

# The Use of Cannabis by Patients with Sickle Cell Disease Increased the Frequency of Hospitalization due to Vaso-Occlusive Crises

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## Abstract

**Introduction:** The objective of this study was to determine if patients with sickle cell disease using cannabis had decreased frequency of acute vaso-occlusive crises (VOCs) that required hospitalization.

**Method:** This was a retrospective study in which 270 urine drug screen tests were done on 72 patients: 40 males and 32 females.

**Results:** Cannabinoids were found in 144 urine tests from 37 patients and were negative in 126 tests from 35 patients. Males who used cannabis were significantly younger ( $p < 0.001$ ) than males who did not. Patients who tested positive used benzodiazepines, cocaine, and phencyclidine significantly more often than patients who tested negative. There was no significant difference in the amounts of opioids consumed by users and non-users of cannabis. The cannabis cohort was seen in the clinic significantly ( $p < 0.05$ ) less often than controls, but hospital admissions were significantly greater in the cannabis group than controls ( $p < 0.05$ ).

**Conclusion:** These data show an unexpected negative effect of cannabis on the frequency of VOCs. This may be due to the effect of cannabis on the brain and/or the severity of the disease in the cannabis users. More controlled studies are needed to clarify these findings.

**Keywords:** cannabinoid; cannabis; sickle cell disease; VOC

## Introduction

The distinguishing insignia of sickle cell disease (SCD) in general and sickle cell anemia in particular is the recurrent acute painful vaso-occlusive crisis (VOC).<sup>1</sup> Treatment of VOC is mostly symptomatic with analgesics and additional supportive therapies, such as rest, heat, massage, physical therapy, meditation, etc.<sup>2,3</sup> Opioid therapy, however, has been the major approach to VOC therapy as shown by evidence from some randomized controlled trials (RCTs), observational studies, and reviews.<sup>4-8</sup> Moreover, in about 55% of adults and 9% of children persistent pain occurs between recurrent VOCs and requires treatment with opioids at home.<sup>9-11</sup> Adjuvants and NSAIDs are often used in addition to opioids.<sup>12,13</sup> Recently, novel therapies such as rivipansel (GMI-1070), intravenous magne-

sium, polaxamer-188, inhaled nitric oxide, lidocaine, and low-molecular-weight heparin are being tried or have been tried for the treatment of VOCs.<sup>14-19</sup>

More recently, there has been popular interest in using cannabis as an analgesic for various types of pain.<sup>20</sup> Medical cannabis is used to treat many indications, a few of which have evidence to support treatment with cannabis and many that do not.<sup>21</sup> There is some evidence supporting the idea that cannabis may reduce symptoms of spasticity associated with multiple sclerosis (MS),<sup>22</sup> HIV/AIDS-related cachexia,<sup>23</sup> and chemotherapy-induced nausea and vomiting.<sup>24</sup> Moreover, cannabis may reduce neuropathic pain<sup>25,26</sup> and possibly some other pain conditions.<sup>22,27,28</sup> However, for the almost 30 other indications for which medical cannabis has been approved across the U.S., the

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evidence is of very low quality.<sup>28</sup> That cannabis should have “beneficial” effects for conditions as diverse as amyotrophic lateral sclerosis, MS, ulcerative colitis, or posttraumatic stress disorder,<sup>29</sup> which have no common pathophysiology, raises questions about the evidence supporting its use. Furthermore, cannabis is associated with abuse, dependence, psychosis, cognitive deficits, etc.<sup>30–32</sup> Given the advent of the legal status of cannabis, RCTs on the efficacy and safety of cannabis or its constituent cannabinoids are urgently needed.<sup>25,33–35</sup>

This state of affairs raised the question about the role of cannabis in the management of VOC. Studies in the transgenic sickle cell mouse showed that cannabinoid receptor-specific mechanisms ameliorate pain through inhibition of mast cell activation and neurogenic inflammation.<sup>36</sup> A questionnaire study from the United Kingdom showed that 36% of the patients with SCD have used cannabis in the previous 12 months to relieve symptoms of SCD.<sup>37</sup> In another longitudinal questionnaire study, Knight-Madden et al. found that cannabis smoking is common in adults with SCD in Jamaica, but its usage was not related to the clinical severity of the disease.<sup>38</sup>

The objective of this study is to report the epidemiological and clinical features of the patients with SCD who were found to be taking cannabis by using random urine drug screening. The frequency of VOCs in these patients was compared with patients with SCD, whose urine drug screening showed no cannabis. The term cannabis and cannabinoid will be used interchangeably in this report.

