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Original Articles

# Acceptability of and attitudes to the therapeutic use of cannabis and cannabidiol in people with Parkinson's disease: A French survey

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ABSTRACT

*Introduction:* Cannabis and cannabidiol (CBD) may potentially alleviate symptoms and improve the quality of life of people with Parkinson's disease (PD), although clinical results to date have provided conflicting evidence. In France, cannabis use is illegal outside the current restricted medical cannabis experimental framework which does not include PD as an eligible condition. In contrast, CBD products are legal and are easily available. We aimed to evaluate the acceptability of therapeutic cannabis and CBD use, and to assess cannabinoid-related attitudes among people with PD in France, with a view to assessing the potential inclusion of medical cannabinoids in PD treatment options.

*Methods:* We conducted a French nationwide online survey among people with PD. Cannabis and CBD acceptability levels were derived from the answers to four questions. Logistic regressions were performed to identify factors associated with these levels. We also collected data on knowledge, information-seeking, and barriers to self-medication.

*Results:* Of 1136 participants, acceptability levels of medical cannabis and CBD use were 81.7% and 87.4%, respectively. For both substances, acceptability was associated with the presence of anxiety symptoms, greater knowledge about cannabinoids, seeking information on medical cannabis, and considering the risk of cannabis dependence to be low. A fear of dependence was one of the main barriers to using either substance; healthcare providers were rarely mentioned as sources of information on medical cannabis.

*Conclusions:* Acceptability levels of cannabis and CBD were high. Acceptability was associated with knowledge and perceptions of cannabinoids. Given ongoing misconceptions about the effects and risks associated with CBD, disseminating accurate information could increase its acceptability in people with PD.

## 1. Introduction

People living with Parkinson's disease (PD) have an impaired quality of life (QoL) in most domains [1] largely because of disease-associated symptoms [2–4]. One example is anxiety [5,6], which can precede motor symptom onset, but may also be exacerbated by it [7]. Treatment side effects also contribute to impaired QoL in this population [3]. Long-term dopaminergic therapy for PD may lead to motor and non-motor complications which impair QoL [8,9]. Poor response to levodopa is also common in late-stage PD. Moreover, the treatment options for non-motor symptoms – such as sleep disorders, depressive symptoms, and fatigue – are limited [8]. Deep brain stimulation is a surgical intervention that aims to improve the clinical state of PD patients; it has also been shown to improve patient QoL [10]. However, it is only available for patients who meet a certain number of criteria. Similarly, continuous subcutaneous apomorphine infusion, indicated in some patients who present motor fluctuations when taking oral medication, may improve PD patients' QoL [11].

These various limitations highlight the importance of identifying alternative approaches to reduce disease and treatment burdens in PD

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patients. One possible approach is cannabis-based products. There are more than 550 chemical compounds in cannabis, with more than 100 phytocannabinoids identified [12]. Cannabinoids are molecules that interact with the endocannabinoid system, a lipid-based signaling system found throughout the human body. The most abundant and studied cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is psychoactive and responsible for the 'high' associated with cannabis use. On the contrary, CBD is well tolerated and non-intoxicating. Both molecules, whether used in combination or isolation in plant extracts or formulations, have multi-target effects on the human body, and may be beneficial in treating a wide range of ailments [13].

Although studies on PD in animal models have shown that cannabinoids may possibly help in alleviating motor symptoms [14], to date no study has provided compelling evidence that cannabinoid use is effective at reducing PD-related symptoms in patients [15,16]. Nonetheless, previous reviews and a *meta*-analysis of clinical studies concluded that cannabinoids most likely constitute a safe option to potentially treat motor symptoms in PD; results for non-motor symptoms and QoL were even more conclusive [15,17,18]. However, a recent small randomized trial found no benefits of a cannabis extract treatment over a placebo on motor symptoms, sleep deterioration, cognition, or activities of daily living [19]. Studies based on real-world data have also highlighted that cannabis-based products may improve PD patients' QoL [20–23].

Patients' attitudes towards medical cannabis may be shaped by their health status [24], and by social factors. The latter include cannabis-related stigma [25–30] and exposure to different sources of information [31]. As cannabis is still primarily associated with recreational consumption, it may be difficult for persons with PD to consider that cannabis-based products may offer tangible therapeutic benefits.

In France, THC-containing products are illegal, except for an ongoing national medical cannabis experimental project initiated in March 2021, which aims to assess the feasibility of providing medical cannabis to individuals with chronic severe conditions not adequately alleviated by other treatments [32]. The project protocol stipulates that pharmacies can dispense cannabis-based products to persons holding a secure prescription from a trained specialist physician. Eligible indications are neuropathic pain, epilepsy, cancer symptoms, palliative situations, and painful spasticity. PD is currently not an eligible indication.

Unlike THC, and despite recent legal twists and turns, CBD is legal in France and is gaining popularity. Approximately 70 % of the French adult population have heard of it [33], and 10 % were users in 2021 and 2022 [33,34]. CBD-based products are generally sold as wellness products or complimentary health products in France, in the form of oils, creams, THC-free cannabis flowers etc.

PD is already a qualifying condition for medical cannabis prescription in many US states [35]. It is possible that medical cannabis will become legal for PD in France in the future (whether as part of the current experimental project or over the longer term). In this context, the present study documents and analyzes French PD patients' attitudes towards cannabis-based products and their acceptability of them, with a view to guiding future policymaking.

## 2. Material and methods

### 2.1. Study design and participants

We conducted the cross-sectional online survey CANNABAPA from 22 May to 14 July 2023. Inclusion criteria were being aged $\geq$ 18 years old and diagnosed with PD. Various sources displayed the link to the survey. One was the France Parkinson website (https://www.france-parkinson.fr/). Created in 1984 and a member of the European Parkinson's Disease Association, France Parkinson is a national association recognized as being of public benefit; it has 75 local committees throughout France. Invitations to participate were sent by email to all contacts in the France Parkinson database (>35 000 addresses, including those of approximately 5000 association members). The survey link was also included in the France Parkinson newsletter, and published on its social media. Another source displaying the survey link was Carenity, a social network for people living with chronic conditions; it invited its members to participate through private messages on the network's platform (1857 contacts, including relatives of PD patients). Furthermore, local associations of people living with PD promoted the survey. Finally, participants were encouraged to disseminate the link.

CANNABAPA was designed in accordance with the declaration of Helsinki, and was approved by the INSERM ethics committee (IRB00003888, CD/EB 23–045, 4 April 2023). It was powered by Voxco. Before accessing the survey questionnaire, participants had to provide informed consent.

### 2.2. Questionnaire and data collection

The self-administered online questionnaire collected data on socio-demographic characteristics including gender, age, type of area of residence (large city (defined as 200,000 inhabitants or more), medium-sized city/town, rural area), educational level, professional situation, and self-perceived household economic status.

Patients' experience with their disease and treatment was measured using the following variables (i.e., questionnaire items): time since PD diagnosis, current intake of dopamine precursors and dopamine agonists (Yes/No), undergoing deep brain stimulation therapy (Yes/No), and two brief screening measures for anxiety and depression, specifically the Generalized Anxiety Disorder-2 (GAD-2) [36] and the Patient Health Questionnaire-2, (PHQ-2) [37]. The impact of fatigue was assessed with a question ('Does fatigue or lack of energy limit your daytime activities?', five possible answers) adapted from the Non-Motor Symptoms Scale for Parkinson's Disease [38–40]. Disability level was assessed with the following item adapted from the Parkinson's Disease Composite Scale: 'To estimate your daily limitations, choose the statement that best corresponds to your current situation' (six possible answers) [41,42]. Pain was measured with three questions adapted from the Graded Chronic Pain Scale-Revised (frequency of pain, frequency of pain as a limiting factor in activities, and visual analog scale of average pain) [43]. Sleep quality was assessed with the following item: 'During the past month, how would you rate your sleep quality overall?' (four possible answers), taken from the Pittsburgh Sleep Quality Index [44].

Cannabinoid knowledge was assessed with four *ad hoc* statements each with three possible answers (True/False/Do not know) (see Supplementary Table 1), with an overall score ranging from 0 (no correct answer) to 4 (four correct answers). Self-information about medical cannabis was assessed with the question 'Do you inform yourself about the medical use of cannabis for Parkinson's disease?' (three possible answers). Participants who responded 'yes' then reported between one and three primary sources of information, in their order of importance, from a list of pre-defined answers. Participant-perceived risk of dependence was assessed with the question 'In your opinion, how great is the risk of becoming dependent on cannabis?' (six possible answers). The participant's position regarding the current legal status of cannabis in France was assessed with two questions: 'Are you in favor of alleviating legal restrictions on medical [respectively, non-medical] use of cannabis in France?' (three possible answers). Barriers to self-medication with cannabis and CBD were assessed with two questions: 'What are the current barriers to your use of cannabis [respectively, CBD] as a self-medication for Parkinson's disease?'. Participants could choose up to five barriers in order of importance (i.e., biggest to smallest barrier) from a pre-defined list of answers.

In the survey, cannabis was defined as containing THC above the French authorized level (0.3 %), and CBD was defined as any type of CBD-containing product with THC levels equal to or below the authorized level.

### 2.3. Study outcomes

The two study outcomes (i.e., acceptability of each of the two substances studied) were based on the following two questions: i) 'Would you be inclined to use medical cannabis [respectively, CBD] (of controlled quality) for Parkinson's disease if it were prescribed to you?'; and ii) 'Would you be inclined to use medical cannabis [respectively, CBD] (of controlled quality) for Parkinson's disease without prescription (i.e., over-the-counter)?'. Possible answers for each question were Yes/No/Do not know. Acceptability was classified as follows: 'low', for 'No' or 'Do not know' answers to both questions, 'moderate' for one 'Yes' answer, and 'absolute', when both answers were 'Yes'.

### 2.4. Statistical analyses

We compared participants' characteristics according to their cannabis and CBD acceptability level, using pairwise comparison (low vs. moderate, low vs. absolute, moderate vs. absolute). Chi-square and Mann-Whitney tests were performed for the qualitative and quantitative variables, respectively. Bonferroni corrections were applied to adjust for the higher risk of a type 1 error.

We then performed two separate binary logistic regression models, one for CBD and the other for cannabis, with a dichotomized moderate/absolute vs. low acceptability (reference category) status as the outcome. The following potential explanatory variables were included: socio-demographic characteristics, health-related variables, cannabinoid knowledge, self-information, and perceived risk of cannabis dependence. A p-value $< 0.20$ (Wald test) was the threshold value for eligible variables in the univariable analyses. A backward selection procedure was then used to obtain the two final multivariable models, with the p-value threshold for statistical significance set at 0.05.

Self-reported barriers to self-medication with cannabis-based products were presented separately for cannabis and CBD. A Chi-squared test was used to test for differences in the pattern of answers according to participants' acceptability level. Self-reported primary sources of information were presented as percentages for participants who reported that they informed themselves about medical cannabis use. Stata/SE 16.1 software (StataCorp LP) was used for all analyses.

## 3. Results

### 3.1. Study sample characteristics

The survey was completed by 1136 participants (54.8 % men, median [interquartile range (IQR)] age 68 [62–74] years). Median [IQR] time since PD diagnosis was 7 [4.0–11.0] years. A third (34.6 %) of the study population experienced 'limitations performing basic daily activities' or a greater level of disability. The vast majority of participants (89.1 %) were directed to the survey through France Parkinson; 2.9 % were directed through Carenity. The respective distribution of participants according to cannabis and CBD acceptability level was as follows: 18.3 and 12.6 % low acceptability, 49.3 and 45.0 % moderate acceptability, and 32.4 and 42.4 % absolute acceptability (Fig. 1). The proportion of persons indicating absolute acceptability was significantly higher for CBD than for cannabis (proportion z-test, $p < 0.001$), and the proportion of persons indicating low acceptability was significantly higher for cannabis than for CBD ($p < 0.001$). The proportions of participants who answered 'do not know' to the prescription-based question (see above) were 14.1 % and 9.7 % for cannabis and CBD, respectively, while the proportions of participants answering 'do not know' to the non-prescription (i.e., over-the-counter) question were 23.7 % and 19.5 %. Study sample characteristics according to acceptability level are provided in Table 1.

Across all three acceptability level groups, for both cannabis and CBD, differences were observed in cannabinoid knowledge, self-information, the perceived risk of cannabis dependence, and positions regarding the relaxation of current cannabis laws in France. Acceptability levels for cannabis and CBD were positively correlated (Table 1).

### 3.2. Factors associated with acceptability of medical cannabis and CBD.

The results of the multivariable analyses are provided in Table 2. For both cannabis and CBD, moderate/absolute acceptability levels were associated with a GAD-2 score $\geq 3$, better cannabinoid knowledge, seeking information on medical cannabis, and considering the risk of cannabis dependence to be low (as compared to high/very high). Furthermore, CBD acceptability was associated with a better self-perceived household economic status.

### 3.3. Self-reported barriers to self-medication with cannabis and CBD.

Supplementary Table 2 presents the reported barriers to self-medication with cannabis and CBD according to how frequently they were reported, and irrespective of their order of importance (see above). For cannabis, the most-cited barriers were 'a lack of information about the right way to use it' (42.4 %), 'the fear of drug-drug interactions' (42.2 %), and 'the fear of other adverse effects' (39.7 %). For CBD, the most-cited barriers were 'a lack of information about the right way to use it' (45.3 %), 'the fear of drug-drug interactions' (41.1 %), and 'the absence of a recommendation from my physician' (37.9 %).

