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The Medicinal Use of Cannabis and Cannabinoids—An International Cross-Sectional Survey on Administration Forms

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Abstract — Cannabinoids, including tetrahydrocannabinol and cannabidiol, are the most important active constituents of the cannabis plant. Over recent years, cannabinoid-based medicines (CBMs) have become increasingly available to patients in many countries, both as pharmaceutical products and as herbal cannabis (marijuana). While there seems to be a demand for multiple cannabinoid-based therapeutic products, specifically for symptomatic amelioration in chronic diseases, therapeutic effects of different CBMs have only been directly compared in a few clinical studies. The survey presented here was performed by the International Association for Cannabinoid Medicines (IACM), and is meant to contribute to the understanding of cannabinoid-based medicine by asking patients who used cannabis or cannabinoids detailed questions about their experiences with different methods of intake. The survey was completed by 953 participants from 31 countries, making this the largest international survey on a wide variety of users of cannabinoid-based medicine performed so far. In general, herbal non-pharmaceutical CBMs received higher appreciation scores by participants than pharmaceutical products containing cannabinoids. However, the number of patients who reported experience with pharmaceutical products was low, limiting conclusions on preferences. Nevertheless, the reported data may be useful for further development of safe and effective medications based on cannabis and single cannabinoids.

Keywords — administration form, cannabinoids, cannabis, comparative study, survey

INTRODUCTION

In recent years, cannabinoid-based medicines (CBMs) have become increasingly available to patients in many countries. These include several pharmaceutical preparations containing pure cannabinoids or cannabis extracts, as well as herbal cannabis (marijuana) products. The most commonly prescribed cannabinoid-based medicines are dronabinol (marketed as Marinol® since 1986, Abbott Products Inc.) and nabilone (marketed as Cesamet® since 1981, Valeant Pharmaceuticals International). Dronabinol is the INN (international non-proprietary name) of the nat-

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ural cannabinoid (-)-*trans*-delta-9-tetrahydrocannabinol, usually abbreviated THC (WHO 2006). It may be extracted from the plant, gained by isomerization of cannabidiol (CBD), or manufactured synthetically. Marinol® is a synthetic form of THC dissolved in sesame oil and prepared in gelatin capsules, while nabilone is a synthetic agonist of the human cannabinoid receptor (CB1), structurally derived from a major human metabolite of THC. Both products are registered for the symptomatic treatment of nausea and vomiting associated with cancer chemotherapy, while dronabinol is also approved for treating anorexia and cachexia related to HIV/AIDS. The patent on Marinol® expired in 2011, and an authorized generic version has become available from Watson Pharmaceuticals. A generic formulation of nabilone is now available in Canada from Pharmascience Inc. In Germany, generic THC is supplied by two companies (THC Pharm and Bionorica Ethics) from which pharmacies can prepare capsules and solutions (in oil or alcohol). The alcoholic solutions of THC can either be used orally or inhaled by using a vaporizer (IACM 2009). About 7.5 kg of THC is delivered by German pharmacies per year (WHO 2006).

Nabiximols (marketed as Sativex® since 2005 by GW Pharmaceuticals, UK, and partners) is a sublingually administered oromucosal spray based on a mixture of two distinct standardized cannabis extracts. Its principal active components are the plant-derived cannabinoids THC and CBD. Sativex is currently registered in Canada, the UK, Spain, Germany, Denmark, and New Zealand to treat spasticity due to multiple sclerosis. In Canada, it is also approved for the relief of neuropathic pain and advanced cancer pain. Further approval is expected in other European countries, based on the European Mutual Recognition Procedure (GW Pharmaceuticals 2012).

Parallel to the development of pharmaceutical CBMs, the number of countries providing a legal source of medicinal-grade cannabis to chronically ill patients has been growing as well. Canada (since 2001) and The Netherlands (since 2003) have had government-run programs for the last decade, where quality-controlled herbal cannabis is supplied by the specialized companies Prairie Plant Systems Inc. and Bedrocan BV, respectively. Several other countries are now setting up their own program (Israel, Czech Republic) or importing products from the Dutch program (Italy, Finland, Germany). In the US, the number of states that introduced laws to permit the medical use of cannabis has grown to 18 plus the District of Columbia (DC), even though these state-level initiatives are still prohibited by the federal government (IACM 2012).

In general, CBMs are used for symptomatic treatment of chronic diseases refractory to standard treatments. Because multiple biologically active cannabinoids have been identified (including THC, CBD, tetrahydrocannabivarin (THCV) and THC-acid (THCA)), and because CBMs can be administered in multiple ways (oral, sublingual, inhaled), there seems to be a demand for multiple cannabinoid-based therapeutic products. Nevertheless, therapeutic effects of different CBMs have only been directly compared in a few clinical studies. Most of these studies compared an unregistered oral cannabis extract (Cannador®) to Marinol® (Zajicek 2003; 2005; Killestein 2002; Freeman 2006; Strasser 2006), while a few others compared smoked cannabis to Marinol® (Haney 2005; 2007). The survey presented here was designed to contribute to the understanding of cannabinoid-based medicine by asking patients to compare the effects of different CBMs and different administration forms. To the best of our knowledge, this survey represents the largest systematic study on actual patient experiences with cannabinoid-based medicines currently available anywhere.

