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# Cannabis use in sickle cell disease: a questionnaire study

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## Summary

Cannabinoids are increasingly being considered for the management of various painful conditions, and could be considered as an option for treating acute pain in sickle cell disease (SCD). The objective of this study was to determine the extent of use of cannabis in the community for pain and other symptom relief, and its side effects during self-administration in patients with SCD. Patients attending Central Middlesex Hospital in London were invited to complete a structured self-administered anonymous questionnaire. Eighty-six young adults with HbSS, HbSC and HbSβthalassaemia disease (median age 30 years) participated in the study. Results showed that 31 (36%) had used cannabis in the previous 12 months to relieve symptoms associated with SCD. The main route in all but two patients was by smoking. The main reasons for use were to reduce pain in 52%, and to induce relaxation or relieve anxiety and depression in 39%. Symptoms related to sedation and mood effects were reported in 77% of patients. The majority of patients (58%) expressed their willingness to participate in studies of cannabis as a medicine. We conclude that research in the use of cannabinoids for pain relief in SCD would be both important and acceptable to adult patients.

**Keywords:** sickle cell disease, pain, cannabis, cannabinoids.

Pain is one of the predominant symptoms in sickle cell disease (SCD), and is challenging in its management. This pain can be severe enough to require opioid analgesics for relief, can recur acutely at unpredicted intervals, is associated with inflammation and can become chronic, requiring regular analgesic medication with drugs, such as non-steroidal anti-inflammatory analgesics (Rees *et al*, 2003). When SCD management at home was monitored with diaries in children and adolescents, pain was frequent and many patients used single analgesics that were described as ineffective (Fuggle *et al*, 1996; Dampier *et al*, 2002). The frequency and duration of painful episodes in adults has been reported to vary widely between individuals; coping strategies influence the number of painful episodes and pain intensity (Anie *et al*, 2002), with mood being a significant component in opioid analgesia use (Anie & Steptoe, 2003).

Patients with SCD are often treated unsatisfactorily with opioids in both hospital and community settings, and this may be due to inherent problems of pain assessment or the perception of dependency on opioids (Shapiro *et al*, 1997; Maxwell *et al*, 1999). In a recent semi-structured questionnaire study of symptoms of substance dependence and abuse in patients with SCD in London, the results revealed that some coping methods could be perceived as analgesic dependence (Elander *et al*, 2003). One area of SCD pain management that has not been investigated is the use of non-proprietary preparations, such as the illicit cannabinoids found in the cannabis plant. Cannabis is commonly available in the community, and it is plausible that some patients could use it for the relief of pain associated with various medical conditions, including SCD. Nonetheless, little is known about the use of cannabis in the SCD population, and the question arises as to whether patients are using cannabis as an additional drug to improve pain relief in the community.

Cannabis contains a mixture of phytocannabinoids whose synthetic congeners have been extensively been investigated in the laboratory for their effects on pain sensation (Walker *et al*, 1999). In humans, there are few pharmaceutical preparations because of legal restrictions but a whole-plant extract (with the active cannabinoids delta-9-tetrahydrocannabinol, THC, and cannabinoid, CBD, in equal portions) has been reported to significantly improve pain relief in patients with intractable neurogenic pain (Wade *et al*, 2003). In addition, one of the active cannabinoids in cannabis, cannabinoid has been

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demonstrated in rats to have both immunosuppressive and anti-inflammatory effects in chemically induced arthritis (Malfait *et al*, 2000). The combined effects of cannabinoids as analgesics and anti-inflammatory agents suggest that they may have a beneficial therapeutic effect in SCD.

We had anecdotal evidence of cannabis used as analgesia from confidential patient accounts, however the extent of use has never been studied in a systematic way. The aims of this study were therefore to determine the extent of use of cannabis in a cross-sectional sample of adult patients, to document the medical reasons for its administration, and to explore the willingness of patients to consider cannabinoids as an alternative or complementary treatment for pain associated with SCD.

## Methods

Following Local Research Ethics Committee approval we recruited adults with SCD to an anonymous questionnaire survey at the Central Middlesex Hospital (Clinic, Inpatient & Daycare Units). All adult patients were offered a patient information sheet and those who consented verbally were then entered into the study. Written consent was not taken in order to protect anonymity. Questions arising from the survey were addressed during consultations either with the medical, psychology or nursing staff in the Clinic. Patients were requested to complete the questionnaire whilst waiting or given an addressed envelope to return it to the staff.

