Effects of Medical Cannabis on Patients with Charcot-Marie-Tooth Disease

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Abstract

Background: Charcot-Marie-Tooth (CMT) disease, also known as hereditary motor and sensory neuropathy, is a rare disease that affects 1 in 2,500 people. CMT can damage the nerves themselves or the myelin sheath surrounding them. CMT can cause symptoms such as neuropathic pain, weak ankles, claw-like hands, and muscle wasting in the extremities. Although treatments can help patients manage their symptoms, no known cure exists. In this study, we sought to determine the efficacy of using medical cannabis as a method of symptom relief in CMT patients.

Methods: We collected patient-reported surveys through the Hereditary Neuropathy Foundation's patient registry: Global Registry for Inherited Neuropathies. The online survey contained 52 multiple-choice questions. We analyzed the data through IBM SPSS and created figures through GraphPad Prism. The sample participants (N=56) consisted of 71.4% females. Ages ranged from 18 to 87. The majority (48.5%) were CMT1, 18.2% were CMT2, and 6.1% were CMT4.

Results: Women were more likely to report experiencing pain than men ($p<.05$). Participants who perceived support from their providers were more likely to inform them of their cannabis use ($p<.05$). When asked about how much relief they experience from using cannabis as a method of symptom relief, respondents reported an average of 69.6% (SEM $\pm$ 2.6) relief.

Conclusion: Our results indicate that patients reported receiving substantial symptom relief from medical cannabis. Further prospective or controlled research is necessary to extend upon these findings.

Introduction

Charcot-Marie-Tooth (CMT) disease is one of the most common inherited neuromuscular disorders, affecting about 1 in 2,500 people. It can be caused by mutations in over 90 genes that affect peripheral nerves or by diabetes or chemotherapy (1). There are five CMT types, with type 1 being the most prevalent. Mutations can either affect nerves themselves or the myelin sheath. In both cases, weaker messages travel between the brain and the extremities.

Mutations can be inherited through autosomal dominant, autosomal recessive, or X-linked patterns (2). CMT1 is an autosomal dominant (3), demyelinating neuropathy (4). CMT2 is an autosomal dominant axonal peripheral neuropathy (4). CMT4 is a rare autosomal recessive demyelinating neuropathy (5). Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant peripheral neuropathy, which leads to demyelination (6). Demyelinating forms lead to degradation of the myelin sheath. Axonal forms lead to axon deterioration in the peripheral nerves (7).

Although CMT has a broad genetic heterogeneity, patients display similar phenotypes (8). Patients with CMT experience various motor deficit symptoms, such as clumsiness, ankle twisting, muscle atrophy of the extremities, hammertoes, and claw hands. They also experience sensory deficit symptoms, such as pain, pins and needles, and burning (9). Symptoms usually worsen over time, but the severity of symptoms vary from person to person.

There are several ways to diagnose CMT disease. It can be diagnosed through genetic testing or through electrophysiological examination, which measures motor conduction velocity (VCM). Those with CMT will display a decreased VCM if they have demyelinating neuropathy (9). Genetic tests can be conducted to receive a CMT diagnosis. Although there is no known cure for CMT, there are treatments available such as physical therapy, occupational therapy, pain medication, and orthotics to manage symptoms.

In the past, there has been taboo surrounding the use of cannabis. Researchers conducted a qualitative descriptive study on the stigma surrounding cannabis use. People who use cannabis for therapeutic purposes (CTP) feel they are perceived as "potheads" by their families and healthcare providers. They also state that when they explain the medical benefits of cannabis, their providers and families respond with mistrust. Due to negative reactions, many participants choose to keep their use undercover (10). Withholding information from providers can have negative consequences due to possible drug interactions. CBD has potential inhibitory effects on CYP3A4, which is a vital liver enzyme responsible for removing drugs from the body (11). CYP3A4 substrates include benzodiazepines, opioids, and antidepressants (12). Another cytochrome that is inhibited by THC and more so, CBD, is CYP2D6 (13). This enzyme is primarily active in the liver and its substrates include medications such as antipsychotics and antidepressants (14). Inhibition of enzymes leads to increased blood levels of substrate. As a result, there is a greater possibility of adverse effects, such as overdosing

on medications (12). Researchers conducted a survey study where they gathered oncologists' thoughts regarding medical cannabis. Seventy percent of physicians said they did not feel as though they had enough knowledge on medical cannabis to recommend it to their patients (15). In another survey study, investigators found that 38.7% of primary care providers feel medical cannabis should be recommended for managing symptoms associated with medical illnesses (16). Currently, 36 states have legalized medical cannabis, furthering research, and encouraging clinicians to consider cannabis as a therapeutic alternative for patients.