## Materials and Methods

### Patients

The patients described in this study were adult African Americans with SCD that were followed-up in our sickle cell center from 1994 through 2009. The Sickle Cell center was supported by the Sickle Cell Program of the Department of Health of the Commonwealth of Pennsylvania for the Philadelphia Region. Written consent was obtained from patients for enrollment in the program. The patients agreed to have random urine drug testing be done as needed. The Department of Health required the submission of quarterly reports describing the activities of our center. These included, among other things, the number of admissions to the emergency department (ED), admissions to the hospital, clinic visits, and types of SCD, complications, and management. The program and its various activities

were approved by the IRB. Some data in this study were obtained retrospectively from patients’ paper charts and electronic medical records (laboratory data, demographics, discharge summaries, etc.).

### Laboratory data

Types of SCD were initially determined by solubility testing, hemoglobin electrophoresis in alkaline and acidic media, and thin-layer isoelectric focusing, and later, by high-performance liquid chromatography. Urine samples, collected randomly, were analyzed for the presence of amphetamine, benzodiazepines, opiates, barbiturate, cannabinoid, propoxyphene, methadone, and phencyclidine. The analytical cutoff for amphetamine was 1000 ng/mL; for benzodiazepine and barbiturate 200 ng/mL; for opiates, cocaine, propoxyphene, and methadone 300 ng/mL; for phencyclidine 25 ng/mL; and for cannabinoid 50 ng/mL. (The cannabinoid chemical tested in urine is actually 11-nor-9-carboxy- $\Delta^9$ -tetrahydrocannabinol.) Samples were classified as either positive or negative for cannabinoid.

### Statistical analysis

The paired *t*-test was used to compare the epidemiological data of the patients in the study. The chi-square statistic and Fisher’s exact tests with 2×2 contingency tables were used to compare the samples that were positive or negative for cannabinoid.

## Results

A total of 322 urine drug screen tests were done on 85 patients with SCD during the study period. Of these, 52 tests did not include screening for cannabinoid and 13 patients were not tested for cannabinoid. These were excluded from this study. The remaining 270 urine drug screen tests done on 72 patients (10% of our patients with SCD during the period of the study) are included in this retrospective report.

Table 1 shows the major epidemiological and clinical feature of the patients studied. Although the number of males who used cannabis was 2.4 times the number of females, there was no significant difference in their ages ( $p > 0.05$ ). Similarly, there was no significant difference between the ages of males and females who tested negative for cannabinoid ( $p > 0.05$ ). However, males who used cannabis were significantly younger ( $p < 0.001$ ) than males who did not (Table 1). Moreover, the ages of females who tested positive for cannabinoid were not significantly different from women who tested negative (Table 1).



**Table 1. Epidemiological and Clinical Features of the Studied Patients with Sickle Cell Disease**

|                                 | Positive for cannabinoid     | Negative for cannabinoid     | <i>p</i> <sup>a</sup> | Total                        |
|---------------------------------|------------------------------|------------------------------|-----------------------|------------------------------|
| Age (years)                     | (37) 32.1 ± 7.3 <sup>b</sup> | (35) 36.0 ± 8.4 <sup>b</sup> | < 0.05                | (72) 33.3 ± 7.8 <sup>b</sup> |
| Age of males (years)            | (26) 31.6 ± 8.0 <sup>b</sup> | (14) 36.3 ± 8.0 <sup>b</sup> | < 0.001               | (40) 32.5 ± 8.2 <sup>b</sup> |
| Age of females (years)          | (11) 32.8 ± 6.1 <sup>b</sup> | (21) 35.9 ± 8.7 <sup>b</sup> | > 0.05                | (32) 34.1 ± 7.4 <sup>b</sup> |
| Number of urine tests           | 144                          | 126                          | > 0.05                | 270                          |
| Sickle cell anemia <sup>a</sup> | 28                           | 27                           | > 0.05                | 55                           |
| Hb SC disease                   | 8                            | 7                            | > 0.05                | 15                           |
| Hb SO arab                      | 1                            | 1                            | > 0.05                | 2                            |

