



Individual application patterns of Cannabis-based Medicines in Germany – Descriptive evaluation of a patient survey and discussion from a forensic perspective

Marica Hundertmark^{a,1,*}, André Ihlenfeld^b, Assaf Landschaft^c, Jörg Röhrich^a, Tanja Germerott^a, Cora Wunder^{a,2}

^a Department of Forensic Toxicology, Institute of Legal Medicine, University Medical Center, Am Pulverturm 3, Mainz D-55131, Germany

^b Anaesthesiology and Intensive Care Medicine, Berlin, Germany

^c Fraunhofer Institute for Intelligent Analysis and Information Systems (IAIS), Schloss Birlinghoven 1, Sankt Augustin D-53757, Germany

ARTICLE INFO

Keywords:

Cannabis based medicines
THC
Medicinal cannabis flowers
Individual application patterns
Cross-sectional observational study
Forensic-toxicological assessments

ABSTRACT

Background: An increasing number of countries have legalised cannabis for medicinal purposes in recent years leading to tensions with other regulatory frameworks. Some countries grant a medical defence according to their drug driving legislations. This may lead to specific medico-legal assessments relating to the participation of cannabis patients in road traffic. In Germany, these enquiries for expert opinions are opposed by incomplete statistics on medicinal cannabis patients, which limits the assessment of individual cases.

Methods: A cross-sectional, anonymous patient survey was carried out nationwide in the first quarter of 2022 using an online questionnaire. The overall collective (n = 1030) was analysed with regard to application patterns of cannabis-based medicines. In particular, a detailed evaluation of the cannabis flower sub-collective was carried out.

Results: Taking into account patients with health insurance prescription and, for the first time, self-payers, a high proportion of cannabis flower patients was observed (89.9 %). On average, the intake of cannabis flowers is associated with substantially higher daily THC doses (336 mg) compared to the usage of other cannabis-based medicines (≤ 17 mg). In addition, 16.2 % of patients reported complex usage patterns consisting of combinations of different types of cannabis-based medicines. Over a quarter (28.4 %) of respondents stated a smoking intake of cannabis flowers which is not recommended from a medicinal point of view.

Conclusions: Descriptive information on individual application patterns of cannabis-based medicines provide a valuable source of information for medico-legal expert statements as well as a basis for further research projects.

1. Introduction

In recent years, a rising number of countries have legalised cannabis for medical purposes. By 2021, 64 countries have developed provisions on the medicinal use of cannabis in their national legislation or at least developed corresponding guidelines [1]. The variety of cannabis-based medicines (CBM) ranges from a few licensed finished products to a multitude of unauthorised formulations. Sativex® is an oromucosal spray with a balanced CBD/THC-content which is authorised in

Germany to treat adult patients with spasticity due to multiple sclerosis. In Canada, it is also licensed for treatment of pain refractory to opiates in cancer patients. Nabilon is a synthetic THC-analogue marketed as Canemes® in Germany (Cesamet® in other countries) and can be prescribed to treat nausea and emesis associated with chemotherapy. Dronabinol, the pharmaceutical name for Δ^9 -THC, is available as finished product (Marinol®) and a formulated drug (drops and capsules). While dronabinol is authorised in its form as Marinol® in the US, it can also be prescribed as a 'no-label'-use in Germany [2].

* Corresponding author.

E-mail addresses: hundertmark@uni-mainz.de (M. Hundertmark), ihlenfeld@me.com (A. Ihlenfeld), assaf.landschaft@iais.fraunhofer.de (A. Landschaft), roehrich@uni-mainz.de (J. Röhrich), tanja.germerott@uni-mainz.de (T. Germerott), wunder@uni-mainz.de (C. Wunder).

¹ ORCID: 0009-0008-7261-6628

² ORCID: 0000-0002-5150-268X

An amendment of the German law in March 2017 allowed the prescription of extracts and medicinal cannabis flowers which are not approved under medicinal law. Moreover, the possibilities to prescribe CBM at the expense of the statutory health insurances were expanded. Costs can be covered in case of a serious illness in which no other appropriate therapeutic option is available after approval according to the Social Insurance Code [3]. Private health insurances also reimburse costs of CBM without the need for prior approval, provided that the eligibility criteria for cannabis therapy are met [4]. However, in case (statutory) health insurances refuse to grant cost coverage, a private prescription and a therapy as a self-payer is also possible [5]. At present, only incomplete statistics on medicinal cannabis patients in Germany are available including exclusively patients with reimbursement by statutory health insurances. On the one hand, prescription statistics are delivered by the National Association of Statutory Health Insurance Funds; on the other hand, the Federal Institute for Drug and Medical Devices carried out an anonymised five-year monitoring survey [6]. Comparing both of these sources, it furthermore becomes apparent that the monitoring survey has only collected incomplete data, which considerably limits its representativeness [7].

Depending on the national legislation, the introduction of cannabis as a medicine may create conflicts with drug-driving regulations under traffic law. In case of recreational legalisation THC-limits for impairment may be defined in blood which also apply to medicinal cannabis patients without exemptions [8]. Contrastingly, some countries with medical only access framework grant a medical exemption even though they have a zero-tolerance policy [9]. In Germany, medical cannabis patients are allowed to take part in road traffic as long as they do not show signs of impairment. The legislation includes a 'medical defence' stating that penalties will not be imposed if 'the substance (detected in blood serum) is derived from the intended use of a medicinal product prescribed for a specific case of illness' [10]. In context of such a 'medical defence' specific legal questions may arise regarding the participation of medicinal cannabis patients in road traffic, which are to be addressed as part of a forensic-toxicological assessment or by an expert witness in court. However, even from a forensic-toxicological point of view, answering such specific questions can be difficult in individual cases: In order to justify a recreational use, the protective claim of obtaining a prescription for medicinal cannabis may be made or prescriptions dated after the time of the incident may be presented. A typical assessment question can therefore be a differentiation between the intake of CBM and a recreational use which is currently only possible to a very limited extent analytically. In case of a prescription of extremely high quantities of medicinal cannabis flowers or non-recommended smoking as 'joint', the question of an 'intended use' in distinction to a misuse may arise. In contrast to a range of other central active pharmaceuticals, therapeutic ranges of THC in blood serum have not yet been established and daily THC-dosages can vary over a wide range, making it difficult to verify an intended use. From a forensic perspective, it would therefore be useful to know the modes of application and the magnitude of common THC-dose ranges, but corresponding statistics on medicinal cannabis patients are very incomplete in Germany.

