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Summary of Experience of Medical Marijuana Use in Canadian Military Veterans Diagnosed with Post-Traumatic Stress Disorder

EXECUTIVE SUMMARY

INTRODUCTION Post-Traumatic Stress Disorder (PTSD) is a mental illness related to a traumatic event. It is a severe disorder which can be chronic and can result in disabilities at the social, occupational and interpersonal level. PTSD symptoms are intrusive symptoms such as flashbacks, avoidance symptoms, and arousal symptoms (anger). PTSD is treated with pharmacotherapy and psychotherapy. However, many do not respond to these treatments. The objective of this study is to describe changes in patient-reported outcomes (PRO) and PTSD related medication consumption of military veterans with PTSD undergoing treatment with medical marijuana.

METHODS We conducted a single centre review of military veterans diagnosed with PTSD who had failed standard pharmacotherapy and psychotherapy and were managed with medical marijuana. PRO and medication use was assessed at baseline and at a follow up visit (3-18 months). Patients rated severity of PTSD symptoms, the impact of PTSD on social and family life, and pain severity on a 10-point scale, where 10 is the most negative. We analyzed changes in PRO from baseline to follow-up and changes in PTSD related medication use, and report percent change and magnitude of effect, as measured by effect size (ES).

RESULTS Patients were primarily male (97%) and on average 43 years old. Average severity of symptoms, severity of social impacts of PTSD and pain severity were all reduced from baseline to follow-up: 59%, 59% and 48% reductions respectively. The aggregate score of PTSD symptoms improved from a mean score of 7.0 to 2.9 (59% reduction, ES 1.5, very large effect). Notably, suicidal thoughts decreased from a baseline score of 4.1 to a follow-up score of 0.9 (77% reduction, ES 1.0, large effect). Aggregate score for social impacts improved from 6.6 to 2.7 (59% reduction, ES 1.2, large effect). Specifically drug and alcohol overuse mean score decreased from 6.0 to 1.1 (82% reduction, ES 1.4, very large effect) and marital/relationship harmony improved from 8.1 to 2.8 (65% reduction, ES 2.6, very large effect). Pain severity decreased from an average of 6.6 to 3.4 (48% reduction, ES 1.5, very large effect). Patients on PTSD related medications reduced consumption by 50% from baseline to follow-up.

CONCLUSION Initiation of medical marijuana in military veterans with PTSD who had failed conventional therapy resulted in significant improvements across all PTSD symptoms as well as social and family impact outcomes and pain severity. There was a 50% reduction in the consumption of PTSD related medications.

HEADLINES Treatment with medical marijuana for military veterans with PTSD improved aggregate patient reported outcomes 50-60%. There was a 77% decrease in suicidal thoughts. Patients on PTSD related medications at baseline reduced consumption by 50% to follow-up.

BACKGROUND Post-Traumatic Stress Disorder (PTSD) is a mental illness related to a traumatic event. Diagnostic criteria for PTSD in DSM-5 include: experiencing or witnessing a severe, traumatic event resulting in symptoms in each of four categories (intrusion, negative alteration in mood and cognitions, avoidance, and arousal); social or occupational impairment; and symptoms and impairment lasting at least one month after the trauma (American Psychiatric Association).

PTSD is treated with pharmacotherapy and psychotherapy. Pharmacotherapy for PTSD includes SSRI, other antidepressants, mood stabilizers, atypical antipsychotics, prazosin, tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs) and benzodiazepines. However, many do not respond to these treatments. PTSD carries high comorbidities with major depressive disorder and substance use disorders, and is associated with suicide attempts and poor quality of life (Sareen J).

The medicinal use of cannabis, or marijuana, is deeply rooted though history, dating back to ancient times. It once held a prominent position in the history of medicine, recommended by many eminent physicians for numerous diseases. Cannabinoids (the psychoactive components of unrefined marijuana and various derivative products) activate endogenous cannabinoid receptors, modulating neurotransmitter release and producing a wide range of central nervous system effects, including increased pleasure and alteration of memory processes. These effects provide a pharmacologic rationale for the use of cannabinoids to manage the three core PTSD symptom clusters: re-experiencing, avoidance and numbing, and hyperarousal.

EPIDEMIOLOGY The lifetime prevalence of PTSD ranges from 6.8 to 12.3 percent in the general adult population in the United States and Canada (Resnick HS) (Kessler RC) (Hoge CW). PTSD can be associated with many types of traumatic injury and it is an important public health problem. Studies have reported lifetime PTSD rates of 10 to 31% amongst military veterans. The prevalence of PTSD was estimated at 4.2 percent at one month and 12.2 percent by four months post injury in a study of soldiers hospitalized for military-related injuries (Hoge CW).