Barriers to self-medication reported as the primary (i.e., the biggest) barrier by > 5 % of the participants are provided in Fig. 2. For cannabis, the most cited primary barriers were 'putting oneself in an illegal situation', and 'the fear of dependence'. The two most-cited primary

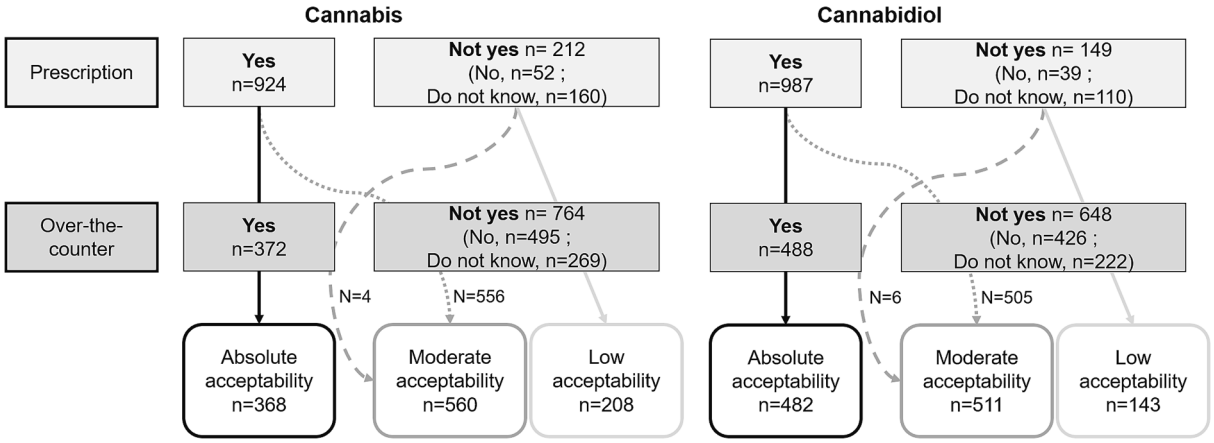


**Fig. 1.** Classification of study participants according to their answers to the two outcome questions (n = 1136).

**Table 1**
Study sample characteristics according to cannabis and cannabidiol acceptability.

| Characteristics (% of 'do not know') | All study sample N (%) | Low cannabis acceptability N (%) | Moderate cannabis acceptability N (%) | Absolute cannabis acceptability N (%) | Intergroup differences[1] | Low cannabidiol acceptability N (%) | Moderate cannabidiol acceptability N (%) | Absolute cannabidiol acceptability N (%) | Intergroup differences[1] |
|---|---|---|---|---|---|---|---|---|---|
| **All study sample** | 1136 (100) | 208 (18.3) | 560 (49.3) | 368 (32.4) | | 143 (12.6) | 511 (45.0) | 482 (42.4) | |
| **Gender** | | | | | | | | | |
| Men | 623 (54.8) | 122 (58.7) | 291 (52.0) | 210 (57.1) | | 81 (56.6) | 274 (53.6) | 268 (55.6) | |
| Women | 511 (45.0) | 86 (41.3) | 268 (47.9) | 157 (42.7) | | 61 (42.7) | 237 (46.4) | 213 (44.2) | |
| Other | 2 (0.2) | 0 (0) | 1 (0.2) | 1 (0.3) | | 1 (0.7) | 0 (0) | 1 (0.2) | |
| **Age (in years, median [IQR])** | 68 [62–74] | 69 [62–74] | 69 [62–74] | 67 [60–74] | | 68 [62–73] | 70 [63–75] | 67 [60–73] | ¤ |
| **Area of residence** | | | | | | | | | |
| Rural area | 376 (33.1) | 59 (28.4) | 195 (34.8) | 122 (33.2) | | 42 (29.4) | 175 (34.2) | 159 (33.0) | |
| Medium-sized city | 484 (42.6) | 99 (47.6) | 236 (42.1) | 149 (40.5) | | 73 (51.0) | 215 (42.1) | 196 (40.7) | |
| Large city (>200 000 inhabitants) | 276 (24.3) | 50 (24.0) | 129 (23.0) | 97 (26.4) | | 28 (19.6) | 121 (23.7) | 127 (26.3) | |
| **Educational level** | | | | | | | | | § ¤ |
| < upper secondary school certificate | 282 (24.8) | 57 (27.4) | 154 (27.5) | 71 (19.3) | | 44 (30.8) | 149 (29.2) | 89 (18.5) | |
| upper secondary school certificate | 166 (14.6) | 34 (16.3) | 80 (14.3) | 52 (14.1) | | 23 (16.1) | 74 (14.5) | 69 (14.3) | |
| Tertiary educational diploma (< Master's degree) | 404 (35.6) | 76 (36.5) | 190 (33.9) | 138 (37.5) | | 44 (30.8) | 174 (34.1) | 186 (38.6) | |
| Tertiary educational diploma (≥ >Master's degree) | 284 (25.0) | 41 (19.7) | 136 (24.3) | 107 (29.1) | | 32 (22.4) | 114 (22.3) | 138 (28.6) | |
| **Professional situation** | | | | | | | | | ¤ |
| Retired | 841 (74.0) | 161 (77.4) | 426 (76.1) | 254 (69.0) | | 108 (75.5) | 406 (79.5) | 327 (67.8) | |
| Working | 153 (13.5) | 20 (9.6) | 74 (13.2) | 59 (16.0) | | 13 (9.1) | 56 (11.0) | 84 (17.4) | |
| Other (including occupational disability) | 142 (12.5) | 27 (13.0) | 60 (10.7) | 55 (14.9) | | 22 (15.4) | 49 (9.6) | 71 (14.7) | |
| **"Presently, would you say that in your household, financially speaking…?"** | | | | | | | | | |
| It's difficult to make ends meet/ You can't manage without going into debt | 110 (9.7) | 23 (11.1) | 46 (8.2) | 41 (11.1) | | 21 (14.7) | 40 (7.8) | 49 (10.2) | |
| You just get by | 265 (23.3) | 52 (25.0) | 128 (22.9) | 85 (23.1) | | 33 (23.1) | 127 (24.9) | 105 (21.8) | |
| You are ok | 445 (39.2) | 85 (40.9) | 230 (41.1) | 130 (35.3) | | 59 (41.3) | 197 (38.6) | 189 (39.2) | |
| You are comfortable | 316 (27.8) | 48 (23.1) | 156 (27.9) | 112 (30.4) | | 30 (21.0) | 147 (28.8) | 139 (28.8) | |
| **Time since Parkinson's disease diagnosis (in years, median [IQR]) (0.3)** | 7 [4.0–11.0] | 7.5 [4.0–11.5] | 7.0 [4.0–11.0] | 7.0 [4.0–11.0] | | 7.0 [4.0–12.0] | 7.0 [4.0–12.0] | 7.0 [4.0–11.0] | |
| **Taking dopamine precursors (0.6)** | | | | | | | | | |
| No | 86 (7.6) | 14 (6.8) | 37 (6.6) | 35 (9.6) | | 13 (9.2) | 30 (5.9) | 43 (9.0) | |
| Yes | 1043 (92.4) | 191 (93.2) | 521 (93.4) | 331 (90.4) | | 128 (90.8) | 478 (94.1) | 437 (91.0) | |
| **Taking dopamine agonists (3.0)** | | | | | | | | | |
| No | 487 (44.2) | 93 (45.1) | 235 (43.8) | 159 (44.2) | | 59 (41.8) | 219 (44.8) | 209 (44.3) | |
| Yes | 615 (55.8) | 113 (54.9) | 301 (56.2) | 201 (55.8) | | 82 (58.2) | 270 (55.2) | 263 (55.7) | |
| **Receiving deep brain stimulation** | | | | | | | | | |
| No | 1046 (92.1) | 189 (90.9) | 515 (92.0) | 342 (92.9) | | 130 (90.9) | 467 (91.4) | 449 (93.2) | |
| Yes | 90 (7.9) | 19 (9.1) | 45 (8.0) | 26 (7.1) | | 13 (9.1) | 44 (8.6) | 33 (6.8) | |

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**Table 1** (*continued*)

| Characteristics (% of 'do not know') | All study sample N (%) | Low cannabis acceptability N (%) | Moderate cannabis acceptability N (%) | Absolute cannabis acceptability N (%) | Intergroup differences[1] | Low cannabidiol acceptability N (%) | Moderate cannabidiol acceptability N (%) | Absolute cannabidiol acceptability N (%) | Intergroup differences[1] |
|---|---|---|---|---|---|---|---|---|---|
| **GAD-2 score[3] (median [IQR]) (7.0)** | 2.0 [1.0–4.0] | 2.0 [0.0–3.0] | 2.0 [1.0–4.0] | 2.0 [1.0–4.0] | | 1.0 [0.0–3.0] | 2.0 [1.0–4.0] | 2.0 [1.0–4.0] | # § |
| **GAD-2 score ≥ 3[3] (7.0)** | | | | | | | | | # |
| No | 664 (62.9) | 129 (68.6) | 324 (62.4) | 211 (60.5) | | 96 (73.3) | 286 (60.7) | 282 (62.1) | |
| Yes | 392 (37.1) | 59 (31.4) | 195 (37.6) | 138 (39.5) | | 35 (26.7) | 185 (39.3) | 172 (37.9) | |
| **PHQ-2 score (median [IQR])[4] (6.1)** | 2.0 [0.0–3.0] | 2.0 [0.0–3.0] | 2.0 [0.0–3.0] | 2.0 [1.0–3.0] | | 1.0 [0.0–3.0] | 2.0 [0.0–3.0] | 2.0 [1.0, 2.0] | |
| **PHQ-2 score ≥ 3[4] (6.1)** | | | | | | | | | |
| No | 772 (72.4) | 143 (74.5) | 372 (70.7) | 257 (73.6) | | 99 (74.4) | 330 (69.0) | 343 (75.2) | |
| Yes | 295 (27.6) | 49 (25.5) | 154 (29.3) | 92 (26.4) | | 34 (25.6) | 148 (31.0) | 113 (24.8) | |
| **Experiencing fatigue as a limit to daily activities[5]** | | | | | | | | | |
| Never / Rarely (< once/week) | 220 (19.4) | 40 (19.2) | 104 (18.6) | 76 (20.7) | | 33 (23.1) | 87 (17.0) | 100 (20.7) | |
| Regularly (once a week) | 238 (21.0) | 49 (23.6) | 112 (20.0) | 77 (20.9) | | 31 (21.7) | 103 (20.2) | 104 (21.6) | |
| Often (several times a week) | 373 (32.8) | 65 (31.3) | 192 (34.3) | 116 (31.5) | | 48 (33.6) | 170 (33.3) | 155 (32.2) | |
| Very often (every day) | 305 (26.8) | 54 (26.0) | 152 (27.1) | 99 (26.9) | | 31 (21.7) | 151 (29.5) | 123 (25.5) | |
| **Disability level[6]** | | | | | | | | | |
| Able to perform daily activity without problems. | 297 (26.1) | 52 (25.0) | 150 (26.8) | 95 (25.8) | | 34 (23.8) | 130 (25.4) | 133 (27.6) | |
| Limitations carrying out demanding daily activities or activities requiring fine motor skills. | 446 (39.3) | 83 (39.9) | 218 (38.9) | 145 (39.4) | | 63 (44.1) | 190 (37.2) | 193 (40.0) | |
| Limitations performing basic daily activities. | 202 (17.8) | 38 (18.3) | 91 (16.3) | 73 (19.8) | | 27 (18.9) | 94 (18.4) | 81 (16.8) | |
| Need help to perform some basic daily activities. | 140 (12.3) | 24 (11.5) | 74 (13.2) | 42 (11.4) | | 14 (9.8) | 68 (13.3) | 58 (12.0) | |
| Dependent on other persons to perform all basic daily activities. | 51 (4.5) | 11 (5.3) | 27 (4.8) | 13 (3.5) | | 5 (3.5) | 29 (5.7) | 17 (3.5) | |
| **Over the past three months, how often did you have pain?[7]** | | | | | | | | | |
| Never | 118 (10.4) | 21 (10.1) | 49 (8.8) | 48 (13.0) | | 13 (9.1) | 48 (9.4) | 57 (11.8) | |
| Some days | 403 (35.5) | 78 (37.5) | 205 (36.6) | 120 (32.6) | | 57 (39.9) | 179 (35.0) | 167 (34.6) | |
| Most days | 267 (23.5) | 49 (23.6) | 132 (23.6) | 86 (23.4) | | 30 (21.0) | 129 (25.2) | 108 (22.4) | |
| Every day | 339 (29.8) | 59 (28.4) | 167 (29.8) | 113 (30.7) | | 42 (29.4) | 148 (29.0) | 149 (30.9) | |
| Do not know | 9 (0.8) | 1 (0.5) | 7 (1.3) | 1 (0.3) | | 1 (0.7) | 7 (1.4) | 1 (0.2) | |
| **Over the past three months, how often did pain limit your life or work activities?[7]** | | | | | | | | | |
| Never | 236 (20.8) | 52 (25.0) | 108 (19.3) | 76 (20.7) | | 38 (26.6) | 99 (19.4) | 99 (20.5) | |
| Some days | 492 (43.3) | 95 (45.7) | 241 (43.0) | 156 (42.4) | | 61 (42.7) | 219 (42.9) | 212 (44.0) | |
| Most days | 219 (19.3) | 32 (15.4) | 121 (21.6) | 66 (17.9) | | 26 (18.2) | 107 (20.9) | 86 (17.8) | |
| Every day | 169 (14.9) | 25 (12.0) | 80 (14.3) | 64 (17.4) | | 14 (9.8) | 78 (15.3) | 77 (16.0) | |
| Do not know | 20 (1.8) | 4 (1.9) | 10 (1.8) | 6 (1.6) | | 4 (2.8) | 8 (1.6) | 8 (1.7) | |
| **Chronic pain[8] (1.1)** | | | | | | | | | |
| Absent | 521 (46.4) | 99 (48.1) | 254 (46.0) | 168 (45.9) | | 70 (49.6) | 227 (45.0) | 224 (46.8) | |