The questionnaire was initially piloted on a small number of patients during a Clinic. The first questions were about the demographics and clinical characteristics of the patient: this was followed by questions on the use of cannabis. For those patients with a history of cannabis use we asked specific questions about their pattern of use, its effectiveness in symptom control, symptoms or side effects experienced, and whether used recreationally or medicinally. Finally, all patients were asked if they would be willing to use cannabis in the future as part of a clinical trial.

Statistical analysis was performed using GRAPHPAD PRISM (version 3.00). We compared the demographic and clinical characteristics of the patients in the study with profiles from our Sickle Cell Clinic.

## Results

### *Demographics and clinical characteristics*

Eighty-six questionnaires were completed over a period of 6 months, representing about 34% of those who could have participated. Table I shows the distribution of gender, age and haemoglobin types in this study in the 31 patients (36%) who had used cannabis and the non-users (51 patients, 64%). These figures are representative of our total clinic population, where 10% have HbSβthalassaemia, 20% HbSC, and 70% HbSS.

**Table I.** Demographic and clinical characteristics: users and non-users of cannabis.

| | Users | Non-users | Total |
|---|---|---|---|
| Age (years): | 29 [24–40] | 30 [22–39] | 30 [23–39] |
| median, [interquartile] | 18–46 | 15–54 | 15–54 |
| and range | | | |
| Gender | | | |
| Male | 13 (42) | 18 (33) | 31 (36) |
| Female | 14 (45) | 30 (54) | 44 (51) |
| Unknown | 4 (13) | 7 (13) | 11 (13) |
| Haemoglobin type | | | |
| HbSS | 13 (42) | 38 (69) | 51 (59) |
| HbSC | 8 (26) | 12 (22) | 20 (23) |
| HbSBthal | 6 (19) | 2 (4) | 8 (9) |
| Unknown | 4 (13) | 3 (5) | 7 (8) |

Values within parentheses are expressed in percentage.

### *Severity of sickle cell disease*

Sickle cell disease severity was assessed by the frequency of painful episodes in the past year in the community, and resulting hospitalisations. Pain episodes were further subdivided by disrupted or undisrupted activities. SCD severity was further determined by surrogate markers, i.e. number of complications, blood transfusions and hydroxyurea treatment (Table II). The two groups were not significantly different using the chi-square test.

**Table II.** Severity of SCD: users and non-users of cannabis.

| | Total | Users | Non-users |
|---|---|---|---|
| Pain episodes: frequency | | | |
| Less than once a year | 16 (19) | 4 (13) | 12 (22) |
| 1–10 per year | 31 (36) | 13 (42) | 18 (33) |
| Once a month | 15 (17) | 6 (19) | 9 (16) |
| Once a week | 13 (15) | 4 (13) | 9 (16) |
| Daily | 4 (5) | 3 (10) | 1 (2) |
| Pain episodes: disruptive | | | |
| Less than once a year | 26 (30) | 5 (16) | 21 (38) |
| 1–10 per year | 33 (38) | 15 (48) | 18 (33) |
| Once a month | 11 (13) | 3 (10) | 8 (14) |
| Once a week | 6 (7) | 3 (10) | 3 (5) |
| Daily | 1 (1) | 1 (3) | 0 (0) |
| Emergency visits, median [range] | 1 [0–13] | 1 [0–13] | 1 [0–11] |
| Transfusions | 20 (23) | 7 (23) | 13 (24) |
| Hydroxyurea | 13 (15) | 4 (13) | 9 (16) |
| SCD complications | | | |
| Strokes/transient ischaemic attacks | 11 (13) | 4 (13) | 7 (13) |
| Chest syndrome | 28 (33) | 14 (45) | 14 (25) |
| Priapism | 3 (4) | 2 (6) | 1 (2) |
| Gall stones | 23 (27) | 10 (32) | 13 (24) |
| Avascular necrosis | 17 (20) | 5 (16) | 12 (22) |
| Retinopathy | 2 (4) | 0 (0) | 2 (4) |

Values within parentheses are expressed in percentage. SCD, sickle cell disease.

### *First and last cannabis use*

Cannabis was first used at a median age of 16 years of age (range 15–26, interquartile range 15–21). Twelve respondents (39%) had used cannabis within the past week, six (19%) had used it within the past month, two (6%) within the past 6 months and eight people (26%) had not used cannabis for over a year.

### *Frequency, route and time of cannabis use*

In the 31 respondents who reported any cannabis use, detailed questions were asked about route, frequency and time of use. The majority of patients took the cannabis by inhalation (smoking) with only three patients (10%) using the oral route (one patient used both routes). The frequency of use was reported as daily by four patients (13%), weekly by 10 patients (32%), monthly by four patients (13%) and the rest occasionally. Respondents were also asked to state how many times they used cannabis over the period of one week or one day. For the 10 responders (32%) who used cannabis at least once a week the median frequency of use was 3·5 times per week (range 1–6). For the eight responders (26%) who said they used cannabis at least once a day the median number of episodes per day was 2·5 (range 2–6).