Yurkil and Stein concluded, based on a prospective, longitudinal study of US Marines deployed in Iraq or Afghanistan that experiencing traumatic brain injury during military deployment was a strong predictor of subsequent PTSD symptoms (Yurgil KA) (Stein MB). Richardson LK et al did a critical review of the prevalence estimates of combat-related PTSD among military personnel and veterans and discussed the potential factors that may account for the variability of estimates. (Richardson LK)

METHODS

Setting & Patients: We conducted a review of the medical marijuana treatment records at a single medical practice. This medical practice has experience in the treatment of medical marijuana and serves a large number of military veterans. In addition, the practice has standardized assessment tools which have been in place for several years. We reviewed 100 consecutive patients with a confirmed diagnosis of PTSD who initiated medical marijuana after January 2014. The patients reviewed had to have a confirmed diagnosis of PTSD and meet the criteria of being military veterans. Patients were referred to the clinic by the physician who was managing their pharmacotherapy. Patients had to have at least a baseline visit documented before starting medical marijuana treatment and at least one follow-up visit post starting treatment.

Interventions: Self-reported Patient-Related Outcomes (PRO) were captured at baseline and at a follow up visit between 3 and 18 months post-initiation of medical marijuana. Current medication use was recorded in the treatment record. Patients self-rated severity of PTSD symptoms, the impact of PTSD on social and family life, and pain severity on a ten point scale, where 10 is the most negative.

We analyzed changes in PRO from baseline to follow-up and changes in PTSD related medication use, and report percent change and magnitude of effect.

Statistical Methods: We analyzed changes in the average score across all participants for each PRO measure from baseline to follow-up. For each outcome, responses were included in the average only if patient had information available at both the baseline and follow-up visit; likewise, reported n numbers reflect number of patients with information available at both visits. We report percentage change from baseline to follow-up, and magnitude of effect, as measured by effect size. We considered an effect size of 0.8 to be large, and an effect size of 1.3 to be very large (Sullivan GM). Minimal clinically important difference (MCID) was calculated for each outcome, to determine the minimal level indicating real change for the quality of life scales (Norman GR), and changes from baseline to follow-up were compared against the MCID.

Changes in PTSD related medication use are also detailed in terms of averages and percent change in number of medications, for those patients with information available at both baseline and follow-up. Medications considered related to PTSD include medications for pain, depression, anti-psychotic medications, medications for bipolar disorder, anxiety, ADHD, seizures, muscle relaxants, nightmares, sleep and related effects (erectile dysfunction, nausea).

No information was captured relating to adverse events experienced on PTSD or other medications, and no information was captured on hospitalization or other physician visits.

RESULTS We present demographic information in Table 1. Of the 100 patients, they were primarily male (97%) and on average 43 years old. Two-thirds of patients were unable to work or had retired.

Table 1 Demographic Information

All patients reviewed, n (%)	100 (100%)
Average age in years	43
Male sex, n (%)	97 (97%)
Age Distribution, n (%)	
<40 years	34 (34%)
40-49 years	41 (41%)
50-59 years	21 (21%)
60+ years	4 (4%)
Employment Status at time of baseline visit	
Working	21 (21%)
Student	2 (2%)
Retired/ Unable to work	63 (63%)
Unknown	14 (14%)

Data presented as n (%) unless indicated otherwise

Analysis was performed on the difference from patients' baseline score to their follow-up visit score, within 18 months of their baseline visit. Distribution of time from baseline to follow-up visit can be found in Table 2.

Table 2 Time to follow-up visit

Distribution of time to follow up visit	n (%)
< 3 months	25 (25%)
4-6 months	12 (12%)
7-10 months	11 (11%)
11-12 months	25 (25%)
13-15 months	20 (20%)
16-18 months	7 (7%)
60+ years	4 (4%)

Dose of Medical Marijuana

Patients were prescribed on average 9.4 grams / day of medical marijuana. Patients were started on a dose of 1 gram, and self-titrated until desired results were met with instructions of a ceiling dose of 10 grams. There were many varieties of medical marijuana used by these patients; patients were often on multiple strains with varying CBD and THC content. Patients utilized various varieties of cannabis supplied by MedReleaf Corp. including "Luminarium^{MR}", "Midnight^{MR}", "AviDekel^{MR}" and others.

Table 3 Dose of medical marijuana at follow-up visit

Dose of medical marijuana (n=99)	n (%)
<5 grams	5 (5%)
5 to 9 grams	20 (20%)
10 grams	66 (67%)
More than 10 grams	8 (8%)

Change in severity of PTSD Symptoms

The mean score for severity of each PTSD symptom showed significant improvement from baseline to follow-up; each symptom had a reduction in average score over the minimal clinically important difference (MCID). The aggregate score of PTSD symptoms improved from a mean score of 7.0 to 2.9 (59% reduction, ES 1.5, very large effect). Notably, suicidal thoughts decreased from a baseline score of 4.1 to follow-up score 0.9 (77% reduction, ES 1.0, large effect). Full results can be found in Table 4.

