assess the efficacy of different cannabis varieties in patients using medical cannabis from one Canadian licensed provider. Information pertaining to current medical conditions, symptoms, and quality of life were collected through a voluntary online survey administered to patients after registration, and at 4 and 10 month follow-up intervals. 837 patients provided information about their experience with medical cannabis at 4-month follow-up. Patients reported that the variety *Midnight[MR]* (*sativa*-leaning, 8-11% THC, 11-14% CBD) was most efficacious for reducing pain (27.4%), and that *Luminarium[MR]* (very *sativa*-dominant, 25-28% THC, 0% CBD) was effective for managing both anxiety disorder (30.4%) and depression (35.5%). Patients most commonly attributed improvements in sleep (29.0%), appetite (24.8%), and bowel function (24.6%) to *Midnight[MR]*, improvements in concentration (22.0%) to *Cognitiva[MR]* (*sativa*-leaning, 15-18% THC, 0% CBD), and improvements in sexual function (26.5%) to *Luminarium[MR]*. The efficacy of different cannabis varieties in managing various symptoms should be further investigated in a controlled clinical setting, to enable patients and physicians to make informed decisions on which varieties are best suited to achieve optimal symptom management.

Keywords: Medical cannabis, cannabis varieties, survey

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Introduction

Cannabis contains over 421 different chemical compounds of several molecular classes, including flavonoids, terpenes, steroids, and cannabinoids. Of these compounds, cannabinoids are perhaps the most well studied group, in particular tetrahydrocannabinol (THC) and cannabidiol (CBD) (1). Both THC and CBD bind to endogenous cannabinoid receptors of the mammalian endocannabinoid system, resulting in a variety of downstream effects related to the modulation of mood, memory, appetite, pain, and inflammation (2). Thus, medical cannabis is used in the management of a variety of conditions and symptoms related to these modulatory effects, including pain, nausea and vomiting, depression, anxiety, and insomnia (3–5).

The physiological effects of cannabis are a product of the composition and concentration of active constituents found in each variety, as well as their complex pharmacological interactions and metabolism in the human body. In addition, the pharmacokinetics of cannabinoids also varies depending on the route of administration (4).

The endocannabinoid system contains two types of receptors known as CB-1 and CB-2. THC has an affinity for both receptor types, with a slight preference for CB-1 (2). CB-1 is found on the presynaptic membranes of neurons in the central and peripheral nervous system, as well as in peripheral tissues, such as the heart and spleen (6, 7). The activation of CB-1 receptors in the nervous system plays a role in cognition and pain signalling (2). CB-2 receptors are found mainly on cells of the immune system, and are the predominant cannabinoid receptors expressed by leukocytes. The activation of CB-2 receptors leads to a downregulation of the inflammatory response, which contributes to analgesic effects (6).

Because of the ability of THC to bind to both of these receptors and activate these different pathways, it is administered in the clinical setting for its analgesic, anti-emetic, anti-spastic, and psychotropic effects. Early clinical research suggests it may be efficacious in the management of symptoms such as chronic and neuropathic pain, and spasticity (8).

The molecular mechanism of CBD is less well understood, but it is thought to be polypharma-cological. CBD is a weak antagonist of CB-1 receptors, and an agonist of the serotonergic 5-HT$_{1A}$ receptor, which is found in central and peripheral nervous systems and controls varying physiological and psychological pathways, including regulation of mood, appetite, and sleep (9). Some evidence exists that suggests CBD may have some effect on the metabolism of THC or on THC's interaction with the body's endocannabinoid system (10). The anti-inflammatory, anti-spastic, and anxiolytic effects of CBD lead to its use in the management of pain, insomnia, and epilepsy in the clinical setting (7, 11).

In addition to cannabinoids, terpenes are another important class of compounds thought to be associated with the physiological effects of the plant. 120 unique terpenes have been isolated in the cannabis plant (1). Terpenes produce their own range of pharmacological activities, and it is possible that they are equally, if not more important, than cannabinoids in terms of therapeutic effects. Clinical and anecdotal evidence suggest that the delivery of whole-plant products is more effective than isolated cannabinoids for symptom management. This is believed to be a consequence of synergistic interactions between cannabinoids, terpenes, and other plant constituents, often described as the "Entourage Effect" (12).