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**Table 1** (*continued*)

| Characteristics (% of 'do not know') | All study sample N (%) | Low cannabis acceptability N (%) | Moderate cannabis acceptability N (%) | Absolute cannabis acceptability N (%) | Intergroup differences[1] | Low cannabidiol acceptability N (%) | Moderate cannabidiol acceptability N (%) | Absolute cannabidiol acceptability N (%) | Intergroup differences[1] |
|---|---|---|---|---|---|---|---|---|---|
| Mild or bothersome | 238 (21.2) | 53 (25.7) | 110 (19.9) | 75 (20.5) | | 33 (23.4) | 105 (20.8) | 100 (20.9) | |
| High impact | 365 (32.5) | 54 (26.2) | 188 (34.1) | 123 (33.6) | | 38 (27.0) | 172 (34.1) | 155 (32.4) | |
| **Over the past three months, what number best describes your pain on average?[7] (median [IQR])** | 5.0 [2.0–6.0] | 5.0 [0.0–6.0] | 5.0 [2.0–7.0] | 4.0 [2.0–6.0] | | 5.0 [0.0–7.0] | 5.0 [2.0–7.0] | 4.0 [2.0–6.0] | |
| **During the past month, how would you rate your sleep quality overall?[9]** | | | | | | | | | |
| Very good | 87 (7.7) | 13 (6.3) | 39 (7.0) | 35 (9.5) | | 9 (6.3) | 40 (7.8) | 38 (7.9) | |
| Quite good | 456 (40.1) | 90 (43.3) | 226 (40.4) | 140 (38.0) | | 68 (47.6) | 205 (40.1) | 183 (38.0) | |
| Quite poor | 441 (38.8) | 79 (38.0) | 225 (40.2) | 137 (37.2) | | 46 (32.2) | 206 (40.3) | 189 (39.2) | |
| Very poor | 152 (13.4) | 26 (12.5) | 70 (12.5) | 56 (15.2) | | 20 (14.0) | 60 (11.7) | 72 (14.9) | |
| **Cannabinoid knowledge (median [IQR])[10]** | 2.0 [1.0–3.0] | 2.0 [0.0–3.0] | 2.0 [1.0–3.0] | 3.0 [2.0–4.0] | # § ¤ | 1.0 [0.0–2.0] | 2.0 [1.0–3.0] | 3.0 [2.0–4.0] | # § ¤ |
| **Do you inform yourself about the medical use of cannabis for Parkinson's disease?** | | | | | # § ¤ | | | | # § ¤ |
| Not at all | 409 (36.0) | 117 (56.3) | 232 (41.4) | 60 (16.3) | | 96 (67.1) | 214 (41.9) | 99 (20.5) | |
| Yes, somewhat | 509 (44.8) | 68 (32.7) | 251 (44.8) | 190 (51.6) | | 36 (25.2) | 232 (45.4) | 241 (50.0) | |
| Yes, absolutely | 218 (19.2) | 23 (11.1) | 77 (13.8) | 118 (32.1) | | 11 (7.7) | 65 (12.7) | 142 (29.5) | |
| **In your opinion, how great is the risk of becoming dependent on cannabis?** | | | | | # § ¤ | | | | # § ¤ |
| There is no risk | 75 (6.6) | 4 (1.9) | 21 (3.8) | 50 (13.6) | | 3 (2.1) | 26 (5.1) | 46 (9.5) | |
| Low risk | 216 (19.0) | 12 (5.8) | 92 (16.4) | 112 (30.4) | | 9 (6.3) | 84 (16.4) | 123 (25.5) | |
| Moderate risk | 188 (16.5) | 20 (9.6) | 99 (17.7) | 69 (18.8) | | 13 (9.1) | 82 (16.0) | 93 (19.3) | |
| High risk | 289 (25.4) | 74 (35.6) | 143 (25.5) | 72 (19.6) | | 48 (33.6) | 123 (24.1) | 118 (24.5) | |
| Very high risk | 95 (8.4) | 40 (19.2) | 43 (7.7) | 12 (3.3) | | 24 (16.8) | 42 (8.2) | 29 (6.0) | |
| Do not know | 273 (24.0) | 58 (27.9) | 162 (28.9) | 53 (14.4) | | 46 (32.2) | 154 (30.1) | 73 (15.1) | |
| **Are you in favor of alleviating legal restrictions on medical use of cannabis in France?** | | | | | # § ¤ | | | | # § ¤ |
| No | 81 (7.1) | 46 (22.1) | 27 (4.8) | 8 (2.2) | | 39 (27.3) | 28 (5.5) | 14 (2.9) | |
| Yes | 845 (74.4) | 77 (37.0) | 430 (76.8) | 338 (91.8) | | 53 (37.1) | 373 (73.0) | 419 (86.9) | |
| Did not adopt a position | 210 (18.5) | 85 (40.9) | 103 (18.4) | 22 (6.0) | | 51 (35.7) | 110 (21.5) | 49 (10.2) | |
| **Are you in favor of alleviating legal restrictions on non-medical use of cannabis in France?** | | | | | # § ¤ | | | | # § ¤ |
| No | 373 (32.8) | 92 (44.2) | 199 (35.5) | 82 (22.3) | | 64 (44.8) | 185 (36.2) | 124 (25.7) | |
| Yes | 477 (42.0) | 39 (18.8) | 208 (37.1) | 230 (62.5) | | 31 (21.7) | 189 (37.0) | 257 (53.3) | |
| Did not adopt a position | 286 (25.2) | 77 (37.0) | 153 (27.3) | 56 (15.2) | | 48 (33.6) | 137 (26.8) | 101 (21.0) | |
| **Cannabis acceptability status** | | | | | | | | | # § ¤ |
| Low acceptability | | – | – | – | | 126 (88.1) | 43 (8.4) | 39 (8.1) | |
| Moderate acceptability | | | | | | 15 (10.5) | 441 (86.3) | 104 (21.6) | |
| Absolute acceptability | | | | | | 2 (1.4) | 27 (5.3) | 339 (70.3) | |

IQR, interquartile range; GAD, general anxiety disorder; PHQ, patient health questionnaire.

[1] For a given substance (i.e., cannabis and cannabidiol), distribution differences between acceptability groups were tested with Chi-square test for categorical variables, and Mann-Whitney test for continuous variables, applying the Bonferroni correction for multiple comparison. The threshold of significance was set at 0.05. Only significant comparisons are displayed in the columns. # refers to low vs. moderate, § refers to low vs. absolute, and ¤ refers to moderate vs. absolute acceptability.

[3] Generalized Anxiety Disorder scale-2, GAD-2 [36].

[4] Patient Health Questionnaire, PHQ-2 [37].

[5] Item adapted from the Non-Motor Symptoms Scale for Parkinson's Disease [38–40].

[6] Item adapted from the Parkinson's Disease Composite Scale [41,42].

[7] Items adapted from the Graded Chronic Pain Scale-Revised [43].

[8] Rated according to the two previous questions [43].

[9] Item taken from the Pittsburgh Sleep Quality Index [44].

[10] Scoring (0–4) based on correctly answering four *ad hoc* statements.

barriers for CBD were 'the fear of dependence', and 'the fear of drug-drug interactions'. Patterns of self-reported primary barriers differed according to acceptability level (Fig. 2).

### 3.4. Cannabinoid knowledge and self-reported sources of information

Of the four ad-hoc statements used to assess cannabinoid knowledge (see above), the highest rate of correct answers was for 'Cannabidiol (CBD) is an active ingredient naturally present in the cannabis plant' (73.5 %). The two statements on the abilities of CBD and THC to induce a high had high rates of 'do not know' answers (41.8 and 48.7 %, respectively). Finally, 24.3 % of the participants inaccurately thought that CBD was illegal (Supplementary Table 1).

Among the subgroup who reported seeking information about medical cannabis (n = 727), the most cited sources of information (irrespective of their ranking by respondent) were scientific and/or medical media (printed or online), and general media (including print press, television and internet sources). The two most cited primary sources of information (i.e., cited in first position by respondents) were scientific and/or medical media (printed or online), and patients and/or users on the internet (social media, forums etc.). Less than 30 % of participants cited their health professional as a source of information (Supplementary Table 3).

## 4. Discussion

This is the first study to investigate the factors associated with the acceptability of cannabis and CBD for medical purposes among patients with PD in France. Notably, both substances were deemed acceptable (i.e., moderate/absolute acceptability) by over 80 % of the participants. For both substances, acceptability was associated with a higher level of anxiety, actively seeking information for medical cannabis, greater knowledge of cannabinoids, and considering the risk of cannabis dependence to be low. Notably, knowledge gaps and the fear of dependence were very frequent barriers to patients choosing to self-medicate with either substance.

Previous studies on people living with PD investigating cannabis and/or CBD use focused on real-world prevalence of use [20,22,45–49]. Our acceptability measures were based on hypothetical situations ('Would you be inclined to […] if […]'), and therefore provide a different kind of information from those studies. Accordingly, we cannot directly compare our findings with those from other studies. However, the 81.3 % and 86.8 % of participants who declared they would use, respectively, cannabis and CBD, if they were prescribed are similar to acceptability indicators in other settings and in patients with different medical conditions [50–54]. For example, more than 80 % of a preoperative patient cohort in the US reported that they would use cannabis if prescribed by a physician for pain after surgery or acute injury [55]. A study in the UK found that 86 % of participants with psychotic disorder were willing to try CBD as a treatment [56]. In the German general population, 48.3 % of CBD non-users declared they could imagine consuming CBD-containing products in the future [57].

We hypothesize that the high levels of acceptability for prescribed cannabis and CBD in our study were related to a high degree of patient trust in medical providers, although we have no data to support this. In a large quota-based sample of US individuals, Kurtzman et al. found that those who 'completely' trusted their usual clinician were more than twice as likely to report that they would definitely use medical cannabis if it were recommended [58].

In our study, 32.7 % and 43.0 % of participants declared they would use cannabis and CBD, respectively, without prescription (i.e., over-the-counter). Unlike the regulated use of prescription drugs, self-medication requires active engagement in self-management strategies and access to reliable information sources [59,60]. In a US study involving a sample of patients with PD, only half reported using complementary or alternative medicine [22].

In our study, CBD use was much more acceptable than cannabis use. One possible reason is greater familiarity with the former, given the widespread distribution of specialized CBD shops in France. A second possible reason is that CBD is perceived as less harmful than cannabis. In a study of the French general population, fewer than 20 % of adults considered CBD to be 'quite harmful' or 'very harmful' [33]. We found that the fear of dependence and the fear of psychoactive effects as barriers to self-medication were more frequently cited for cannabis than for CBD.

Furthermore, after multiple adjustment, we found that the higher the perceived risk of dependence on cannabis, the lower the acceptability level for both cannabis and CBD. The fear of dependence was the second most frequently cited primary barrier to self-medication for cannabis, and the foremost barrier for CBD (though participants with higher levels of acceptability were significantly less likely to cite it). This vigilance and awareness of the risk of dependence may be related to dopaminergic treatments which can cause impulse control disorders in people with PD [61,62]. PD patients with knowledge or experience of these treatments and their consequences may be particularly reluctant to use any substance linked to potential dependence.

Our findings concerning the perceived risk of dependence were similar for cannabis and CBD, which would suggest conflation of the characteristics of both substances in our sample of PD patients. Only 40.8 % of participants knew that CBD does not provoke a high, and 56.4 % that it is legal in France. In Germany, Yenilmez et al. reported that only 8.8 % of their sample of PD patients knew the difference between CBD and THC [46].

Better knowledge about cannabinoids was associated with greater willingness to use both cannabis and CBD in our study. Active information seeking was also associated with greater acceptability. Accordingly, providing accurate information about the potential of dependence on cannabinoids and their safety profile may enhance their acceptability.

Health professionals were rarely mentioned as a source of information on medical cannabis in our study; scientific and/or medical media, general media, and other patients and/or users on the internet were the principal sources cited. These two findings reflect results from a US study where the most common sources of information were from the internet/news and from friends or other people with PD [45]. In the Czech Republic, Venderová et al. reported that patients with PD mostly

**Table 2**
Factors associated with absolute/moderate (vs. low) cannabis and cannabidiol acceptability levels (n = 1136, multivariable logistic regression models).

| | Cannabis aOR [95 % CI] | p-value | Cannabidiol aOR [95 % CI] | p-value |
|---|---|---|---|---|
| **"Presently, would you say that in your household, financially speaking…?"** | | | | |
| It's difficult to make ends meet/You can't manage without going into debt | – | – | 1 | |
| You just get by / You are ok | | | 2.10 [1.17–3.76] | 0.012 |
| You are comfortable | | | 3.18 [1.63–6.22] | 0.001 |
| **GAD-2 score ≥ 3**[1] | | | | |
| No | 1 | | 1 | |
| Yes | 1.48 [1.03–2.11] | 0.033 | 1.92 [1.24–2.98] | 0.003 |
| Missing value (n = 80) | 0.95 [0.54–1.69] | 0.865 | 1.38 [0.69–2.77] | 0.362 |
| **Cannabinoid knowledge (median [IQR])**[2] | 1.25 [1.09–1.43] | 0.001 | 1.44 [1.22–1.69] | <0.001 |
| **Do you inform yourself about the medical use of cannabis for Parkinson's disease?** | | | | |
| Not at all | 1 | | 1 | |
| Yes, somewhat / absolutely | 1.8 [1.27–2.55] | 0.001 | 2.73 [1.80–4.14] | <0.001 |
| **In your opinion, what is the risk of becoming dependent on cannabis?** | | | | |
| There is no risk/a slight risk[3] | 1 | | 1 | |
| Moderate risk | 0.54 [0.27–1.08] | 0.082 | 0.62 [0.27–1.42] | 0.261 |
| High/ Very high risk | 0.16 [0.09–0.28] | <0.001 | 0.23 [0.12–0.44] | <0.001 |
| Do not know | 0.32 [0.17–0.59] | <0.001 | 0.38 [0.19–0.77] | 0.007 |

aOR, adjusted odds ratio; CI, confidence interval.
[1] Generalized Anxiety Disorder scale-2 [36].
[2] Scoring (0–4) based on correctly answering four *ad hoc* statements.
[3] 'There is no' and 'slight' were aggregated, as were 'high' and 'very high'.

decided to take cannabis based on information presented in the media [47]. In Argentina, Micheli et al. reported that in their study sample of patients with PD, the main sources of information were friends, family or acquaintances, television, and the internet [49]. Our results regarding the principal sources also reflect findings in different populations, specifically older adults [63] and patients with multiple sclerosis [64].

