Therapeutic Satisfaction and Subjective Effects of Different Strains of Pharmaceutical-Grade Cannabis

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Abstract: In The Netherlands, pharmaceutical-grade cultivated cannabis is distributed for medicinal purposes as commissioned by the Ministry of Health. Few studies have thus far described its therapeutic efficacy or subjective (adverse) effects in patients. The aims of this study are to assess the therapeutic satisfaction within a group of patients using prescribed pharmaceutical-grade cannabis and to compare the subjective effects among the available strains with special focus on their delta-9-tetrahydrocannabinol and cannabidiol content. In a cross-sectional and natural design, users of pharmaceutical-grade cannabis were investigated with questionnaires. Medical background of the patients was asked as well as experienced therapeutic effects and characteristics of cannabis use. Subjective effects were measured with psychometric scales and used to compare among the strains of cannabis used across this group of patients. One hundred two patients were included; their average age was 53 years and 76% used it for more than a year preceding this study. Chronic pain (53%; n = 54) was the most common medical indication for using cannabis followed by multiple sclerosis (23%; n = 23), and 86% (n = 88) of patients (almost) always experienced therapeutic satisfaction when using pharmaceutical cannabis. Dejection, anxiety, and appetite stimulation were found to differ among the 3 strains of cannabis. These results show that patients report therapeutic satisfaction with pharmaceutical cannabis, mainly pain alleviation. Some subjective effects were found to differ among the available strains of cannabis, which is discussed in relation to their different tetrahydrocannabinol/cannabidiol content. These results may aid in further research and critical appraisal for medicinally prescribed cannabis products.

Key Words: medicinal cannabis, delta-9-tetrahydrocannabinol, cannabidiol, subjective effects, visual analog scale

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Throughout history, the cannabis plant (*Cannabis sativa* L.) has been applied medicinally worldwide for a variety of clinical and subclinical conditions. The main pharmacologic constituents of current medicinal interest in the plant are its cannabinoids, foremost delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).[1] Tetrahydrocannabinol is the main psychoactive constituent, producing cannabis' main subjective effects for which it is renowned and which has led to its worldwide recreational use.[2,3] Cannabidiol, on the other hand, seems to lack any psychoactive effects. Tetrahydrocannabinol and CBD are formed in the plant through different enzymes and enzymatic routes, both cannabinoids occur at the same time in the plant as well as their precursors.[4]

The pharmacodynamic mechanism underlying a major difference between both cannabinoids is the fact that they show a different interaction with the endocannabinoid receptor system in the brain; CBD binds as an antagonist to the cannabinoid receptor CB_1 but with much lower affinity than THC (in fact, in the order of >100 times less potent binding).[5,6] In addition, CBD also antagonizes the action of THC on the cannabinoid G protein-coupled receptor GPR55, which is believed to be responsible for different neuromodulatory actions as the CB_1 receptor.[7]

The effects of cannabis in humans are diverse, complex, and not yet fully understood. Alongside its well-known desirable subjective effects, such as relaxation, improved mood, and increased senses, THC is also known for causing anxiety, dizziness, depressed mood, agitation, panic disorder, and even psychosis.[8,9] It is mainly these undesirable effects together with its alleged potential for dependency and illegal status in many countries that has overshadowed the possible beneficial properties of cannabis for a long time in the medical community.[10,11]

However, THC has been increasingly associated with medicinal effects, such as muscle-relaxing, antiemetic, analgesic, anxiolytic, appetite-enhancing, and ophthalmologic properties.[1] By far, the most evidence for therapeutic efficacy for cannabinoids is in the disease multiple sclerosis (MS), where a beneficial effect on spasticity and on pain are the main reasons for treatment with cannabis.[12] However, randomized controlled trials have yielded heterogeneous results and have not yet resulted in practical guidelines for the prescription of cannabis.[13] Cannabis has also been shown effective as antiemetic and in increasing appetite in patients experiencing certain types of cancer or acquired immunodeficiency syndrome, and antiproliferative and immunomodulating properties have been shown as well.[1,14] Most studies describing its beneficial potential have also reported THC's adverse effects on treatment with various cannabis extracts in patients, many of which are known adverse subjective effects of nonmedicinal cannabis use as mentioned previously.[3,9,15] Therefore, the current scientific emphasis lies on this precarious balance between beneficial effects and lack of adverse effects.[1]