While cannabis speciation has been a topic of debate, the current scientific consensus is that it is a single species known as *Cannabis sativa* L. with three commonly recognized sub-species, *indica*, *sativa,* and *ruderalis* (13). Interbreeding of these subspecies has resulted in the creation of over 700 hybrid varieties that span the morphological and pharmacological characteristics of both *sativa* and *indica* plants (14). Different cannabis hybrids express differing cannabinoid ratios and terpene profiles. Moreover, identical strains grown in different environments may also produce different cannabinoid and terpene profiles. The varying physiological effects induced by *indica* and *sativa* strains leads to different clinical uses of cannabis varieties. For example, *indica* dominant varieties are traditionally associated with more sedative or relaxing effects, while *sativa* dominant varieties are thought to produce more stimulating or energizing effects (14).

Although numerous medical cannabis varieties are available, only anecdotal or self-reported evidence

exists to suggest which strains are best indicated for the management of particular symptoms or conditions. Based on existing knowledge, doctors may recommend specific parameters on cannabinoid content or method of administration depending on a patient's condition or experience with the medication. Patients may also use a trial-and-error method to find a variety that works optimally for their specific condition or symptoms, and adjust strain and dosage depending on how and when it is administered (14). This selection process can be complicated by the fact that differences in every individual's biochemistry can play a role in their experience with the medication, as well as the fact that there is still a limited understanding of the role and interactions between terpenes and cannabinoids in vivo. Therefore, intensive investigation is required to better understand the clinical utility of different cannabis strains as a function of their unique chemical profiles.

The aim of the present study was to assess patient reported efficacies of different cannabis varieties in managing their conditions and symptoms based on information provided through a voluntary online survey. These results will allow physicians to better recommend different strains of medical cannabis for future patients to more effectively and efficiently address their medical needs.

Methods

An online survey was designed by a Canadian medical cannabis provider in consultation with physicians and nurses experienced in prescribing medical cannabis, and with reference to relevant scientific literature. Existing validated questionnaires that assessed pain and quality of life were adapted to assess specific attributes of the target patient population. Questions assessing patients' pain levels were measured on a scale of 0-10 (with 0 being no pain and 10 being worst possible pain), and patients' ability to cope with their pain was assessed based on an adaption of the Pain Self-Efficacy Questionnaire (15). Quality of life (QOL) questions were based on two commonly used and validated methods of QOL assessment (16,17). The survey was dynamic, and

patients were given questions based on relevance as determined by their answers to earlier questions (e.g., patients were not asked about their pain experience if they did not indicate pain as a symptom or condition). Since the survey was customized to best assess each patient's unique characteristics, not all questions were mandatory and not all patients answered every question.

Baseline

Patients of one licensed medical cannabis producer were invited to complete an intake survey at the time of registration, which is considered "baseline." The survey collected demographic information and information pertaining to current medical conditions and symptoms. Condition and symptom severity was reported as mild, moderate, or severe. Patients were asked additional detailed questions relevant to the symptoms or conditions they selected. QOL was assessed by asking patients to report on their experiences with items such as sleep, appetite, concentration, bowel activity, and sexual function, by selecting from the options "severe difficulty," "moderate difficulty," "no difficulty," "good," and "very good."

Follow-up

Patients were invited to complete a follow-up survey 4 and 10 months following completion of the initial intake survey. Patients were asked to report any changes they had experienced to their symptoms, conditions, or QOL. They were also asked about their experience with medical cannabis, and if they had experienced any changes in their symptoms or conditions, which of the cannabis varieties they perceived the changes could be attributed to. Cannabis varieties were categorized based on their approximate *sativa* and *indica* character. *Sativa*-leaning strains consist of 50-60% *sativa* character, *sativa*-dominant strains consist of 61-70% *sativa* character, and very *sativa*-dominant strains consist of >70% *sativa* character. *Indica* strains are similarly characterised.

Data analysis

Patients who completed surveys between January 2015 and January 2017 were included in this analysis. Baseline survey data was filtered to include only patients who indicated which strains they took at the 4-month follow-up for analysis.