All these findings highlight that in France, as elsewhere, in order to have reliable information on the medical use of cannabinoid, an individual needs to show active interest in the topic, and have the capacity to access and understand the information discovered. The fact that health professionals were cited so little as information sources in our study may suggest that patients were less likely to ask them for advice. Such reticence could be related to patients' fear of disapproval by the provider, or explicit disapproval by physicians [65–68] (including neurologists [69,70]). Indeed, one can presuppose that given the lack of an approved cannabinoid-based product for PD in France, not all physicians may feel comfortable discussing this topic with their patients. As cannabis-based products cannot be prescribed by doctors, and pharmaceutical-grade CBD is not available over-the-counter in France, one cannot expect health professionals to initiate such a discussion or proactively provide information to patients.

Cannabis and CBD acceptability levels were only associated with one disease-related symptoms in the present study which was anxiety (positive association). Anxiety is very prevalent in people with PD [7,71], although it is commonly underrecognized and undertreated [72]. Moreover, anxiety is a major independent predictor of QoL in PD patients [5,7]. The associations we found between anxiety and acceptability levels may therefore be driven by both a strong unmet need for treatment to alleviate anxiety, and a perception that cannabis-based products are anxiolytic.

Clinical results to date for the benefits of CBD and cannabis in treating anxiety [73–75] are inconclusive. Both substances are commonly used in general populations for managing this condition [76–79]. This is partly driven by as yet unproven claims transmitted through social media [80–82] and commercial marketing [83] that these products alleviate anxiety.

Participants in our study who perceived their household financial situation as difficult were more likely to have a low CBD acceptability level. One possible reason for this is that despite multiple adjustment for perceptions and knowledge, having financial difficulties was related to less favorable perceptions and/or less knowledge of CBD. In a large sample of older US adults, lower income was associated with higher perceived risks associated with cannabis consumption [84]. We can hypothesize that the same is true for CBD, given the highlighted conflation between both products. It has also been shown that lower income and lower socioeconomic status are associated with a lower likelihood of seeking online medical information [85–88]. A second possible reason for lower acceptability in persons on a lower income is that the current prices of CBD products deterred them from buying them. Cost is a major issue for medical cannabis use in patients with chronic pain [89] and one can expect the same is true for CBD products. Prices for CBD products can be freely consulted by everybody in France.

This study has several strengths. First, it is the first to explore acceptability and attitudes to the therapeutic use of cannabis and CBD in PD patients in France. Second, the sample size was large, meaning good statistical power. Third, we assessed a complex mix of socio-demographic, health-related and perception-related variables, which allowed us to comprehensively characterize patients according to their acceptability level.

The study also has limitations. First, the sample cannot be considered representative of all French people with PD, and therefore we cannot generalize our results. More specifically, a very large percentage of the participants were directed to the survey from the national association France Parkinson. These people were therefore already engaged in information seeking and community-based exchanges. Accordingly, the relevant findings may be overestimated. Second, the web-based format of the survey may have disproportionally selected patients with fewer disabilities. However, one possible advantage of online surveying is reduced desirability bias, especially for a topic like cannabis-based products. However, it is likely that people interested in using cannabinoids were overrepresented, potentially leading to overestimations of acceptability. Third, the male-to-female ratio of our study sample was slightly lower than what would be expected in the national French PD population, as was the median age [90]. PD severity was only estimated, but not clinically validated. Finally, fatigue, sleep, and pain levels were assessed with isolated questionnaire items that do not reflect the psychometric properties of the validated scales they were taken from.

## 5. Conclusions

In conclusion, acceptability levels among people with PD for cannabis and CBD use were high, the latter substance being more acceptable. Our findings underscore that knowledge and perceptions of cannabinoids had a major impact on acceptability levels. As misconceptions persist about the negative effects of CBD and the risk of dependence, disseminating accurate information should increase acceptability.

## CRediT authorship contribution statement

**Tangui Barré:** Writing – original draft, Methodology,

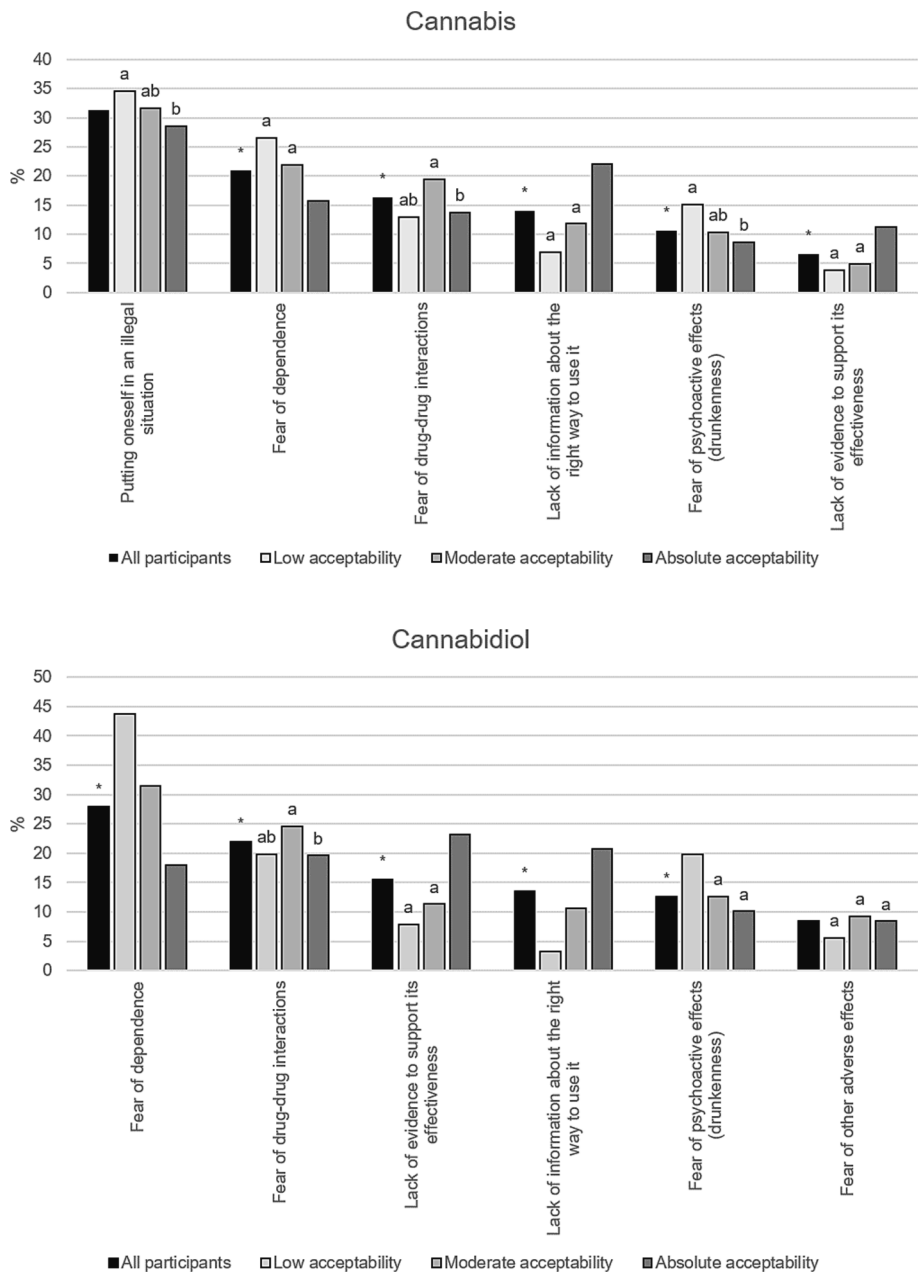


**Fig. 2.** Percentages of cited primary barriers to self-medication for cannabis and cannabidiol according to acceptability level. Only barriers cited by more than 5 % of participants are shown. * indicates a global p-value $< 0.05$ (Chi-square test). For a given barrier, groups with a similar letter were not statistically different ($p \geq 0.05$, Chi-square test). 'Putting oneself in an illegal situation' was not proposed as a possible answer for cannabidiol, as it is legal in France.

Conceptualization. **Géraldine Cazorla:** Writing – review & editing, Methodology, Conceptualization. **Vincent Di Beo:** Writing – review & editing, Formal analysis. **Fabienne Lopez:** Writing – review & editing, Methodology. **Lise Radoszycki:** Writing – review & editing, Investigation. **Gwenaëlle Maradan:** Writing – review & editing, Investigation. **Christelle Baunez:** Writing – review & editing, Conceptualization. **Patrizia Carrieri:** Writing – review & editing, Methodology, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2024.100286.

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**Patterns of use and patient-reported effects of cannabinoids in people with PD: a nationwide survey**

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## Abstract

**Background**. People with Parkinson's disease (PD) may use cannabis-based products for symptom management. In France, products containing tetrahydrocannabinol are prohibited, while cannabidiol (CBD)-products are readily available. However, data on cannabinoid use in French people with PD are lacking.

**Objectives**. To identify correlates of the use of cannabis-based products and to document their patterns of use and perceived effects.

**Methods**. A French nationwide online survey was conducted from May to July 2023. Regression analyses helped identify factors associated with current cannabis and with CBD use. Patterns of use and self-reported effects were also documented.

**Results**. The study sample comprised 1136 participants, with a median age of 68 years. Six percent (5.9%) and 17.9% reported using cannabis and CBD, respectively. Both substances were associated with better knowledge of cannabinoids and a poor self-perceived household economic situation. The most common routes of cannabis administration were oral ingestion (44.8%) and smoking (41.4%); for CBD they were oral ingestion (82.8%) and smoking (6.4%). Users reported that cannabis and CBD were very effective for sleep disorders, pain, and rigidity/cramps. The satisfaction level for both substances was also high.

**Conclusion**. Cannabis and CBD use among people with PD were associated with better knowledge about cannabinoids and a poor self-perceived household economic situation. Furthermore, users reported high levels of satisfaction for both substances. Enhanced communication with healthcare providers and facilitated access to safe cannabis/CBD products are needed in France to enable people with PD to maximize the benefits of cannabinoids when clinically appropriate.

**Key words: Parkinson's disease; cannabis; cannabidiol; sleep disorders; pain;**

# Introduction

Parkinson's disease (PD) is characterized by a number of cardinal motor manifestations including bradykinesia, rigidity, and rest tremor [1]. Dopamine replacement strategies are commonly used to treat these symptoms. PD development is also accompanied by several and varied non-motor symptoms such as pain and sleep disorders [2], for which treatment options are limited [3]. Long-term dopaminergic treatment may also bring about motor and non-motor symptoms [4,5]. All these symptoms weigh heavily on patients' quality of life [6–8]. Compared to healthy persons, people with PD have a lower quality of life in most domains [9].

In this context of suboptimal symptom management, PD patients may seek alternative approaches to care [10,11], including consuming cannabis-based products. In line with findings from subsequent reviews [12,13], Urbi et al.'s 2021 meta-analysis concluded that in terms of cannabis use in PD patients, "a potential benefit was identified with respect to alleviation of PD-related tremor, anxiety, pain, improvement of sleep quality and quality of life" [14]. In contrast, a recent small-sized randomized trial found no superiority of a cannabidiol (CBD)-dominant oil over placebo regarding motor and non-motor symptoms in people with PD [15]. These diverging conclusions contrast with more positive results observed elsewhere from the patients' perspective [11,16–18].

User-reported effects, profiles and patterns of use of cannabis-based products in the sphere of self-medication vary according to the product type and are influenced by sociocultural and legal contexts. Unlike countries where medical cannabis is authorized, tetrahydrocannabinol (THC)-containing products (over 0.3%) are prohibited in France. The only exception is an ongoing national field experiment aimed at assessing the relevance and feasibility of providing medical cannabis to individuals with chronic severe conditions not sufficiently alleviated by other treatments [19]. PD was not considered to be an eligible indication for enrolment in this experiment.

Unlike THC-containing products, CBD-based products are authorized in France, as in most European countries [20,21], and are used by a substantial proportion of French adults [22]. Therefore, French PD patients seeking cannabis-based symptom relief have two options: obtaining CBD products of uncontrolled quality or purchasing THC-containing cannabis from the black market. The latter likely has high concentrations of THC [23] and is potentially adulterated [24].

Due to stigma, including in medical settings [25–31], PD patients may not disclose their use of cannabis-based products to healthcare providers. This is concerning because both THC-containing cannabis and CBD can cause adverse effects and may interact with concurrently prescribed drugs [32].

CBD-based self-medication is rarely studied in PD [33], and no research has examined cannabis use in French PD patients. Identifying PD patients prone to using and understanding their usage patterns could assist healthcare providers in initiating discussions and offering appropriate guidance and harm reduction counseling.

In this context, the present study aimed to identify factors associated with cannabis and CBD use among PD patients living in France, and document their patterns of use and self-reported effects.

# Methods

## Study design and participants

A cross-sectional online self-administered survey was implemented from 22 May to 14 July 2023. The two inclusion criteria were being ≥ 18 years old and having diagnosed PD. The link to the survey was displayed on the France Parkinson website. France Parkinson is a national public utility association with 75 local committees and is part of the European Parkinson's Disease Association. Invitations to participate in the survey were sent by email to all France Parkinson's contacts (over 35 000 addresses, including approximately 5000

paying members). The association also featured the survey in its newsletter and on its social media. Carenity, a social network for people living with chronic conditions, also invited its members to participate via email and/or private messages on the network's platform (n=1857, including relatives of people with PD). Local associations of people living with PD also helped to disseminate the survey. The survey was closed when a sample size of 1000 participants was reached.

The survey was designed in accordance with the declaration of Helsinki, and approved by the INSERM Ethic committee (IRB00003888, CD/EB 23-045 dated 4 April, 2023). It was powered by Voxco. Prior to accessing the questionnaire, participants were required to provide informed consent.

## Questionnaire and data collection

Socio-demographic data collected included gender, age, type of area of residence, educational level, professional situation, and self-perceived household economic status. Health-related data collected included time since PD diagnosis, current intake (Yes/No) of dopamine precursors and/or agonists, receiving deep brain stimulation (Yes/No), and measures for anxiety and depression from the Generalized Anxiety Disorder scale-2, (GAD-2) [34] and Patient Health Questionnaire (PHQ-2) [35]. The impact of fatigue was assessed with a question adapted from the Non-Motor Symptoms Scale for Parkinson's Disease [36–38]. Disability level was assessed with an item adapted from the Parkinson's Disease Composite Scale [39,40]. Pain was assessed with three questions adapted from the Graded Chronic Pain Scale-Revised [41]. Sleep quality was assessed with a question taken from the Pittsburgh Sleep Quality Index [42].