Despite of this, scientific attention into the medicinal properties of cannabis has not waned over the last decade. Rather, it seems to be increasing over the years, partly because of new insights into pharmacologic mechanisms of action of nonpsychoactive cannabinoids, such as CBD.[16] Cannabidiol has been suggested to have therapeutic potential in a variety of pathologies, such as inflammatory disease, diabetes, cancer, neurodegenerative diseases, and psychosis.[16–18] In fact, CBD has been shown to counteract THC's adverse psychoactive effects in a dose-dependent fashion.[19,20]

Although in most countries, cannabis is considered an illegal drug, a number of countries have made an exception in the law in the case of cannabis for medicinal purposes. In The Netherlands,

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the Office for Medicinal Cannabis (OMC) is in charge of the cultivation of high-grade pharmaceutical cannabis for medicinal purposes.[21] It is available at specialized pharmacies, and patients are advised through information brochures about the different strains of cannabis available and the methods of consumption. For instance, the OMC advises to either use a vaporizer or to prepare tea to avoid damage to the lungs. The method of administration affects the pharmacokinetics of THC. Drinking tea is associated with an enduring and mild effect, whereas inhalation causes a faster and larger delivery of THC to the blood, resulting in a higher peak value.[22] However, only very small amounts of THC are soluble in boiling water.[21] Currently, the OMC offers different strains of medicinal cannabis, which are cultured according to stringent pharmaceutical standards. Each strain differs in their THC content and only 1 variant contains a noteworthy level of CBD, and with this strain, the OMC advises inhalation as the only administration route because CBD is insoluble in boiling water.

Most of the scientific evidence on medicinal cannabis involve pharmaceutical cannabis products, which are orally administered or by buccal sprays, such as Sativex (GW Pharmaceuticals, Salisbury, UK) or Marinol (AbbVie, Chicago, IL). So far, only a few limited studies have been conducted on pharmaceutical-grade cultivated cannabis as medicinal therapy and have marginally described patient groups that use it.[21,23,24] This study describes more than 100 patients reporting about the therapeutic satisfaction with their pharmaceutical-grade cannabis product. Furthermore, differences in subjective effects among the available strains are investigated.

MATERIALS AND METHODS

Study Population and Recruitment

In collaboration with the OMC, 150 study questionnaires were dispersed to all of the pharmacies across The Netherlands that are specialized in distribution of medicinal cannabis. The questionnaires were accompanied with a letter describing the aims and containing explicit ethical guidelines of consent for participation in this study. Patients received their medicinal cannabis product together with this letter and the questionnaire after handing in their prescription at a pharmacy. Questionnaires were dispersed between September 2011 and January 2012; inclusion criterion was the use of 1 of the available variants of medicinal cannabis. Exclusion criteria were co-use of other forms of medicinal cannabis extracts, such as Sativex, and co-use of cannabis from Dutch coffee shops.

Pharmaceutical-Grade Cultivated Cannabis

Dried flower tops are sterilized by γ-irradiation to eliminate microbiological contamination. Cannabis products are then analyzed by a number of chemical techniques (Farmalyse BV, Zaandam, The Netherlands) for ensuring high-quality standards and to test for undesirable contaminants, such as pesticides. The amount of ingredients, such as THC and CBD, are always kept the same for every product. A liquid chromatography method is routinely used to verify the presence of active and inactive (carboxylated) cannabinoids in dry volume. This guarantees a final product with a reproducible and reliable potency and quality.

Psychometric Measures (Subjective Effects)

Subjective effects were measured using visual analog scales (VAS). Visual analog scale is one of the most frequently used psychometric instruments to measure the extent and nature of subjective effects and adverse effects.[25] This instrument has previously been used in a number of studies investigating subjective adverse effects of cannabis.[26–29] The VAS questionnaire consisted of a series of 100-mm lines labeled "not at all" at 1 end to "extremely" at the other end.[26] Each VAS scale consisted of an adjective describing a subjective effect of cannabis use, and the patient was asked to give a rating on the scale that fitted his/her subjective feeling best after using their own prescribed cannabis product. The 12 adjectives used for this study were as follows: alertness, tranquility, confidence, dejection, dizziness, confusion/disorientation, fatigue, anxiety, irritability, appetite, creative stimulation, and sociability. These adjectives were selected based on earlier studies on the subjective effects of medicinal and nonmedicinal cannabis.[26,29,30]

Questionnaires

Besides the VAS, a second questionnaire contained 11 categorical multiple-choice items dealing with the use of pharmaceutical cannabis. Patients were asked for which medical indication they used pharmaceutical-grade cannabis, which strain of cannabis they used, the method of administration (drinking tea or inhalation), frequency and dose of use, the nature of therapeutic effect, and to which extend it occurred (4 degrees of rating). Inhalation included both smoking and inhalation through a vaporizer. In the questionnaire, space for open comments was included. Patients were able to provide contact details for further information.