Results

In total, 837 patients reported which cannabis varieties they consumed at 4-month follow-up. The demographic and lifestyle characteristics of these patients at baseline are presented in Table 1. The majority of patients were male (68.8%), Caucasian (83.4%), and reported that they have prior experience with cannabis at the time of survey completion (78.9%). The average age of patients was 44.9 years old, with an age range from one year to 80 years old. Most patients belonged in the age bracket of 50-59 (28.7%). The most common medical conditions reported in this patient cohort at baseline included depression (34.5%), anxiety disorder (34.3%), post-traumatic stress disorder (PTSD, 25.9%), and sleep disorder (25.7%). Pain was reported by 33.0% of patients at baseline. The most common symptoms at baseline included anxiety (40.7%), sleep problems (38.4%), depression (29.9%), insomnia (29.3%), and headache (20.4%).

Table 1. Baseline demographics of patients who indicated cannabis varieties associated with symptom improvement

Demographic	n (%)
Gender (Total n = 837)	
Male	575 (68.8%)
Female	259 (30.9%)
Other	3 (0.4%)
Ethnicity (Total n = 836)	
Caucasian	697 (83.4%)
Spanish/Hispanic/Latino	4 (0.5%)
Native Canadian	40 (4.8%)
Black/African American	8 (1.0%)
Asian	10 (1.2%)
Pacific Islander	1 (0.1%)
Prefer not to answer	31 (3.7%)
Demographic	**n (%)**
Other	45 (5.4%)
Age in Years (Total n = 833)	
0 - 19	22 (2.6%)
19 - 29	66 (7.9%)
30 - 39	209 (25.1%)
40 - 49	179 (21.5%)
50 - 59	239 (28.7%)
60 - 69	96 (11.5%)
≥70	22 (2.6%)
Average (min, max)	44.9 (1, 80)
Other Conditions (Total n = 837)	
Depression	289 (34.5%)
Anxiety disorder	287 (34.3%)
PTSD	217 (25.9%)
Sleep disorder	215 (25.7%)
Previous Experience with Cannabis (Total n = 835)	
Yes	659 (78.9%)
No	118 (14.1%)
Prefer not to answer	58 (6.9%)

PTSD: Post-traumatic stress disorder.

Properties of cannabis varieties to which improvement was most often attributed

651 patients reported on which cannabis varieties they felt contributed most to any improvements in overall health. These are presented in Table 2, along with information pertaining to each variety's composition, THC and CBD content, as well as price. The variety *Midnight^MR* (*sativa*-leaning, 8-11% THC, 11-14% CBD, $12.50/g) was the most popular strain overall, with 18.7% of all patients perceiving it to be the most beneficial cannabis strain contributing to improvements in overall health. This was followed by *Avidekel^MR* (*indica*-leaning, 0.1-0.8% THC, 15-18% CBD, $12.50/g) preferred by 13.7% of patients, and *Sedamen^MR* (*indica*-dominant, 21-24% THC, 0% CBD, $12.50/g) preferred by 9.4% of patients.

Improvements in conditions, symptoms, and QOL items

Table 3 lists the top five conditions reported by patients, and the three cannabis varieties to which improvements in conditions at 4-month follow up were attributed. These conditions include anxiety, depression, sleep disorder, arthritis, and post-traumatic stress disorder. Improvement was most commonly reported by patients experiencing anxiety as a condition at intake. Out of 69 patients, 35.5% attributed their anxiety reduction to the variety *Luminarium^{MR}* (very *sativa*-dominant, 25-28% THC, 0% CBD, $12.50/g). This was followed by *Midnight^{MR}* (27.5%) and *Avidekel^{MR}* (21.7%).

Six of the most common symptoms for which patients reported improvements after 4 months of medical cannabis use include anxiety (as a symptom rather than condition), sleep problems, depression, insomnia, headaches, and exhaustion (Table 4). 27.3% of 341 patients attributed improvements in their symptom of anxiety to *Sedamen^{MR}*. This was followed by *Luminarium^{MR}* (25.2%), and *Cognitiva^{MR}* (22.0%). 27.7% out of 321 patients attributed improvements in sleep problems to *Luminarium^{MR}*, followed by *Midnight^{MR}* (24.6%), and *Avidekel^{MR}* (20.2%).