Table 4 Severity of Symptoms (Scale of 0-10)

Symptom	**Number of responses**	**Mean Baseline Score + SD**	**Mean Follow-up Score**	**Improvement** (%Improvement over Baseline)	**Effect Size**
Anger and irritability	93	7.9 ± 2.1	3.0 + 2.1	5.0 (63%)	2.4
Anxiety	93	7.8 ± 1.5	3.3 + 1.5	4.6 (59%)	9.0
Avoidance of trigger related people and situations	90	8.1 ± 2.3	3.7 ± 2.3	4.3 (54%)	1.9
Depression	92	7.3 ± 2.1	2.9 ± 2.1	4.4 (60%)	2.1
Distorted sense of blame for the events	78	6.7 ± 2.8	2.9 ± 2.8	3.8 (57%)	1.4
Easily startled	90	7.5 ± 2.3	3.3 ± 2.3	4.2 (57%)	1.8
Feeling disconnected from oneself (depersonalization)	78	7.0 ± 2.7	2.5 ±2.7	4.4 (64%)	1.6
Flashbacks and intrusive memories	89	6.9 ± 2.4	2.8 ±2.4	4.2 (60%)	1.7
Hypervigilance	84	7.4 ± 2.2	3.0 ± 2.2	4.4 (59%)	2.0
Nightmares	87	6.8 ± 2.5	2.5 ± 2.5	4.2 (62%)	1.7
Poor concentration	92	8.0 ± 1.8	4.2 ± 1.8	3.8 (47%)	2.0
Sense of felling that one's surroundings are not real	76	4.8 ± 3.4	1.9 ± 3.4	2.9 (60%)	0.9
Stuck in severe emotions related to the event	79	6.8 ± 2.5	2.6 ± 2.5	4.3 (63%)	1.7
Suicidal thoughts	80	4.1 ± 3.3	0.9 ± 3.3	3.1 (77%)	1.0
Aggregate score		7.0 ± 2.7	2.9 ± 2.7	4.1 (59%)	1.5

Change in Social/ Family Impacts

All domains of social/ family impacts showed a decrease, with a range of reductions from 46% to 82%. For all impacts, improvement over baseline was larger than the minimally clinically important difference. Aggregate score for social/ family impacts improved from 6.5 to 2.7 (59% reduction, ES 1.2, large effect). Specifically, drug and alcohol overuse mean score decreased from 6.0 to 1.1 (82% reduction, ES 1.4, very large effect) and marital/relationship harmony improved from 8.1 to 2.8 on average (65% reduction, ES 2.6, very large effect). Full results can be found in Table 5.

Table 5 Social and Family Impact (Scale of 0-10)

Impact	Number of responses	Mean Baseline Score + SD	Mean Follow-up Score	Improvement (%Improvement over Baseline)	Effect Size
Drug and alcohol overuse	66	6.0 ± 3.6	1.1 ± 1.7	4.9 (82%)	1.4
Marital or relationship harmony	70	8.1 ± 2.0	2.8 ± 2.4	5.3 (65%)	2.6
Relationship with brothers / sisters / parents	73	7.1 ± 2.8	3.7 ± 2.6	3.4 (48%)	1.2
Your belief that good things will happen in the future	72	6.1 ± 3.1	3.0 ± 2.3	3.1 (50%)	1.0
Your belief that you are a valuable and appreciated member of society	47	6.1 ± 2.9	3.3 ± 2.5	2.8 (46%)	1.0
Your belief that you belong in the “Human Race” or your concepts of society	35	5.8 ± 3.1	2.3 ± 2.0	3.4 (59%)	1.1
Your relationship with children	66	6.7 ± 2.9	2.3 ± 2.3	4.3 (65%)	1.5
Your trust in the relationship with “the creator” or your concept of “God”	51	5.7 ± 3.8	3.0 ± 2.9	2.8 (48%)	0.7
Aggregate score		7.0 ± 2.7	2.9 ± 2.7	4.1 (59%)	1.5

Change in Pain Severity

Pain severity decreased from an average of 6.6 to 3.4 (48% reduction, ES 1.5, very large effect).

Table 6 Pain Severity (Scale of 0-10)

Number of responses	Mean Baseline Score + SD	Mean Follow-up Score	Improvement (%Improvement over Baseline)	Effect Size
80	6.6 ± 2.1	3.4 ± 1.5	3.2 (48%)	1.5

PTSD Related Medication Consumption

Of 100 patients, PTSD related medication information was available for 87. Of these 87 patients, 59 (68%) were on PTSD related medications at the baseline visit with a mean of 3.2 such medications (SD 1.9). The number of PTSD related medications for these patients was reduced to a mean of 1.6 (SD 1.8), or a 50% reduction in number of medications. 21 of 59 patients (36%) had discontinued all PTSD related medications by the time of their follow up visit. Another 19 patients of 59 (32%) discontinued some of their PTSD medications. 14 patients (24%) had no change to their PTSD medications and 5 patients (8%) added some PTSD related medications.