Statistical Analyses

The normality of distribution of the VAS scores was tested with the Kolmogorov-Smirnov test, and the homogeneity of variance was tested with Levene test. Analysis of variance and Levene test were used to determine whether the dose of medicinal cannabis used per occasion or per day (cumulative dose) differed among the strains of cannabis. Then, differences in the subjective effects were investigated among the cannabis strains. Because this study included a diverse population of patients differing in sex, age, medical indication, dose, and method of cannabis administration (drinking tea or inhalation), these important covariates were included in a multivariate covariance analysis. This corrects for the influence of these covariates in the statistical comparison among the different groups. Finally, multiple comparisons were done among the different cannabis groups followed by Bonferroni post hoc test. Statistical analysis was performed with SPSS version 19.0.

RESULTS

In total, 113 participants completed and returned the research questionnaires (response rate of 75%), 6 participants were dismissed on account of co-use of cannabis from coffee shops, and 5 participants were dismissed on account of co-use of another form of medicinal cannabis (Marinol). Missing or unclear items were completed afterward by consensual telephonic contact.

Characteristics of the Study Population

The average age of the 102 patients who were included was 52.8 (SD, 12.3) years; sexes were almost equally represented (Table 1). Most patients (76%; n = 78) had used their particular cannabis strain for more than a year preceding this study. Chronic pain was by far the most prevalent medical indication (52.9%), followed by MS (22.5%). In accordance with this, pain relief (analgesia) was the therapeutic effect of pharmaceutical cannabis reported by most patients, followed by sleep improvement and alleviation of muscle spasms (Table 1). A total of 90.1% of the participants were daily users and 35.3% used it multiple times a day. The mean dose of pharmaceutical cannabis used per occasion was 0.31 (SD, 0.32) g, and the mean daily cumulative dose was 0.65 (SD, 0.63) g. Inhalation was the most common method of cannabis administration among the

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TABLE 1. Patient Characteristics (n = 102)

Characteristic	n	%
Age	52.8*	(24–81)*
Sex		
Male	50	(49.0)
Female	52	(51.0)
Strain pharmaceutical cannabis		
Bedrocan (THC high)	48	(47.1)
Bedrobinol (THC medium)	29	(28.4)
Bediol (THC low)	25	(24.5)
Medical indication		
MS	23	(22.5)
Chronic pain	54	(52.9)
Nausea	6	(5.9)
Cancer	11	(10.8)
Psychologic problems	8	(7.8)
Therapeutic effect†		
Pain alleviation	89	(87.3)
Sleep improvement	47	(46.1)
Spasm alleviation	43	(42.2)
Mood improvement	15	(14.7)
Stress alleviation	10	(9.8)

*Age is given in average and range, respectively.
†Two answer categories were required.

participants (81%; n = 83), and the rest prepared tea out of the pharmaceutical cannabis.

Cannabis Strains and Dose

The analysis of the questionnaires revealed 3 different cannabis strains manufactured by the OMC that were used by these patients. The 3 groups of cannabis strains across this group of patients were as follows: 19% THC/less than 1% CBD (n = 48), 12% THC/less than 1% CBD (n = 29), and 6% THC/7.5% CBD (n = 25), which are coded for the purpose of legibility in the results section as THC high, THC medium, and THC low, respectively. In accordance with the advice of the OMC, the THC low strain was administered through inhalation only.

To investigate if the differences in THC content could be of consequence to the dose used by these patients, it was determined whether the dose cannabis that was used per occasion or throughout the day (cumulative dose) differed among these 3 strains of cannabis. Figure 1 shows the mean doses per strain of cannabis. Analysis of variance analysis showed that there was no difference in variance between the doses used among any of the 3 strains based on the Levene statistic.

