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TITLE

Clinical trials of medicinal cannabis for appetite-related symptoms from advanced cancer: A survey of preferences, attitudes and beliefs among patients willing to consider participation

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ABSTRACT

Background

Australian clinical trials are planned to evaluate medicinal cannabis in a range of clinical contexts.

Aims

To explore the preferences, attitudes and beliefs of patients eligible and willing to consider participation in a clinical trial of medicinal cannabis for poor appetite and appetite-related symptoms from advanced cancer.

Methods

A cross-sectional anonymous survey was administered from July to December 2015 in 8 adult outpatient palliative care and/or cancer services, and online. Respondents were eligible if they were ≥18 years, had advanced cancer and poor appetite/taste problems/weight loss, and might consider participating in a medicinal cannabis trial. Survey items focused on medicinal rather than recreational cannabis use and did not specify botanical or pharmaceutical products. Items asked about previous medicinal cannabis use, preferences for delivery route, and invited comments and concerns.

Results

There were 204 survey respondents, of whom 26 (13%) reported prior medicinal cannabis use. Tablets/capsules were the preferred delivery mode (n=144, 71%), followed by mouth-spray (n=84, 42%) and vaporiser (n=83, 41%). Explanations for preferences (n=134) most commonly cited convenience (n=66; 49%). Eighty-two percent (n=168) of respondents indicated they had no trial-related concerns, but a small number volunteered concerns about adverse effects (n=14) or wanted more information/advice (n=8). Six respondents volunteered a belief that cannabis might cure cancer, while 2 wanted assurance of efficacy before participating in a trial.

Conclusion

Justification of modes other than tablets/capsules and variable understanding about cannabis and trials will need addressing in trial-related information to optimise recruitment and ensure that consent is properly informed.

KEYWORDS

Cannabis, cancer, clinical trials, attitudes, anorexia

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MANUSCRIPT

Introduction

Legislative frameworks for medicinal cannabis provision are the focus of much current debate among Australian healthcare professionals and the general public,[1] with the federal government announcing changes to the Narcotic Drugs Act (1967) in February 2016.[2] More than two-thirds of Australians support the use of medicinal cannabis,[3] despite limited evidence for many indications.[4] Australian clinical trials (complemented by laboratory research) are planned to evaluate medicinal cannabis in a range of clinical contexts, including management of poor appetite and appetite-related symptoms in advanced cancer. These trials aim to provide important new information about the net benefits of medicinal cannabis, assessing both efficacy and adverse effects. As with any clinical trial, success will depend on patients' willingness to participate based on acceptability of the intervention and methods.

Internationally, several studies have surveyed people with chronic health conditions who have used medicinal cannabis (e.g. [5-13]), but older studies may not reflect changing views on cannabis and none have focused on cancer patients or canvassed perspectives on clinical trials. Findings suggest that medicinal cannabis users perceive a range of symptom benefits, including pain, appetite, sleep and nausea, and also a range of psychological benefits and enhanced wellbeing.[9 13 14]

Survey results concerning delivery routes for self-administering medicinal cannabis in the community have tended to be dominated by smoking [8 10 13]- a route associated with carcinogenicity and respiratory toxicity both to the smoker and those in proximity that cannot be used in healthcare and other environments where smoking is banned. Tablets or capsules are the most commonly used delivery mode for medicines, but a broader range needs to be considered for medicinal cannabis to enable tailoring to the indication and optimisation of pharmacokinetic and pharmacodynamic properties of specific products. For example, some cannabinoids have low oral bioavailability and variability in pharmacodynamic effects. A range of delivery routes is also needed because oral and inhalation modes may not be feasible for people with swallowing and respiratory problems. For use in clinical trials, cannabis plant-derived products will also need to meet Australian Therapeutic Goods Administration's (TGA) standards for Good Manufacturing Processes (GMP).[15] Standardisation of dosage is important for both clinical trials and (if a benefit is demonstrated) subsequent therapy. Future clinical trials will also require tight documentation of the major cannabinoid content of agents tested in view of evidence for differing effects and risks associated with content of tetrahydrocannabinol (THC) and cannabidiol (CBD).[16]

Failing to align drug delivery route with patient preferences may impact on trial feasibility, recruitment and retention rates, and therefore study completion. Research with other medications has shown mode of administration to be an important predictor of adherence and outcomes for cancer patients.[17] Preferences for mode of delivery for analgesics has been found to vary according to patient characteristics (e.g. gender), previous experience and perceived differences in efficacy and side effects.[18] For this reason, a better understanding of the perspectives of potential participants on Australian medicinal cannabis trials is important for informing choice of delivery mode, the content of trial-related patient information, and optimising recruitment, adherence and retention.