Cannabis has cannabidiol (CBD) and tetrahydrocannabinol (THC) components. Both components have been found to have anti-inflammatory and analgesic effects, while THC has an added psychoactive component (17). There are three types of strains: indica, sativa, and hybrids. Each produces different effects and combats separate issues. Indica is often recommended for medical conditions such as chronic pain, anxiety, insomnia and muscle spasms (18). As stated in the MMP directory website, benefits of sativa use include reduced fatigue, pain, headaches, nausea, and increased focus. Hybrid strains provide the effects of both sativa and indica strains. Dispensary staff commonly recommends hybrid strains for amyotrophic lateral sclerosis (ALS) (18).

Humans have an endocannabinoid system (ECS) with cannabinoid receptors (CB_1 and CB_2) and endogenous lipid ligands (19). Endocannabinoid receptors recognize and bind exogenous plant-derived cannabinoids (20). Cannabinoids target nociceptors, which are receptors associated with painful stimuli. They exert their effects on nociceptors in the brain, spinal cord, and peripheral nerves, which conversely are the locations of CB_1 receptors. When chronic or neuropathic pain is rooted in inflammation, cannabinoids also target CB_2 receptors (20). CBD has potential therapeutic effects, such as anti-inflammatory, anti-anxiety, and anti-nausea. According to animal studies, cannabis is effective for treating chronic pain, specifically neuropathic and inflammatory pain.

In a case study, a 67-year-old female with multiple sclerosis (MS) reported neuropathic pain and rated the pain a 9 out of 10. She was prescribed 1 g of a 2.5% THC and 5% CBD strain per day through vaporizer. She reported that this strain was unsuccessful at treating her symptoms, so they changed the prescription to a 9% THC and 13% CBD strain. During her 60 day follow-up, she rated her pain a 5 out of 10 and reported that she planned on lowering the dose of other medications (21). Thus, the effectiveness of medical cannabis may be dose dependent.

Additionally, the substitution effect can occur when medical cannabis replaces recreational or pharmaceutical drug use (22). A cross-sectional survey study shows that medical cannabis use was correlated with a 64% decrease in opiate use (23). Another survey study found that cannabis served as a replacement for opiates (30%), alcohol (25%), benzodiazepines (16%), and antidepressants (12%) (24). Cannabis has been ruled a Schedule I drug under federal law. A Schedule I drug is said to have no medical purpose and to have high abuse potential. This creates a limitation in the research that can be conducted to determine its efficacy and safety. In this study, we seek to determine the efficacy of using medical cannabis as a source for symptom relief as reported by CMT patients.

Methods

Participants

Participants (N=56, 71.4% female, Age= 48.9, Min= 18, Max=87, Figure 1). Further demographic information was not collected to maintain anonymity.

Survey

The survey used for this study was modified from (22). Most of the items were kept the same, but some were tailored to address the sample we are studying. Surveys are posted on the Hereditary Neuropathy Foundation (HNF) website. A link was also created and sent to all the members of the foundation. Those affected by CMT were free to take the survey. It contained 52 questions, which were all multiple choice. The survey questions can be accessed in the Appendix section. The surveys were anonymous to maintain privacy and to minimize bias. Generally, it took participants about 10 minutes to complete. The survey was designed to gather information on the effectiveness of medical cannabis as a treatment for symptom relief for those affected by CMT. The purpose was to gather this information from a patient perspective. Since this study does not cause any harm to participants, the study was IRB approved as exempt by Advarra.