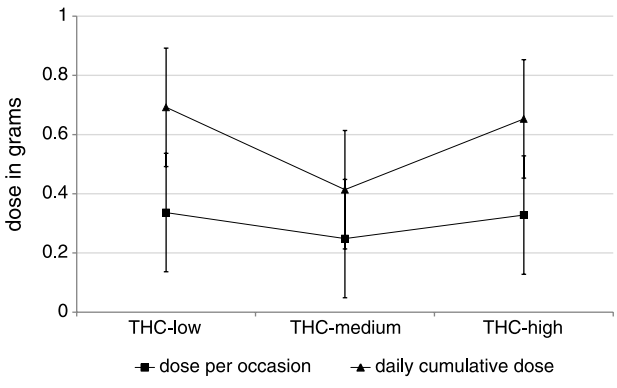


FIGURE 1. Average dose of the 3 strains of pharmaceutical cannabis used per occasion and throughout the day.

TABLE 2. Therapeutic Satisfaction of Pharmaceutical Cannabis Reported by the Patients

	Frequency of Therapeutic Effect			
Fulfillment of Therapeutic Effect	Always	Usually	Sometimes	Never
Always	27	11	—	—
Usually	30	20	2	—
Sometimes	4	3	1	—
Never	2	2	2	—

Therapeutic Satisfaction

There were 2 parameters used in defining the therapeutic satisfaction of the pharmaceutical cannabis in these patients; these are frequency of reported therapeutic effects (alleviation of symptoms associated with disease) and fulfillment of these effects. Both parameters were asked in a 4-point scale. Therapeutic effects were reported always in 63 (62%) cases and usually in 36 (35%) of the cases, respectively, when cannabis was used. Fulfillment of these effects was reported always in 38 (37%) cases and usually in 50 (49%) of the cases, respectively. Thus, most of the participants reported a high degree of therapeutic satisfaction with pharmaceutical cannabis (86%; n = 88; Table 2). Therapeutic satisfaction was independent of the different strains of pharmaceutical cannabis used (Fig. 2).

Subjective Effects

The comparison of subjective effects in VAS scores among the 3 cannabis groups with multivariate analysis of covariance revealed the presence of a significant interaction (correcting for age, sex, medical indication, dose, and method of administration). The means for all 12 VAS scores divided across the 3 cannabis strains are expressed in Figure 3. No differences were observed for alertness ($F_{2,93} = 0.12$; $P = 0.89$), confidence ($F_{2,93} = 0.06$; $P = 0.94$), tranquility ($F_{2,93} = 1.91$; $P = 0.15$),

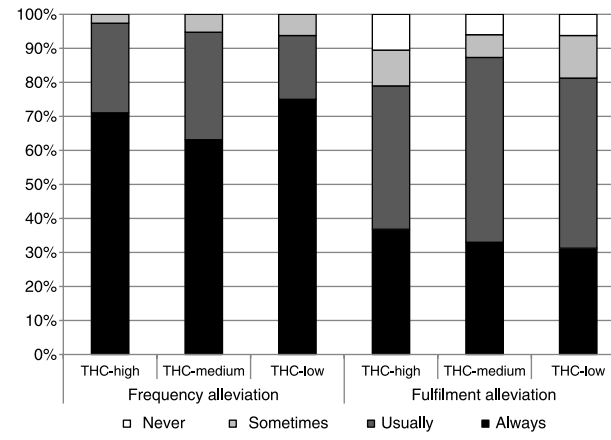


FIGURE 2. Frequency and fulfillment of alleviation of symptoms (therapeutic satisfaction) as reported by the study population, expressed per pharmaceutical strain of cannabis.