This report therefore aims to analyse data regarding application patterns of CBM from a patient survey and to discuss the results from a forensic-toxicological point of view. A particularly common constellation is the assessment of self-paying patients with a prescription for cannabis flowers in combination with high THC concentrations detected in serum. Since so far there is no data available on self-payers, the application patterns of patients with cost coverage by health insurances and self-paying patients are to be compared. In particular, the patient sub-collective with a prescription for cannabis flowers is analysed in greater detail with regard to the type of flower prescribed and the modes of application.

2. Material and methods

2.1. General information on the patient survey

The non-interventional patient survey was carried out by Copeia GmbH between 17th January and 30th April 2022 [11]. Using a standardised online questionnaire, patients across Germany were asked about their course of treatment with CBM. Patients were recruited via a network of pharmacies (German Association of Cannabis Supplying Pharmacies e.V.), and associations of CBM-prescribing physicians (Professional Association of Physicians and Psychological Psychotherapists in Pain and Palliative Medicine in Germany e.V., Working Group Cannabis as Medicine e.V.). The practical implementation of the survey was carried out using a QR code, which was handed out to patients on an information sheet. This QR code took the participants directly to the web page (<https://copeia.de/cannabis-patientenbefragung>) of the survey. The survey was conducted interactively in the form of a dialogue and could be completed on a browser of a mobile phone, a tablet, a laptop or a stationary computer. Inclusion criteria were an age of at least 18 years and a medical prescription for CBM. Due to the study design of a non-interventional, retrospective study with the collection of anonymised data in compliance to data protection regulations, ethics approval was not required.

2.2. Statistical analysis

Raw data were provided by Copeia GmbH to the Institute of Legal Medicine in Mainz, which subsequently analysed the aspects presented here. Data were evaluated at a descriptive level using Microsoft Excel 365 (Version 16.83, ©2024) and SPSS (Version 23.0.0.3, ©2016).

2.3. Evaluation of the entire patient collective

2.3.1. Frequency of prescription for different types of CBM

The collective was analysed regarding the frequency of prescription for different types of CBM. The question "In what form were you prescribed CBM?" allowed the following answers: Cannabis flowers, cannabis extracts, dronabinol drops, dronabinol capsules, cannabidiol solution, cannabidiol capsules, Sativex® and Canemes®. In the evaluation, dronabinol (capsules and drops) and CBD (solution and capsules) were each recorded as one category. The possibility of obtaining a combination of several CBM was taken into account. Furthermore, a subdivision was made into patients with and without cost coverage by health insurances.

2.3.2. Daily THC doses

After specifying the type of CBM, the respondents were asked about the THC-content and the daily amount administered in ranges of usual dose units (e.g. millilitres, drops, weight). Exemplified for flowers, the following choices were possible: up to 100 mg, 101–300 mg, 301–500 mg, 501–750 mg, 751–1000 mg, 1–2 g, 2–3.5 g, more than 3.5 g, other/free text and unknown. The calculation of the daily THC dose was based on the THC-content of the specified preparation and the mean value of the given dose range (in the case of flowers, e.g. 75 mg, 200 mg, 400 mg, 625 mg, 875 mg, 1.5 g, 2.75 g, 4 g).

2.4. Detailed evaluation of patient sub-collective with prescription for medicinal cannabis flowers

If a prescription of cannabis flowers was indicated, subsequent questions asked about the type of flower obtained (answer options, THC/CBD: 25/1, 22/1, 20/1, 18/1, 14/1, 12/1, 10/10, 8/8, 1/8, 1/12, 1/14, other/free text, unknown) and the preferred route of administration (answer options: vaporising, smoking, edible administration, tea preparation and other/free text). Up to 4 flower varieties could be specified per patient, each with a route of administration. The

prescription frequency of the different flower types, the number of varieties prescribed per patient and the frequency of the different routes of administration were evaluated.

3. Results

3.1. General information on the patient survey

1582 patients participated in the survey. Only complete data sets (n = 1030) with consent of the respondents for data storage were included in the analysis (completion rate 65.1 %). The evaluable collective consisted of 72.9 % males, 26.0 % females and 1.1 % diverse patients. The proportion of (statutory) health insurance patients (46.1 %) and self-paying patients (53.9 %) in the sample was almost balanced. The participants were on average 42 years old (median 41, range 18–89).

3.2. Evaluation of the entire patient collective

3.2.1. Frequency of prescription for different types of CBM

Most of patients (83.8 %) were treated with only one type of CBM, although the remaining 16.2 % received a combination of several CBM (Fig. 1). A high percentage of patients were prescribed cannabis flowers (89.9 %), and of these patients 74.5 % were exclusively prescribed cannabis flowers. 15.5 % of respondents had a prescription for cannabis extracts out of which only 5.2 % stated the isolated intake of extracts. 8.1 % of participants reported taking dronabinol and 3.5 % of these patients were not prescribed other CBM besides dronabinol. The percentage of patients in the collective who were prescribed Sativex (4.3 %) and CBD (2.1 %) was lower. Notably low was the number of patients who took Sativex (0.4 %) or CBD (0.3 %) in isolation. In case of a combination of several CBM, the three most common combinations were cannabis flowers and extracts (6.7 %), cannabis flowers and dronabinol (2.6 %) and cannabis flowers and Sativex (1.7 %). The intake of the synthetic THC-analogue Canemes was reported by only one patient, in this case in combination with cannabis flowers.

The proportion of patients who were prescribed cannabis flowers was higher among self-payers (97.5 %) than among patients with cost coverage by health insurances (81.1 %). The prescription of a combination of several CBM was reported more frequently by patients with health insurance cost coverage (23.4 %) compared to self-paying patients (10.1 %).

3.2.2. Daily THC doses

Means, medians, minima and maxima of daily THC-doses depending on the type of CBM administered as well as age patterns of the sub-collectives are shown in Table 1. Median daily THC-doses of cannabis flowers are up to 19-fold higher compared to the intake of extracts, Dronabinol and Sativex (Mann-Whitney-U-Test $p < 0.001$). The intake of a combination of flowers and extracts resulted in significantly higher daily THC-doses compared to the isolated intake of flowers (Mann-Whitney-U-Test $p < 0.05$). The highest reported daily THC dose in the entire collective was 4071 mg (4000 mg in the form of flowers, 69 mg in the form of extracts, 3 mg as Sativex). It was reported by a 38-year-old male who has been prescribed CBM for 3–5 years for treatment of fibromyalgia on a health insurance prescription. Moreover, flower patients were the youngest sub-collective with a median age of 39 years.