Data analysis

After the surveys were collected, we input the data into IMB SPSS, version 26. Through this software program, we conducted Chi-square and t-tests to find associations between variables. We created figures and tables through GraphPad Prism, version 8. A $p<0.05$ was considered statistically significant. The variability was reported as the Standard Error of the Mean (SEM). For the results listed in Table 1, the percentages do not add up to 100 because respondents were allowed to choose more than one symptom/mobility device. For the symptom category in Table 1, we combined the results for two variables, symptoms, and characteristics.

Results

A total of 56 people answered the survey. When asked if they experienced pain associated with CMT, 90.9% of participants answered yes. The majority (48.5%) of respondents had CMT type 1A, which is the most prevalent CMT type; 27.3% were HNPP; 18.2% were CMT2; and 6.1% were CMT4 (Figure 1).

In this sample population, about three-quarters of respondents had weak ankles, about one-third had muscle atrophy and/or tremors, and about a quarter had temperature sensitivity and/or poor or absent reflexes (Table 1). Other symptoms alleviated by medical cannabis according to participants were pain, substance cravings, and anxiety (Table 2). Furthermore, many respondents needed the aid of mobility devices. About one-fifth needed canes/walking sticks and/or braces, one-sixth needed custom foot orthotics/inserts, and about one-tenth needed walkers (Table 1).

Of the sample population, 33.9% possessed a medical cannabis certificate. Most (90.9%) respondents said they experienced pain. When prompted with "How effective is medical cannabis in alleviating your symptoms with CMT?" respondents provided the percent of relief they experienced from medical cannabis.

Characteristic	Percent
Symptoms	
Weak ankles	72.2%
Muscle atrophy	36.1%
Tremors	33.3%
Temperature sensitivity	27.8%
Poor or absent reflexes	27.8%
Clumsiness	25.0%
Coordination/balancing problems	25.0%
Restless leg syndrome	25.0%
Arm or leg weakness	22.2%
Difficulty with physical activity	22.2%
Neuropathic pain	22.2%
Numbness	22.2%
Rigid muscles	22.2%
Hammer or curled toes	19.4%
Spasticity	19.4%
Weakness	19.4%
Mobility Device	
Cane/walking sticks	19.4%
Braces (leg, AFOs, KFOs, etc.)	19.4%
Custom foot orthotics/inserts	16.7%
Walker	11.1%
Scooter/electric chair	8.3%
Night splints	5.6%
Occupational Therapy	2.8%
Physical Therapy	2.8%
None	13.9%

Table 1. Symptoms experienced and mobility devices used by respondents.

Characteristics	Percent
Pain	42.9%
Substance cravings	17.9%
Anxiety	7.1%
Other	32.1%

Table 2. Other symptoms alleviated by medical cannabis.