At the 4-month follow-up, patients were asked about which cannabis varieties they felt were responsible for changes, if any, in five quality of life measures, including sleep, appetite, concentration, bowel activity, and sexual function (see Table 5). 224 and 175 patients attributed improvements in sleep and bowel function to three specific strains: *Midnight^{MR}* (29.0% and 24.6%, respectively), *Sedamen^{MR}* (22.8% and 21.1%, respectively), and *Avidekel^{MR}* (16.5% and 20.6%, respectively). Improvements in appetite, with 302 total responses, were attributed to *Midnight^{MR}* (24.8%), *Cognitiva^{MR}* (24.2%), and *Sedamen^{MR}* (22.8%). For improvements in concentration, responses from 191 patients indicate that *Cognitiva^{MR}* (22.0%), *Midnight^{MR}* (20.4%), and *Avidekel^{MR}* (19.4%) were perceived to be the most beneficial strains.

Improvements in pain as a symptom at 4 months and 10 months

At four months, 259 patients reported on the cannabis varieties that they perceived had caused the greatest reduction in pain levels (see Table 6). A majority of these patients identified *Midnight^{MR}* (27.4%) as the most helpful, followed by *Sedamen^{MR}* (22.8%), and *Avidekel^{MR}* (22.4%). Of the 138 patients who also reported improvement in pain in the 10-month follow-up, most attributed their pain reduction to the variety *Sedamen^{MR}* (29.0%), followed by *Luminarium^{MR}* (26.1%) and *Midnight^{MR}* (26.1%).

Table 2. Properties of fifteen most popular cannabis strains perceived to be most beneficial overall

Strain	Patients Found Most Beneficial n (%)	Composition	% THC	% CBD	$/Gram
Midnight^{MR}	122 (18.7%)	*sativa*-leaning	8 - 11%	11 - 14%	12.5
Avidekel^{MR}	89 (13.7%)	*indica*-leaning	0.1 - 0.8%	15 - 18%	12.5
Sedamen^{MR}	61 (9.4%)	*indica*-dominant	21 - 24%	0	12.5
Luminarium^{MR}	57 (8.8%)	*sativa*-dominant	25 - 28%	0	12.5
Cognitiva^{MR}	51 (7.8%)	*sativa*-leaning	15 - 18%	0	5
Remissio^{MR}	29 (4.5%)	*indica*-dominant	24 - 27%	0	12.5
Alaska^{MR}	26 (4.0%)	*sativa*-dominant	20 - 23%	0	15
Erez^{MR}	24 (3.7%)	*indica*-dominant	20 - 23%	0	**7.5**
Eran Almog^{MR}	20 (3.1%)	very *indica*-dominant	25 - 28%	0	15
Contenti^{MR}	16 (2.5%)	*indica*-leaning	15 - 18%	0	**5**
Cerebri^{MR}	14 (2.2%)	very *indica*-dominant	25 - 28%	0	12.5
Voluptas^{MR}	14 (2.2%)	very *sativa*-dominant	20 - 23%	0	12.5
Elevare^{MR}	13 (2.0%)	very *sativa*-dominant	24 - 27%	0	12.5
Stellio^{MR}	11 (1.7%)	*indica*-dominant	23 - 26%	0	12.5
Or^{MR}	10 (1.5%)	*indica*-dominant	20 - 23%	0	15

Table 3. Top three cannabis strains associated with condition improvement

Condition (Total n)	1st	2nd	3rd
Anxiety disorder (69)	*Luminarium*[MR]	*Midnight*[MR]	*Avidekel*[MR]
	n = 21 (30.4%)	n = 19 (27.5%)	n = 15 (21.7%)
Depression (62)	*Luminarium*[MR]	*Avidekel*[MR]	*Alaska*[MR]
	n = 22 (35.5%)	n = 18 (29%)	n = 16 (25.8%)
Sleep disorder (53)	*Eran Almog*[MR]	*Sedamen*[MR]	*Midnight*[MR]
	n = 17 (32.1%)	n = 17 (32.1%)	n = 11 (20.8%)
Arthritis (46)	*Midnight*[MR]	*Avidekel*[MR]	*Sedamen*[MR]
	n = 18 (39.1%)	n = 15 (32.6%)	n = 13 (28.3%)
PTSD (41)	*Stellio*[MR]	*Luminarium*[MR]	*Sedamen*[MR]
	n = 15 (36.6%)	n = 13 (31.7%)	n = 12 (29.3%)

PTSD: Post-traumatic stress disorder.

