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Clinical impact of Medicinal Cannabis on Patients with Sickle Cell Disease Pain: A scope review

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ABSTRACT

Clinical impact of Medicinal Cannabis on Patients with Sickle Cell Disease Pain: A scope review.

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Objective: A systematic review to investigate the efficacy and safety of medicinal cannabis on clinical outcomes of patients suffering from sickle cell anemia pain. *Data sources*: The following databases were searched: PubMed, COCHRANE, LILACS and Science Research from inspection up to March 8th, 2022. No restrictions applied. The terms used for search were sickle cell anemia and cannabis and their synonyms. *Study selection*: We included Non-Randomized Studies (NRS) and Randomized controlled trials (RCTs) evaluating Cannabis Medicinal for Pain originating from Sickle Cell Disease (SCD). *Data extraction*: Reviewers independently screened potentially eligible articles; extracted data from included studies on populations, interventions and outcomes and assessed their risk of bias. *Data synthesis*: 1 RCT including 34 participants and 5 NRS, including a total of 37871 participants, proved eligible. We could not find enough publications to further proceed with a meta-analysis. *Conclusions*: There is no evidence in the literature about treating pain

from sickle cell anemia with cannabis. There is an association between cannabis use and hospital emergency department visits.

Keywords: medicinal cannabis, sickle cell anemia, pain

INTRODUCTION

Sickle cell disease (SCD) is an umbrella term that defines a group of inherited diseases (including sickle cell anaemia (SCA), HbSC and HbSβ-thalassaemia) characterized by mutations in the gene encoding the haemoglobin subunit β[1]. One of the most frequent and debilitant complications of the disease is the vaso-occlusive crisis (VOC), which is mediated by multicell adhesion between red blood cells (RBCs), white blood cells, platelets, and endothelial cells and causes intense pain in consequence of impaired oxygen supply, but also infarction-reperfusion injury[2,3].

Previous studies suggest that more than 90% of acute hospital admissions from SCD patients are due intense pain crisis[4,5]. Episodes of acute pain vary in frequency, with an average from one to three episodes per year, and although pain presentation in vaso-occlusive crisis is primarily nociceptive. Yet, since SCD patients exhibits a significative degree of central sensitization and hypersensitivity of nociceptors associated with neuropathic pain neuropathic pain may also implicated in this process[6].

Long-term daily oral hydroxyurea treatment has been shown to reduce or prevent many acute and chronic complications of SCD, as well the need of erythrocytes transfusions and hospitalizations. Therefore, it's recommended to adults with SCD who had experienced more than 3 vaso-occlusive crises during the previous year or in those in which SCD results in significant interference with daily activities or quality of life. Parenteral opioids are the flagship treatment for patients facing an acute pain caused by vaso-occlusive crises[7]. Still, a multicenter randomized controlled trial showed 44% reduction in the median incidence of painful crisis per year (2.5 crisis per year in hydroxyurea group vs 4.5 in control group, $p<0.001$)[8]. However, the use of hydroxyurea is associated with increased presence of neuropathic pain in this population, which may reflect the severeness of disease as a criterion for this substance use[9].

Current American Society of Hematology guidelines for SCD recommends that patients with acute pain should receive opioid therapy within 1 hour of emergency department arrival, with frequent reassessments, associated with short courses of non-steroidal antiinflammatory drugs (NSAIDs)[10]. Regarding the neuropathic character of SCD pain, first-line treatment includes antidepressants, especially tricyclic ones (such as amitriptyline), and serotonin norepinephrine reuptake inhibitors, such as duloxetine and venlafaxine; while opioids are considered as second-line therapy, primarily due to their side effects and potential for abuse[6]. Despite the

great need for the use of opioids by patients with SCD, which theoretically would make them more susceptible to addiction, data show even a lower prevalence than in other painful syndromes or the general population, with prevalence for opioid addiction among patients with sickle cell disease ranging from 0.5% to 8% vs 3% to16% in patients with other chronic pain syndromes and 4.8% in general population (excluding heroin)[11].

Recently, *Cannabis* has been associated with analgesic and anti-inflammatory effects in oncologic and non-oncologic pain. Its main components with therapeutic action are δ9-Tetrahydrocannabinol (THC), the main component with psychoactive action in the Central Nervous System (CNS), and Cannabidiol (CBD), with pharmacological action in the CNS but without psychoactive action[12]. A systematic review and meta-analysis suggested that cannabis is moderately efficacious for treatment of chronic pain, however its use may cause significative side effects, specially related to the central nervous system[13].

Despite the growing number of studies on the therapeutic potentials of medicinal cannabis, there is no systematic review addressing this topic in populations of SCD patients. Therefore, the objective of this study was to assess the efficacy of cannabinoid derivates in thetreatment of pain related to this condition and their potential adverse effects.

METHODS

The present systematic literature review was conducted in accordance with the PRISMA (Preferred Reposting Items for Systematic Reviews and Meta-analysis) statement, as mentioned in the Cochrane Handbook for Intervention Reviews[14-23]. It was registered at PROSPERO International Prospective Register of Systematic Reviews (http:// www.crd.york.ac.uk/prospero/index.asp), under the number CRD 42020212950.