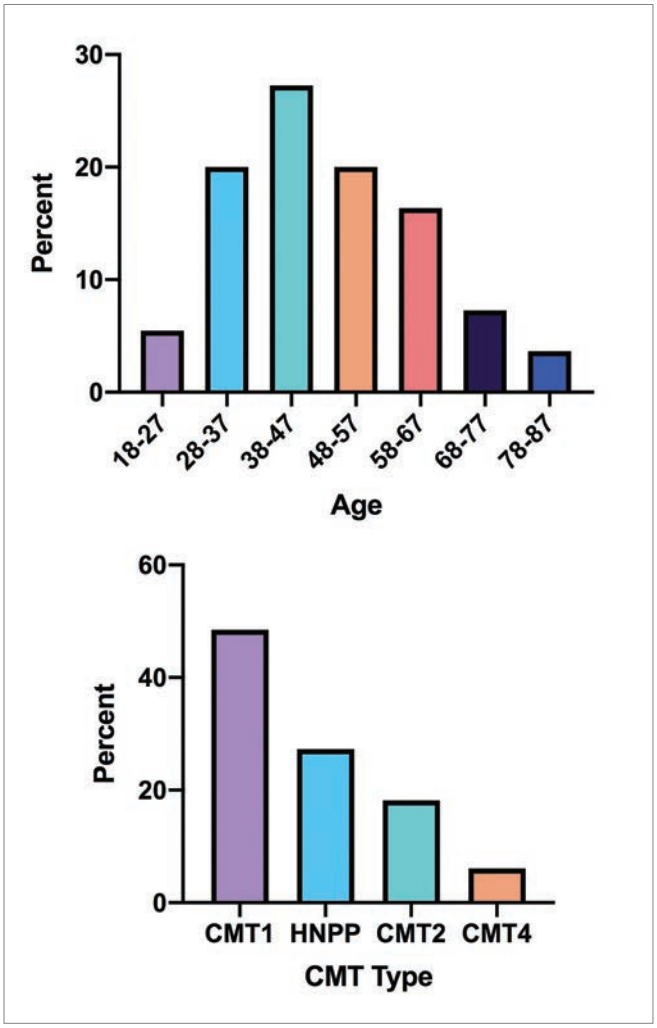

Figure 1. Participants' CMT types (bottom) and age of participants (top). HNPP: Hereditary neuropathy with liability to pressure palsies.

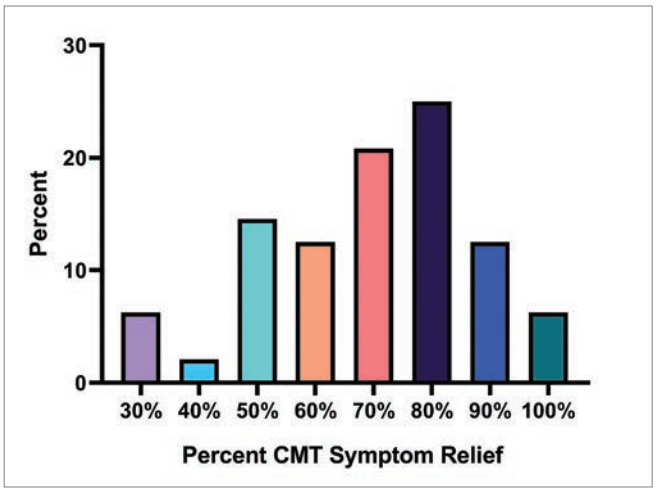

Figure 2. Percent CMT symptom relief from using medical cannabis (mean= 69.6, SEM= 2.6).

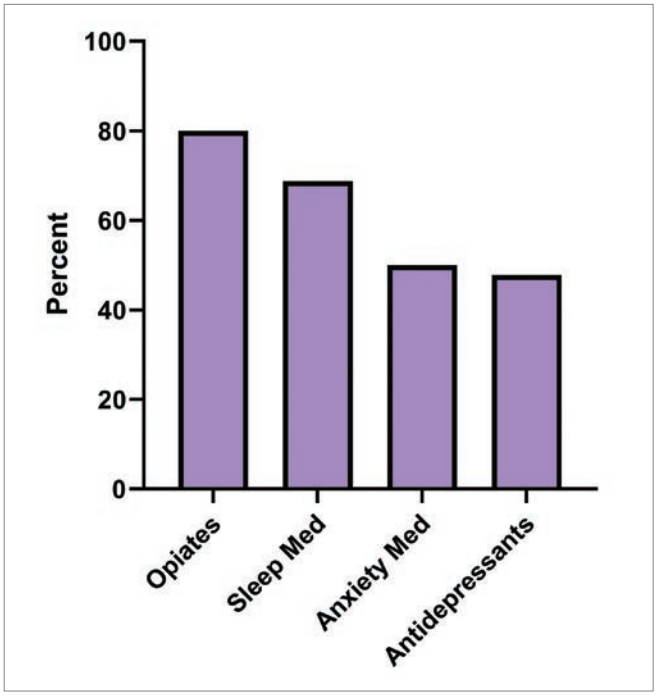

Figure 3. Percent reducing medication use after using medical cannabis.

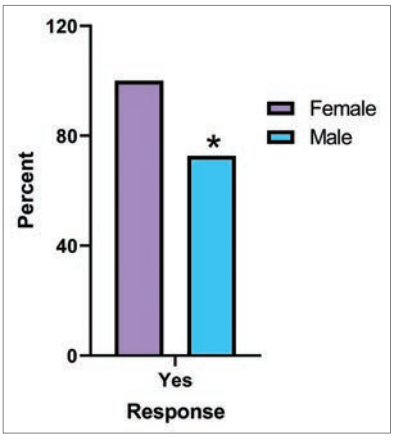

Figure 4. Gender differences in pain reporting.