<sup>a</sup>Includes patients with *Sβ<sup>0</sup>* Thalassemia.

<sup>b</sup>(Number) mean ± standard deviation.

Hb, hemoglobin; N/A, not applicable.

Table 2 shows that the patients who tested positive for cannabinoids used other illicit drugs more often than patients who tested negative for cannabinoid. Thus positivity for benzodiazepines, cocaine, and phencyclidine were significantly higher in patients who used cannabis than the nonusers (*p* < 0.001 for benzodiazepines and *p* < 0.01 for cocaine and phencyclidine). None of the patients in both groups tested positive for amphetamine. Given that the analytical cutoff for amphetamine was relatively high (1000 ng/mL), the absence of amphetamine may not be true. Notably, there was no significant difference in the amounts of opioids consumed by users and nonusers of cannabis.

Table 3 shows that hospital admissions were significantly greater in the cannabis group than controls (*p* < 0.05). However, the cannabis cohort was seen in the clinic significantly (*p* < 0.05) less often than controls, but the ED admissions were similar in both cohorts (*p* > 0.05).

## Discussion

Patients whose urine was positive for cannabinoid were counseled and referred to Psychiatry and/or Addiction Medicine for further management. Repeat testing was negative and remained negative in some patients, but

**Table 2. Number of Urine Tests Positive for Other Drugs in Each Cohort of Patients**

| Drug                 | Positive for cannabinoid | Negative for cannabinoid | <i>p</i> <sup>a</sup> |
|----------------------|--------------------------|--------------------------|-----------------------|
| Amphetamine          | 0                        | 0                        | —                     |
| Barbiturate          | 7                        | 2                        | 0.1.0                 |
| Benzodiazepine       | 45                       | 2                        | < 0.001               |
| Cocaine              | 37                       | 16                       | < 0.01                |
| Opioids <sup>b</sup> | 122                      | 109                      | 0.07                  |
| Phencyclidine        | 14                       | 1                        | < 0.01                |

<sup>a</sup>Fisher's exact test.

<sup>b</sup>Includes codeine, dilaudid, methadone, morphine, opiates, oxycodone, oxymorphone, and propoxyphene.

fluctuated between positive and negative for cannabinoid in others.

All patients who tested positive for cannabinoid admitted smoking cannabis on a regular basis and indicated that the reason for doing this was to achieve better pain relief. Other reasons included the desire to achieve relaxation and manage anxiety/depression syndromes. Similar to previous reports,<sup>37,38</sup> males used cannabis more often than females and the use of cannabis was significantly higher in younger males than males in the control group.

The most important finding in this study is that, patients who tested positive for cannabinoid were admitted to the hospital for the treatment of VOCs significantly more often than patients in the control group, and they were seen significantly less often in the clinic. Neither the placebo effect of cannabis nor the expectations of pain reduction by its users were operative in this study. It seems the severity of the disease, the use of cannabis, and the use of other illegal drugs conspired to make the disease worse, which required more hospital admissions. Why this combination makes the disease worse is unknown. A possible reason why the use of cannabis did not decrease the frequency of hospital admissions due to VOC may be the severity of their disease as far as pain is concerned. However, priapism (seven in the positive group, eight in the

**Table 3. Frequency of Clinic Visits and Admissions to Emergency Department and Hospital of Patients Positive or Negative for Cannabinoid**

| Positivity to cannabinoid | Number of urine tests | Clinic visits | ED admissions | Hospital admissions |
|---------------------------|-----------------------|---------------|---------------|---------------------|
| Negative                  | 126                   | 1325          | 4147          | 1602                |
| Positive                  | 144                   | 1138          | 4977          | 2443                |
| <i>p</i> <sup>a</sup>     | N/A                   | < 0.05        | > 0.05        | < 0.05              |

<sup>a</sup>Chi-square test.

