Validation of Clinical Vignettes to Explore Medical Cannabis Practices

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ABSTRACT: **Background:** The policies and practices related to medical cannabis are currently in flux. These changes have been associated with many controversies, and there is a lack of consensus within the medical community regarding medical cannabis practices.

Objectives: To validate clinical vignettes that can be used to examine and improve medical cannabis practices.

Methods: Ten physicians participated in a Delphi survey of two consequent rounds in which they quantified the eligibility of medical cannabis therapy for six clinical vignettes describing both chronic pain and cancer patients.

Results: Higher consensus was achieved for the vignettes of cancer patients, which were additionally rated as more eligible for medical cannabis therapy. The highest level of consent (4.3 out of 5) was achieved regarding a vignette of a metastatic cancer patient. While in some cases physicians consolidated their ratings toward the group's average, in other cases they remained stable in their responses.

Conclusions: While controversies related to medical cannabis are expected to remain rampant, the validated vignettes may facilitate assessment of clinical practices, which is essential for a successful implementation of medical cannabis policies. These vignettes may additionally be used in medical training for appropriate patient selection for medical cannabis authorization.

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The use of cannabis for medical purposes has been documented since ancient times, but during the previous century cannabis was legally banned and its medical use was neglected [1]. In recent years, however, a shift in medical cannabis policies has occurred throughout the world [2]. Physicians hold a vital role in the implementation of medical cannabis policies, as they are legally entitled to recommend medical cannabis to patients, and in some places to certify it directly [3]. Yet, while different policies are being enacted or considered, medical cannabis clearly remains controversial within the medical community.

Given the dominant role of physicians in patient selection for authorized use of medical cannabis, it is essential to examine the clinical practices related to medical cannabis. Indeed, accurate and valid measurements of clinical practices are essential for any assessment of quality in healthcare [4]. Such assessment needs to rely on measures that are reliable, standardized, and inexpensive [5]. Researchers have used different methods to assess physicians' decisions and practices. One method, clinical vignettes, holds potential as a practical survey instrument as it focuses directly on the process of care provided in actual clinical practice while allowing evaluation of practices across physicians with different backgrounds and across different healthcare systems [6]. A clinical vignette is a written case simulation that includes details of a hypothetical patient, such as age, gender, medical history, and symptoms. Based on these details, which emulate a realistic clinical situation, respondents are asked to answer one or several questions related to the diagnosis or the treatment of this patient [7].

Previous studies have used clinical vignettes to explore physician decision making in realms of medical care that have established guidelines, such as management of hypertension [8] or lower back pain [9]. While medical cannabis is an evolving field in healthcare, there are currently no defined guidelines for physicians regarding the appropriate patient selection for medical cannabis authorization. Thus, we used the Delphi technique to facilitate the development and validation of clinical vignettes, which could be used, in turn, to assess medical cannabis practices.

The Delphi technique is a valid and reliable method for reaching expert agreement [10]. This technique is a structured method that facilitates the development of consensus among a group of experts by synthesizing their opinions. Development of consensus is achieved in iterative rounds, in which participants respond to a semi-constructed questionnaire. During repeated rounds, the group's collective opinion is fed back to the experts, while maintaining anonymity among respondents, and thus encouraging honest opinions that are free of group pressure [11].

The Delphi technique may be particularly relevant in areas that lack consensus and have inadequate policies and guidelines [12], and where evidence and knowledge are missing [13], as is the

case for medical cannabis. This technique has been widely used in healthcare research to reach consensus on diagnostic criteria, quality of care, and healthcare policies. The Delphi technique has shown important results that have been used to develop expert agreement related to the appropriateness of treatment for patients and to develop treatment guidelines [14].

THE CURRENT STUDY

This study is based on a sample of Israeli physicians. In Israel, the largest groups of patients that hold governmental licenses for medical cannabis are cancer patients and chronic pain patients. According to the detailed criteria set by the Ministry of Health (MoH), cancer patients are eligible for medical cannabis for chemotherapy-induced nausea, vomiting, or pain (for patients who are currently undergoing chemotherapy and up to 6 months after therapy). Alternatively, cannabis is approved for treating cancer pain, but only for metastatic patients and after exhaustion of conventional treatment options. Chronic pain patients are eligible if they suffer from neuropathic pain that has a clear organic origin, and only after being treated at a recognized pain clinic for at least one year [15].

Given that the regulations may be interpreted differently by different physicians, combined with the lack of specific clinical guidelines for patient selection for medical cannabis use, the integration of medical cannabis into healthcare is profoundly challenged. Thus, the objective of the current study was to develop expert consensus on the eligibility for medical cannabis therapy of six clinical vignettes, which could be used, in turn, to assess clinical practices and practice variation, as well as for physicians' training and education.