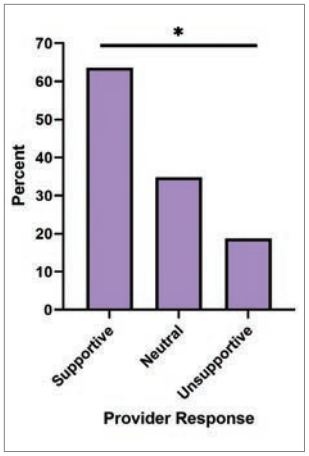

Figure 5. How likely participants are to inform providers of cannabis use based on perceived support.

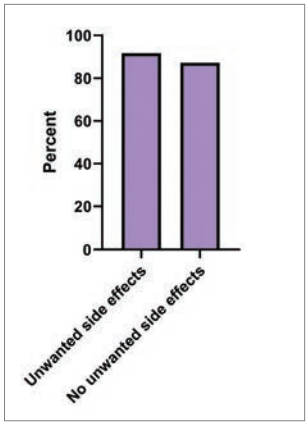

Figure 6. Difference in plans of stopping usage of medical cannabis in participants who have and have not experienced negative side effects.

Most respondents said that cannabis provided 80% relief (Figure 2).

Participants were asked if they noticed a change in their use of other medications after they began using medical cannabis. In Figure 3, we show how many respondents reported a decrease in medication use. Four-fifths (80%) reported using less opiates, 68.8% responded using less sleep medication, 50% reported using less anxiety medication, and 47.8% reported using less antidepressants (Figure 3).

We wanted to see if there was an association between gender and pain. All (100%) of female respondents and 72.7% of male respondents reported feeling pain associated with CMT (Figure 4). Additionally, we ran a 2x2 chi-squared test on gender and pain variables. There was a significant relationship between gender and pain.

Figure 5 shows physicians' attitudes regarding patient medical cannabis use. Based on those attitudes, we measured how likely participants were to inform the provider of their cannabis use. As evident below, the more positive the provider's response, the more likely they are to inform them. For those who reported receiving a supportive response from providers, 63.6% said that they would inform them of their medical cannabis use.

For those who reported unsupportive responses from providers for medical cannabis use, only 18.8% said they would inform providers of cannabis use. We conducted a 2x2 chi-squared test to analyze whether provider attitudes regarding medical cannabis affect patients' decisions to inform them of cannabis use. When providers are perceived by patients as being supportive, patients are significantly more likely to inform them of cannabis use than if providers are unsupportive toward cannabis use ($p < 0.05$).

Participants reported whether they experienced negative side effects due to cannabis use and if they planned on halting their usage. The preponderance (91.7%) of participants who experienced negative side effects and 87.2% of respondents who did not have negative side effects said they did not have plans to stop consuming medical cannabis (Figure 6).

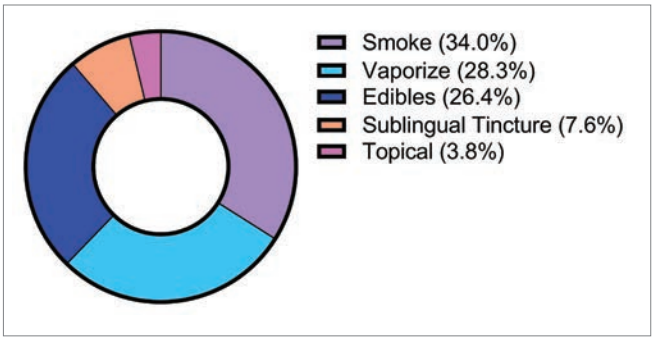

Figure 7. Preferred method of consumption among participants.