For those 21 patients discontinuing all PTSD related medications, the estimated annual savings from discontinuing these prescription medications would range from $48,600 to $78,600 based on average daily dose for these medications, and depending on price of generic where available, versus brand name and assuming a dispensing fee of $10 per month. This translates into an average savings per patient discontinuing all PTSD medications to be between $2,300 and $3,800 per year.

For those patients adding or discontinuing some (not all) of their medications, the average was 1.8 medications per patient for each category.

The widespread use of polypharmacy, as outlined in Table 7 reflects the complexity of treatment for these patients. The percentage of patients on two or more medications dropped from 55% at baseline to 31% at follow-up and correspondingly the percentage of patients on zero or one medications increased from 45% to 69%.

Table 7 Number of related medications at baseline and at follow-up visit, for patients with medication list available (n=87)

Number of PTSD related medications, n (%)	Number of patients on medications at baseline visit	Number of patients on medications at follow up visit
0	28 (32%)	43 (49%)
1	11 (13%)	17 (20%)
2	13 (15%)	11 (13%)
3	12 (14%)	4 (5%)
4	13 (15%)	8 (9%)
5 or more	10 (11%)	4 (5%)

DISCUSSION

PTSD is a severe disorder that results in disabilities at the social, occupational and interpersonal level. PTSD prevalence amongst military veterans is higher than in the general population. Suicide attempts and thinking about suicide is reported amongst veterans with PTSD. Traditional pharmacotherapy has limitations in terms of efficacy. In addition, psychoactive medications have many side effects that can lead to poor adherence on treatment, or may be unacceptable to patients.

Patient-reported outcomes (PROs) is a method used in a clinical setting where responses are collected directly from the patient. These scales are a particularly important assessment tool to measure the impact of PTSD on this patient population as treatment effects in the context of relief of symptoms and quality of life are better known to patients than to their treating physicians.

In demonstrating the outstanding improvement in symptoms relevant to PTSD and social life impacts as evidenced by effect sizes, this study shows that daily treatment with medical marijuana improves the quality of life of military veterans with severe PTSD who have failed pharmacotherapy and psychotherapy.

Our findings of reduced anxiety and improved coping ability are consistent with benefits previously reported in the literature specifically for this population. Betthauser et al. evaluated 11 articles pertaining to cannabis use by military veterans who met standard diagnostic criteria for PTSD. The authors concluded that substantial numbers of military veterans with PTSD use cannabis or derivative products to control PTSD symptoms, with some patients reporting benefits in terms of reduced anxiety, insomnia and improved coping ability. (Betthauser K)

In particular, it is worthwhile to note the decrease in suicidal thinking post-initiation of medical marijuana that we found. In recent months data has begun to surface regarding the suicide rates amongst military veterans. Medical marijuana may be a viable treatment option to help prevent this mounting death toll.

Quality of life improvements in this patient population should also be a significant factor in treatment choice. As evidenced by the changes in social/family impacts, medical marijuana has significantly helped these individuals in their inter-personal relationships; this may help their eventual re-integration into society. The majority of these patients, despite being younger than retirement age, were not working at the time of their baseline visit. Further investigation is required to understand if these patients can return to work once stabilized on treatment with medical marijuana.

These results should be interpreted within the context of military veterans suffering from PTSD for whom traditional pharmacotherapy had not resulted in satisfactory outcomes. This study was limited to a single centre's experience where the treating physician has had extensive experience in treating this patient population. Given the recent availability of medical marijuana as a treatment option, these results provide early Canadian data on its benefits in this unique population.

CONCLUSION Initiation of medical marijuana in military veterans with PTSD who had not responded adequately to conventional therapy resulted in significant improvements across all PTSD symptoms as well as social and family outcomes and pain severity. Furthermore, improvements in outcomes were associated with a 50% reduction in the consumption of PTSD-related medications for patients on these medications at baseline, resulting in lower drug costs and dispensing fees, and a reduction in potential adverse events. 36% of patients on PTSD related medications at baseline discontinued all such medications, for an estimated annual savings of $2,300 to $3,800 per patient. In addition, there was less drug/ alcohol overuse post initiation of medical marijuana, which may reduce adverse events and hospital admissions; information on hospital admissions and adverse events was not captured in this study.

Research results support ongoing access of medical marijuana to military veterans not responsive to traditional pharmacotherapy and psychotherapy for their PTSD, on the basis of improved quality of life in these individuals and reducing polypharmacy and potential adverse events.

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