PATIENTS AND METHODS

The study was approved by the institutional review board of the Faculty of Welfare and Health Sciences at the University of Haifa, Israel.

PREPARATION OF THE CLINICAL VIGNETTES

Six vignettes were initially prepared by S.V. with the objective of developing vignettes of both cancer and pain patients. Each vignette was developed to have either high, medium, or poor compatibility with current medical cannabis regulations in Israel. Each vignette included age, gender, diagnosis, and medical history (procedures, prescribed medications) as well as a description of the medical condition together with signs and symptoms. The six vignettes are summarized in Table 1. The full vignettes are attached in the supplementary material of this paper.

THE DELPHI PANEL

An expert panel comprised of a purposive sample of 10 physicians: 3 oncologists, 3 pain specialists, 3 family physicians, and an additional physician who was formerly the competent authority in the Israeli MoH for medical cannabis licensure. The inclusion criteria for membership to the expert panel were familiarity with the regulations as well as experience with medical cannabis recommendation. Participants were identified through the professional network of the research team. Following Delphi guidelines, participants were anonymous to one another.

Table 1. Summary of clinical vignettes

Clinical vignette	Age	Diagnosis	Conventional medications previously used	Conventional medications currently used	Visual Analogue Scale (VAS)
Chronic pain I	52	Mild osteoarthritis	Ibuprofen, paracetamol, celcox		7
Chronic pain II	65	Ankylosing spondylitis	Tramadol, ibuprofen, naproxen sodium	Oxycodone	8
Chronic pain III	52	Complex regional pain syndrome	Gabapentin. pregabalin, duloxetine	Oxycodon, amitriptyline	9
Cancer I	61	Breast cancer 2 years before		Simple analgesics	7
Cancer II	63	Metastatic prostate cancer		Oxycontin, dipirone, etodolac, zolpidem	7
Cancer III	54	Osteosarcoma (left thigh)		Transdermal fentanyl, transbuccal fentanyl, pregabalin	8

PROCEDURE AND DATA ANALYSIS

Qualtrics XM Platform (Qualtrics^{XM}, United Kingdom) was used for all phases of the date collection. Each participant received a separate email that included a unique and personal link to the survey. Informed consent was obtained from all individual participants included in the study. Physicians who had not responded to the questionnaire within 10 working days were sent a remainder by email.

In the first round, members of the expert panel were asked to rate the appropriateness for medical cannabis therapy for each of the six vignettes from 0 (not at all eligible) to 5 (highly eligible). In accordance with guidelines of the Delphi method, at this point participants had the option to comment freely on each vignette if any information was missing that they deemed necessary to make a decision [16]. The data of the first round was synthesized, and the mean and standard deviation were calculated, as well as Cronbach α. Cronbach α was used as a measure of homogeneity for the rankings, and increasing homogeneity was considered to be an indication of consensus among the panelists [17]. Thus, to achieve expert consensus, we aimed to reduce the standard deviation and to reach Cronbach α larger than 0.9.

In the second round, all of the vignettes were presented to participants once again, with changes that reflected the comments of the first round. Each vignette was presented with both the previous rating given by this participant and the average rating of all panel members. Participants were asked again to rate the eligibility of each clinical vignette for medical cannabis

therapy. This rating allowed participants one of three options: to change their previous rating so that their new rating would be more consolidated with the average, to rate the same as in the previous round, or to change the rating so that their new rating would be more deviant from the average rating.

RESULTS

ROUND 1

The round 1 data was collected within 14 days of distributing the online questionnaire. Eight physicians were sent remainders by email. Table 2 shows physicians' rating to the six clinical vignettes. A total of 33 comments on the vignettes were made by the participants (18 for the pain patients and 15 for the cancer patients). On average 5.5 comments were received per vignette (range 5–7). The comments on the cancer patient vignettes referred to other types and/or higher dosages of anti-pain medications that physicians stated as appropriate prior to becoming eligible for medical cannabis (n=10); inquiries about mood, depression, and psychosocial support (n=3); and information about the specific origin and diagnosis of the cancer pain (n=2).

The comments on the chronic pain vignettes referred to other types and/or higher dosages of anti-pain medications that physicians stated as appropriate prior to becoming eligible for medical cannabis (n=11), speculation on the honesty of patient reports (n=2), inquiries about the treatment and rehabilitation plan (n=3), psychiatric background (n=1), and psychosocial condition (n=1).