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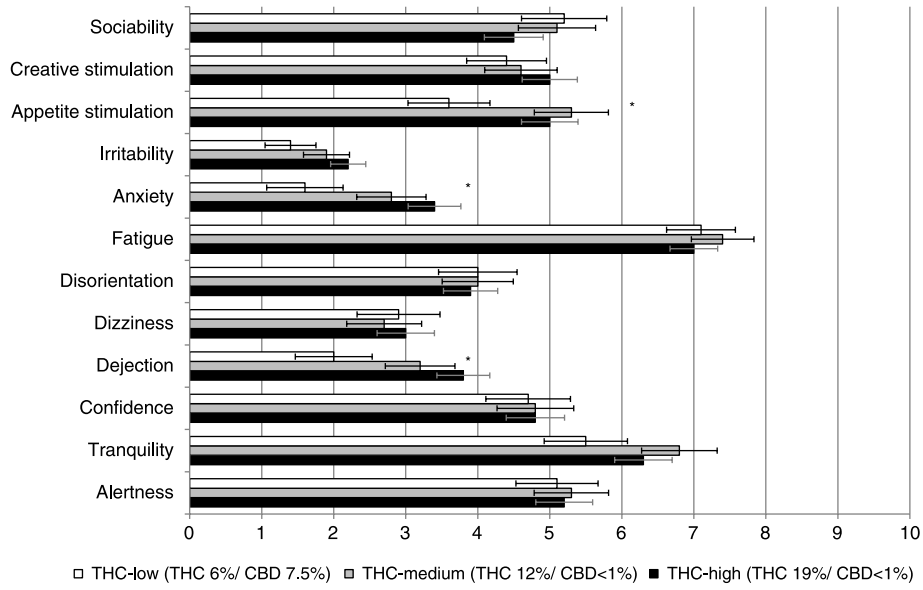


FIGURE 3. Mean VAS scores for 12 subjective effects of medicinal cannabis across the 3 cannabis strains. *Significant differences among the variants as determined with post hoc Bonferroni multiple comparisons.

fatigue ($F_{2,93}$ = 0.24; P = 0.79), creative stimulation ($F_{2,93}$ = 0.36; P = 0.70), irritability ($F_{2,93}$ = 1.57; P = 0.21), disorientation ($F_{2,93}$ = 0.01; P = 0.99), dizziness ($F_{2,93}$ = 0.14; P = 0.87), and sociability ($F_{2,93}$ = 0.87; P = 0.44).

There was a significant difference in VAS scores for appetite stimulation ($F_{2,93}$ = 5.01; P = 0.009), and Bonferroni multiple comparisons among the groups revealed that THC low differed from THC high (P = 0.03) and THC medium (P = 0.01), with the latter 2 groups showing an increased appetite compared with THC low. Visual analog scale scores of dejection differed among the cannabis strains ($F_{2,93}$ = 3.80; P = 0.03). Multiple comparisons revealed a difference between THC high and THC low (P = 0.02), with the level of dejection being higher for the THC high group. The level of anxiety was also different among the cannabis groups ($F_{2,93}$ = 5.44; P = 0.006), with multiple comparisons revealing higher anxiety levels in the THC high group than in the THC low group (P = 0.004).

DISCUSSION

The current study presents some new insights into the reported therapeutic effects of pharmaceutical-grade cannabis by a relevant group of patients. The results indicate that medicinal cannabis offers therapeutic relief for various conditions, many of which are characterized by chronic pain. Therapeutic satisfaction was independent of which strain of medicinal cannabis was used. This finding is in agreement with a multitude of previous studies, describing the therapeutic efficacy of cannabis products against pain, especially neuropathic pain (for some elaborate reviews, see Hall et al,[14] Rahn and Hohmann,[31]Baker et al,[32] and Martín-Sánchez et al[33]). However, it has to be mentioned that these clinical trials and other studies were done with very different cannabis extracts and different ways of administration. To date, this is the second study presenting reported therapeutic effects of cannabis that is grown under stringent pharmaceutical standards and manufactured by the OMC for distribution via Dutch pharmacies.[24] Furthermore, the study provides unique information about the Dutch population of patients who uses this governmental medical service.

There is a large spread in age among these patients, indicating a great diversity of this group. The medical indications that were given in this study correspond to the most important indications given in the previous research.[1,14,32] Therapeutic effect was not asked per indication per se but, overall, to reflect the circumstances as naturally as possible.[34] It is interesting that a therapeutic satisfaction and fulfillment of effects were experienced with all available strains used. An important finding is that satisfaction with medicinal cannabis seems comparable with the satisfaction with other, regular, prescribed medication.[35,36] However, it has to be mentioned that this study only included patients who are actively using medicinal cannabis at the time; unsatisfied customers were likely to have been excluded because of the lack of compliance with their therapy. Also, patient satisfaction studies do not substitute for clinical efficacy per se but merely indicate a subjective measure of tolerability and desired effects.