Thirteen patients (43%) used cannabis when necessary at any time of day or night and the remainder used cannabis in the evening.

### *Reasons for cannabis use*

Patients were asked in some detail about their reasons for cannabis use to elicit those who were using cannabis for medicinal as opposed to recreational reasons. The questions that were asked and the responses obtained are shown in Table III.

Respondents often gave several reasons for using cannabis, leading to considerable overlap between the different answers. When the answers to these questions were combined and the overlapping answers removed, 16 people (52%) used cannabis for medicinal reasons (taken to be those where cannabis was used to reduce or prevent acute or chronic pain, and to reduce the amount of painkillers taken). There was no evidence of more severe disease in these 16 patients except that avascular necrosis of the head of the femur was more common in those who used cannabis non-recreationally rather than recreationally, with four of 16 people having avascular necrosis in the medicinal group and only one of 15 in the recreational group. A further 12 people (39%) used cannabis to relax, to sleep better to reduce anxiety or depression or to improve mood. These factors may also contribute to pain management. No one in the medicinal group reported using cannabis solely to 'get high' or to improve energy levels. In the recreational group, three of five respondents (16%) who said they used cannabis to 'get high' also said they used cannabis to decrease or prevent acute or chronic pain. The other two respondents who used cannabis to 'get high' said they also used it to relax and to help them sleep. Two respondents (6%) gave no reasons why they had used cannabis, one (3%) had tried cannabis to see what it was like; none of these had used cannabis in the previous year.

### *Side effects from cannabis use*

Beneficial or detrimental side effects from cannabis are shown in Table III.

Sleepiness and mood change were the most common side effects. Eleven of the 13 people who said sleepiness was a side effect also stated that a benefit of cannabis was that it made them sleep better, and four of the 11 people who said that mood change was a side effect of cannabis also said that cannabis improved their mood. Some of the effects of cannabis

**Table III.** Cannabis use, symptoms and side effects.

| | Positive responses |
|---|---|
| Question | |
| I use cannabis when I have acute pain due to sickle cell disease | 7 (23) |
| I use cannabis to help reduce chronic pain due to sickle cell disease | 9 (29) |
| I use cannabis to help me relax | 18 (58) |
| I use cannabis to stop me feeling anxious | 7 (23) |
| I use cannabis to stop me feeling depressed | 7 (23) |
| I use cannabis to prevent me getting pain due to sickle cell disease | 3 (10) |
| I use cannabis to give me energy | 1 (3) |
| I use cannabis to 'get high' | 5 (16) |
| Cannabis reduces my pain when I have an acute crisis | 8 (26) |
| Cannabis reduces my chronic pain | 9 (29) |
| Cannabis reduces the frequency of my painful crises | 7 (23) |
| Cannabis reduces the amount of painkillers I need | 13 (42) |
| Cannabis improves my mood | 11 (35) |
| Cannabis helps me relax | 19 (61) |
| Cannabis helps me feel less anxious or depressed | 16 (52) |
| Cannabis makes me sleep better | 19 (61) |
| Cannabis makes me feel more energetic | 4 (13) |
| Symptom or side effect | |
| Blurred vision | 1 (3) |
| Dizziness | 2 (6) |
| Poor appetite | 2 (6) |
| Memory loss | 3 (10) |
| Sleepiness | 13 (42) |
| Mood change | 11 (35) |
| Anxiety | 5 (16) |
| None | 7 (23) |

Values within parentheses are expressed in percentage.

were therefore seen as either beneficial or troubling by different people and sometimes by the same person. In addition, all of the five people who said that anxiety was a side effect of cannabis also reported that cannabis made them feel less anxious when completing the questionnaire section on why they used cannabis. One person apiece reported increased appetite, inability to concentrate and paranoia.

### *Future use of cannabis*

Fifty patients (58%) said they would be willing to participate in future studies using cannabis for the treatment of pain in SCD. This group consisted of 24 (77%) cannabis users and 26 (47%) non-users. In addition, respondents were asked if they were concerned about dependency on cannabis. Thirty-six respondents (42%) said they were concerned about this, including nine cannabis users (29%) and 27 non-users (49%). Twenty-four respondents (28%) said they would be willing to participate in studies using cannabis despite having concerns about dependency.