ROUND 2

Minor changes were implemented into the four vignettes according to participants' comments, mainly regarding the types and dosages of anti-pain medications. For example, the dosage of fentanyl in one of the vignettes was changed from 100 to 125 mcg/hour, and gabapentin and pregabalin were added as non-successful treatments in another vignette.

The data for round 2 were collected within 16 days of distributing the online questionnaire. Six physicians were sent remainders by email. Participants' ratings in the second round are presented in Table 3. Other than one participant, all physicians changed at least one rating. On average, each physician changed the rating of 1.8 vignettes. All the changes in participants' ratings were toward the average of the panel, meaning that participants reconciled their responses to be closer to the general average [Table 3].

In total, there were 18 changes of ratings. Of 14 ratings of 0 in the first round, 4 were changed (to 1). Of 10 ratings of 1 in the first round, 3 were changed (to 2 or 3). Of 6 ratings of 2 in the first round, one was changed (to 3). Of 13 ratings of 3 in the first round, 6 were changed (to 2 or 4). Of 6 ratings of 4 in the first round, 2 were changed (to 3 and 1), and of 11 ratings of 5 in the first round, 2 were changed (to 4).

Table 2. Round 1: Ratings of six clinical vignettes*

	Chronic-pain patients			Cancer patients			
Respondents	I	II	III	I	II	III	Comments
Physician 1	0	4	5	1	5	5	4
Physician 2	0	0	2	0	1	3	6
Physician 3	2	0	4	0	1	3	6
Physician 4	0	0	1	0	2	4	0
Physician 5	3	5	5	5	5	5	2
Physician 6	1	3	4	0	3	5	6
Physician 7	0	3	1	0	0	3	6
Physician 8	0	2	3	3	5	5	1
Physician 9	1	1	1	1	2	3	0
Physician 10	3	3	3	4	2	4	4
Mean	1	2.1	2.9	1.4	2.6	4	
Range	0–3	0–5	1–5	0–5	0–5	3–5	
Standard deviation	1.247	1.791	1.595	1.897	1.837	0.942	
Cronbach α	0.879						

*Vignettes marked as I, II, and III represent, respectively, poor, medium, and high compatibility with current medical cannabis regulations in Israel

Table 3. Round 2: Ratings of six patient vignettes*

	Chronic-pain patients			Cancer patients			Changes of ratings
Respondents	I	II	III	I	II	III	
Physician 1	0	4	4	1	5	5	1
Physician 2	0	0	3	0	1	4	2
Physician 3	2	1	3	1	2	3	4
Physician 4	0	1	1	0	2	4	1
Physician 5	3	5	5	5	5	5	0
Physician 6	1	3	4	1	3	5	1
Physician 7	0	1	3	0	0	4	3
Physician 8	0	2	3	2	4	5	2
Physician 9	1	1	1	2	2	4	2
Physician 10	2	3	3	1	2	4	2
Mean	0.9	2.1	3	1.3	2.6	4.3	
Range	0–3	0–5	1–5	0–5	0–5	3–5	
Standard deviation	1.101	1.595	1.247	1.494	1.647	0.675	
Cronbach α	0.945						

*Vignettes marked as I, II, and III represent, respectively, poor, medium, and high compatibility with current medical cannabis regulations in Israel

Physician #5 was identified as an outlier, since s/he did not change any rating between the rounds, and rated 5 out of the 6 vignettes as 5, that is, highly eligible for medical cannabis therapy. The standard deviations of physicians' ratings were lowered by 17.4% on average from round 1 to round 2 ratings (range 10.4–28.4). The Cronbach α reached 0.94, which indicated homogeneity for the rankings, and thus additional rounds were not required.

DISCUSSION

Medical cannabis remains contentious and subject to professional controversy. Nevertheless, medical cannabis policies are evolving throughout the world, so that cannabis is gradually being integrated into healthcare. To gain a better understanding of physicians' decisions on patient selection for medical cannabis authorization, there is a need for a reliable and standardized measure, such as clinical vignettes [5]. In this study, we used the Delphi technique to reach expert consensus on the eligibility of medical cannabis therapy for six clinical vignettes.

Our reported validation of these vignettes, in a systematic and structured procedure, is a first step toward their wider application. Indeed, previous studies suggest that clinical vignettes accurately reflect decisions of physicians and may be reasonably interpreted as "observations" of clinical decisions [5-7]. The vignettes developed in this study may thus be used in future studies with varied samples of physicians as a behavior simulation to assess physicians' decisions regarding medical cannabis and to evaluate practice variation.