Cannabinoid knowledge was assessed through four Yes/No ad hoc questions (see **Supplementary Table 1**), with a score ranging from 0 (no correct answer) to 4 (four correct answers). Self-information was assessed with the question 'Do you inform yourself on medical use of cannabis for Parkinson's disease?' Perceived risk of dependence was

assessed with the question ‘In your opinion, how great is the risk of becoming dependent on cannabis?’ The participants’ position regarding the legal status of cannabis was assessed with two questions: ‘Are you in favor of alleviating legal restrictions on medical (respectively, non-medical) use of cannabis in France?’

In the survey, cannabis products were defined as containing THC above authorized thresholds, while CBD products were defined as any type of CBD-containing product with THC levels below authorized thresholds.

‘Regular use’ (see next section) of either substance was defined as using it at least once a week. Regular users were asked how long they had regularly used (more or less than a year). Users were also asked to specify the type of product they used most often for each of the two substances (e.g., herb, resin) and the primary route of administration for each (e.g., smoked, oral ingestion). Answers were selected from predefined lists. For cannabis and CBD separately, users were asked to assess the effect of each substance on a list of nine symptoms, using the following predefined response options: ‘I am not concerned by this symptom’, ‘deterioration’, ‘no effect on the symptom’, ‘slight improvement’, ‘moderate or large improvement’, and ‘I do not know’. Having experienced adverse effects from using each substance was assessed using a predefined list. Users also indicated whether each substance had an impact on prescribed medical drugs they were taking. Cannabis users were asked how much attention they paid to the choice of the cannabis strain they used. Finally, user satisfaction was assessed with the question ‘Would you recommend cannabis [respectively, CBD] as self-medication to a friend in a similar health situation? (Please rate your motivation from 1 to 10)’.

## Study outcomes

Two outcomes were defined for the regression analyses: being a cannabis user, and being a CBD user. Cannabis [respectively, CBD] use was determined based on respondents selecting any response other than ‘I do not use it’ to the question ‘How often do you usually

use cannabis [respectively, CBD]?'. Possible predefined answers were 'I do not use it', 'less than once a week', 'once a week', 'more than once a week but not every day', 'once a day', 'twice a day', and 'three times or more per day'.

### Statistical analyses

All participants who completed the survey questionnaire entirely were included in the analyses. Participants' characteristics were described according to their user status of cannabis and CBD, and were compared using Chi-square and Mann-Whitney tests for categorical and continuous variables, respectively.

We ran two separate logistic regression models to identify factors associated with cannabis and CBD use. Sociodemographic and health-related variables as well as cannabinoid knowledge (as a continuous variable) were all tested in the models. A p-value <0.20 was used as the threshold for identifying eligible variables in the univariable analyses (Wald test). A backward selection procedure was then used to obtain the two multivariable models, with the p-value threshold for statistical significance set at 0.05.

For comparability purposes, we built final multivariable models for both outcomes based on a common set of variables. Any variable that was maintained in at least one of the previously ran multivariable models was included in the final models, irrespective of their p-value. Stata/SE 16.1 software (StataCorp LP) was used for all analyses.

## Results

### Study sample characteristics

The study sample comprised 1136 participants, median [interquartile range (IQR)] age was 68.0 [62.0, 74.0] years, and 54.8% were men. Six (5.9) percent of the participants used cannabis, 17.9% used CBD, and 4.0% used both (**Supplementary Figure 1**).

Participants' characteristics according to their cannabis and CBD use are shown in **Supplementary Table 2**. Cannabis users, in comparison to non-users, were more likely to

be younger, to be working, to perceive a poor household economic situation, and to have greater cannabinoid knowledge. CBD users, compared to non-users, were more likely to be working, not to be receiving deep brain stimulation, to experience more impactful chronic pain, and to have greater cannabinoid knowledge.

Cannabis-CBD co-users were more likely to be working, to seek information on medical cannabis, and to be in favor of alleviation of legal restrictions on non-medical cannabis use compared to exclusive CBD users. No difference was observed between cannabis-CBD co-users and exclusive cannabis users (data not shown).

Furthermore, 74.4% of the participants were in favor of alleviating legal restrictions on medical use of cannabis in France, with higher proportions among cannabis and CBD users than among non-users.

## Factors associated with cannabis and cannabidiol use

Results from the two separate logistic regressions are provided in **Supplementary Table 3**. In the final model for cannabis, after multiple adjustment, cannabis use was associated with not being retired, a poor self-perceived household economic situation, and greater cannabinoid knowledge (**Table 1**).

In the final model for CBD, after multiple adjustment, CBD use was associated with self-perceived household economic difficulties, not receiving deep brain stimulation, more severe pain, and greater cannabinoid knowledge (**Table 1**).

As most (68.7%) cannabis users were CBD co-users, we performed a post-hoc analysis by merging cannabis and CBD users into a single group of cannabis and/or CBD users. In the final related model, after multiple adjustment, cannabis and/or CBD use was associated with professional situation other than working (e.g., occupational disability) (reference: retirement), poor self-perceived household economic situation, not receiving deep brain stimulation, more severe pain, and greater cannabinoid knowledge (**Table 1**).

## Patterns of cannabis and cannabidiol use

The frequency of use and duration of regular use (defined as at least once a week) are separately presented for cannabis and CBD users in **Supplementary Table 4**. Daily users accounted for 23.9% and 33.0% of cannabis and CBD users, respectively. Cannabis users were more likely to have regularly used for more than a year than CBD users ($p<0.001$, z-proportion test).

The routes of administration for the two substances are presented in **Figure 1**. The most commonly reported main types of cannabis products were dried herb (38.8%) and tincture/oil (drops) (34.3%), while the most common main routes of cannabis administration were oral ingestion (44.8%) and smoking (41.4%). Among those whose main cannabis products were dried herb or resin, 73.5% reported smoking as the main route of administration. Among cannabis smokers, most mixed it with tobacco.

For CBD users, the most common main products were oil (71.4%) and dried herb (12.3%), while the most common main routes of CBD administration were oral ingestion (82.8%) and smoking (6.4%). Among those whose main CBD products were oil, 95.9% reported oral ingestion as the main route of CBD administration. Among tobacco smokers (n=13), the majority (n=11) mixed CBD with tobacco to some degree.

Among cannabis users, 37.3% paid no attention to the cannabis strain, 26.9% paid moderate attention, and 35.8% paid great attention.

## Self-reported effects

### Beneficial effects

The self-reported effects of cannabis and CBD on PD symptoms are shown in **Figure 2**. Cannabis users reported improvements (slight, moderate or strong) for a median number of 3 [1-7] symptoms out of the nine examined. At least one moderate or strong symptom improvement was reported by 80.6% (62.7% for strong improvement) of cannabis users. The most improved symptoms reported by cannabis users were, in descending order: sleep

disorders (56.7% of all cannabis users), rigidity/cramps (56.7%), pain intensity (52.2%), pain frequency (50.7%), other motor disorders (42.9%), anxiety (41.8%), fatigue (40.3%), tremor (38.8%), and depression (28.4%). Improvement rates exceeded 60% for the three most-cited symptoms (i.e., sleep disorders, rigidity/cramps, and pain intensity) when participants who declared they were not at all affected by each of these three specific symptoms were excluded.

CBD users reported improvements (slight, moderate or strong) for a median number of 3 [2-5] symptoms out of the nine examined. At least one moderate or strong symptom improvement was reported by 87.2% (45.3% for strong improvement) of CBD users. The most improved symptoms reported by CBD users were, in decreasing order: pain intensity (55.2% of all CBD users), pain frequency (50.7%), rigidity/cramps (48.8%), sleep disorders (47.3%), anxiety (46.3%), fatigue (33.5%), tremor (27.1%), other motor disorders (26.9%), and depression (24.1%). Improvement rates exceeded 60% for pain intensity when participants who declared they did not have this symptom were excluded.

## Side effects

For cannabis, the symptoms with the highest levels of self-reported deterioration were fatigue (11.9%), sleep disorders, other motor disorders, and tremor (between 7.5 and 6.0%). For CBD, the symptom with the highest level of self-reported deterioration was fatigue (3%) (**Figure 2**).

Frequencies of self-reported side effects of cannabis and CBD use are presented in **Figure 3**. Cannabis users reported a median [IQR] of 2 [0-5] side effects while CBD users reported a median [IQR] of 0 [0-1] side effects. The most common side effect for both cannabis and CBD was a dry mouth.

Among cannabis users, 80.6% reported that cannabis use had no effect on their use of medical drugs (i.e., for PD or other ailments) consumption; 11.9% reported they decreased their PD drug intake, while 7.5% decreased their intake of drugs for other ailments. In terms

of CBD users, 88.7% reported that it had no effect on their use of drugs (i.e., all ailments); 5.4% reported they decreased their PD drug intake, 1.0% increased it, and 4.9% decreased their use of drugs for other ailments.

Median [IQR] satisfaction rates with cannabis and CBD were 7 [5, 9] and 7 [5, 8], respectively.

## Discussion

To the best of our knowledge, this is the first study to examine cannabis and CBD use among people with PD in France, a country where medical cannabis use is currently not approved. There are two main results: first, cannabis and CBD use were both associated with better knowledge about cannabinoids and a poor self-perceived household economic situation. Second, both cannabis and CBD users reported high effectiveness levels for sleep disorders, pain, and rigidity/cramps, as well as high overall levels of satisfaction with the substances. Dried herb (cannabis) and oil (CBD) were the most commonly used products.

Both cannabis and CBD use was associated with a poor self-perceived household economic situation. One possible reason for this is that that people with PD who need to continue working despite their PD symptoms may more actively seek alternative medicines to better self-manage their symptoms at work. This is partly supported by the association between cannabis use and working conditions in our study. One could also hypothesize that cannabis - which comes from the black market in France - is more easily accessible in deprived socioeconomic areas. In line with findings by Yenilmez et al. [43], both cannabis use and CBD use in our study were associated with better cannabinoid knowledge. This association was expected, as self-medication demands active engagement in self-management strategies and access to reliable information sources [44,45].

CBD use was also associated with greater pain perception. Feeney et al. found pain a common reason for cannabis use [46]. CBD users likely have similar motives, with social media associating CBD with pain relief [47]. A previous study highlighted that CBD users in

France frequently reported pain relief as an expected effect [48], reflecting findings from users in Germany [21]. Patients with chronic pain likely view CBD positively [49]. The lack of association between pain and cannabis use in our study may be due to insufficient statistical power.

CBD use was also associated with not receiving deep brain stimulation. The favored target for deep brain stimulation treatment is the subthalamic nucleus which is a critical node through which nociceptive stimuli enter the basal ganglia circuit [50]. Stimulation of this part of the brain has been shown to reduce pain [51]. This would suggest that PD patients in our study who underwent deep brain stimulation surgery suffered less from pain and were therefore less prone to use CBD to treat it.

For both substances, participants reported the most improvement in sleep disorders, pain, and rigidity/cramps. This ranking aligns with patient-reported results from other studies in people with PD using cannabis [17,18,43,46,52,53]. To our knowledge, this is the first time that such a ranking has been reported for CBD in people with PD. In their meta-analysis, Urbi et al. pointed out the potential benefits of cannabis for people with PD in terms of improved pain and sleep, as well as tremor [14]. On the contrary, another meta-analysis concluded that no motor symptom improvement could be credited to medical cannabis and its derivatives [54]. In the general population, small positive effects of CBD on pain and sleep have been highlighted or suggested with varying levels of certainty [55–57]. Differences between clinical and patient-reported outcomes in PD [16] can partly be explained by the likelihood that surveys attract active users who experience benefits, explaining the high satisfaction levels for both cannabis and CBD.

In our study, CBD was predominantly ingested orally. However, 41.4% of cannabis users smoked it, mostly mixed with tobacco. Previous studies among people with PD have shown significant variations in routes of administration. In some contexts, cannabis was primarily smoked [53], while in others, other routes of administration were frequent [18,43,46,58]. Although it is difficult to draw definitive epidemiological conclusions about the

cannabis smoke's respiratory effects [59], research suggests that cannabis smoke contains higher levels of particulate matter compared to tobacco smoke [60]. Consequently, smoking cannabis is likely to have adverse effects on lung health, particularly when it is obtained on the black market as it may be adulterated. Additionally, the co-use of tobacco-cannabis is likely to exacerbate tobacco and cannabis use and/or dependence, and reduce the likelihood of cessation [61–63].

In our study, the prevalence of cannabis and CBD use was approximately 6% and 18%, respectively. In Norway, whose legal context resembles France, Erga et al. reported a prevalence of current cannabis use of 11.3% among a sample of 530 people with PD recruited through a process quite similar to ours [17].However, because of various legal contexts and data collection methodologies, no conclusion can be drawn from comparisons of cannabis use prevalence from other studies [11,18,43,46,52,58,64]. Studies from countries with medical cannabis programs showed that many PD patients still obtain cannabis through non-medical sources [46,52,58].

The difference in prevalence between cannabis and CBD use which we found for France can be attributed to several factors. First, CBD is easily and legally accessible, whereas cannabis use remains *de jure* criminalized, which limits its accessibility and raises legality and safety concerns regarding its supply. Second, CBD is likely to be perceived as less harmful than cannabis. In the French general population, fewer than 20% of adults reported considering CBD as “quite” or “very harmful” [22].

Most cannabis users among our participants also used CBD, though not vice versa. This aligns with general population data in France, where cannabis use is associated with CBD use [22]. Additionally, regular cannabis users had used it for longer compared to regular CBD users. Taken together, these findings suggest that cannabis users may turn to CBD as they believe it can provide similar health-related benefits with potentially lower associated risks.