METHODOLOGY

We conducted an international, web-based, cross-sectional survey to describe patients' perceptions of different modes of administration for cannabinoid-based medicines (complete survey available from first author). The study was designed and conducted by the International Association for Cannabinoid Medicines (IACM), which has the goal to "advance knowledge on cannabis, cannabinoids, the endocannabinoid system, and related topics especially with regard to their therapeutic potential." The survey was posted on the official IACM website (http://www.cannabis-med.org) from August 2009 until January 2010 in five different languages: English, French, Spanish, German, and Dutch. To improve recruitment, the survey was brought to the attention of the approximately 5500 recipients of the IACM biweekly electronic newsletter. The survey was approved by the Ethics Committee of the Hannover Medical School, Germany.

Subjects were a self-selected "availability sample" of visitors to the IACM website; eligible subjects needed to have experience with at least two different CBMs or administration forms to be included. Participants remained anonymous and received no financial compensation.

The survey consisted of 21 structured (fixed) questions that were answered by yes/no responses, multiple choice lists, and rating scales. In addition, two open-ended questions allowed remarks, comments, and suggestions. Information collected included demographics, details on medical condition and symptoms, medical treatment, cannabis-use patterns, and methods of former and current intake of cannabis or cannabinoids. Participants were asked to rate their personal experience with different modes of delivery using Likert scale-style responses. Only completed surveys were included for final evaluation.

Participants were asked to evaluate different cannabis administration forms, including: smoking of cannabis (*Smoking*); inhalation of cannabis with a vaporizer (*Vaporizer*); oral use of cannabis as a tea (*Tea*); oral use

TABLE 1
(a) Methods of Ingestion Ever Tried (Multiple Answers Possible), Most Preferred Method of Intake; (B) Expressed as Total Number of Participants; and (C) Expressed as Percentage of All Users

	GROUP 1				GROUP 2				OTHER
	Smoking	Vaporizer	Tea	Food/Tinc	Dronabinol	Nabilone	THC vap	Nabiximols	Other
a) Ever tried (N=)	827	450	213	571	74	14	28	7	69
b) Preference (N=)	599	225	23	75	17	1	1	4	8
c) Satisfied users (%)	72.4	50.0	10.8	13.1	23.0	7.1	3.6	57.1	11.6

of cannabis in baked goods/cannabis tincture (*Food/Tinc.*); oral use of dronabinol/Marinol® (*Dronabinol*); oral use of nabilone/Cesamet® (*Nabilone*); inhalation of dronabinol with a vaporizer (*THC vap.*); and oromucosal administration of Sativex® (*Nabiximols*). To facilitate discussion of the results in this article, administration forms were divided into two distinct groups: Group 1 covers herbal cannabis (marijuana)-based products that were prepared by patients themselves; Group 2 includes the pharmaceutical preparations with known content of cannabinoids in a defined administration form (see Table 1). All remaining responses were grouped under "other." This practical classification will be used throughout the discussion of results.

RESULTS AND DISCUSSION

Demographics

The survey was completed by 953 participants, of whom 614 (64%) were male and 339 (36%) were female. The mean age was 40.7 years old (range 14–76) with the following distribution: ≤20 years old (7.9%); 21–30 years (20.1%); 31–40 years (20.7%); 41–50 years (20.8%); 51–60 years (24.1%); 61–70 years (5.8%); >70 years (0.6%).

Participants responded from 31 countries, with the most common nationalities represented being the USA (38.5% of participants), Germany (16.6%), France (7.9%), Canada (7.5%), The Netherlands (5.5%), and Spain (5.1%). Participants from the USA were additionally asked for their state of residence. The top five states, representing 72% of US participants, all have medical marijuana laws (IACM 2012) and were California (36.2% of all US subjects), Oregon (18.5%), Washington (7.6%), Michigan (3.7%), and Colorado (3.5%). In total, participants from 40 US states were included in the survey.