In addition, clinical vignettes are frequently used in medical schools and in examinations of board certification [5]. Previous studies indicated the need for more knowledge regarding medical cannabis among physicians [18]. Indeed, the vignettes validated in this study may be used as educational tools in physician training on medical cannabis to prompt discussion regarding patient selection for medical cannabis authorization in order to develop physicians' clinical skills. These vignettes may additionally be used to evaluate the effectiveness of an educational intervention.

Consensus was reached within the expert panel after two rounds. How physicians changed their ratings between the rounds may enable a deeper insight into physicians' willingness to change their positions toward a consensus, or their aversion to do so. One physician did not change any rating between rounds and three other physicians changed only one of their ratings. Although most of their ratings were deviant from the average, these physicians stayed persistent with their divergent views, which may represent a rigid position toward medical cannabis among certain physicians.

Indeed, although cannabis may potentially serve as a therapeutic agent for different ailments [19,20], its integration into clinical practice remains heavily challenged [21]. A systematic review recently reported that physicians are generally in support of using medical cannabis in practice. Nevertheless, practitioners also reported on low levels of perceived knowledge and raised concerns such as a lack of standardization and a potential for recreational misuse and diversion to the illicit market [22]. In contrast, chronic patients reported on preferences to use cannabis as a supplement or substitute to conventional therapies [23,24], possibly since conventional therapies might entail adverse effects and limited efficacy [25].

Following the guidelines of the Delphi technique, the members of our expert panel remained anonymous to one another. This research design ensured that participants exposed their honest opinions and avoided biases, which may have been the result of social desirability. Given the conundrum related to medical cannabis, this element of the Delphi procedure may be particularly relevant and applicable to resolve conflicts and to enhance consensus on medical cannabis practices. Thus, the Delphi procedure may also serve the development of clinical guidelines. More generally, successful implementations of medical cannabis policies involve other groups, such as patients, government officials, and other healthcare providers, and such diverse groups may have different interests and motivations. By synthesizing anonymous opinions, future studies, as well as policy developments, may benefit from utilizing the Delphi technique to assess the level(s) of consensus around specific aspects of practices and policies.

LIMITATIONS

The main limitation of this study is the small sample size. However, since physicians have a homogenous background and they abide by similar practices and guidelines, the number of experts falls within the recommended guidelines for a Delphi procedure [11]. In addition, the vignettes are compatible with the Israeli regulations at the time of data collection, and thus adjustments might be needed for use within other regulatory frameworks. However, cancer and chronic pain patients are eligible for medical cannabis use across various different medical cannabis regulatory frameworks.

CONCLUSIONS

The Delphi technique was found appropriate to attain professional consensus to validate clinical vignettes, which could be used, in turn, to examine medical cannabis practices. The scientific evidence and subsequent knowledge on medical cannabis are scarce, and the controversies related to medical cannabis practices are thus expected to remain rampant. Nevertheless, as medical cannabis policies are being considered and enacted in many places, assessment of physician practices may be essential for a successful implementation of policies. The clinical vignettes may also be used in medical training about medical cannabis, which is much needed among physicians and other healthcare providers. The development of clinical guidelines, and of policies in general, may benefit from using the Delphi technique to enhance consensus within the medical community, as well as with other stakeholders.

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Capsule

Heterogeneity in old fibroblasts is linked to variability in reprogramming and wound healing

Age-associated chronic inflammation (inflammageing) is a central hallmark of aging, but its influence on specific cells remains largely unknown. Fibroblasts are present in most tissues and contribute to wound healing. They are also the most widely used cell type for reprogramming to induced pluripotent stem (iPS) cells, a process that has implications for regenerative medicine and rejuvenation strategies. **Mahmoudi** and colleagues showed that fibroblast cultures from old mice secrete inflammatory cytokines and exhibit increased variability in the efficiency of iPS cell reprogramming between mice. Variability between individuals is emerging as a feature of old age, but the underlying mechanisms remain unknown. To identify drivers of this variability, the authors performed multi-omics profiling of fibroblast cultures from young and old mice that have different reprogramming efficiencies. This approach revealed that fibroblast cultures from old mice contain 'activated fibroblasts' that secrete inflammatory cytokines, and that the proportion of activated fibroblasts in a culture correlates with the reprogramming efficiency of that culture. Experiments in which conditioned medium was swapped between cultures showed that extrinsic factors secreted by activated fibroblasts underlie part of the variability between mice in reprogramming efficiency, and the authors have identified inflammatory cytokines, including TNF, as key contributors. Notably, old mice also exhibited variability in wound healing rate in vivo. Single-cell RNA-sequencing analysis identified distinct subpopulations of fibroblasts with different cytokine expression and signaling in the wounds of old mice with slow versus fast healing rates. Hence, a shift in fibroblast composition, and the ratio of inflammatory cytokines that they secrete, may drive the variability between mice in reprogramming in vitro and influence wound healing rate in vivo. This variability may reflect distinct stochastic ageing trajectories between individuals, and could help in developing personalized strategies to improve iPS cell generation and wound healing in elderly individuals.

