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 impressive 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 cannabinoid 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 CB1, 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 CB1 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 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,
the Office for Medicinal Cannabis (OMC) is in charge of the
cultivation of high-grade pharmaceutical cannabis for medicinal
purposes. 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
teas 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.23 However, only very small amounts of THC
are soluble in boiling water.24 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 Pharma-
aceuticals, 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 can-
nabis 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 partici-
pation in this study. Patients received their medicinal cannabis
product together with this letter and the questionnaire after
hanging in their prescription at a pharmacy. Questionnaires were
dispersed between September 2011 and January 2012; inclusion
criteria was the use of 1 of the available variants of medicinal
cannabis. Exclusion criteria were co-use of other forms of me-
dicinal 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 elimi-
nate 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 (car-
boxylated) 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 pre-
viously been used in a number of studies investigating subjective
adverse effects of cannabis.26–28 The VAS questionnaire consisted
of a series of 100-mm lines labeled “not at all” at 1 end and “ex-
tremely” 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 stimu-
lation, and sociability. These adjectives were selected based on
earlier studies on the subjective effects of medicinal and nonmedicinal cannabis.29,29,30

Questionnaires

Besides the VAS, a second questionnaire contained 11 cate-
gorical multiple-choice items dealing with the use of pharma-
caceutical cannabis. Patients were asked for which medical indication
they used pharmaceutical-grade cannabis, which strain of canna-
bis they used, the method of administration (drinking tea or inhala-
tion), frequency and dose of use, the nature of therapeutic effect,
and to which extent 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 me-
dicinal 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 im-
portant 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 re-
search 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 im-
provement 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 can-
nabis 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
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.

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 ($F_{2,93} = 1.91; P = 0.15$),

![TABLE 1. Patient Characteristics (n = 102)](image)

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

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

![TABLE 2. Therapeutic Satisfaction of Pharmaceutical Cannabis Reported by the Patients](image)

<table>
<thead>
<tr>
<th>Fulfillment of Therapeutic Effect</th>
<th>Frequency of Therapeutic Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Always</td>
</tr>
<tr>
<td>Always</td>
<td>27</td>
</tr>
<tr>
<td>Usually</td>
<td>30</td>
</tr>
<tr>
<td>Sometimes</td>
<td>4</td>
</tr>
<tr>
<td>Never</td>
<td>2</td>
</tr>
</tbody>
</table>

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.](image)

![FIGURE 2. Frequency and fulfillment of alleviation of symptoms (therapeutic satisfaction) as reported by the study population, expressed per pharmaceutical strain of cannabis.](image)
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 al33). 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.35 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,
effects of CBD has generated widespread scientific interest into its therapeutic potential against inflammatory diseases and cancer.  

In addition, CBD has gained a lot of interest because of its antipsychotic properties and capacity to counteract THC’s adverse effects. In addition, CBD has been suggested to possibly attenuate THC’s reinforcing effects on addictive behavior. 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. In fact, CBD has been demonstrated to independently suppress subjective and physiologic measures for social anxiety. 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. Therefore, it is very interesting to see that the strain with high-CBD content was associated with less anxiety and feelings of depression. 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.

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 of their particular condition. It also contributes to a growing insight into the various effects of cannabinoids in general.

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