Compared to cannabis flower patients without health insurance coverage, those with insurance coverage took higher THC doses per day (median 162 mg vs. 300 mg, Mann-Whitney-U-Test $p < 0.05$, Fig. 2).

3.3. Detailed evaluation of patient sub-collective with prescription for medicinal cannabis flowers

3.3.1. Types of cannabis flowers

Due to the possibility of providing multiple answers up to 4 flower types, a total of 1463 responses were received from the 926 patients underlining the fact that almost half of the patients were prescribed more than one variety (Fig. 3). The median age of patients of this sub-collective was 39 years old (range 18–78). The most common flower type was 22/1 (34.5 %), followed by 20/1 (20.4 %) and 25/1 (19.0 %). Flowers with lower THC-contents were mentioned less frequently (18/1:

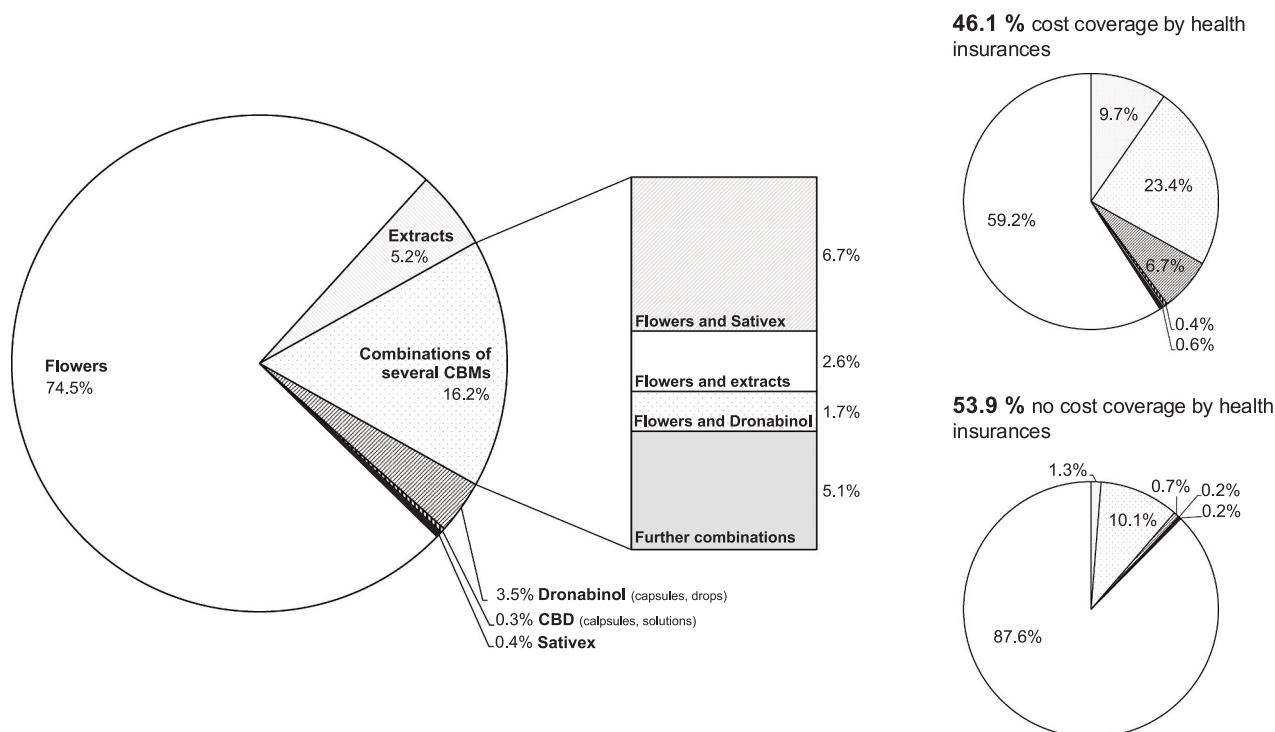


Fig. 1. Classification of the surveyed patient collective according to the type of CBM prescribed and subdivision of the collective depending on whether costs are covered by health insurances.

Table 1

Means, medians, minima and maxima of daily THC doses in mg depending on the type of CBM administered including the three most common combinations as well as age patterns of this sub-collectives. The table covers 91.5 % of the collective. No information on either THC content or dosage was provided for 3.2 %. 5.4 % of patients reported less frequent combinations and the remaining 0.3 % of the patients obtained exclusively CBD. For patients taking a combination of CBM, the daily dose proportion accounted for by the flowers is shown in square brackets [].

	Isolated administration of one type of CBM				Combination of several CBM (3 most common combinations)		
	Flowers (n = 760, 73.8 %)	Extracts (n = 48, 4.7 %)	Dronabinol (n = 34, 3.3 %)	Sativex (n = 4, 0.4 %)	Flowers and extracts (n = 61, 5.9 %)	Flowers and Dronabinol (n = 17, 1.7 %)	Flowers and Sativex (n = 17, 1.7 %)
Daily THC doses (mg)							
Median	193	12	10	12	373 [350]	188 [160]	333 [330]
Mean	336	15	13	17	466 [447]	492 [473]	544 [526]
Minimum	0.8	1.6	1.8	12	22 [15]	20 [15]	31 [6.0]
Maximum	3520	63	44	31	2680 [2640]	1960 [1900]	2094 [2063]
Age patterns							
Median	39	52	63	55	44	51	40
Mean	40	52	63	52	44	47	41
Minimum	18	23	40	36	25	23	23
Maximum	72	66	89	60	73	65	58