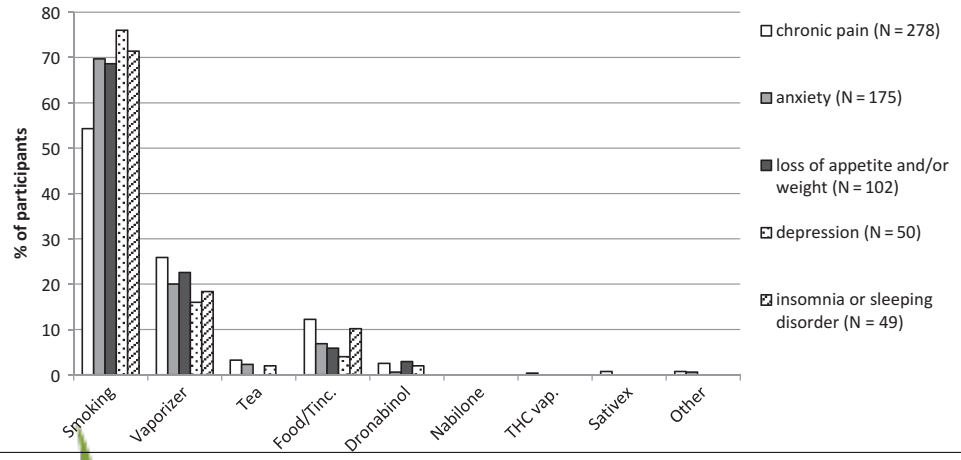
Modes of Delivery

When asked what types of inhaled or oral CBMs had been used, subjects could score all answers that apply. Results are shown in Table 1a. Of 953 participants, 903 (94.8%) reported having tried at least one form of inhaled administration of CBMs, while 653 (68.5%) had experience with some form of oral or sublingual administration. About 5% of participants indicated experience with topical use of CBMs, which included lotions, oils, and skin creams containing powdered cannabis or extracts.

Of the 903 individuals who indicated the use of inhaled CBMs, 827 (91.6%) had tried smoking cannabis herb or resin (hashish). When asked if tobacco was added when smoking cannabis, the responses were: always 16.6%; often 15.2%; sometimes 16.3%; never 51.8%. A distinction between North American and European subjects became apparent: of the 425 North American participants who used inhaled CBMs, 52.7% never used tobacco and only 2.6% always, while among the 410 European participants 14.1% never used tobacco and 29.0% always did so. While the use of tobacco is not encouraged, it may be relevant to study whether the addition of tobacco in these cases is merely a matter of habit or taste, or has an actual pharmacokinetic interaction with cannabis. One study has suggested that the co-administration of tobacco with cannabis releases relatively more THC from cannabis when smoked (Van der Kooy 2009).

As an alternative to smoking, cannabis constituents can be inhaled by using a vaporizer, which volatizes components such as THC, CBD, and terpenes, but with significant reduction of pyrolytic byproducts (Hazekamp 2006). Of the 903 individuals with experience in inhaling cannabinoids, 450 (49.8%) had used a vaporizer in combination with cannabis herb or resin, while 28 had used a vaporizer to inhale some form of pure THC (likely dissolved in alcohol or another solvent). Although many different types and brands of vaporizers are commercially available, almost half (227) of those using a vaporizer had tried the Volcano® vaporizer (Storz & Bickel GmbH, Germany). Another 201 subjects indicated they used another brand of vaporizer, while 30 selected the

FIGURE 1
Preferred Mode of Administration for Subjects in Each of the Top 5 Symptoms



answer "does not apply," which could indicate they assembled their own device for vaporizing.

Of the 653 participants who indicated experience with oral or sublingual forms of CBM, 571 subjects (87.4%) had used herbal cannabis in foods, baked goods, or tinctures. Another 231 subjects (35.4%) had used cannabis prepared as a tea. Fewer participants had experience with dronabinol (74; 11.3%), nabilone (14; 2.1%), or nabiximols (7; 1.1%).

Subjects were asked which method of intake they would prefer, if given a single choice. Preferences are shown in Table 1b. While 97% chose an herbal CBM (Group 1) to treat their medical condition, this may reflect the fact that many patients have not had the opportunity to try any of the pharmaceutical preparations covered by the survey. We therefore compared the total number of users of each CBM to the number of subjects who would choose that particular CBM as their preference. The resulting percentage (Table 1c) may be loosely regarded as a "satisfaction-score," independent of the number of patients who have actually tried each product.

Medical Condition

Participants were asked to select from a list of 47 medical conditions the main condition or disease for which they seek symptomatic relief by using CBMs. The results, as shown in Appendix 1, indicated that participants used CBMs for a wide variety of medical conditions. The top five conditions were back pain (11.9%), sleeping disorder (6.9%), depression (6.7%), pain resulting from injury or accident (6.2%), and multiple sclerosis (4.1%). Eighty participants (8.4%) marked "other." Most participants (80.4%) indicated they were, or had been, under medical treatment by a doctor for their particular condition.

Participants were also asked to select the main symptom for which they sought relief by using CBMs from a list of 22 options. The top five consisted of chronic pain (29.2%), anxiety (18.3%), loss of appetite and/or weight (10.7%), depression (5.2%), and insomnia or sleeping disorder (5.1%) (see Appendix 2). While chronic pain and loss of appetite and/or weight are specifically targeted indications of pharmaceutical products such as Marinol and Sativex, anxiety, depression, and insomnia have not yet been targeted as indications for pharmaceutical drug development.