## Discussion

The use of cannabis in this population of responders is high and clinically important given the frequent presentation of both acute and chronic pain in this sickle cell community. Severity of SCD did not appear to be a factor in determining cannabis use as there was no significant difference in severity between the group that used cannabis and the group that did not, and the median number of hospital visits was the same in both groups. Use of cannabis was more common in patients with avascular necrosis, which is associated with severe chronic pain. Increasing severity of SCD was not associated with greater cannabis use and conversely, those who used cannabis did not report markedly reduced levels of pain.

The distribution of age, gender and type of SCD found in this study is similar to that observed in our adult clinic population. The incidence of lifetime use and use in the last year are both higher in our population (36% and 27%) than in the general UK population (27% and 9%) (Ramsay *et al*, 2001). However, when our population was compared with other groups, such as those with chronic pain disorders, human immunodeficiency virus (HIV) or multiple sclerosis patients, their rates of cannabis use are very comparable (Prestage *et al*, 1996; Wesner, 1996; Dansak, 1997; Sidney, 2001; Page *et al*, 2003; Clark *et al*, 2004). For example Ware *et al* (2003) investigated 209 patients with chronic non-cancer pain; 35% reported ever using cannabis and 15% had used cannabis for pain relief. In a questionnaire study also from west London in 523 HIV-positive patients, 27% used cannabis to treat symptoms associated with HIV; in more than 90% of users pain was the main symptom (Woolridge *et al*, in press).

Sickle cell disease is a condition where there is evidence that analgesia for both acute and chronic pain is inadequate (Claster & Vichinsky, 2003). In this context of pain that is difficult to manage, cannabinoids are becoming scientifically valid analgesic agents for clinical trials. There are increasing numbers of randomised controlled trials investigating the use of different synthetic as well as plant-derived cannabinoids as analgesic agents. An early review of these studies found that there was no evidence for their efficacy in pain relief, but small numbers of patients were involved, together with different preparations with differing pharmaceutical properties (Campbell *et al*, 2001). Several small studies have shown improvement in pain control in patients with multiple sclerosis and post-operatively when cannabinoids have been used (Noyes *et al*, 1975a,b; Zajicek *et al*, 2003; Svendsen *et al*, 2004). There is evidence therefore that cannabis may have a role as an analgesic agent in patients with SCD.

Cannabis may have a further role as an adjuvant analgesic agent to allow decreased use of other analgesic agents, such as opioids. A synergistic interaction between opioids and cannabinoid systems has been described (Welch & Eads, 1999), but further work is needed to clarify the hypothesis of synergy between cannabinoids and opioids. This interaction was suggested by the findings of Holdcroft *et al* (1997) where the use of oral THC enabled a patient with 'Familial Mediterranean Fever' to decrease their intake of opioids. In the present study, 42% of cannabis users stated that they used cannabis to decrease the amounts of other pain analgesia required.

There was a high rate of side effects from cannabis use described in this study, and was reported in 78% of users. Some were beneficial, for example 11 of the 13 people who described sleepiness as a side effect of cannabis also described help with sleeping as a benefit of taking cannabis. Similarly, all of those who described anxiety as a side effect of cannabis also described cannabis as making them less anxious. These varied effects may explain why the high incidence of side effects does not seem to deter patients from taking cannabis. In addition, opioid analgesics that are used to treat acute SCD pain also have high rates of side effects that are also more life-threatening, so that patients are likely to be attracted to any methods of decreasing the dose and frequency of opioid analgesia.

This study investigated the issues of concern about the use of cannabis in clinical trials. In the community, the main route of administration is by inhalation, often with tobacco, but this cannot be encouraged in the sickle cell population because of their risk of acute and chronic chest disease. For clinical trials different preparations are being developed, such as capsules, sublingual sprays, suppositories and topical formulations. Concerns about dependency have been raised by our respondents and in the scientific community about the psychiatric side effects of cannabis, particularly in adolescence (Arseneault *et al*, 2004) and in the black community. Confounding factors in such analyses are the problems of recreational use with the potential for high doses to be used and the lack of standardised preparations. It is reassuring that a recent meta-analysis (Macleod *et al*, 2004) found no evidence for causation of mental health problems in young cannabis users, however a

possibility that such a relationship exists cannot be excluded. Also of concern in this group of patients, who have a high incidence of stroke, is the reported association between stroke and cannabis use (Mateo *et al*, 2005).

This study provides a degree of evidence that cannabis is efficacious in this group of patients in whom current treatments are inadequate. To allow them to use cannabis safely there is a need for a standardised legal preparation and clinical evidence of its efficacy. The next stage of investigation should be to develop a trial protocol to use oral cannabinoids in the treatment of acute sickle cell pain for which there is adequate support in our clinic population.

## Competing interest

Anita Holdcroft is a member of the Napp Specialist Opioid Advisory Group on drug dependency.

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