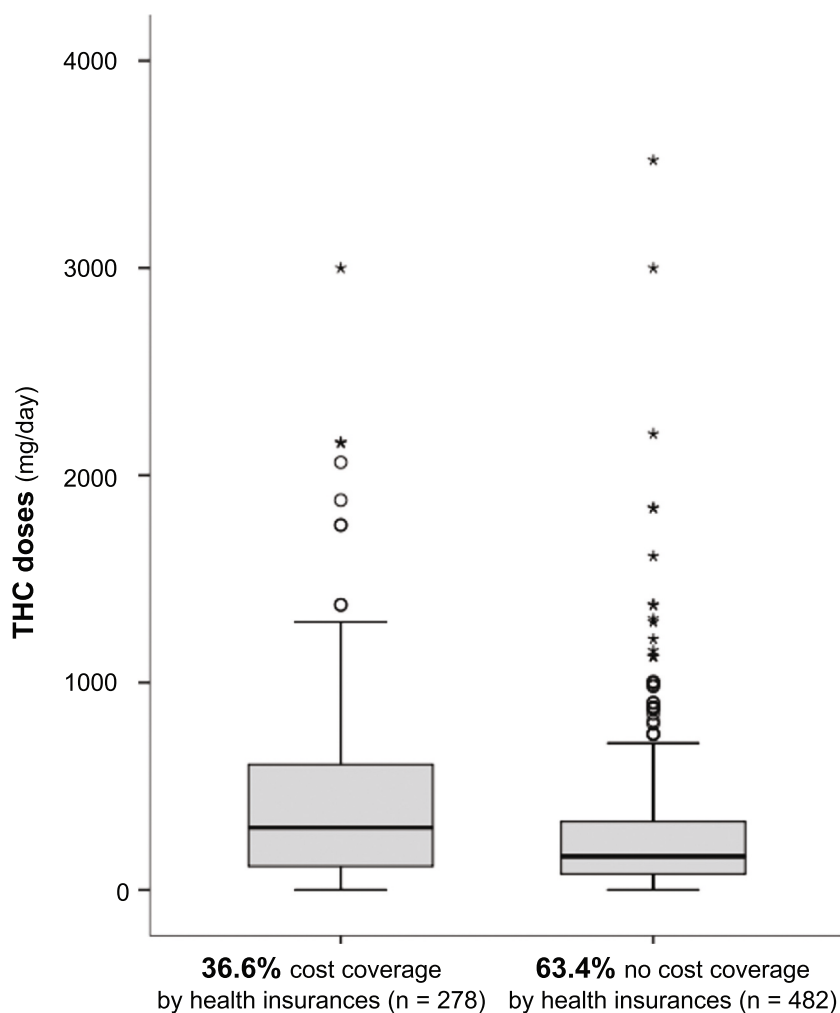


Fig. 2. Comparison of daily THC doses of patients with a prescription for cannabis flowers (73.8 %) depending on whether costs are covered by health insurances.

8.1 %; 14/1: 3.3 %; 12/1: 0.3 %). The two varieties with balanced THC/CBD content, 10/10 and 8/8, were named at 6.4 % and 3.9 % respectively. Only a small number of patients was treated with CBD-dominant material (1/8: 0.3 %; 1/12: 0.8 %; 1/14: 1.6 %). In 1.3 % of responses, an intake route or dose range was given without specifying the type of flower prescribed.

3.3.2. Routes of administration

Inhalation using a vaporiser was reported as most frequent route of administration (69.7 %, Fig. 4). Over a quarter of patients (28.4 %) stated that they smoke the flowers. Oral intake (edible administration 4.4 %; tea preparation 1.1 %) was mentioned considerably more seldom. 5.5 % of patients reported more than one route of

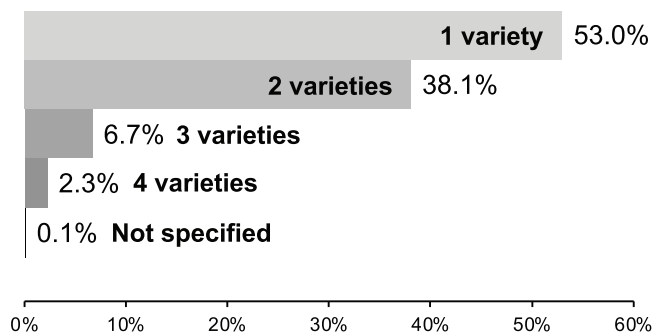


Fig. 3. Number of medicinal cannabis flower varieties per patient among the sub-collective of patients with a prescription for flowers.

administration, and a combination of smoking and vaporising (2.9 %) was most frequently mentioned. While more patients with health insurance coverage use a vaporiser (75.6 % vs. 65.4 %), more self-payers smoke the flowers (33.8 % vs. 21.0 %).

A detailed analysis of the patients with the isolated answer ‘smoking’ (n = 228, Fig. 5) shows that the proportion of therapy beginners among self-payers is higher than among patients with cost coverage by health insurances (duration of therapy ≤ 1 year: 28.7 % vs. 12.3 %). The age of the subgroup of ‘smoking patients’ was slightly below that of the overall flower patients, with a median of 36 years (range 19–70).

4. Discussion

In Germany, medical cannabis patients are granted exemptions from restrictions on driving under the influence of drugs. This requires specific medical and legal assessments of the participation of medicinal cannabis patients in road traffic, including difficulties in analytically differentiating between the uptake of CBM and a recreational

consumption as well as the verification of an ‘intended use’ due to the lack of therapeutic ranges for THC in blood serum. Thus closing the gaps in incomplete statistics on medicinal cannabis patients, especially regarding application patterns and usual THC-dose ranges, is desirable. The survey aimed to depict a representative cross-section of German cannabis patients in the first quarter of 2022 and, for the first time, also included self-paying patients. The collective is characterised by a high prevalence of patients with prescriptions for cannabis flowers (89.9 %), while other types of CBM are of secondary importance. These statistics are contradictory to data from the monitoring survey by the Federal Institute for Drug and Medical Devices and the National Association of Statutory Health Insurance Funds. In both of these sources Dronabinol prescriptions make up a higher proportion (62.2 %, [6] and 35.5 % [12] respectively), while prescriptions for flowers were recorded much less frequently (16.5 % [6] and 30.2 % [12] respectively). In particular, the high percentage among self-payers indicates that the prevalence of cannabis flower patients in Germany may have been greatly underestimated in the past.

This observation is in line with experience from the field of forensic toxicology since the majority of assessments relating to medicinal cannabis are requested in situations involving road traffic offences against patients with a prescription for medicinal cannabis flowers. In context of the ‘medical defence’ of German Traffic Law it may be of legal interest whether a differentiation between an intake of medicinal cannabis and a recreational consumption can be made. Such a ‘plausibility check’ on the basis of a blood sample taken during traffic control, as has already been enquired by prosecution authorities, is currently only possible to a limited extent. While there are approaches to differentiate between the intake of Sativex and Dronabinol based on minor cannabinoid profiles, in particular a distinction between the intake of medicinal cannabis flowers and a recreational use of herbal cannabis material is currently not yet analytically possible [13]. However, the data presented here demonstrates that the latter distinction is likely to