Our results have several implications. First, CBD use does not seem uncommon among French people with PD, underscoring the importance for healthcare providers to inquire about CBD use to address symptom management needs and manage potential adverse effects and drug interactions. Second, most cannabis users in our study smoked it mixed with tobacco; posing significant cancer-related risks [65] and health risks associated with the quality of unregulated products. Third, initiating discussions about CBD use is crucial for implementing harm reduction strategies, such as promoting smoke-free administration methods like vaporizing. Finally, despite legal constraints in France, users perceive cannabis and CBD as effective for managing PD symptoms, highlighting the need to consider PD as an eligible indication for controlled cannabinoid use under medical supervision.

The study's strengths include pioneering documentation of cannabinoid behaviors among people with PD in France, separate documentation of CBD use and effects from cannabis use, a robust national sample size, and comprehensive collection of sociodemographic and health-related variables.

The study also has limitations. The sample may not be representative of all French people with PD, potentially limiting the generalizability of our findings. Specifically, recruitment primarily targeted individuals affiliated with a particular association, possibly overrepresenting those actively seeking information and engaging in community-based interactions. Additionally, the online survey format might have favored the participation of individuals with milder disabilities. There was also a slight underrepresentation of men and overrepresentation of younger patients compared to the typical national French PD population [66]. Furthermore, self-administered questionnaires may be subject to desirability bias particularly regarding such a sensitive topic. However, the online format likely mitigated any such bias. Finally, PD diagnosis and severity were not clinically validated in our study.

To conclude, unlike cannabis use, CBD use was common in our sample of people with PD in France. Both uses were associated with better knowledge of cannabinoids and a poor self-perceived household economic situation. Users commonly reported improvements

312 in sleep disorders, pain, and rigidity/cramps. Enhanced communication with healthcare
313 providers and facilitated access to safe products are needed in France so that people with
314 PD can maximize the benefits of cannabinoids when clinically appropriate.

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## Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## Authors' contributions

Design: TB, GC, FL, CB, PC

Data collection: TB, GC, LR, GM

Data analyses: VDB

Writing of original draft: TB

Writing of revisions: TB, GC, VDB, FL, LR, GM, CB, PC.

## Disclosures

### Funding Sources and Conflict of Interest

This study was funded by the France Parkinson association.

The funder helped collecting the data. It had no role in the analysis, interpretation of data, and writing the manuscript.

The authors declare that there are no conflicts of interest relevant to this work.

### Financial Disclosures for the previous 12 months

The authors declare that there are no additional disclosures to report.

## Ethical Compliance Statement

The survey was designed in accordance with the declaration of Helsinki, and approved by the INSERM Ethic committee (IRB00003888, CD/EB 23-045 dated 4 April, 2023).

Prior to accessing the questionnaire, participants were required to provide informed consent by ticking a box on the online survey.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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**Table 1. Factors associated with cannabis and cannabidiol use (final multivariable binary regression models)**

| | Cannabis | | Cannabidiol | | Cannabis and/or cannabidiol | |
|---|---|---|---|---|---|---|
| | **aOR [95% CI]** | **p-value** | **aOR [95% CI]** | **p-value** | **aOR [95% CI]** | **p-value** |
| **Professional situation** | | | | | | |
| Retired | 1 | | 1 | | 1 | |
| Working | 2.57 [1.34-4.91] | **0.004** | 0.94 [0.57-1.56] | 0.809 | 1.18 [0.74-1.91] | 0.484 |
| Other (including occupational disability) | 2.63 [1.39-4.95] | **0.003** | 1.53 [0.98-2.38] | 0.061 | 1.59 [1.03-2.44] | **0.036** |
| **"Presently, would you say that in your household, financially speaking…?"** | | | | | | |
| You are ok / You are comfortable | 1 | | 1 | | 1 | |
| You just get by | 1.24 [0.67-2.31] | 0.490 | 1.22 [0.82-1.82] | 0.324 | 1.16 [0.78-1.71] | 0.468 |
| It's difficult to make ends meet / You can't manage without going into debt | 2.28 [1.11-4.69] | **0.025** | 1.77 [1.02-3.05] | **0.041** | 1.99 [1.18-3.34] | **0.010** |
| **Receiving deep brain stimulation** | | | | | | |
| No | 1 | | 1 | | 1 | |
| Yes | 0.85 [0.35-2.10] | 0.725 | 0.39 [0.19-0.83] | **0.014** | 0.42 [0.21-0.84] | **0.014** |
| **"Over the past three months, what number best describes your level of pain on average (0-10)?"** ***Per one-unit increase*** | 1.03 [0.94-1.14] | 0.492 | 1.09 [1.02-1.16] | **0.008** | 1.07 [1.01-1.14] | **0.021** |
| **Cannabinoid knowledge (0-4)** [1] ***Per one-unit increase*** | 1.53 [1.23-1.90] | **<0.001** | 2.26 [1.93-2.65] | **<0.001** | 2.25 [1.94-2.61] | **<0.001** |

CI, confidence interval. Bold indicates p-values ≤ 0.05.

[1] Scoring based on the correctness of four ad hoc questions

**Figure 1. Types of products and routes of administration among cannabis (n=67) and cannabidiol (n=203) users**

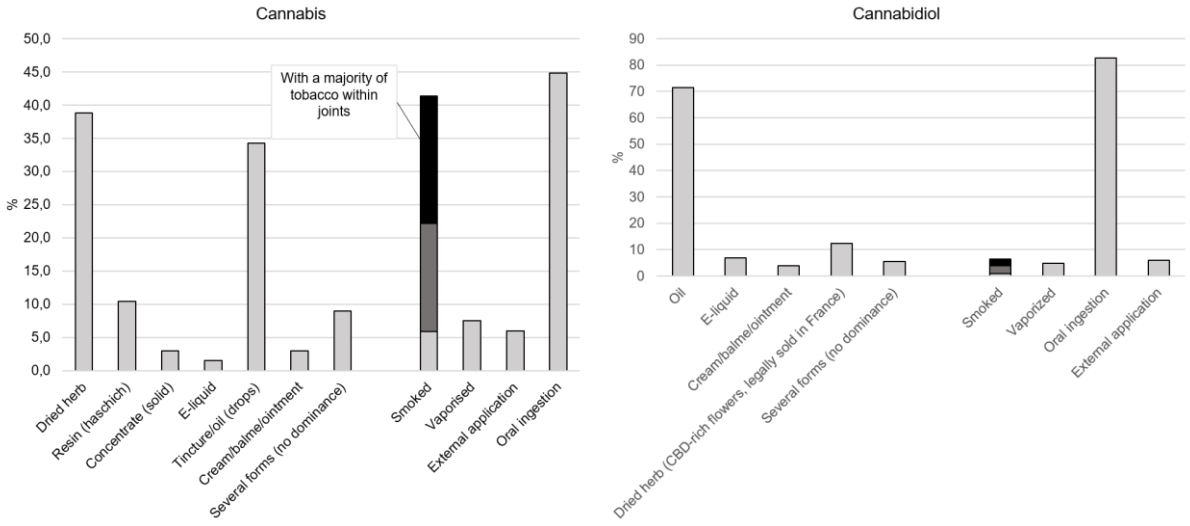


**Figure 2. Self-reported effects of cannabis (n=67) and cannabidiol (n=203) use on symptoms**

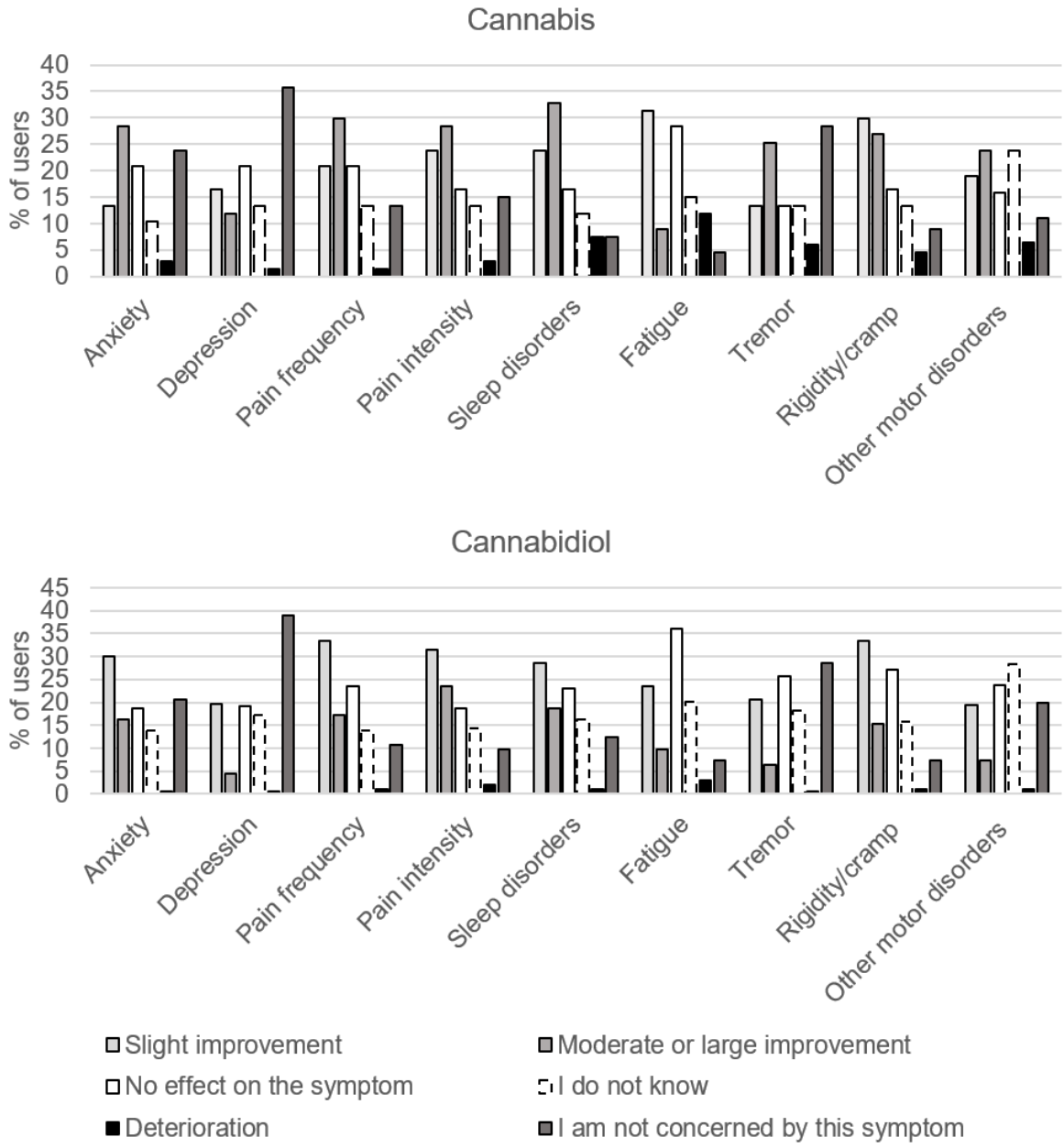
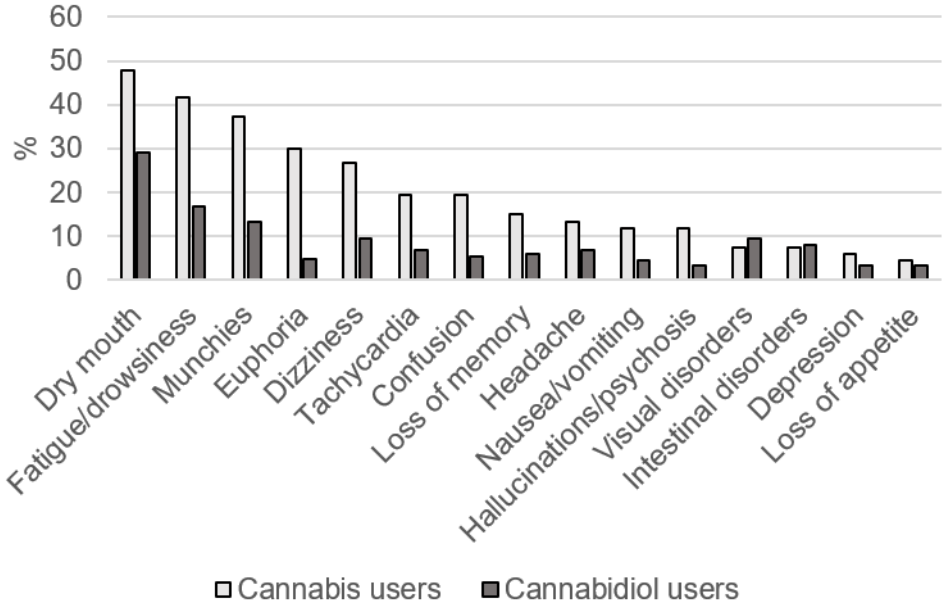


**Figure 3. Self-reported side effects in cannabis (n=67) and cannabidiol (n=203) users**



# Supplementary Material

**Supplementary Figure 1. Distribution of participants according to cannabis and cannabidiol use**

**Supplementary Table 1: Questions assessing participants' knowledge about cannabis and cannabinoids**

**Supplementary Table 2: Study sample characteristics according to cannabis and cannabidiol use**

**Supplementary Table 3. Factors associated with cannabis and cannabidiol use (multivariable binary regression models)**

**Supplementary Table 4. Frequency and duration of use for cannabis and cannabidiol use**

**Healthcare providers' acceptability of cannabis and cannabidiol to manage Parkinson's disease in France**

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**Running title**: Acceptability of cannabinoids for PD

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VDB: Data curation, formal analysis, review & editing

CB: Data curation, formal analysis, review & editing

ChB: Review & editing

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**Conflicts of interest:**

The authors have no conflict of interest to declare

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**Supplementary Materials:**

There are three supplementary tables.

Supplementary Table 1. Answers to *ad hoc* statements assessing knowledge about cannabinoids, according to participants' occupation (i.e., physicians vs. non-physicians) (n=218)

Supplementary Table 2: Answers to the two separate acceptability questions according to participants' occupation (i.e., physicians vs, non-physicians) (n=218)

Supplementary Table 3: Primary barriers to agreeing to the use of cannabis and cannabidiol for the therapeutic management of PD according to participants' occupation (i.e., physicians vs. non-physicians) (n=218)

The authors have checked to make sure that our submission conforms as applicable to the Journal's statistical guideline.