ED, emergency department.



negative group), mortality (six patients in each group), and other complications of SCD were not significantly different ( $p > 0.05$ ) in both cohorts. Patients who tested positive for cannabinoid seem to be a subgroup of patients with severe SCD associated with constantly increasing transmission of painful stimuli associated with central sensitization, glial activation, and rewiring of the brain.<sup>39</sup> Consequently, these patients constantly seek more legal and illegal medications in search for pain relief. This may explain why these patients used more benzodiazepines, cocaine, and phencyclidine than patients who did not use cannabis. Interestingly the patients with positive urine drug screen for cannabinoid did not use opioids more frequently than the control group.

Another possibility is that the patients smoked cannabis. Utilization of cannabis by other routes may have a better effect; specifically in an experiment with transgenic sickle mice, pain was attenuated when given cannabinoids intraperitoneally.<sup>40</sup> Accordingly, the administration of cannabis by other routes than smoking may be more beneficial. The reason why patients taking cannabis went to the clinic less frequently is not known. One possibility is that the patients believed that the analgesics prescribed by the provider would not be helpful to them anyway. Another possibility is that since they were in the hospital most of the time, they had less days as outpatients to go to the clinic.

### Neuronal mechanism of action of cannabis

Neurologically the reason why cannabis increased the frequency of VOCs that required hospitalization may be related to the shift from goal-oriented to habit-oriented behavior caused by cannabis. Cannabinoids exert their action through binding to G-protein receptors located throughout the body.<sup>36</sup> These include CB1 and CB2 receptors. THC binds preferentially to CB1 receptors and CBD binds preferentially to CB2 receptors. CB1 receptors mediate the psychoactive aspects of cannabinoids and CB2 receptors play a role in pain relief. Normally, activity of orbitofrontal cortex (OFC) neurons project to OFC-dorsal striatum (DS) neurons. Activity of the OFC-DS terminals is believed to be necessary for goal-directed behavior. Deletion of CB1 receptors from OFC-DS neurons in mice prevented the shift from goal-directed to habit-directed behavior.<sup>41,42</sup> Accordingly, a herbal cannabis drug that is THC-rich may preferentially activate the CB1 Receptors which, in turn, may promote the shift from goal-oriented to habit-oriented behavior and maximize

the psychoactive effects of the drug. In clinical terms, this shift may encourage patients to reflexively seek help in the hospital rather than in the clinic.

In summary, the role of cannabis in treating the VOC of patients with SCD needs further exploration. The longitudinal questionnaire study in Jamaica<sup>38</sup> showed no relation between the use of cannabis and the clinical severity of SCD. This study showed a negative correlation between the use of cannabis and the frequency of VOCs that required hospitalization. Controlled trials that utilize standardized doses of cannabis are needed to clarify the role of cannabinoids in the treatment of sickle cell pain. Such a trial is in its early phase.<sup>43</sup>

### Acknowledgment

This study is supported in part by the Sickle Cell Program of the Commonwealth of Pennsylvania for the Philadelphia Region.

### Author Disclosure Statement

No competing financial interests exist.

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**Cite this article as:** Ballas SK (2017) The use of cannabis by patients with sickle cell disease increased the frequency of hospitalization due to vaso-occlusive crises, *Cannabis and Cannabinoid Research* 2:1, 197–201, DOI: 10.1089/can.2017.0011.

#### Abbreviations Used

DS = dorsal striatum  
ED = emergency department  
MS = multiple sclerosis  
OFC = orbitofrontal cortex  
SCD = sickle cell disease  
VOC = vaso-occlusive crisis

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