Although a variety of conditions and symptoms were covered in this survey, we found no clear differences between perceived symptomatic amelioration and preferred method of intake. This is visualized in Figure 1, where the top five symptoms represent 69% of participants.

Background of CBM Use

Of 953 participants, 87.4% were current users of CBMs, while the remaining 12.6% had used it in the past. Most participants (76.5%) indicated having used cannabis products prior to the onset of their medical condition. When asked how long CBMs had been used for medical purposes, 14.5% responded they used it less than one year, 32.8% used it for one to five years, and 52.7% had used it for over five years. In about half of the cases (47.6%), a medical professional was (or had been) involved in recommending or prescribing the therapeutic use of cannabinoids. This may be dependent on the country of origin of participants, as many countries do not allow the medical use of cannabis or cannabinoids in any form, so it may be difficult for patients to find a medical professional to be involved.

When asked where they obtained their CBMs, participants reported official sources (such as pharmacy or

FIGURE 2
Source of CBMS, Comparing Participants Using CBMS with Prescription Vs. No Prescription; Totals Exceed 100% Because Participants Could Check Multiple Sources

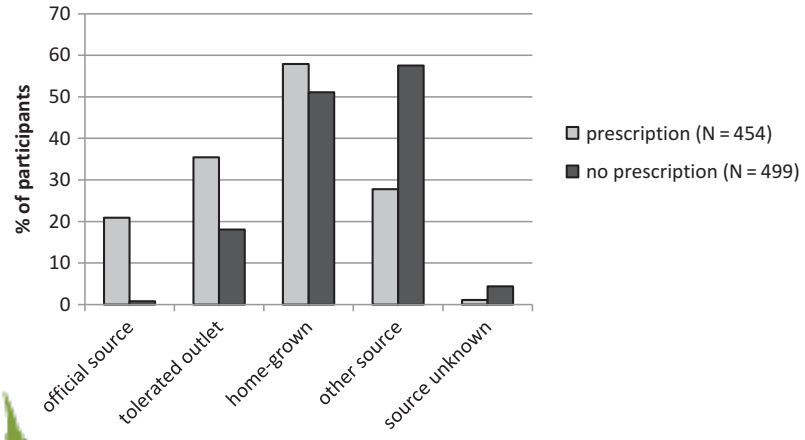


TABLE 2
Daily Dose, Daily Frequency, and Onset of Effects; Mean Values are Shown

	Smoking	Vaporizer	Tea	Food/Tinc	Dronabinol	Nabilone	THC vap	Nabiximols	Other
a) Daily use (units are indicated)	3.0 gram	3.0 gram	2.4 gram	3.4 gram	30.1 mg	4.4 mg	35.1 mg	17.3 sprays	3.2 gram
b) Daily frequency (times per day)	6.0	5.2	1.9	1.8	2.5	3.2	8.8	10.9	3.3
c) First onset of effects (minutes)	7.0	6.5	28.9	45.5	52.9	39.4	2.5	13.1	15.3

government program; 10.4%); unofficial or tolerated outlet (such as coffee shop, medical marijuana dispensary, or buyer's club; 26.3%); homegrown either legal or illegal (54.4%); other source (43.3%); do not know or does not apply (2.8%). Home-growing of cannabis was popular among all participants, including those using CBM by prescription; of those using CBM by prescription, 57.9% also reported home-growing as a source of cannabis. Among those without prescription, this was virtually the same, with 51.1% (Figure 2). Although the survey did not ask subjects to further specify "other sources," it is likely that this category includes illicit sources, and perhaps obtaining cannabis products from friends, family, or caregivers.

Dosing and Effects

Daily dose. When asked about daily quantities of CBMs used, participants provided a range of answers. Mean scores are shown in Table 2a. One participant reported a smoked dose of 500 gram cannabis per day and was removed from the summary as an outlier.

Within Group 1, the different administration forms required very similar amounts daily. The daily dose reported seemed to be slightly higher among those who used edibles (mean 3.4 g/day – median 1.5 g/day) compared to those using cannabis as tea (mean 2.4 g/day – median 1.5 g/day). This may be remarkable given the fact that cannabinoids are only sparingly soluble in cannabis tea (Hazekamp 2007). Vaporizing and smoking both required similar amounts of cannabis, with mean values of 3.0 grams daily each (median 2.0 and 1.5 g/day, respectively).

Within Group 2, while small numbers preclude definitive conclusions, patients using nabilone reported the lowest daily dose (mean 4.4 mg). Based on discrimination studies of healthy volunteers comparing nabilone to THC,

it may be estimated that 1 mg of nabilone equals about 7-8 mg of THC (Lile 2011; Bedi 2012). For nabiximols, when converting the number of sprays to total dose of THC and CBD (2.7/2.5 mg per spray, respectively), the reported daily dose of cannabinoids was a mean of 46 mg THC and 43 mg CBD per day.