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APPENDIX 1. Supplementary material: validated clinical vignettes

Chronic pain patients

Clinical vignette I

A 52-year-old woman reported on self-medication with cannabis for pain relief in the hand joints. On physical examination, mild osteoarthritis in her finger joints was apparent. She reported having taken ibuprofen, paracetamol, and celcox in the past. She stopped the medications because of adverse effects that she was not able to recall (possibly nausea and abdominal pain). She rated her pain as 7 out of 10 on the visual analogue scale (VAS) for pain.

Clinical vignette II

A 65-year-old man presenting with ankylosing spondylitis was referred to the pain clinic by his primary care physician for consideration of medical cannabis treatment. He endured intense pain in his neck and the lower back. He was previously treated with tramadol, ibuprofen, and naproxen sodium, which were stopped due to abdominal pain and/or constipation. He received a biological treatment, as well oxycodone/naloxone (with no reported constipation) as well as sleeping tablets. His pain was rated as 8 out of 10 on the VAS for pain.

Clinical vignette III

A 52-year-old male presented with complex regional pain syndrome in his right hand as a result of a work accident one year ago. He was treated with oxycodon 120 mg/day, amitriptyline 50 mg/day, and physical therapy. Previous treatments with gabapentin and pregabalin failed because of adverse effects, and duloxetine was inefficient. On physical examination, his hand seemed swollen and cyanotic, and allodynia and hyperesthesia were present. His wrist and fingers did not seem to function, and his wrist joint had minimal passive movement, with no active movement. He was not interested in spinal cord stimulation. He experienced sleep disturbances and was nonresponsive to sleeping tablets. He was involved with a multidisciplinary rehabilitation program. His pain was rated as 9 out of 10 on the VAS for pain.

Cancer patients

Clinical vignette I

A 61-year-old woman underwent mastectomy 2 years previously due to breast cancer (stage 1 T1N0M0). She underwent chemotherapy and radiotherapy, and was followed with no further treatment. She complained of bilateral shoulder pain, fatigue, weakness, and loss of appetite. Occasionally she experienced nausea and her weight had decreased by a few kilograms in just a few months. She received simple analgesics for her pain. The patient presented with considerable anxiety, and underwent re-evaluation due to the suspicion of recurrent malignancy. Her pain was rated as 7 out of 10 on the VAS for pain.

Clinical vignette II

A 63-year-old man diagnosed with metastatic prostate cancer, with metastases mainly in his buttock and the lower spinal cord, started hormonal treatment. He experienced pain in his pelvis and had difficulty sitting and ambulating. Lying down was pain free. He was treated with oycontin 10 mg × 2/day, dipirone 500 mg, 2 × 3/day, etodolac 500mg × 2/day, and zolpidem 7.5 mg (for sleep). His pain was rated as 7 out of 10 on the VAS for pain.

Clinical vignette III

A 54-year-old male presented with osteosarcoma of the left thigh. He had undergone chemotherapy and was preparing for surgery planned for tumor removal with wide margins. He complained of pain radiating from the upper thigh along his leg for 4 months. The pain was not relieved following radiotherapy. The pain had been described as burning and stabbing along the leg. He received the following medications: transdermal fentanyl 125 mcg/hour, transbuccal fentanyl 800 mcg × 4/day, and pregabalin 225 mg × 2/day. He had good emotional support from his family and from the oncology staff. His pain was rated as 8 out of 10 on the VAS for pain.

Capsule

The toll of measles on the immune system

Many of the deaths attributable to the measles virus are caused by secondary infections because the virus infects and functionally impairs immune cells. Whether measles infection causes long-term damage to immune memory is unclear. This question has become increasingly important given the resurgence in measles epidemics worldwide. Using a blood test called VirScan, **Mina** and colleagues analyzed the antibody repertoire in children before and after natural infection with measles virus as well as in children before and after measles vaccination. They found that measles infection can greatly diminish previously acquired immune memory, potentially leaving individuals at risk for infection by other pathogens. These adverse effects on the immune system were not seen in vaccinated children.

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