Furthermore, the reported profile of subjective (adverse) effects offers a source of information for consideration, which strain or variant to prescribe. The different ways of cannabis administration may have contributed to different subjective effects, although the statistical analyses controlled for it. Most of the sample in this study inhaled the product, which has an established impact on the pharmacokinetics and can produce unwanted physical harm and psychologic adverse effects.[1,14,30,32,33] A cannabis product that is inhaled generally produces a stronger high but also more dizziness, irritability, feelings of depression, stronger feelings of dependence, and withdrawal, among others.[26,29,31]

Because differences were anticipated for the different strains of cannabis based on their pharmacologic composition, these were compared. Remarkably, the dose of cannabis used did not differ among the different cannabis strains. It would have been expected that patients may have compensated lower content of THC with higher doses and vice versa.[37] The differences found among the available strains in this study confirmed the hypothesis that THC/CBD content is important to the ultimate effect experienced. As recent insights have already made clear, CBD is a cannabinoid with quite distinct effects from THC.[19,20] The lack of psychotropic, unwanted,

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effects of CBD has generated widespread scientific interest into its therapeutic potential against inflammatory diseases and cancer.[16,38–40] In addition, CBD has gained a lot of interest because of its antipsychotic properties and capacity to counteract THC's adverse effects.[20] In addition, CBD has been suggested to possibly attenuate THC's reinforcing effects on addictive behavior.[41]

The current results suggest that CBD may have a modulatory effect on some of the THC's well-known subjective adverse effects, such as anxiety or depressed mood.[42–45] In fact, CBD has been demonstrated to independently suppress subjective and physiologic measures for social anxiety.[46] However, few studies have tried to show the difference in effects between CBD and THC on mood or anxiety by actual inhalation, the most common way of administration in medicinal use.[1] Therefore, it is very interesting to see that the strain with high-CBD content was associated with less anxiety and feelings of dejection. Another finding was significantly lower appetite stimulation in patients using the low-THC/high-CBD strain. This is in line with a number of studies that have shown appetite-enhancing properties of THC specifically.[6,14,47]

This study may contribute to the rapidly evolving insights into the pharmacologic properties of various cannabis products, including commercially grown cannabis, and their detrimental or beneficial subjective effects. On the other hand, it has to be noted that no differences were found for any of the other adverse subjective effects (fatigue, dizziness, irritability) or potential beneficial effects, such as confidence, alertness, or sociability. Perhaps a bigger study population could have drawn out more of these differences.

Inherent to the natural design chosen for this study, there are a number of factors that limit conclusions based on it. First of all, this is a very diverse group of patients. Given that these patients will have different medical prognostic risk profiles and the severity of their illness is not known, the results could suffer from confounding by indication. This could generate biased results. Confounding by indication occurs frequently in studies of drugs not widely prescribed because the narrow indications for their use and comparison groups are usually absent (as in this study). Second, it makes it difficult to generalize the findings of this study to other patients or patient groups. The total number of Dutch pharmaceutical cannabis users has been estimated by the Dutch Minister of Public Health to be 560 in 2010.[48] Nonetheless, although the total population of pharmaceutical cannabis users was not reached in this study, given the brief collection period, the participation rate (75%) for this kind of study could be considered satisfactory. Finally, it is important to consider that some of these patients have indicated to use medicinal cannabis for a considerable period. This has probably led most to carefully dose and use the product to their optimal needs, and some might have minimized the chance of certain subjective (adverse) effects in this way, which is possible with these standardized pharmaceutical cannabis preparations. In fact, it is quite conceivable that patients were titrating on the level of THC as a more determining factor than the level of CBD. Others, who are not satisfied with these products, might have just dropped out of therapy altogether. This possible bias could be underlying the appreciation of the medicinal cannabis products in this study. However, it has to be stressed that this is inherent to a natural study design and the dose used did not differ among the strains of cannabis used.

In summary, the present results present a unique insight into a previously unstudied population of Dutch consumers of a pharmaceutically cultivated product, which has continuously raised both interest and controversy in the clinical community. It seems that this unique array of pharmaceutical cannabis products has a high therapeutic satisfactory profile within this group of patients. It largely confirms earlier findings that chronic pain and neuropathic pain are alleviated to the patient's satisfaction. Interestingly, the pharmacologic composition of the different strains available affected the extent of different subjective (adverse) effects, with a high-THC/low-CBD product leading to more appetite stimulation but also to feelings of dejection and anxiety in comparison with a low-THC/high-CBD product. The results of this study may aid medical practitioners and patients alike in selecting which strain of pharmaceutical cannabis could be most suited for their particular condition. It also contributes to a growing insight into the various effects of cannabinoids in general.

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