Number of intakes. CBM preparations were further evaluated according to the number of daily doses used to treat the symptoms or condition of the participants. Mean values are shown in Table 2b. Oral use of cannabis in the form of tea, together with baked products or tincture, required the fewest intakes, with little less than two administrations daily. Smoking and vaporizing cannabis required a higher number of intakes, with an average of five to six administrations daily. Oral cannabinoids are known to have a longer, although more erratic, duration of effect (Grotenhermen 2003; McGilveray 2005). As a result, cannabis smokers may use more doses per day because they are able to titrate to desired effect with multiple smaller doses that have rapid onset. The sublingual product nabiximols required the highest number of administrations (mean 10.9) per day.

First onset of effects. The time needed to first onset of effects is an important pharmacodynamic consideration of a medicine. Together with total duration of effect, it has a major impact on how quickly patients attain drug efficacy, and therefore may influence adherence to the drug regimen. The survey therefore asked how long it took on average before first therapeutic effects became apparent using the different preparations. Mean scores are shown in Table 2c. Comparing CBMs in Group 1, subjects using inhalation (smoking and vaporizing) reported a first effect after the same time, about seven minutes. This is in agreement with a study (Abrams 2007) which showed that smoking and vaporizing the same quantity of cannabis, respectively, resulted in similar blood serum levels of THC over time. Although tea and baked goods/tincture are both taken orally, subjects using cannabis as tea reported more rapid onset of effect (mean 29 min.) than other oral preparations (mean 46 min.). Uptake of cannabinoids can be significantly delayed depending on the nature of the food present in the gastrointestinal (GI) tract. For example, fatty foods can significantly delay absorption (Grotenhermen 2002).

Subjects using vaporizers reported the onset of effects more rapidly with pure THC (mean 2.5 min) than herbal cannabis (mean 6.5 min). It is possible that non-cannabinoid constituents present in the plant, such as terpenes, delay or modulate the onset of effects of cannabinoids (Russo 2011). Patients using nabilone or dronabinol reported the longest time before first onset of effect, likely due to the delay in GI absorption, resulting in similar scores compared to cannabis taken in food or as a tincture. Participants using nabiximols experienced first effects after an average of 13 minutes, suggesting that nabiximols may be absorbed (at least in part) sublingually, speeding up the process of absorption of cannabinoids.

Advantages of Different Modes of Delivery

Subjects were asked to compare their satisfaction with nine parameters regarding their experience using different modes of delivery. These parameters included: dose needed, onset of effect, duration of effect, ease of dose finding, ease of exact dosing, ease of preparation and intake, irritation of lungs (if applicable), side-effects, and cost involved. The satisfaction rating scale ranged from 0 to 10, with 0 representing absolutely no satisfaction and 10 representing perfect satisfaction by the participant. A total number of 4414 ratings were obtained. The results are shown in Table 3.

Daily dose needed. The highest rating of dose satisfaction (representing "only low dose needed") was obtained for inhalation of herbal cannabis with a vaporizer (6.4), closely followed by smoking (5.8). The inhalation of pure THC, using a vaporizer, received the lowest score. This is notable, since laboratory studies have shown pure THC to evaporate more efficiently (at the same temperature) than an equivalent amount of THC present in herbal material (Hazekamp 2006). Synergetic effects between multiple herbal cannabis components may explain this effect (Izzo 2009). The use of products in Group 2 (range 3.5 – 4.8) scored consistently lower in dose satisfaction than plant-based preparations in Group 1 (range 4.8 – 6.4).

The lower scores for Group 2 may be related to the fact that these pharmaceutical preparations are generally perceived as more costly than the preparations in Group 1 (see section on "cost" below), which may subjectively add to the sense of needing "too much" for a single dose. It should be noted that the dose units are different between Groups 1 and 2 (gram versus milligram), and that the herbal cannabis mentioned in the majority of cases has no standardized or known chemical composition.

Onset of effects. Participants were asked to rate their satisfaction with the time needed before first (therapeutic) effects became apparent. The faster the first onset of effects, the higher CBMs are scored on this scale (Table 3b). Note that this scoring system assumed that rapid onset of effect is always more satisfactory, which may not always be the case for chronic stable conditions.

The highest satisfaction score for onset of action was obtained for smoking (8.0), vaporizing of herbal cannabis (7.8), and inhaled administration of pure THC (6.9). Indeed, the inhaled administration of cannabinoids is known to be the most rapid way to get measurable serum levels of cannabinoids (Grotenhermen 2003). The obtained results are compatible with Table 2c, where these three administration forms all showed first effects in less than 10 minutes. The administration forms with lowest scores were all oral preparations with slow GI absorption and potential first-pass effects by liver metabolism. Nabiximols received an intermediate score, suggesting that patients experience pharmacodynamic effects somewhere between inhaled and oral administration.