**Healthcare providers' acceptability of cannabis and cannabidiol to manage Parkinson's disease in France**


## Abstract

**Background**. Some people living with Parkinson's disease (PD) self-administer cannabis-based products to manage symptoms. However, using non-prescribed products can pose risks. In France, PD is not an eligible condition for prescribed cannabis-based products. Investigating healthcare providers' perspectives on this topic is critical as PD might be considered for inclusion in future French medical cannabis programs.

**Aims**. To explore healthcare providers' acceptability, knowledge, and perceptions regarding the therapeutic use of cannabis and cannabidiol (CBD) to manage PD in France.

**Design**. A cross-sectional study.

**Methods**. An online survey was conducted among healthcare professionals actively managing patients with PD in France. Logistic regressions were performed to identify factors associated with their acceptability of cannabis and CBD use to manage PD.

**Results**. The study population comprised 218 professionals, including 45 physicians. Acceptability levels were greater for CBD than for cannabis. Providers very concerned about cannabis dependence were less likely to agree with cannabis use to manage PD. Physicians were 87% and 90% less likely than other providers to agree with the use of cannabis and CBD, respectively, to manage PD. Among physicians, the primary barrier identified to the use of both substances was a lack of evidence to support their therapeutic effectiveness.

**Conclusion**. Physicians' acceptability of cannabis and CBD for therapeutic use to manage PD was lower than for other healthcare providers. Acceptability was generally higher for CBD than cannabis.

**Relevance to clinical practice**. To mitigate reluctance about discussing the possible use of cannabis-based products to manage PD, people living with the disease may prefer to talk to non-physician healthcare providers; the latter should be adequately prepared for such conversations. Irrespective of their stance on cannabis-based products, physicians should be trained on cannabinoid use and should proactively initiate discussions on this topic with patients to ensure they receive appropriate guidance.



**Keywords**: Parkinson's disease; cannabis; cannabidiol; physicians


**What does this paper contribute to the wider global community?**

- This study addresses, for the first time, the issue of healthcare providers' acceptability of cannabis-based products to manage Parkinson's disease in France
- We found that acceptability levels were higher in non-physicians, and that general healthcare provider acceptability was higher for cannabidiol than cannabis

## Introduction

People with Parkinson's disease (PD) often experience a reduced quality of life (QoL)[1] due to associated symptoms[2–4]. Treatment side effects can further decrease QoL[3,5,6]. When standard treatments are insufficiently effective or have side effects, some patients turn to alternative remedies, such as cannabis and cannabidiol (CBD), whether medically prescribed or not. Systematic reviews and a meta-analysis have highlighted the potential of these products to relieve symptoms and improve QoL [7–9]. However, solid evidence is still needed[10,11].

Patients with PD who use cannabis-based products outside of medical supervision [12–18] risk adverse effects, including drug-drug interactions with prescribed medications [19,20]. Healthcare provider support is therefore essential not only for the safe integration of cannabis-based therapies in PD care in contexts where these therapies are legal, but also for contexts where the use of cannabis-based products for therapeutic reasons is not legal. Even in jurisdictions with authorized medical cannabis programs, patients may face reluctance from healthcare providers to prescribe or support its use, as highlighted by data from Canada[21–23], and in Rønne et al.'s systematic review[24]. For example, a survey among international neurologists primarily from the US found that although 95% had been asked to prescribe medical cannabis by patients, only 39% encouraged its use[25]. This reluctance may stem from providers' lack of knowledge[26–28], or their fear that medical cannabis users will be socially stigmatized [29].

In France, products containing tetrahydrocannabinol (THC) are prohibited, except within the framework of a national medical cannabis experimental project which started in 2021. This project aims to evaluate the feasibility of providing medical cannabis to individuals with severe chronic conditions who do not respond to conventional treatment[30]. PD is not included among the list of eligible conditions, despite patient-reported benefits[12,31]. Unlike THC, CBD is legal in France despite recent legal to-ing and fro-ing. Approximately 10% of the adult population uses CBD[32,33] which is typically marketed as a wellness or complementary health product, and is available in various forms including oils, creams, and THC-free cannabis flowers.

There is a lack of data on French healthcare providers' attitudes towards cannabis-based products to manage PD. In a context where PD might be considered for inclusion in future French medical cannabis programs, it is essential to collect healthcare providers' current perspectives on these products. We aimed to examine the acceptability, knowledge, and perceptions of healthcare providers regarding the therapeutic use of cannabis and CBD for PD in France, as well as barriers to their agreeing with this therapeutic use.

# Material and methods

## Study design and participants

A cross-sectional online survey was conducted from 16 September 2023, to 30 January 2024 utilizing the Voxco survey platform. Inclusion criteria were being a healthcare provider in France and actively managing patients with PD. The survey link was displayed through multiple channels. One was the France Parkinson association website (https://www.franceparkinson.fr/). Created in 1984 and a member of the European Parkinson's Disease Association, France Parkinson is a national association recognized as being of public benefit, with 75 local committees throughout French territory.

Besides publicizing the survey link, invitations to participate in the survey were sent by email to approximately 5000 professionals in healthcare, social, and medico-social sectors via their professional mailing list. Additionally, regional unions representing general practitioners, nurses, pharmacists, physiotherapists, and speech therapists were contacted by email or through their websites to disseminate the survey. National and local neurologist societies and neurology networks were also asked to forward the survey link to their members. Participants were encouraged to share the survey link to increase reach and participation.

The survey was designed in accordance with the declaration of Helsinki, and was approved by the INSERM ethics committee (IRB00003888, CD/EB 23-045, 4 April 2023). Before accessing the survey questionnaire, participants had to provide informed consent.

## Questionnaire and data collection

The self-administered online questionnaire collected data on socio-demographic characteristics (age, gender, city size), and practice details (occupation, private or public sector, number of PD patients, years of experience with PD patients). Participants' cannabinoid knowledge was assessed using four *ad hoc* statements with three response options (True/False/Do not know), resulting in a score ranging from 0 (no correct answer) to 4 (four correct answers) (**Supplementary Table 1**).

In the survey, cannabis was defined as containing THC above the French authorized threshold (0.3%), while CBD was defined as any product containing CBD with THC levels at or below this threshold.

Acceptability levels of cannabis and CBD were assessed using two questions for each: i) "Might you encourage the use of (quality-controlled) medical cannabis [respectively, CBD] for Parkinson's disease if it were only available on prescription?"; and ii) "Might you encourage the use of (quality-controlled) medical cannabis [respectively, CBD] for Parkinson's disease if

it were available without prescription (i.e., over the counter)?". Respondents could answer Yes/No/Do not know to each question. For each of the two substances, acceptability was categorized as 'moderate' for one 'Yes' answer, 'high', when both answers were 'Yes', and 'low' for all other situations.

The perceived risk of cannabis dependence was assessed by asking: "In your opinion, how great is the risk of becoming dependent on cannabis?" with six possible response options. Participants' views on the current legal status of cannabis in France were evaluated through two questions: "Are you in favor of easing legal restrictions on the medical use of cannabis in France?" and "Are you in favor of easing legal restrictions on the non-medical use of cannabis in France?", each with three possible responses. Barriers to the therapeutic use of cannabis and CBD for PD were assessed using the question: "What are the barriers currently preventing you from agreeing with the use of cannabis [respectively CBD] for therapeutic purposes for Parkinson's disease (that is to say, outside of official recommendations)?" Participants could choose one to five responses from fifteen and thirteen options for cannabis and CBD, respectively.

## Statistical analyses

Participants' characteristics were compared based on their occupation which we dichotomized into two groups: physicians and non-physicians. This choice was based on the assumption that physicians would have different views on cannabis-based products as they are the only professionals who can prescribe medications. Chi-square and Mann-Whitney tests were used for categorical and continuous variables, respectively.

Two separate binary logistic regression models were run - one for cannabis and the other for CBD - using a binary outcome: moderate/high versus low acceptability (with low acceptability as the reference category). Explanatory variables included age, gender, city size, occupation (i.e., physician or non-physician), practice sector (i.e., public or private), number of PD patients, years of experience managing PD patients, cannabinoid knowledge (scored from 0 to 4), and perception of the risk of cannabis dependence. Variables were initially selected based on a p-value threshold of <0.20 (Wald test) in univariable analyses. A backward selection procedure was then employed to finalize the two multivariable models, with a significance threshold of 0.05. To ensure comparability, a common set of variables was included in the final multivariable models. Any variable retained in at least one of the initial multivariable models was retained in the final models, regardless of its p-value.

Answers to the two questions on position regarding the current legal status of cannabis in France and barriers to its use were compared between the two groups using a Chi-square test.

# Results

## Study sample characteristics

The survey was completed by 218 participants (79.4% women, median [interquartile range (IQR)] age 41 [34, 50] years (**Table 1**). Participants accessed the survey through various channels, listed here in descending order of frequency: 'other' channels (39.0%), the France Parkinson association (26.6%), neurology networks (20.6%), and healthcare providers (13.8%). The study population comprised 82 speech therapists, 58 physiotherapists, 45 physicians (including 42 neurologists), 21 nurses, three dieticians, three occupational therapists, two neuropsychologists, one pharmacist, one clinical psychologist, one psychomotor therapist, and one naturopath. Physicians therefore represented 20.6% of the study population; they differed significantly from other participants across all the surveyed characteristics except for the perceived risk of cannabis dependence, where the difference was not statistically significant (p=0.101).

One quarter (27.5%) of the study population had low acceptability of cannabis for PD management; 11.9% had low acceptability for CBD (**Table 1**). The proportion of physicians with low acceptability was higher compared to non-physicians for both substances (p<0.001, z-proportion test). The proportion of low acceptability was significantly higher for cannabis than for CBD in both sub-populations (p≤0.020, z-proportion test). Answers to the separate acceptability questions can be found in **Supplementary Table 2**.

## Factors associated with acceptability of medical cannabis and CBD

The results of the multivariable analyses are summarized in **Table 2**. For both cannabis and CBD, moderate/high acceptability was inversely associated with being a physician (adjusted odds ratio (aOR) [95% confidence interval (CI)] 0.13 [0.06;0.28], p<0.001; 0.10 [0.04;0.27], p<0.001, respectively). Participants who considered that there was a very serious risk of becoming dependent on cannabis were 75% less likely to report moderate/high cannabis acceptability (aOR [95% CI] 0.26 [0.08;0.88], p=0.031).

## Positions regarding the legal status of cannabis and barriers to use

The vast majority (71.6%) of participants supported easing legal restrictions on medical cannabis use in France. However, support for reducing restrictions on non-medical use was considerably lower, at 23.9%. Physicians were significantly less likely to favor easing legal restrictions in both cases, as shown in **Table 1**.

The top three barriers to agreeing with the use of therapeutic cannabis for PD as reported by physicians were: 'the absence of recommendations from medical authorities'

(82.2%), ‘a lack of evidence to support its effectiveness’ (80.0%)’, and ‘a fear of psychoactive effects (i.e., drug *highs*)’ (62.2%). Among non-physicians, the most cited barriers were ‘a fear of drug-drug interactions’ (63.0%), ‘a lack of information (61.8%), and ‘the absence of recommendations from medical authorities’ (50.3%) (**Table 3**).

The three most cited barriers to agreeing with the use of therapeutic CBD for PD were ‘the absence of recommendations from medical authorities’ (84.4%), ‘a lack of evidence to support its effectiveness’ (77.8%)’, and ‘a lack of information about proper usage’ (53.3%) for physicians. Among non-physicians, the primary barriers were ‘a lack of information about proper usage’ (78.0%), ‘the absence of recommendations from medical authorities’ (61.3%), and ‘a fear of drug-drug interactions’ (59.5%) (**Table 3**).

For physicians, ‘a lack of evidence to support its effectiveness’ was overwhelmingly the primary barrier to agreeing with the use of both cannabis and CBD for the therapeutic management of PD, while no singular primary barrier stood out among non-physicians (**Supplementary Table 3**).

## Discussion

This is the first study to investigate acceptability, knowledge and perceptions regarding therapeutic cannabis and CBD use for PD among French healthcare providers. Acceptability of cannabis use in physicians – the only participants interviewed who could prescribe medications – was lower than for other healthcare providers, with a lack of evidence to support its effectiveness emerging as a major barrier. Similar differences between physicians and non-physicians were observed for the acceptability of using CBD. For both groups, acceptability rates for CBD were higher than for cannabis.

Differences in attitudes towards medical cannabis between physicians and non-physicians have been highlighted in previous research. In their systematic review of healthcare providers’ beliefs, knowledge, and concerns about medical cannabis, Gardiner et al. reported that nurses and other allied health professionals were “largely supportive of medicinal cannabis”. No such result was given for medical practitioners[26]. In a study involving clinicians from the District of Columbia, nurse practitioners were more likely to acknowledge a medical role for cannabis than oncologists[27]. Another systematic review indicated that physicians with specialties - reflecting our interviewed sample of physicians - were less supportive of the legal use of medical cannabis[24]. Our findings broaden these observations to include CBD-based products.

There have been relatively few studies exploring healthcare providers’ attitudes towards therapeutic cannabis use specifically for PD. Bega et al. reported that among an

international sample of 56 PD neurologists, 10% had recommended cannabis use to their patients, with 39% endorsing its use when requested by patients[25]. In a quota-based survey conducted among US-based neurologists, pharmacists, nurses, and nurse practitioners, Szaflarski et al. revealed that neurologists generally held less favorable views on therapeutic cannabis for PD than nurses and nurse practitioners. They also noted that attitudes across all professions surveyed were linked to their levels of knowledge about cannabis[28].

The less favorable attitude of physicians towards the therapeutic use of cannabinoids for PD may stem partially from their deeper understanding of potential adverse effects, such as cognitive impairment[34] and drug-drug interactions[19], which could be prevalent among self-medicated patients (i.e, whether for PD or another condition) [35]. However, the primary barriers to agreeing with the use of cannabis and CBD for the therapeutic management of PD cited by physicians in our study seemed to be largely driven by the lack of robust scientific evidence and official recommendations. These barriers were less frequently reported by non-physicians. The fact that in our sample physicians were older may also have had an effect on their acceptability, as older age may be correlated with higher risk perception in terms of cannabis use [36–38].