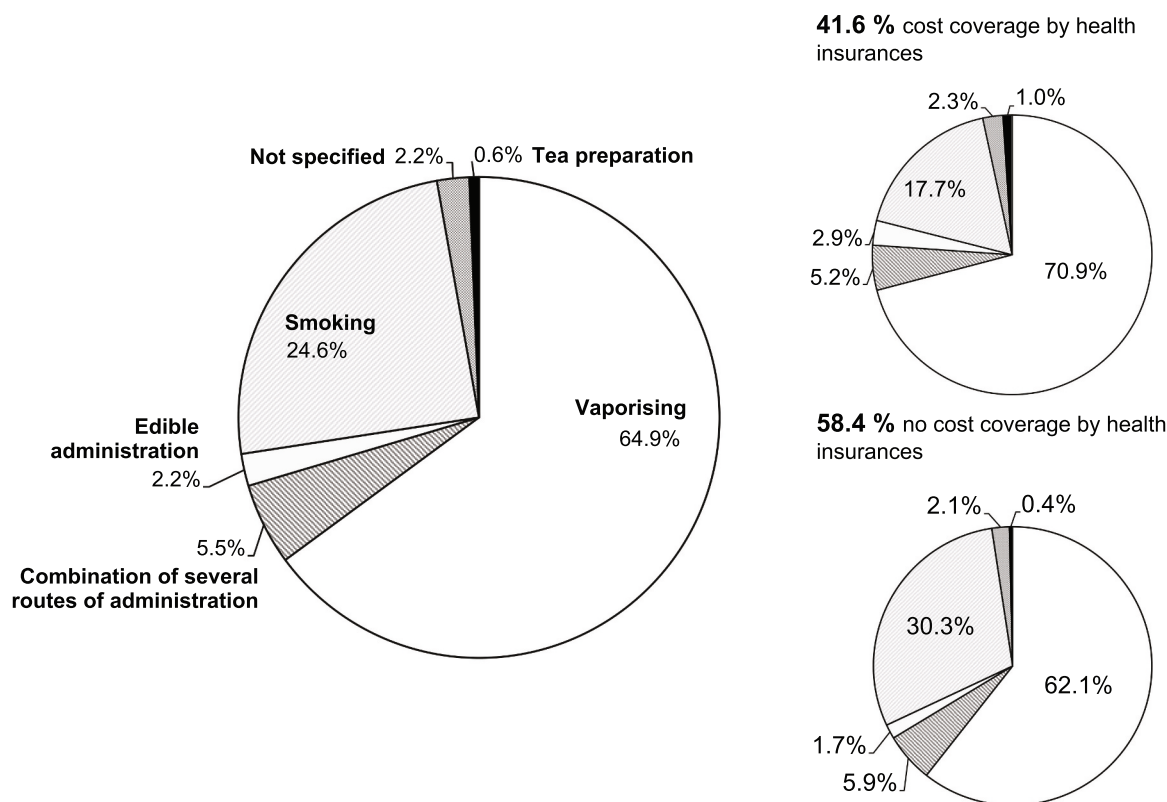


Fig. 4. Evaluation of the sub-collective with prescription of medicinal cannabis flowers by route of administration and subdivision of the collective depending on whether costs are covered by health insurances.

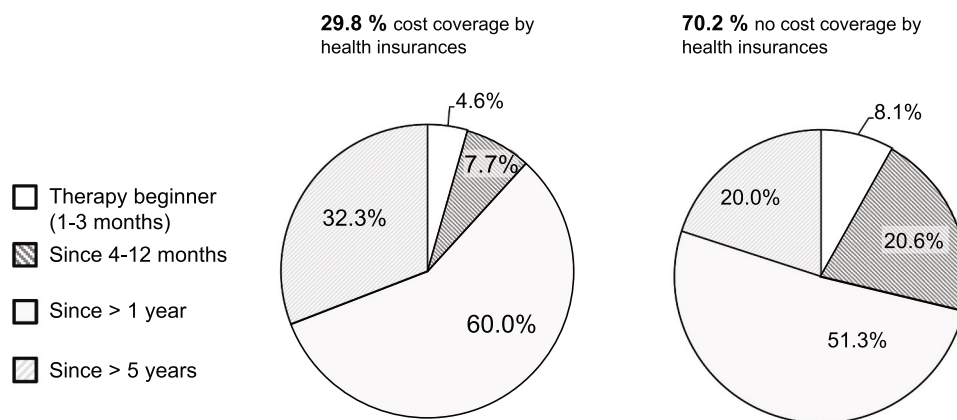


Fig. 5. Duration of therapy within the medicinal cannabis flower patient collective with the isolated response 'smoking' as a route of administration depending on cost coverage by health insurances.

be of highest relevance in practice. Likewise, it is currently subject to forensic-toxicological research projects using complex metabolomic approaches [14,15]. A desirable objective in the future could therefore be the development a refined, possibly even variety-specific, differentiation possibility of the consumed cannabis flower material by means of laboratory analysis based on blood samples. A noteworthy aspect is that application patterns of CBM may be more complex than previously assumed: While no combinations were reported in the governmental monitoring survey [6], 16.2 % of respondents in this collective stated the usage of several categories of CBM in parallel. Moreover, patients are often prescribed a combination of several flower types, on average 1.6 varieties. In a further survey conducted in 2020, as many as 66 % of German flower patients stated that they are treated with 2 varieties simultaneously. When asked about 'ever used', patients even indicated on average that they had used 5.9 strains (SD = 5.1, range 1–36) [5]. This finding may limit analytical differentiation approaches due to mixing effects. Finally, the question of differentiation may not always be trivial to answer, as further patient surveys show that motives for intake may represent a fluent transition between medicinal and recreational use. Furthermore, the major part of patients has previous experience with recreational use or (illegal) self-treatment attempts [5,16,17].

In cases undergoing forensic toxicological assessment, trends towards high daily THC doses and prescriptions of varieties with high THC-content are observed. Another remarkable finding against this background is the up to 19-fold increase in median daily THC dose when being treated with cannabis flowers (336 mg) compared to every other type of CBM. An analogous observation has already been described by the governmental monitoring survey. It was hypothesised that due to the rapid onset and short duration of action in case of inhalation, a different type of effect could be present [6]. Such daily doses are about an order of magnitude higher than THC individual doses of around 20–54 mg, which have usually been investigated in inhalative kinetic studies [18–21]. Interestingly, despite large fluctuations in THC dose ranges of both groups, self-payers tend to take slightly lower daily doses than patients with cost coverage by health insurances. As mentioned repeatedly in the free text field, the price of medicinal cannabis flowers can be a dose-limiting factor for self-paying patients or may even lead to co-consumption of non-medical material. However, its price has significantly declined since the cultivation of medicinal cannabis in Germany was controlled by the authorities at contractually agreed selling prices of around 10 euros per gram in 2021 [22]. Prices have thus equalised with those for 'street cannabis', which was sold between 6 and 25 euro per gram in 2021 [23]. Nonetheless, there has recently been a trend towards substantial increases in THC-contents in the prescribable flower material. These varieties also appear at the top of the prescription statistics [6]. According to an online survey of German patients using medicinal cannabis flowers in 2020, the most commonly prescribed strains were

Bedrocan (THC/CBD = 22/<1), Bakerstreet (19/<1) and Pedanios 22/1 [5]. Also in the present collective, the three flower types with the highest THC-contents (22/1, 20/1 and 25/1) were prescribed most frequently. While the maximum THC-content at the time of the survey was 25 % [24], flowers up to 31 % are currently available [22]. These THC-contents are significantly higher than the average content of seized herbal cannabis in Europe, which was around 10 % in 2021 [23]. Moreover, the market for medicinal cannabis is growing rapidly, with the number of available varieties increasing exponentially. While only 14 varieties were on offer in the first quarter of 2017 [25], there are currently several hundred varieties available [22].