TABLE 3
Ad vantages and Disadvantages of CBM Use, Expressed by Satisfaction Rating (Mean Score on a 0–10 Likert Scale)

	Smoking	Vaporizer	Tea	Food/Tinc	Dronabinol	Nabilone	THC vap	Nabiximols	Other
a) Daily dose needed	5.8	6.4	4.8	4.8	4.3	4.8	3.5	4.2	5.2
b) Onset of effects	8	7.8	3.9	2.8	3.5	2.8	6.9	5.6	5.6
c) Duration of effects	5.6	5.9	6.7	7.8	5.3	6.5	5.4	4.2	5.5
d) Ease of dose finding	7.7	7.2	4.8	4	4.5	5.9	6.2	5.4	5.5
e) Ease of dose finding	7.4	7.3	4.9	4	4.9	6.3	5.7	5	5.6
f) Preparation & intake	8.7	7.4	6.6	4.4	9	9	7.4	9.2	6.3
g) Irritation of lungs	5.7	8.1	n.a.	n.a.	n.a.	n.a.	5.4	n.a.	7
h) Side effects	7.6	8.5	7.9	7.2	5.8	4.8	5.4	6	7.1
i) Costs involved	4.5	5	5	4.5	2	1.3	4.1	2.7	4.6

N.A.: Not Applicable

Duration of effects. The duration of effects experienced for each type of CBM was also assessed using the satisfaction score (Table 3c). A longer duration of effect reduces the need for frequent dosing. Since inhaled and oral administration of cannabinoids display different pharmacokinetics (Grotenhermen 2003; McGilveray 2005), we expected that smoking and vaporizing would receive the lowest satisfaction scores regarding duration of effect. However the lowest scores were observed for nabiximols, followed by oral use of dronabinol and the inhaled use of pure THC. The oral use of cannabis in foods, tincture, or tea received the highest satisfaction scores for duration of effects.

Ease of dose finding and dosing exactly. THC has a narrow therapeutic window between desired benefits and adverse effects. When taken orally, THC absorption may vary strongly between different patients, as well as within the same patient over different days (Pertwee 1999). Each patient therefore initially has to focus on finding a dose range that works for their specific condition, and it may take up to several weeks before a steady-state is reached. For the CBMs in Group 1, administering the desired dose from day-to-day may be complicated by the fact that most are not available as standardized products, so that while patients may know what dose they wish to administer, this may not be easily achievable. We therefore evaluated patient satisfaction with dose finding as well as ease of dosing.

Cannabis smoking, closely followed by vaporizing, scored highest for satisfaction with ease of dose titration, while oral use of cannabinoids scored lowest (see Table 3d). This may be because rapid onset of effects (Table 3b) of inhaled cannabinoid use allows easier titration of dose (Grotenhermen 2002).

Satisfaction with ease of stable dosing is indicated in Table 3e. We expected that the standardized CBMs in Group 2 (with a known concentration of active ingredients) would score significantly higher than the non-standardized preparations in Group 1. However, the results were similar to the scores given for the previous question (compare to Table 3d), perhaps because the resolution between these questions was not clear enough to participants.

Preparation and intake. The satisfaction of participants with the effort needed for preparation and intake of different CBMs is summarized in Table 3f. A distinction between products in Group 1 and 2 emerged: standardized

and ready-to-use pharmaceutical preparations scored generally higher than the herbal cannabis-based preparations. One notable exception is the smoked use of cannabis, which receives a high score. A possible reason may be that most participants had experience with smoking cannabis, and many also had experience with cannabis previous to onset of their illness. It is likely that those participants are familiar with preparing cannabis cigarettes and therefore do not find it bothersome to do so when they get ill. It is also possible that participants conveniently used a pipe or bong to inhale herbal cannabis (not evaluated in this study). The low score for baked products or tincture may be due to the extended time needed to prepare such products. With baked products specifically, limited shelf-life stability may also play a role.

Irritation of the lungs. Satisfaction with lung irritation (Table 3g; low scores suggest more irritation) is only relevant for inhaled preparations. While smoking and vaporizing herbal cannabis received similar scores in previous questions, the advantage of vaporizing (score 8.1) over smoking (score 5.7) now becomes more obvious. This advantage was not recognized for using the vaporizer with pure THC, which scored similar to smoking. Although pyrolytic by-products of combustion may be responsible for pulmonary irritation, it seems that THC alone is also capable of this (Tashkin 1977; Naef 2004). Higher satisfaction with vaporized cannabis compared to THC alone may be due to the presence of non-THC constituents, including anti-inflammatory terpenes that protect the lungs from irritation (Russo 2011). Another potential cause of irritation from pure THC preparations may be the presence of residual solvents (e.g., ethanol) that are needed to solubilize the sticky pure THC (Žuškin 1981).