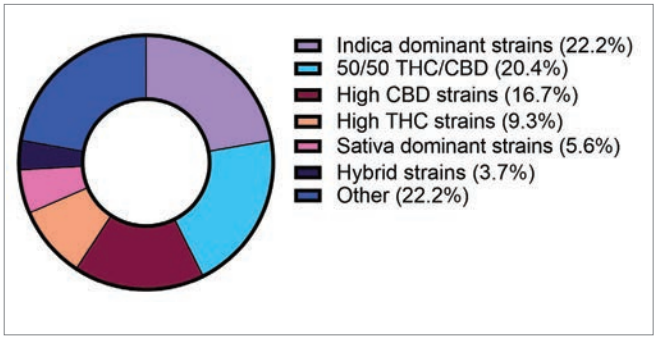

Figure 8. Commonly used strains among participants.

Preferred methods of consumption among participants are smoking (34%), vaporize (28.3%), edibles (26.4%), sublingual tinctures (7.6%), and topical (3.8%) (Figure 7). Preferred strains were indica dominant strains (22.2%), 50/50 THC/CBD strains (20.4%), high CBD strains (16.7%), high THC strains (9.3%), sativa dominant strains (5.6%), and hybrid strains (3.7) (Figure 8).

Discussion

This novel study shows that medical cannabis provides symptom relief for CMT patients. Studies have examined the efficacy of medical cannabis for MS-related symptoms, such as spasticity and tremors. For MS patients with spasticity, oral cannabis extract (OCE) and THC are effective at reducing patient-reported pain scores. However, for MS patients with tremors, OCE and THC are likely ineffective for treating this symptom (19). In a randomized controlled trial conducted among MS patients, those who smoked medical cannabis scored about 2.7 points lower on the Ashworth Scale than those in the control group (25). The Ashworth Scale measures spasticity in MS patients, with 0 being no resistance and 4 being rigidity. The U.S. FDA has approved a mucosal spray (nabiximols) that consists of CBD and THC in a 1:1 ratio for clinical trials. This drug may aid in decreasing spasticity in MS patients (26).

In patients with amyotrophic lateral sclerosis (ALS), cannabis possibly aids in muscle relaxation, appetite stimulation, and pain reduction (27). In a survey examining the effects of cannabis on ALS patients, researchers found that cannabis is moderately effective at relieving symptoms such as spasticity, pain, and depression (28). Additionally, in open-label observational study, Parkinson's disease (PD) patients showed an improvement in tremors, rigidity, and pain 30 minutes after smoking cannabis (29). Symptoms experienced in CMT overlap with those experienced in MS, ALS, and PD. Almost all participants said they experienced pain, one-third had tremors and one-fifth had spasticity and/or muscle rigidity.

In general, patients with unmanaged neuropathic pain have poorer health outcomes and have an increased probability of developing anxiety and depression. The ECS plays an important role in regulating neuropathic pain. A series of studies have shown that compared to placebo groups, those exposed to short-term use of medical cannabis experienced significant alleviation of neuropathic pain (30, 31, 32). Additionally, in a randomized, double-blind control study, THC reduced neuropathic pain in patients with MS or with traumatic nerve injury (20). Per the literature (19, 20, 28,32), medical cannabis provides relief for symptoms such as spasticity and pain. Cannabis appears to be a promising therapy option for CMT-related symptoms.

There was a significant association ($p<0.05$) between gender and pain. It is unknown whether there were biological differences or/and sociocultural expectations that lead to the differences in pain sensation. A literature review suggests that females are more sensitive to experimentally induced pain and have a higher prevalence of common forms of pain (33). Social and cultural factors also contribute to the differences in expression of pain between genders. By societal standards, it is more acceptable for females to display pain expression. In turn, this can lead to respondent bias, where men downplay their perception of pain (34). Additionally, studies show that neuropathic pain is more prevalent in females than in males (33).

In an online survey study, researchers found that twice as many consumers preferred indica strains to sativa strains (22). In this study, we discovered that about a quarter of respondents preferred indica dominant strains, which are used to provide relaxing and sedating effects. One-fifth of respondents said they use 50/50 THC/CBD strains. One-sixth said they used high CBD strains to provide more relaxing effects and are used to relieve symptoms. One-tenth of participants said they use high THC strains that are more potent and provide the effect of being "high." Only 5.6% of participants said they used sativa dominant strains, which provide an uplifting effect. Participants used hybrid strains, which provide a combination of indica and sativa effects, the least.