Another typical forensic-toxicological assessment question, also against a background of high THC intake, refers to the 'intended use' of CBM. This issue can be discussed from various perspectives, including a legal or medical perspective. In forensic-toxicological assessments, the serum concentrations measured of a central active pharmaceutical is usually compared with its therapeutic range. So far, this is not possible with regard to THC due to the lack of such ranges. From a legal context, current assessment enquiries therefore often also focus on route of administration. According to medical recommendations, patients are advised to inhale cannabis flowers using a vaporiser or ingest them orally using tea preparations. It is not recommended to smoke the flowers due to the formation of toxic combustion products [26]. Furthermore, edible administration is not advised due to poorer dose-ability [27]. For this reason, it is especially remarkable that around a quarter of patients (28.4 %) reported an administration by smoking. This proportion is even higher in the sub-collective of self-payers (33.8 %). Since medically recommended vaporisers in Germany cost at least 300 euros [28], one possible reason could be that the 'expensive purchase' of a vaporiser is initially postponed until the therapy is regarded to be successful. Accordingly, a higher proportion of therapy beginners with the statement 'smoking' is observed among self-payers. Nevertheless, a significant proportion of the 'smoking' patients had been in treatment for more than 5 years (around a third of the patients covered by health insurance), which suggests that some may have already tried self-therapy and do not appreciate switching to the usage of a vaporiser. The combination of vaporising and smoking, however, as reported by around 3 % of the collective, is particularly questionable. In case of oral administration, medically non-recommended edible formulations were reported four times more frequently than tea preparations. In general, the data demonstrates that oral intake of flowers plays a minor role compared to inhaled intake.

From a medical point of view, the indication is decisive for the physician in choosing which application route and dose is suitable for a patient. An oral administration is appropriate for most, chronic conditions due to a slow onset and persistent effects whereas inhalative intake is preferable only in few, acute events such as spasms [29,30]. Due to the

better dosage and data availability as well as a lower risk of misuse, oral administration of finished products or standardised extracts is to be preferred over inhalative intake of cannabis flowers [27]. For cannabis flowers, there is a very imprecise dosage recommendation advising to start with low THC varieties and a quantity of 0.05–0.1 g (approx. 3–10 mg THC). Whilst this recommendation does not suggest any indication-specific routes of administration, ‘smoking’, ‘edibles’ and ‘tea preparations’ are listed as possibilities, ‘inhalation’ is not explicitly mentioned [31]. Contrastingly, current guidelines describe exclusively oral intake with usual THC dose ranges of 5–20 mg, in individual cases up to 40 mg. For dose finding, increases are usually made every 1–3 days until the desired symptom relief or unpleasant side effects are observed [30,32,33]. The application patterns observed are thus in substantial contrast to current medical prescription recommendations. It seems questionable why so many patients - possibly at their own explicit request - are prescribed flowers for inhalation. Also in other studies, it has already been noticed that the high-dose group consists mainly of young male patients. The medically incomprehensible doses suggest many years of ‘pre-experience’, an addiction or abuse [34]. The data presented here also reveal the trend that flower patients, who are taking by far the highest daily THC doses, also represent the youngest sub-population of cannabis patients. As the current prescription trends are now also being more critically questioned from a medical perspective, cannabis flower prescriptions at the expense of the statutory health insurances must be specifically justified since 2023 [35]. As an outlook, it will be interesting to see how the prescription trends in Germany will develop against the background of this decision and the recent partial legalisation of cannabis for recreational consumption [36].

4.1. Limitations of the data collection

As this evaluation focusses on assessing application patterns of CBM, a major advantage is that is the data collection from the patient’s perspective. Aspects for which no data was previously available, including self-payers, combinations of CBM and routes of applications, could be studied in greater detail. The collective is regarded as a representative sample of the point prevalence of treatment with CBM in Germany in the first quarter of 2022. However, due to the method of patient recruitment using QR codes and online questionnaires, it is conceivable that primarily younger patients were addressed (median 41 years). As the majority of patients reported a significant improvement in symptoms, it can be assumed that successful treatments were preferably covered and fewer treatment discontinuations were recorded than in the governmental monitoring survey. Furthermore, the truth of the statements cannot be verified. In order to further standardise the datasets and simplify their processing, the total THC daily dose was recorded in dose ranges. Although this allows for a rough but representative estimate, it should be emphasised that this is not an exact calculation. However, it is highly likely that the daily amount of THC administered is divided into several individual doses over the course of a day.

5. Conclusion

The patient survey indicates a high, possibly previously underestimated point prevalence of medicinal cannabis flower patients in Germany, especially among self-payers. In addition, these patients take significantly higher daily THC-doses (approx. 19-fold) than patients with prescriptions for other types of CBM. The individual application patterns and combinations of different types of CBM turned out to be extremely complex. The prescription statistics, predominantly high-dose inhalation intake of cannabis flowers, are in substantial contrast to current medical recommendations, advising a low-dose intake of oral preparations. In individual cases, doubts may arise relating to an ‘intended use’, taking into account the application route and doses, and misuse may be suspected. Finally, these descriptive statistics can be an important source of information for medical and legal assessments, a

critical impulse of thoughts for physicians as well as a basis for further forensic-toxicological research projects.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The survey was self-financed by Copeia GmbH (Bergisch Gladbach, Germany).

CRediT authorship contribution statement

Marica Hundertmark: Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **André Ihlenfeld:** Writing – review & editing, Resources, Methodology, Investigation. **Assaf Landschaft:** Software, Formal analysis, Data curation. **Jörg Röhrich:** Writing – review & editing, Conceptualization. **Tanja Germerott:** Writing – review & editing. **Cora Wunder:** Writing – review & editing, Supervision, Conceptualization.