In a previous study involving general practitioners in France, having a good knowledge of the effects of cannabinoids was associated with a willingness to become a medical cannabis prescriber [39]. The low levels of acceptability found in physicians in our study may therefore be at least partly attributed to a lack of knowledge, as illustrated by the substantial proportion of respondents who declared the lack of information about proper usage as a barrier to use. The fear of drug-drug interactions, cited less often, may also stem from a lack of knowledge about them. Rønne et al. also identified a knowledge gap in their study of physicians[24].

There is currently no formal education on cannabinoids in French healthcare curricula. Previous studies have shown that brief educational interventions can effectively enhance healthcare providers' knowledge and shift their attitudes regarding the possible benefits of cannabis-based medicine[35,40]. Incorporating such training into healthcare education programs could meet the demand for greater understanding of cannabinoids[25,26] and interrupt reliance on erroneous beliefs when prescribing or when providing guidance[27,41], all within the context of the goal of improving patient QoL.

Irrespective of the type of provider (i.e., physician or non-physician), we observed that perceiving the risk of cannabis dependence as very serious was associated with poor acceptability of using medical cannabis for PD. This reflects Bega et al.'s study where 84% of participants perceived cannabis as potentially addictive[25]. A recent meta-analysis by Dawson

et al. estimated the prevalence of cannabis use disorder at 25% among users of medical cannabis[42]. However, it included participants using cannabis for “medicinal reasons”, a term which does not necessarily reflect medical supervision (i.e., versus self-medication) of dosages and frequencies. Moreover, their meta-analysis did not exclude dual use motives (i.e. recreational and medical). The authors also noted that younger age may be a risk factor for cannabis use dependence, which is important when considering that PD affects older people. Moreover, following appropriate training, clinicians may be able to reduce dependence risks by implementing key recommendations such as proper screening of patients and monitoring of medical cannabis use[43].

Healthcare providers' opinions on legalizing medical cannabis may influence political decisions regarding its authorization. In our study, we observed significant differences in attitudes between physicians and non-physicians. Specifically, while 42.2% of physicians supported easing legal restrictions on medical cannabis use in France, 79.2% of other healthcare providers endorsed this stance. Szaflarski et al. reported that over 80% of healthcare providers in their study agreed that cannabis products for medical purposes should be legal if prescribed by a medical provider[28]. Similarly, in Bega et al.’s study, nearly 70% of neurologists expressed belief that cannabis should be permissible for medicinal prescribing[25].

The hesitance among French physicians to support loosening legal restrictions on medical cannabis may stem from doubts about its therapeutic value, as indicated by our analysis of barriers to use. A study of general practitioners in France also suggested that physicians might oppose the legalization of medical cannabis due to concerns over potential risks to their own security[41]. Additionally, physicians are wary that legalizing medical cannabis could lead to broader legalization of non-medical cannabis use[41].

We found that non-physician healthcare providers generally held a positive view towards the use of cannabis-based products; whereas physicians in France were less supportive. Should there be changes in French regulatory framework allowing access to cannabis-based products for therapeutic purposes, our findings suggest that a model granting physicians discretion to determine specific indications for cannabis prescriptions (a practice common in many jurisdictions[44]) may not effectively facilitate access for people with PD. Our results highlight the need for specific evidence-based guidelines from medical institutions and proper training to garner physician support for such practices. This requirement appears particularly crucial for cannabis compared to CBD, suggesting a more nuanced situation for CBD.

Another implication of our findings is that, as long as CBD and cannabis remain somehow accessible outside of medical prescriptions in France, it is essential for physicians, regardless of their personal views, to engage openly in discussions about these substances with people with PD. This proactive approach is necessary to prevent or mitigate potential adverse effects associated with cannabinoid use. Without establishing a non-judgmental and supportive dialogue, patients may opt to conceal their use of such substances from their physician[21,45,46], or may seek advice from non-physician healthcare providers who are generally more receptive to their use. For example, nurses often demonstrate better listening skills, are less inclined towards top-down decision-making, and hold a more positive view towards cannabis-based products, thereby potentially reducing stigma, compared to physicians[29,47,48]. However, these healthcare professionals may lack comprehensive education on this topic in their training, which could hinder their ability to effectively counsel patients, particularly on the risks of drug interactions. Given the higher acceptability of CBD compared to cannabis, healthcare professionals may find it easier to use CBD as a gateway to initiate discussion with the patients about cannabis-based products.

The primary strength of our study lies in its pioneering nature, being the first to investigate healthcare providers' perspectives on cannabis-based products for PD within France's restrictive legal framework. Additionally, we successfully collected and compared responses from both physicians and non-physician healthcare providers, thereby revealing distinctions based on occupation. Furthermore, our study comprehensively assessed both cannabis and CBD, with the latter receiving comparatively less scrutiny regarding its acceptability among healthcare providers. However, the relatively modest sample size may have limited our ability to identify other factors influencing the acceptability of cannabis and CBD. Moreover, the broad range of professions within the 'non-physician' category necessitates a careful interpretation and cautious generalization of our findings.

## Conclusion

Our study highlights that among a sample of healthcare providers in France, physicians showed lower acceptability towards cannabis and CBD for therapeutic use in PD compared to other healthcare professions. CBD was generally more accepted than cannabis. If cannabis-based products were to be authorized for symptom alleviation in PD patients, physicians may require more robust scientific evidence and training before prescribing these treatments.

**Table 1. Study sample characteristics according to their occupation (physicians/non-physicians) (n=218)**

| Variables | **Total sample N (%)** | **Physicians N (%)** | **Non-physicians N (%)** | **p-value[1]** |
|---|---|---|---|---|
| **Total** | 218 (100) | 45 (100) | 173 (100) | |
| **Gender** | | | | <0.001 |
| Men | 45 (20.6) | 22 (48.9) | 23 (13.3) | |
| Women | 173 (79.4) | 23 (51.1) | 150 (86.7) | |
| **Age** (in years, median [IQR]) | 41 [34;50] | 47 [39;53] | 40 [32;50] | 0.003 |
| **Age** (in years, by quartile) | | | | 0.054 |
| 23-34 | 58 (26.6) | 6 (13.3) | 52 (30.1) | |
| 35-41 | 54 (24.8) | 11 (24.4) | 43 (24.9) | |
| 42-50 | 52 (23.9) | 11 (24.4) | 41 (23.7) | |
| 51-75 | 54 (24.8) | 17 (37.8) | 37 (21.4) | |
| **Area of residence** | | | | <0.001 |
| Rural area | 63 (28.9) | 1 (2.2) | 62 (35.8) | |
| Medium-sized city | 87 (39.9) | 16 (35.6) | 71 (41) | |
| Large city (>200 000 inhabitants) | 68 (31.2) | 28 (62.2) | 40 (23.1) | |
| **Type of practice** | | | | <0.001 |
| Public only | 60 (27.5) | 38 (84.4) | 22 (12.7) | |
| Private (with or without public practice) | 158 (72.5) | 7 (15.6) | 151 (87.3) | |
| **Number of PD patients currently followed** | | | | <0.001 |
| <10 | 152 (69.7) | 3 (6.7) | 149 (86.1) | |
| ≥10 | 66 (30.3) | 42 (93.3) | 24 (13.9) | |
| **Number of years of experience with people with PD** | | | | 0.029 |
| <5 | 44 (20.2) | 5 (11.1) | 39 (22.5) | |
| 5-9 | 45 (20.6) | 6 (13.3) | 39 (22.5) | |
| 10-19 | 71 (32.6) | 15 (33.3) | 56 (32.4) | |
| ≥20 | 58 (26.6) | 19 (42.2) | 39 (22.5) | |
| **Cannabinoid knowledge (median [IQR])** | 4 [3;4] | 4 [3;4] | 4 [3;4] | 0.047 |
| **Cannabinoid knowledge (mean)** | 3.25 | 3.55 | 3.17 | 0.033[2] |
| **In your opinion, how great is the risk of becoming dependent on cannabis?** | | | | 0.101 |
| There is no risk | 5 (2.3) | 0 (0) | 5 (2.9) | |
| Weak | 21 (9.6) | 7 (15.6) | 14 (8.1) | |

| | | | | |
|---|---|---|---|---|
| Moderate | 51 (23.4) | 14 (31.1) | 37 (21.4) | |
| Serious | 81 (37.2) | 18 (40) | 63 (36.4) | |
| Very serious | 45 (20.6) | 5 (11.1) | 40 (23.1) | |
| I do not know | 15 (6.9) | 1 (2.2) | 14 (8.1) | |
| **Cannabis acceptability status** | | | | <0.001 |
| Low acceptability | 60 (27.5) | 26 (57.8) | 34 (19.7) | |
| Moderate acceptability | 108 (49.5) | 16 (35.6) | 92 (53.2) | |
| High acceptability | 50 (22.9) | 3 (6.7) | 47 (27.2) | |
| **Cannabidiol acceptability status** | | | | <0.001 |
| Low acceptability | 26 (11.9) | 15 (33.3) | 11 (6.4) | |
| Moderate acceptability | 80 (36.7) | 19 (42.2) | 61 (35.3) | |
| High acceptability | 112 (51.4) | 11 (24.4) | 101 (58.4) | |
| **Are you in favor of alleviating legal restrictions on medical use of cannabis in France?** | | | | <0.001 |
| No | 26 (11.9) | 15 (33.3) | 11 (6.4) | |
| Yes | 156 (71.6) | 19 (42.2) | 137 (79.2) | |
| I do not know | 36 (16.5) | 11 (24.4) | 25 (14.5) | |
| **Are you in favor of alleviating legal restrictions on non-medical use of cannabis in France?** | | | | <0.001 |
| No | 91 (41.7) | 31 (68.9) | 60 (34.7) | |
| Yes | 52 (23.9) | 3 (6.7) | 49 (28.3) | |
| I do not know | 75 (34.4) | 11 (24.4) | 64 (37) | |

IQR, interquartile range; PD, Parkinson's disease.

[1]Chi-square test for categorical variables, and Mann-Whitney test for continuous variables.

[2] Student's t-test

**Table 2. Factors associated with high or moderate cannabis and cannabidiol acceptability levels (n=218, multivariable logistic regression models)**

| | **Cannabis** | | **Cannabidiol** | |
|---|---|---|---|---|
| | aOR [95% CI] | p-value | aOR [95% CI] | p-value |
| **Healthcare occupation** | | | | |
| Non-physician | 1 | | 1 | |
| Physician | 0.13 [0.06;0.28] | <0.001 | 0.10 [0.04;0.27] | <0.001 |
| **In your opinion, how great is the risk of becoming dependent on cannabis?** | | | | |
| There is no risk/Small risk | 1 | | 1 | |
| Moderate risk | 1.3 [0.37;5.49] | 0.681 | 1.46 [0.33;6.46] | 0.615 |
| Serious risk | 0.67 [0.21;2.12] | 0.500 | 1.56 [0.38;6.35] | 0.535 |
| Very serious risk | 0.26 [0.08;0.88] | 0.031 | 1.18 [0.23;5.91] | 0.843 |
| I do not know | 0.45 [0.09;2.22] | 0.330 | 0.23 [0.04;1.30] | 0.096 |

aOR, adjusted odds ratio; CI, confidence interval

**Table 3: Barriers to therapeutic use of cannabis and cannabidiol of participants according to their occupation (i.e., physicians vs non-physicians) (n=218)**

| | Cannabis | | | Cannabidiol | | |
|---|---|---|---|---|---|---|
| | Physicians | Non-physicians | p-value[1] | Physicians | Non-physicians | p-value[1] |
| | Cited N (%) | Cited N (%) | | Cited N (%) | Cited N (%) | |
| Putting oneself or one's patients in an illegal situation | 14 (31.1) | 86 (49.7) | 0.026 | - | - | - |
| Fear that patients would become dependent on the substance | 16 (35.6) | 62 (35.8) | 0.972 | 2 (4.4) | 26 (15) | 0.059 |
| Fear of psychoactive effects (i.e., drug *highs*) | 28 (62.2) | 85 (49.1) | 0.117 | 5 (11.1) | 20 (11.6) | 0.933 |
| Fear of drug-drug interactions | 6 (13.3) | 109 (63) | 0.000 | 7 (15.6) | 103 (59.5) | 0.000 |
| Fear of other adverse effects | 20 (44.4) | 81 (46.8) | 0.776 | 13 (28.9) | 89 (51.4) | 0.007 |
| Lack of evidence to support its effectiveness | 36 (80) | 36 (20.8) | 0.000 | 35 (77.8) | 73 (42.2) | 0.000 |
| Lack of information about proper usage | 16 (35.6) | 107 (61.8) | 0.002 | 24 (53.3) | 135 (78) | 0.001 |
| Difficulties in supply | 4 (8.9) | 20 (11.6) | 0.610 | 2 (4.4) | 11 (6.4) | 0.629 |
| Cost of substance | 4 (8.9) | 31 (17.9) | 0.142 | 12 (26.7) | 47 (27.2) | 0.946 |
| The lack of recommendations from medical authorities | 37 (82.2) | 87 (50.3) | 0.000 | 38 (84.4) | 106 (61.3) | 0.003 |
| My colleagues' reluctance | 0(0) | 0(0) | - | 1 (2.2) | 0 (0) | - |
| My relatives' reluctance (other than colleagues) | 0(0) | 0(0) | - | 0 (0) | 2 (1.2) | - |
| Fear of stigmatization (social disapproval) of patients | 1 (2.2) | 9 (5.2) | - | 0 (0) | 13 (7.5) | - |
| Fear of stigmatization (social disapproval) of myself | 0 (0) | 1 (0.6) | - | 0 (0) | 5 (2.9) | - |
| Its form/mode of administration (e.g., dried herb/resin) is poorly adapted to certain patients | 2 (4.4) | 28 (16.2) | 0.042 | - | - | - |

[1] Chi-square test

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