Table 4. Top three cannabis strains associated with symptom improvement

Symptom (Total n)	1st	2nd	3rd
Anxiety (341)	*Sedamen*[MR]	*Luminarium*[MR]	*Cognitiva*[MR]
	n = 93 (27.3%)	n = 86 (25.2%)	n = 75 (22.0%)
Sleep problems (321)	*Luminarium*[MR]	*Midnight*[MR]	*Avidekel*[MR]
	n = 89 (27.7%)	n = 79 (24.6%)	n = 65 (20.2%)
Depression (250)	*Luminarium*[MR]	*Avidekel*[MR]	*Alaska*[MR]
	n = 80 (32%)	n = 63 (25.2%)	n = 50 (20%)
Insomnia (245)	*Eran Almog*[MR]	*Sedamen*[MR]	*Midnight*[MR]
	n = 68 (27.8%)	n = 61 (24.9%)	n = 45 (18.4%)
Headache (171)	*Midnight*[MR]	*Avidekel*[MR]	*Sedamen*[MR]
	n = 53 (31%)	n = 40 (23.4%)	n = 39 (22.8%)
Exhaustion (164)	*Stellio*[MR]	*Luminarium*[MR]	*Sedamen*[MR]
	n = 43 (26.2%)	n = 38 (23.2%)	n = 29 (17.7%)

Table 5. Top three strains associated with QOL improvement

Symptom (Total n)	1st	2nd	3rd
Sleep (224)	*Midnight*[MR]	*Sedamen*[MR]	*Avidekel*[MR]
	n = 65 (29.0%)	n = 51 (22.8%)	n = 37 (16.5%)
Appetite (302)	*Midnight*[MR]	*Cognitiva*[MR]	*Sedamen*[MR]
	n = 75 (24.8%)	n = 73 (24.2%)	n = 69 (22.8%)
Concentration (191)	*Cognitiva*[MR]	*Midnight*[MR]	*Avidekel*[MR]
	n = 42 (22.0%)	n = 39 (20.4%)	n = 37 (19.4%)
Bowel function (175)	*Midnight*[MR]	*Sedamen*[MR]	*Avidekel*[MR]
	n = 43 (24.6%)	n = 37 (21.1%)	n = 36 (20.6%)
Sexual function (170)	*Luminarium*[MR]	*Sedamen*[MR]	*Cognitiva*[MR]
	n = 45 (26.5%)	n = 44 (25.9%)	n = 36 (21.2%)

QOL: quality of life.

Table 6. Top ten strains associated with pain improvement at 4-month follow-up and 10-month follow-up

4-months		10-months	
Strain	**n (%)**	**Strain**	**n (%)**
Midnight[MR]	71 (27.4%)	*Sedamen*[MR]	40 (29.0%)
Sedamen[MR]	59 (22.8%)	*Luminarium*[MR]	36 (26.1%)
Avidekel[MR]	58 (22.4%)	*Midnight*[MR]	36 (26.1%)
Luminarium[MR]	46 (17.8%)	*Avidekel*[MR]	34 (24.6%)
Cognitiva[MR]	45 (17.4%)	*Remissio*[MR]	22 (15.9%)
Eran Almog[MR]	39 (15.1%)	*Cognitiva*[MR]	22 (15.9%)
Stellio[MR]	35 (13.5%)	*Eran Almog*[MR]	22 (15.9%)
Alaska[MR]	30 (11.6%)	*Alaska*[MR]	21 (15.2%)
Bellis[MR]	24 (9.3%)	*Cerebri*[MR]	20 (14.5%)
Remissio[MR]	20 (7.7%)	*Stellio*[MR]	19 (13.8%)
Total n	259	**Total n**	138