A study was designed to explore the preferences, attitudes and beliefs of people with advanced cancer who self-identified as willing to consider participating in a clinical trial of medicinal cannabis for poor appetite and appetite-related symptoms.

Materials and Methods

A cross-sectional survey design was used. The study was approved by South Western Sydney Local Health District Human Research Ethics Committee (HREC number LNR/15/LPOOL/185**)**.

Patients were eligible if they self-reported as: 1) being ≥18 years of age, 2) having advanced cancer and poor appetite, taste problems and/or weight loss, 3) being willing to consider participating in a trial of medicinal cannabis for these problems. Appetite and appetite-related symptoms are among the most common and serious problems in advanced cancer that may benefit from medicinal cannabis,[19] and are the focus for a planned trial.

The volunteer effect expected from open surveys was considered likely to support the study's aims by biasing selection towards patients likely to participate in future trials. Surveys were administered electronically online and via hard copy in the waiting rooms of 8 adult outpatient palliative and/or cancer services, seven in NSW and one in South Australia between July and December 2015. Participant anonymity was protected by approval from the HREC to assume completion of the survey constituted informed consent without this needing to be collected via reference to name and address. Online data collection did not record Internet Protocol (IP) addresses or other information that could be used to identify respondents, and surveys completed in waiting rooms were returned via ballot-style boxes rather than directly to clinical or research staff. To minimise response bias associated with a reticence to disclose illegal activity, respondent anonymity was ensured and focused on medicinal not recreational cannabis use. Study information highlighted exemption from prosecution under the New South Wales (NSW) Terminal Illness Cannabis Scheme.[20]

Survey content was developed by a multi-disciplinary team of cannabis and clinical trials experts, palliative care physicians and nurses, and was reviewed by consumers (see Box 1 for items). Experts were scientific committee members and site investigators of the Palliative Care Clinical Studies Collaborative (PaCCSC). Item suggestions were circulated via email, responses collated and revised items circulated iteratively until agreement was reached.

Quantitative data were summarised descriptively using SPSS V23.0 statistical software. Medicinal cannabis users and non-users were compared for age (</≥60 years), sex and trial-related concerns (yes or unsure/no). These variables were also used to compare groups expressing particular preferences with regard to route/mode of cannabis delivery. Age </≥60 years was chosen because people in the younger age group might have been more likely to be use cannabis recreationally during their early adulthood. For this reason, we were also interested to find out whether patients who took part in the survey (and therefore were willing to consider taking cannabis in a clinical trial) were younger than the national average. Bivariate analyses were used to identify unadjusted relationships, with a significance level of $p<0.10$ used to select variables for inclusion in multiple logistic regression analyses of adjusted relationships, with the calculation of 95% Confidence Intervals (CIs). A Type I error of 5% was adopted for all analyses. Comments were coded inductively by two researchers.

Results

Respondent characteristics

Two hundred and eleven respondents completed the survey. Seven surveys were removed because participants reported diagnoses other than cancer, leaving 204 for inclusion in analyses. Of these, 175 (86%)

completed the survey at participating services, and 29 (14%) completed it online. The median number of surveys collected at each outpatient service was 21 (range 3-50). Variability in numbers of surveys per site was due, in part, to some sites commencing later than others. See Table 1 for a summary of respondent characteristics.

Previous use of medicinal cannabis

Twenty-six (13%) respondents reported prior use of medicinal cannabis. The most common indications were pain and appetite loss (n=9 each), followed by psychological problems (n=5), insomnia (n=4) and nausea (n=2). The majority of users reported smoking cannabis either on its own (n=18) or with tobacco (n=15), while 12 had consumed it orally and 10 had used a vaporiser. Of the 25 users who answered the question, 21 indicated that being asked to stop their current medicinal use would not prevent them from participating in a trial, 3 indicated it would prevent them, and one indicated that she was unsure. Compared with non-users, users were significantly more likely to be aged less than 60 years (χ^2 =11.67, p=0.001) but did not differ significantly with regard to sex (χ^2 =3.24, p=0.07) or the likelihood of having trial-related concerns (χ^2 =1.92, p=0.17).