Side-effects. Participants were asked to rate their satisfaction with side-effects experienced with the different CBMs (Table 3h). Unfortunately, the survey did not ask more explicitly what side-effects were experienced, as this could have added significantly to our understanding of CBMs in a large population. Here, more than for any other parameter that we assessed, the differences between preparations in Group 1 and 2 were very distinct. The herbal cannabis-based products received mean scores in the range of 7.2 – 8.5 (meaning high overall satisfaction with side-effect profiles), while the pharmaceutical preparations scored notably lower with a range of 4.8 – 6.0. The major reason for this may be that the majority of herbal cannabis users (76%) admitted to using cannabis products before onset of their condition, potentially giving them more experience with these CBMs and, hence, with their potential side-effects. The lowest satisfaction with side-effects was reported with the use of nabilone. The average daily dose of nabilone reported by subjects (4.4 mg; Table 2) was nevertheless below the maximum of 3 mg twice daily suggested by the product monograph. Vaporizing cannabis had the highest side-effect satisfaction score (score 8.5), which was higher than that reported for smoking (score 7.6).

Costs involved. For chronically ill patients, disability and unemployment render "cost" to be an important factor in CBM use. Overall, low satisfaction ratings were observed (highest mean score was 5.0; see Table 3i), suggesting that the cost of using CBMs is a major issue for patients everywhere.

Open Questions

In order to assess what the perfect CBM would look like, if participants could develop their own product, the survey concluded with two open-ended questions. A total of 375 suggestions were obtained (39.3% response) for factors not covered by existing pharmaceutical products.

A tincture based on whole cannabis was found to be the most popular choice for a new product to be developed, mainly because it can be used in a multitude of ways: as oral drops, in baking and tea, and for vaporizing as well as smoking. According to participants, this allows for maximal flexibility of using cannabinoids throughout the day. Furthermore, a tincture can be used discretely in public (i.e., at work, visiting friends) and does not have a strong, distinct smell. Other common suggestions were legally growing your own cannabis, developing standardized edibles, and capsules containing whole powdered cannabis plant.

Issues that participants wanted to see addressed included bad taste, adverse events such as drowsiness, uncontrollable appetite (munchies), and mental effects (getting high). The latter observation is of particular interest, as getting high is generally the sought-after effect for recreational users. Multiple participants further suggested that different administration forms may be preferred in the privacy of one's home and in public.

CONCLUSION

To our knowledge, this survey represents the largest systematic study of patient experiences with CBMs conducted to date. Although other, and sometimes larger, surveys have been reported, they did not compare patients' experiences with multiple CBM products or administrations forms, or they were restricted to a single country and/or focused on a single medical condition (Hazekamp 2013; Corless 2009; O'Connell 2007; Chong 2006; Ware 2005; Prentiss 2004; Page 2003; Ware 2003; Braitstein 2001; Ogborne 2000). The majority of subjects in our study were current users who had a health professional involved in the management of their illness, and were using CBMs for at least several years. The inclusion criterion that participants should have had experience with at least two administration forms was easily met in the study population; on average, those who (ever) tried smoking cannabis had experience with 2.4 different administration forms (lowest value), while those who had (ever) used nabiximols (Sativex®) had tried 4.4 different administration forms (highest value) in total.

The main goal of this survey was to compare different administration forms of cannabinoids and identify their relative advantages and disadvantages as described by actual users. Before any conclusions may be drawn, however, the potential limitations of the study must be clearly addressed. Most participants of the survey had experience with herbal cannabis before onset of their medical condition, and smoking of cannabis was the most common method of intake participants had tried. So although many different methods of intake were represented in the survey, the results may be biased towards the use of herbal cannabis. Also, people who were satisfied with their first cannabinoid medication (e.g., smoked cannabis, dronabinol, nabiximols) and used it without problems were not included, because they did not meet the inclusion criterion of having experience with multiple methods of intake. As homemade cannabis products allow more experimentation with administration forms and dosing than standardized oral products, the survey consequently may have favored participants who use herbal cannabis. Because of this potential for bias, we caution against drawing any conclusions with respect to the efficacy of any CBM from this study. In addition, circulating the survey through the IACM may have attracted responses from subjects who are already familiar with cannabis effects and may have produced a bias towards more positive responses overall. In addition, one should keep in mind that some CMBs (such as nabiximols) have been available only for a relatively short time. But despite these limitations, we believe that these results contribute to our understanding of patient preferences for specific methods of intake (administration forms) for cannabinoids.

Patient-reported advantages and disadvantages for each administration form varied widely. Many parameters measured (e.g., time before first onset, duration of effects) showed a distinction between oral and inhaled forms of cannabinoids, reflecting known differences in pharmacokinetics and/or pharmacodynamics. Nabiximols was often rated between oral and inhaled administration, reflecting the different nature of the oromucosal administration form. Many participants also provided scores in the category "other use," suggesting there may have been administration forms that were overlooked in this study. Future surveys may want to further identify such products.

In general, products in Group 1 (i.e., herbal non-pharmaceutical CBMs) received the higher scores in most categories. Products of Group 2 scored consistently higher than the herbal preparations only for "ease of preparation and intake." Indeed, herbal products are generally lacking convenient, reliable, and standardized administration forms, in contrast to conventional approved medicines.