Declaration of Competing Interest

André Ihlenfeld: Financial competing interests - Copeia GmbH, Bergisch Gladbach, Germany. Assaf Landschaft: Financial competing interests - Copeia GmbH, Bergisch Gladbach, Germany. The Copeia GmbH is a software company that develops digital health applications. All other authors have no conflicts of interest to be declared.

References

- [1] United Nations Office on Drugs and Crime, Word Drug Report - Herbal Cannabis for Medical Use: A spectrum of regulatory Approaches. (https://www.unodc.org/res/WDR-2023/WDR23_B3_CH3_Medical_Cannabis.pdf), 2023 (accessed May 05, 2024).
- [2] K. Müller-Vahl, F. Grotenhermen, Verschreibungsfähige cannabisbasierte Medikamente [Prescribable cannabis-based medicines], Cannabis und Cannabinoide in der Medizin [Cannabis and cannabinoids in medicine], Medizinisch Wissenschaftliche Verlagsgesellschaft, Berlin, 2019, pp. 165–186.
- [3] German Bundestag, Gesetz zur Änderung betäubungsmittelrechtlicher und anderer Vorschriften [Act to Amend Narcotic Drugs Provisions and Other Related Provisions] Bundesgesetzblatt [Federal Law Gazette] I(11) (2017) 403–405.
- [4] Association of German Private Health Insurance Companies, Erstattet die PKV die Kosten für eine Cannabis-Therapie? [Does private health insurance cover the costs of cannabis therapy?]. (<https://www.privat-patienten.de/arzneien-und-hilfsmittel/erstattet-die-pkv-die-kosten-fuer-eine-cannabis-therapie/#:~:text=Medizinalcannabis%20ist%20durch%20das%20neue,die%20PKV%20die%20Kosten%20übernimmt>). 2024 (accessed May 05, 2024).
- [5] N. Szejko, E. Becher, F. Heimann, F. Grotenhermen, K.R. Müller-Vahl, Medicinal use of different cannabis strains: results from a large prospective survey in Germany, Pharmacopsychiatry (2024), <https://doi.org/10.1055/a-2261-2269>.
- [6] Federal Institute for Drugs and Medical Devices, Abschlussbericht der Begleiterhebung nach § 31 Absatz 6 des Fünften Buches Sozialgesetzbuch zur Verschreibung und Anwendung von Cannabisarzneimitteln [Final report of the accompanying survey in accordance with Section 31 (6) of the Fifth Book of the German Social Insurance Code on the prescription and use of cannabis medicinal products]. (https://www.bfarm.de/DE/Bundesopiumstelle/Medizinisches-Cannabis/Begleiterhebung/_node.html), 2022 (accessed May 05, 2024).
- [7] C. Kurz, T. Lau, Begleiterhebung zu medizinischem Cannabis - Bedingt aussagekräftig [Monitoring survey on medicinal cannabis - Conditionally meaningful], Deutsches Ärzteblatt 119, 29–30 (2022) 1290–1291.
- [8] Government of Canada, Frequently Asked Questions - Drug-Impaired Driving Laws. (<https://www.justice.gc.ca/eng/cj-cp/sid/rlcfa/qa2-qr2.html>), 2021 (accessed May 05, 2024).
- [9] D. Perkins, H. Brophy, I.S. McGregor, P. O’Brien, J. Quilter, L. McNamara, J. Sarris, M. Stevenson, P. Gleeson, J. Sinclair, P. Dietze, Medicinal cannabis and driving: the intersection of health and road safety policy, Int J. Drug Policy 97 (2021), <https://doi.org/10.1016/j.drugpo.2021.103307>.
- [10] Federal Ministry of Justice, § 24a Straßenverkehrsgesetz [§ 24a Traffic Law]. [https://www.gesetze-im-internet.de/stvg/_24a.html#:~:text=\(1\)%20Ordnungswidrig%20handelt%2C%20wer,solchen%20Atem%2D%20oder%20Blutalkoholkonzentration%20führt,](https://www.gesetze-im-internet.de/stvg/_24a.html#:~:text=(1)%20Ordnungswidrig%20handelt%2C%20wer,solchen%20Atem%2D%20oder%20Blutalkoholkonzentration%20führt,) (accessed May 05, 2024).
- [11] K. Gastmeier, A. Ihlenfeld, A. Gastmeier, G. Hirt, A. Landschaft, S. Wirz, Patient-reported outcomes“ bei chronischen Erkrankungen unter Therapie mit Cannabisarzneimitteln: Analyse der Ergebnisse der Befragung von Copeia [Patient-reported outcomes in chronic diseases under treatment with cannabis medicines: Analysis of the results of the Copeia survey], Schmerz (2024), <https://doi.org/10.1007/s00482-024-00802-4>.