Preferences for route/mode of delivery

Of the seven modes of medicinal cannabis delivery offered, respondents identified a median of 2 preferences (range 0 – 7), with 9 (4%) indicating a willingness to use any mode (see Table 2). Reasons for preferences were offered by 134 (66%) respondents, and most commonly related to perceived ease/convenience (n=66, 49%) followed by considerations relating to taste, nausea or lack of appetite (n=17, 13%), a familiarity with the mode for taking other medications (n=11, 8%), perceived faster speed of action (n=11, 8%), control over dose (n=7, 5%), enjoyment (n=5, 4%), and perceived advantages in efficacy (n=4, 3%), unobtrusiveness (n=3, 2%) and adverse effects (n=2, 1%). Reasons given for preferences against certain modes included a wish not to take any more tablets (n=6, 4%) and limitations from reduced capacities to swallow (n=7, 5%), inhale (n=2, 1%) or use suppositories (n=2, 1%). Four (3%) further patients indicated a more general distaste for suppositories. A small number (n=14, 11%) reported preferences for alternative (n=4, 3%) or additional (n=10, 8%) modes, including smoking (e.g. in a 'joint' or 'glass pipe') (n=7, 6%), percutaneous endoscopic gastrostomy (PEG) (n=4, 3%) and oil (n=3, 2%).

Given the sample's strong preference for tablets/capsules and the limited range of cannabinoid-based products deliverable via this mode, inferential analyses were focused on characteristics and attitudes of respondents citing this as an exclusive preference (see Table 3). The logistic regression model found female sex to be significantly and positively associated with an exclusive preference for tablets/capsules (odds ratio [OR]=1.86 [95% CIs 0.96-3.61]) and previous experience of medicinal cannabis to be negatively associated (OR=0.23 [95% CIs 0.05-1.03]); there was no evidence of interaction between the variables.

Trial- and cannabis-related attitudes and beliefs

Of the 204 respondents, 168 (82%) said they had no trial-related concerns, 12 (6%) indicated they did, and 25 (12%) indicated they were unsure. Concerns elucidated in comments included potential psychological adverse effects (n=14), a need for more information/advice to help them decide about participating (n=8), and concerns regarding addictiveness (n=3), compatibility with other medications (n=2) and legal issues (n=2). Five respondents perceived a need to limit access or expressed concern about a 'slippery slope' to legalisation for recreational use, and 3 others expressed a belief that cannabis would be unlikely to benefit

everyone. Two respondents said they would need to be reassured of evidence for efficacy before participating in a clinical trial. Factors highlighted by single respondents as influencing their decision to participate included the dose required, trial duration, risk of allergy to cannabis, and tolerability in the context of poor liver function.

General comments (n= 122) frequently went beyond poor appetite to refer to symptoms in general or specific others such as pain or nausea. Sixteen (13%) respondents believed that there was sufficient evidence for medicinal cannabis without further clinical trials. Four (3%) respondents reported being in favour of clinical trials because of their potential to facilitate legalisation and so improve access to cannabis. Eleven (9%) reported first-hand anecdotal evidence for efficacy of cannabis in managing symptoms, 8 (6%) reported hearing others report such benefits, and 3 (2%) reported being influenced by positive reports in the media or medicinal cannabis advocates. Five (4%) compared cannabis favourably with other medications in terms of side effects, and one (1%) indicated that he was unable to use alternative medications for symptoms, leaving cannabis as his only option. Six (5%) respondents reported a belief that cannabis might have potential to cure cancer.

Discussion

This study is the first to survey people with advanced cancer willing to consider participation in a clinical trial of medicinal cannabis. It therefore yields new insights into related preferences, attitudes and beliefs, with important implications for future trials.