Discussion

Different medical cannabis varieties were found to have varying efficacies for the management of different symptoms or conditions. For example, *Eran Amog*[MR] (very *indica*-dominant, 25-28% THC, 0% CBD, $15.00/g) was the strain most beneficial for insomnia and sleep disorder, but was the ninth most popular strain overall, and did not appear in the top three varieties for the management of any other condition, symptom, or QOL measure. Similarly, *Stellio*[MR] was identified as the most beneficial for PTSD and exhaustion, but was reported to be the 14th most effective for overall health, and did not appear to be associated with any other common conditions or symptoms.

On the other hand, several varieties such as *Avidekel*[MR] and *Midnight*[MR] were found to be effective across a range of conditions and symptoms. Both varieties contain high CBD content (*Midnight*[MR] 11-14% CBD, *Avidekel*[MR] 15-18% CBD), with *Midnight*[MR] also containing moderate levels of THC (*Midnight*[MR] 8-11% THC, *Avidekel*[MR] 0.1-0.8% THC). These two varieties often appeared together as two of the top three strains perceived to be most effective for multiple indications including anxiety disorder, arthritis, sleep problems, and headache. Moreover,

Midnight[MR] and *Avidekel*[MR] both appeared as the top strains for improvements in three out of five QOL items including sleep, concentration, and bowel activity. In these QOL categories, *Midnight*[MR] was always found to be preferred over *Avidekel*[MR]. This suggests that a combination of CBD and THC may be more clinically useful than THC or CBD on their own.

Reported improvements in pain 4 and 10 months after intake was remarkably consistent, with the varieties *Midnight*[MR], *Sedamen*[MR], *Avidekel*[MR], and *Luminarium*[MR] identified as the top four strains by patients at both follow-up intervals. This suggests that these strains may be optimal for pain management. In particular, *Midnight*[MR] and *Avidekel*[MR] are likely to contribute to pain reduction in this population due to the anti-inflammatory effects associated with CBD (9). Further investigation should be conducted to determine the optimal CBD:THC ratio for moderating pain in different patient populations. It is also unclear if the efficacy of specific varieties changes over time, and whether they are effective for long-term pain management, past 10-months.

An interaction between CBD and THC has been observed in many physiological studies. For example, studies in mice have found that CBD alters the effect of THC on the protein expression of neurons in

multiple brain regions. This is complicated by the fact that the characteristics of CBD-THC interactions vary between different brain regions. In some areas such as the hypothalamus, CBD exerts an antagonistic effect, while in other areas such as the locomotor regions, the effect is synergistic (18). These factors likely play a role in the varying efficacies of different cannabis varieties, and support the finding that varieties containing both CBD and THC may be optimal for many different types of symptom management, as opposed to varieties containing solely CBD or THC.

One of the limitations of this study includes the lack of ability to correlate reported responses of cannabis varieties tried, to patients' actual ordering history from their provider(s). This, in addition to extended follow-up periods, may have led to some level of recall bias influencing results. Improvements in condition or symptoms could also be due to the combination of strains patients tried, making it difficult to accurately attribute any changes in their symptoms or conditions to one isolated product. Moreover, patients' product selection may have been influenced by factors such as differences in strain availability and cannabis variety price.

Conclusion

The most frequently reported cannabis strains effective for managing commonly reported conditions or symptoms such as depression, anxiety disorder, and pain include *Midnight[MR]*, *Luminarium[MR]*, and *Sedamen[MR]*. Strains with high CBD content such as *Avidekel[MR]* and *Midnight[MR]* were effective, particularly for improving pain. These are just a few out of numerous medical cannabis varieties that are available for patients to choose from in the Canadian medical cannabis market. Despite this, limited quality scientific evidence exists to help patients and clinicians with appropriate strain selection. By identifying patient-perceived efficacies of different cannabis varieties, this study provides a platform for clinicians to make accurate strain recommendations to patients presenting a variety of symptoms for which cannabis may be indicated. These results will also help contribute to the strategic design of future efficacy studies.

Acknowledgment

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