- [12] National Association of Statutory Health Insurance Funds, Sonderbeilage zur GKV-Arzneimittel-Schnellinformation für Deutschland [Monthly Drug Utilisation Information System of the National Association of Statutory Health Insurance Funds]. <https://www.gkv-gamsi.de/startseite/startseite.jsp>, 2022 (accessed May 05, 2024).
- [13] A. Scheunemann, K. Elsner, T. Germerott, S. Groppa, C. Hess, I. Miederer, A. Poplawski, J. Rohrich, Identification of potential distinguishing markers for the use of cannabis-based medicines or street cannabis in serum samples, *Metabolites* 11 (5) (2021), <https://doi.org/10.3390/metabo11050316>.
- [14] M.C. Monti, P. Frei, S. Weber, E. Scheurer, K. Mercer-Chalmers-Bender, Beyond Delta9-tetrahydrocannabinol and cannabidiol: chemical differentiation of cannabis varieties applying targeted and untargeted analysis, *Anal. Bioanal. Chem.* 414 (13) (2022) 3847–3862, <https://doi.org/10.1007/s00216-022-04026-2>.
- [15] M. Hundertmark, A. Scheunemann, Von „Amnesia Haze“ bis „Zour Apple“ – die Vielfalt des (Medizinal-)Cannabis [From “Amnesia Haze“ to “Zour Apple“ – the diversity of (medicinal) cannabis, *Toxicchem Krimtech* 91 (2) (2024) 179–186.
- [16] C.E. Grella, L. Rodriguez, T. Kim, Patterns of medical marijuana use among individuals sampled from medical marijuana dispensaries in los angeles, *J. Psychoact. Drugs* 46 (4) (2014) 267–275, <https://doi.org/10.1080/02791072.2014.944960>.
- [17] G.L. Schauer, B.A. King, R.E. Bunnell, G. Promoff, T.A. McAfee, Toking, vaping, and eating for health or fun: marijuana use patterns in adults, U.S., 2014, *Am. J. Prev. Med* 50 (1) (2016) 1–8, <https://doi.org/10.1016/j.amepre.2015.05.027>.
- [18] M.A. Huestis, J.E. Henningfield, E.J. Cone, Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana, *J. Anal. Toxicol.* 16 (5) (1992) 276–282, <https://doi.org/10.1093/jat/16.5.276>.
- [19] S.W. Toennes, J.G. Ramaekers, E.L. Theunissen, M.R. Moeller, G.F. Kauert, Comparison of Cannabinoid Pharmacokinetic Properties in Occasional and Heavy Users Smoking a Marijuana or Placebo Joint, *J. Anal. Toxicol.* 32 (2008) 470–477.
- [20] M.A. Huestis, A. Barnes, M.L. Smith, Estimating the time of last cannabis use from plasma delta9-tetrahydrocannabinol and 11-nor-9-carboxy-delta9-tetrahydrocannabinol concentrations, *Clin. Chem.* 51 (12) (2005) 2289–2295, <https://doi.org/10.1373/clinchem.2005.056838>.
- [21] D.M. Schwoppe, W.M. Bosker, J.G. Ramaekers, D.A. Gorelick, M.A. Huestis, Psychomotor performance, subjective and physiological effects and whole blood Delta(9)-tetrahydrocannabinol concentrations in heavy, chronic cannabis smokers following acute smoked cannabis, *J. Anal. Toxicol.* 36 (6) (2012) 405–412, <https://doi.org/10.1093/jat/bks044>.
- [22] Arbeitsgemeinschaft Cannabis als Medizin e.V., Cannabissorten in Deutschland und ihre Inhaltsstoffe [Cannabis varieties in Germany and their constituents]. (https://www.arbeitsgemeinschaft-cannabis-medizin.de/wp-content/uploads/2023/09/Cannabissorten_inhaltsstoffe-1.pdf), 2023 (accessed May 05, 2024).
- [23] European Monitoring Centre for Drugs and Drug Addiction, Cannabis - the current situation in Europe, European Drug Report 2023: Trends and Developments. (https://www.emcdda.europa.eu/publications/european-drug-report/2023/cannabis_en), 2023 (accessed May 05, 2024).
- [24] F. Grotenhermen, P. Timte, Cannabissorten in Deutschland [Cannabis varieties in Germany], (2022).
- [25] Federal Union of German Associations of Pharmacists, Verordnung von Arzneimitteln mit Cannabisblüten, -extrakt und Cannabinoiden - Informationen für verschreibende Ärzte/innen [Prescribing medicinal products containing cannabis flowers, extract and cannabinoids - Information for prescribing physicians], (2017).
- [26] K. Müller-Vahl, F. Grotenhermen, Pharmakokinetik der Cannabinoide [Pharmacokinetics of Cannabinoids], Cannabis und Cannabinoide in der Medizin [Cannabis and cannabinoids in medicine], Medizinisch Wissenschaftliche Verlagsgesellschaft, Berlin, 2019, pp. 75-83.
- [27] Associations of Statutory Health Insurance Physicians, Cannabisarzneimittel [Cannabis-based medicines]. https://www.kbv.de/media/sp/WirkstoffAktuell_3-23_Cannabisarzneimittel.pdf, 2023).
- [28] B. Jung, Cannabis-Vaporisator auf Rezept: Was Apotheker wissen sollten [Cannabis vaporiser on prescription: what pharmacists should know]. (<https://www.deutsche-apotheke-zeitung.de/news/artikel/2019/03/01/cannabis-vaporizer-auf-rezept-t-noch-kein-routine-hilfsmittel>), 2019 (accessed May 05, 2024).
- [29] S.L. MacPhail, M.A. Bedoya-Perez, R. Cohen, V. Kotsirilos, I.S. McGregor, E. A. Cairns, Medicinal cannabis prescribing in Australia: an analysis of trends over the first five years, *Front Pharm.* 13 (2022) 885655, <https://doi.org/10.3389/fphar.2022.885655>.
- [30] S. Gottschling, T. Herdegen, J. Horlemann, I. Hornke, H.G. Kress, I. Kuhlen, R. Likar, S. Mieke, Expertenkonsens: Medizinischer Einsatz von Cannabinoiden [Expert consensus: Medical use of cannabinoids], (2018).
- [31] Arbeitsgemeinschaft Cannabis als Medizin e.V., Cannabisblüten - Dosierung von Cannabisblüten [Cannabis flowers - Doseability of cannabis flowers]. (<https://www.arbeitsgemeinschaft-cannabis-medizin.de/cannabisbluten/>), (accessed June 10, 2024).
- [32] J. Horlemann, N. Schürmann, DGS-Praxisleitlinie - Cannabis in der Schmerzmedizin, Version 2.0 für Fachkreise [DGS Practice Guideline - Cannabis in Pain Medicine, Version 2.0 for healthcare professionals], 2024.
- [33] T. Schlereth, Diagnose und nicht interventionelle Therapie neuropathischer Schmerzen, S2k-Leitlinie [Diagnosis and non-interventional treatment of neuropathic pain, S2k guideline]. www.dgn.org/leitlinien, (2019).
- [34] C. Maier, G. Glaeske, Green Rush – schlimmer als befürchtet? Daten zur Fehlversorgung mit medizinischem Cannabis, *Schmerz* 35 (3) (2021) 185–187, <https://doi.org/10.1007/s00482-021-00560-7>.
- [35] Federal Joint Committee, Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie: § 4a und Abschnitt N §§ 44 bis 45 (Cannabisarzneimittel) [Decision of the Federal Joint Committee on an amendment to the Medicinal Products Directive: § 4a and Section N §§ 44 to 45 (cannabis-based medicines)]. https://www.g-ba.de/downloads/39-261-5915/2023-03-16_AM-RL_Paragraf-4a-Abschnitt-N-Paragrafen-44-46-Cannabisarzneimittel_BAnz.pdf, 2023 (accessed May 05, 2024)..
- [36] German Bundestag, Gesetz zum kontrollierten Umgang mit Cannabis und zur Änderung weiterer Vorschriften (Cannabisgesetz — CanG) [Act on the Controlled Use of Cannabis and on the Amendment of Further Regulations (Cannabis Law - CanG)], Bundesgesetzblatt [Federal Law Gazette] I(109), 2024.