Tablets/capsules were by far the most preferred mode of delivery for reasons of ease/convenience and familiarity, although a small minority were opposed to tablets/capsules on the grounds that they were already taking large numbers for other medications or had problems with swallowing. Univariate analyses suggested that women and those with no experience of medicinal cannabis were more likely to express an exclusive preference for tablets/capsules. However, these variables showed reduced association in multivariate analysis, with results suggesting that the more common preference for tablets/capsules reported by women was largely accounted for by their lesser experience with medicinal cannabis. This finding may suggest that attitudes vary between people who are considering taking medicinal cannabis for the first time because they are newly conceptualising it as a sanctioned medication versus those whose who have used cannabis outside the auspices of medical care.

After tablets/capsules, the most preferred modes of delivery were mouth-spray and vaporiser. In Australia, nabiximols (a Schedule 8 medication) is currently the only pharmaceutical on the Australian Register of Therapeutic Goods that delivers cannabinoids via the oro-mucosal route, although other oral pharmaceutical products (nabilone, dronabinol) have been accessible via the TGA Special Access Scheme. There is an emerging interest in vaporisation of cannabis for management of symptoms, including neuropathic pain.[21] A recent study has provided evidence of vaporiser acceptability among a large national sample of US cannabis users (N=2,910),[22] suggesting that it may represent a satisfactory alternative to smoking for people used to that mode of delivery.

Comments offered by respondents to the current survey are consistent with findings from previous survey and qualitative studies on medicinal cannabis use. Cannabis users have consistently reported anecdotal evidence for symptom improvement, although the proportion reporting benefit has varied widely.[5-7 10-12 23] The only previous Australian survey (N=128) found that around a quarter of medicinal cannabis users across a variety of health conditions used it for appetite loss, and nearly all reported ‘great’ or ‘good’ relief.[10]

Compared with efficacy, previous studies have paid less attention to side effects of medicinal cannabis use. Side effects have tended to be reported by only a small proportion of respondents, with the exception of a German study which found almost a third of respondents to rate these as 'moderate' or 'strong'. [6] Results from qualitative studies suggest the low emphasis placed on side effects by survey respondents may, in part, reflect a perception that these are favourable compared to other medicines,[10 14 24 25] a perception also voiced by a small number in the current survey.

Small numbers of respondents also seemed unclear that the primary purpose of clinical trials is to test efficacy and held beliefs that cannabis has potential to cure cancer. This suggests that information associated with a clinical trial aimed at evaluating symptom control needs to describe its purposes using language that potential participants can understand, and also highlights the need to balance the rationale for clinical trials with emphasis on equipoise.

Finally, respondents' requests for further information and advice from the medical community is consistent with previous survey results [26] and of special interest given evidence that health professionals themselves hold varying views on medicinal cannabis and report an unmet need for guidance on how best to advise patients.[27 28]

Limitations

Our study's focus on people willing to consider participating in clinical trials of medicinal cannabis means the results are unlikely to be representative of people with advanced cancer more generally. The services participating in the study served diverse metropolitan communities but did not represent regional and rural patient perspectives. Further, the survey measured patient attitudes rather than behaviours, and the latter cannot be assumed to always follow from the first.[29] Also, some respondents may not have reported previous cannabis use because they regarded this to be recreational rather than medicinal. Prior research suggests that users may vary in the degree they distinguish recreational and medicinal use, especially with regard to perceived psychological benefits, which may be seen as falling in both categories.[9 13 14] We did not ask about previous recreational use because the study aims were focused on cannabis in a medicinal context and we sought to minimise ethical issues and response bias associated with disclosure of illegal activity. More research is needed into the relationship between recreational and medicinal use of cannabis in people with chronic illness to better understand related health beliefs and how these influence use over time.

The low prevalence of previous or current medicinal cannabis use within the sample limited analyses regarding the relationship between experience and various perspectives. However, it also provides encouragement for the feasibility of future trials to accrue participants willing to try cannabis for the first time as well as current or previous users. The fact our sample was somewhat younger than population estimates for Australian cancer patients at diagnosis [30] is consistent with the possibility that younger people may be more willing to consider participation in medicinal cannabis trials due to societal attitudes having become more sympathetic over time.

Finally, differences in the recruitment strategy used for our survey vis-à-vis those typical of a clinical trial mean the numbers taking part should not be used to estimate likely accrual rates.

Conclusion

Future trials of medicinal cannabis for advanced cancer symptoms may be more likely to attract and retain patients if preferences for an oral delivery route can be accommodated or alternative routes justified.