There was low patient satisfaction with costs for all CBMs studied. This may be because most healthcare systems do not provide for reimbursement or health insurance coverage of CBMs, with the exception of the Dutch program, where cannabis is covered by an increasing number of health insurers (NCSM 2012), and Canada where nabilone is covered on most provincial formularies. Indeed, cost factors may have influenced our data: when medication costs are covered by health insurance, patients may be able to use higher doses. Conversely, when patients have to cover the costs by themselves (probably most often when cannabis is used without prescription) the doses used may be lower. Perhaps those patients preferring herbal cannabis are those who need a very high dose of cannabinoids, which cannot be covered by the currently available pharmaceutical cannabinoid preparations, both practically and economically. As a result, costs may also be a reason for patients to grow their own cannabis.

The source where CBMs are obtained is worth further consideration. Patients who use CBMs on prescription, and simultaneously grow their own cannabis, may raise questions about the legitimacy of their medical use of cannabinoids. For researchers as well as policy makers, it would be of interest to understand the motivations for patients to choose a particular source of herbal CBMs, despite the inherent legal risks. Besides cost, another potential reason for continuing home-growing despite having access to a legal source may be a lack of cannabis varieties currently available to patients. Indeed, differences in chemical composition between varieties can be significant (Fischedick 2010; Hazekamp 2012). In Canada, a recent review of the national medical marijuana program indicated that access to multiple cannabis varieties is an important issue for patients (Health Canada 2011).

In conclusion, we believe that this survey presents a broad picture of the current state of real world CBM use. The reported data may be useful to guide the development of safe and effective cannabinoid-based medications that meet the needs of patients. Besides the need for such products to be standardized and quality controlled, our data suggest that overall there is good satisfaction with whole plant preparations that are affordable and administered in an inhaled manner, or in the form of a tincture. Relatively new administration forms of herbal cannabis, such as juicing of raw leaves and buds (Courtney 2012), or the preparation of concentrated extracts such as Simpson oil (Simpson 2012), have not yet been covered by this survey, which was initiated in 2009. Future studies should therefore be aware of newer cannabis preparations, and ask more detailed questions in order to properly explore such upcoming cannabinoid based treatments.

CONFLICT OF INTEREST STATEMENTS

The authors, with the exception of DA, are members of the Board of Directors of the IACM. FG is also the Executive Director of the IACM. AH receives income in his role as head of Research and Development at Bedrocan BV. MW has received grant support from GW, Bedrocan,

and Valeant and has consulted for companies developing cannabinoid medications (AstraZeneca, Boehringer, Ironwood). Apart from this support, no other funding was received for conducting the survey or publishing the data.

The survey results have been presented, in part, at an IACM conference in Bonn, Germany, in September, 2011. An abstract was posted on the website of the IACM (http://www.cannabis-med.org).

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APPENDICES

Appendix 1: List of medical conditions (in alphabetical order) and scores (number of subjects selecting this option) obtained in the survey

33	ADHD or hyperactivity	4	Lupus erythematosus
7	Allergy	5	Menstrual pain
1	Amyotrophic lateral sclerosis	33	Migraine or headache
38	Anxiety disease	39	Multiple sclerosis
35	Arthrosis or degenerative arthritis	9	Neuralgia
15	Asthma	2	Neurodermatitis
4	Autism	23	Neuropathy
113	Back pain	7	Obsessive compulsive disorder
6	Bechterew disease	2	Osteoporosis
13	Bipolar disorder	59	Pain from injury or accident
14	Cancer	2	Parkinson's disease
7	Cancer chemotherapy	7	Phantom limb pain
6	Chronic obstructive pulmonary disease	3	Postpolio syndrome
17	Crohn's disease or ulcerative colitis	31	Posttraumatic stress disorder
14	Dependency from alcohol, opiates, or other	3	Restless legs syndrome
64	Depression	19	Rheumatoid arthritis
15	Epilepsy	7	Schizophrenia or psychosis
33	Fibromyalgia	7	Scoliosis
5	Gastritis or gastric ulcer	66	Sleeping disorder
10	Glaucoma	22	Spinal cord injury
4	Head or brain injury	1	Tinnitus
23	Hepatitis	3	Tourette's syndrome
28	HIV or AIDS	1	Trigeminal neuralgia
13	Irritable bowel syndrome		

Appendix 2: List of symptoms (in alphabetical order) and scores (number of subjects selecting this option) obtained in the survey

174	Anxiety	22	Irritability
102	Appetite loss or weight loss	22	Nausea or vomiting
8	Bladder problems	6	Nightmares
14	Breathing problems	–	Pruritus or itching
35	Chronic inflammation	7	Seizures
278	Chronic pain	49	Sleep disorders or insomnia
50	Depression	28	Spasms
8	Diarrhea	10	Spasticity
17	General malaise	3	Sweating at night
22	Hyperactivity	1	Tics
3	Impotence or decreased sexual desire	1	Tremor
22	Inner unrest		