Perceived provider attitudes affected patients' likelihood to inform providers of their medical cannabis use. Some physicians have conflicting views on medical cannabis. While physicians may be hesitant to endorse medical cannabis, with increasing evidence-based guidelines this hesitance is likely to decrease. Patients are also aware of the social stigma that surrounds cannabis use, so they are less likely to disclose their usage to friends and family (21). In a cross-sectional survey study among medical cannabis users in Canada, 79.3% of respondents said they withheld information regarding their cannabis use, mainly to avoid being judged. Additionally, 10.1% stated that their physicians were unsupportive of their medical cannabis use, while 38% perceived their physicians to be supportive. Furthermore, 32.6% of respondents said that their physician

had refused to provide them with a medical certificate, mostly because the physician was not sure of the therapeutic benefits or because they were afraid of negative consequences on behalf of the medical association (35). This supports the data seen in Figure 7, which shows that when people perceive positive feelings and decreased judgment from their providers, they were more likely to inform them that they are using cannabis to experience symptom relief.

Medical cannabis has been legalized in 36 states, but many providers are hesitant to provide medical cannabis certificates. As seen in our study population, only 33.9% of participants had medical cannabis certificates. In a survey study done in Ohio, where medical cannabis has been legalized, they found that there are geographic limitations to where patients can find physicians that provide medical cannabis certificates. Providers who do provide certificates were usually located in cities, whereas there was a lack of certifying physicians in rural areas (36). Another study found that over time, both adolescents and adults perceive cannabis to be of decreased risk. In physicians, they did not find the same trends. Due to inconvenient reporting requirements, providers do not recommend and often dissuade patients from using medical cannabis (37). This leads to people obtaining cannabis illegally or to patients withholding information regarding cannabis use from their providers.

There are several notable limitations to this study. Inherent to survey studies is respondent bias. In this study, all participants (N=56) used cannabis. Given the branched design of the survey, there were multiple questions where fewer than 20 respondents provided data. Therefore, the data is biased toward a positive cannabis experience, since those who are more inclined to answer the survey generally have more positive experiences with medical cannabis. Although the sample size is relatively small, CMT patients are not easy to come across since this is a relatively rare disease, making these findings exciting. Within the sample, not all the forms of CMT were accounted for, such as CMT3. Additionally, because of the small sample size, there may be a lack of generalizability. Cannabis not being used in a controlled setting (e.g., dosage, composition, methods of delivery) was also a limitation. Cannabis can be absorbed in many ways; whether it's inhaled through vapor or ingested in food or drinks, each method has a different rate of absorption. Though some of the participants had reported a decrease in their pain levels, there is no indication as to how much cannabis they consumed for them to see that decrease. It is possible that those who reported decreased levels of pain consumed an increased dose of cannabis and/or had a different method that was faster at relieving pain than that of those participants who reported no change in their pain levels. Physical and psychological adverse events were not considered. Finally, they did not report if they had psychedelic effects.

Conclusion

Although studies have shown inconclusive results regarding the effectiveness of medical cannabis in pain relief, the findings from the surveys indicate that cannabis provides substantial symptom relief in CMT patients. Since CMT is a rare and relatively new disease, we believe that this sample (N=56) provides valuable insight into the possibility of using cannabis as a method of symptom relief. Additionally, we believe this data is innovative and shows that medical cannabis is a possible avenue to take when assessing treatments for neuropathic pain. For further research, it would be beneficial to continue receiving surveys to get more robust results. We could also build on the results that we have and hopefully provide a new and effective modality for symptom relief for CMT patients. Future studies will benefit with a wider range of participants to account for the missing CMT types. If possible, accounting for medical cannabis effects in a controlled environment and having the possibility of comparing placebo to treatment groups would provide valid data. Since this was the first study exploring CMT and medical cannabis, we believe this is exciting and opens a new door to providing more effective treatments for CMT patients.

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Disclosures

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