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People with advanced cancer may have varying understanding both about cannabis and trials. This should be addressed in trial-related participant information and public communication strategies to optimise recruitment, adherence and retention, and to ensure that consent is properly informed.

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Box 1. Items used in the survey on medicinal cannabis use and related clinical trials

1. Age (in years) 18-25 / 26 – 40 / 41-60 / 61-75 / 76-85 / 85+

2. Sex Male / Female

3. What kind of cancer do you have? _____

4. If you were to take part in a clinical trial of medicinal cannabis for improving loss of appetite, taste problems and weight loss, how would you prefer to take the medication? (Tick all that apply)

Oral – tablets or capsules	
Oral mouth-spray	
Oral – eating (cookies)	
Oral - drinking (tea)	
Inhaled using a special vaporiser	
Suppositories (inserted into the rectum)	
Topical (applied to the skin)	
Other (please describe):	

4a). Please explain the reasons for any preference(s) you have for how to take cannabis

5. Would you have any concerns with using medicinal cannabis in a clinical trial?

Yes / No / Unsure

5a). If 'yes' or 'unsure', please describe any concerns you may have

6). Have you ever used cannabis medicinally for any health problem(s)?

Yes / No (*if no, please skip to question 7*)

6a). If yes, what health problem(s) have you used cannabis for?

6b). How have you usually used cannabis for health problems? (Tick all that apply)

Smoked with tobacco in joint or cone	
Smoked alone in joint or cone	
Vaporiser	

Oral forms/edibles (e.g. cookies, biscuits)

Other (please describe):

6c). If you enrolled in a clinical trial, you would be asked to stop your usual use of medicinal cannabis so that measures could more clearly tell whether any benefits were due to the product being used in the trial. Would this prevent you from taking part?

Yes / No / Unsure

7. Regardless of whether you have used medicinal cannabis, please use the space below to make any other comments you would like to about future cannabis clinical trials

Table 1. Self-reported characteristics of 204 adult patients with advanced cancer and appetite loss, taste problems or weight loss who completed surveys about medicinal cannabis trials and use

Characteristic		**N (%)***
Gender	Male	106 (52)
	Female	96 (47)
Age (years)	18-25	6 (3)
	26-40	14 (7)
	41-60	68 (33)
	61-75	77 (38)
	76-85	30 (15)
	>85	5 (2)
Self-reported cancer type[#]	Blood	37 (18)
	Lung	33 (16)
	Upper GI	36 (18)
	Breast	24 (12)
	Lower GI	17 (8)
	Gynaecological	14 (7)
	Prostate	13 (6)
	Brain	10 (5)
	Other	43 (21)
	Unknown	3 (1)

* Missing data as follows – gender (n=2), age (n=4), cancer type (n=5); [#] 23 patients reported >1 cancer type; GI = gastro-intestinal

Table 2. Patient preferences for modes of delivery in a hypothetical clinical trial of medicinal cannabis for anorexia, appetite loss and taste change from advanced cancer (N=204)

Preferred mode	**N***	**%***
Tablets or capsules	144	71
Mouth-spray	84	42
Vaporiser	83	41
Eating	76	37
Drinking	68	33
Topical	53	26
Suppositories	16	8

* Participants could select >1 preference from the list given

Table 3. Univariate relationships between participant characteristics and an exclusive preference for tablets/capsules as a mode of delivering medicinal cannabis in a hypothetical clinical trial (N=204)

Participant characteristics	Number (%) preferring tablets/capsules only		Results on association
	Yes n=52 (25%)	No n=152 (75%)	
Age*	31 (60%)		
≥60 years	20 (38%)	81 (53%)	χ^2_1 =0.64, p=0.43
<60 years		68 (45%)	
Missing	1 (2%)	3 (2%)	
Sex*			
Male	20 (38%)	86 (57%)	χ^2_1 =4.81, p=0.03
Female	31 (60%)	65 (43%)	
Missing	1 (2%)	1 (0%)	
Trial-related concerns			
Yes/unsure	13 (25%)	24 (16%)	χ^2_1 =2.21, p=0.14
No	39 (75%)	128 (84%)	
Medicinal cannabis user			
Yes	2 (4%)	24 (16%)	χ^2_1 =5.17, p=0.02
No	49 (94%)	122 (80%)	
Missing	1 (2%)	6 (4%)	