Eligibility criteria

We considered all observational studies and randomized controlled trials (RCTs) evaluating the use of medicinal cannabis for SCD patients with chronic pain. We excluded participants under 18 years of age, pregnant women, patients who were unable to read or comprehend an informed consent, patients with neurological or behavioral disorders or with drug addiction. Eligible studies reported one or more of the following: a) Pain measured by any validated tool such as the visual analogue scale (VAS); b) Quality of life; c) Mood; d) Self-reported adverse outcomes such as dizziness or sedation; e) Hospital visits or admissions; and f) Opioid consumption.

Data source and searches

The search was performed in the following electronic databases: The Cochrane Central Register of Controlled Trials (CENTRAL, 2022), PubMed (OvidSP, 1966 to 2022), LILACS (Literatura Latino-americana e do Caribe

emCiências da Saúde) (1982 to 2022). The databases were searched for available published and unpublished studies from inception up to March 8th, 2022. The search was conducted using multiple combinations of the following key words: "Cannabis" and "Sickle Cell Anemia"). No restrictions were placed on language, year of publication or publication status. In addition, a manual search of the reference lists of potential primary studies was conducted, and the ScienceResearch.com database was hand-searched for additional eligible studies.

Selection of studies

Using pre-standardized screening forms and protocols, two reviewers (IPS and JEGP) independently screened all titles and abstracts identified by the literature search, obtained full-text articles of all potentially eligible studies, and evaluated these studies for eligibility. Reviewers resolved disagreement through discussion, with third party adjudication if necessary.

Data extraction and risk of bias assessment

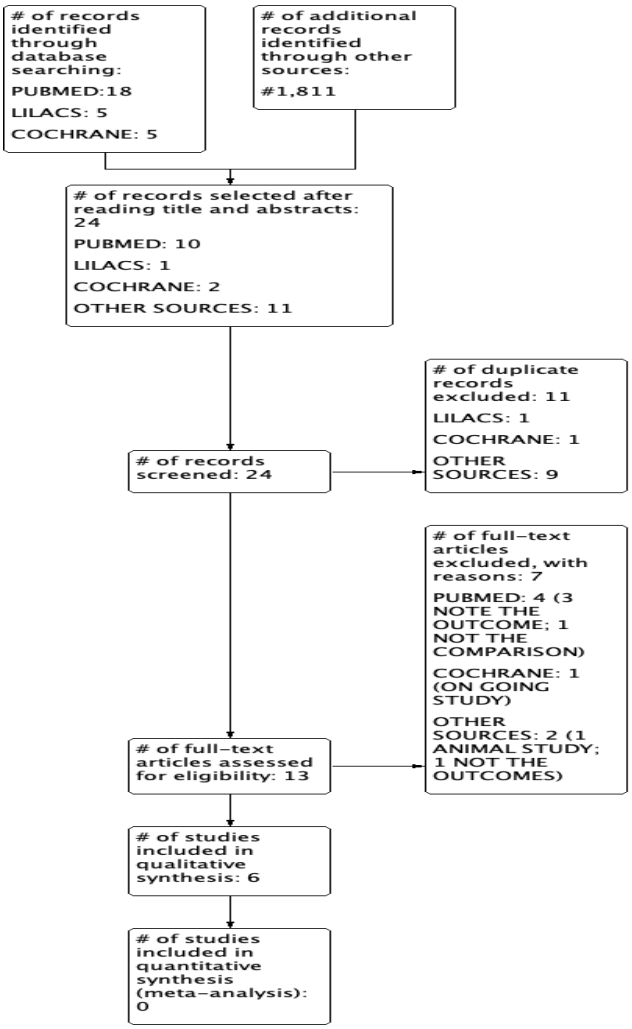
Two reviewers (IPS and JEGP) independently extracted the following data using a pre-standardized data extraction form: characteristics of the study design; participants; interventions; outcomes, event rates and follow-up. Reviewers to identify missing data and confirm data accuracy of eligible studies contacted authors of eligible studies. Reviewers independently assessed risk of bias of included studies by using the risk of bias approaches for Cochrane reviews: modified by Guyatt[15-16] for randomized controlled trials and the risk of bias instrument approach by Morgan for non-randomized studies[23]. We used the following five separate criteria for Randomized Controlled Trials: adequacy of sequence generation, allocation sequence concealment, blinding (investigators, patients, collectors, statistician, outcome assessors), incomplete outcome data, selective outcome reporting. For incomplete outcome data, we considered loss to follow-up of 10% and a difference of 5% in missing data between intervention and control groups as low risk of bias. We also used the risk four separate criteria for Cohort studies: eligibility criteria, measurement of outcome and exposure, adequate control for confoundings and adequate follow-up.

RESULTS

Search results

We identified a total of 1839 citations (Figure 1). After screening by title, and then by abstract, and excluding duplicates, we obtained full-text copies of 13 citations that were potentially eligible for inclusion in the review. Of these, 6 studies did not meet our eligibility criteria and were excluded. We therefore included 01 RCTs[24] with a total of 34 participants and 5 NRS [Ballas; Curtis and Brandow; Howard; Curtis et al; Wilson][24-28] with a total of 37871 participants. No additional eligible studies were identified based on additional search.

Figure 1. PRISMA flowchart.



Characteristics of the included studies

One of the 6 included studies was reported as a RCT. Only one study took place in Europe[25]; 5 studies took place in the USA[24,26-29]. The studies included both male and female participants and the mean age of the participants in the cannabis control groups were 32.2 and 33.6 years of age respectively. Abrams 2020 included adult SCD patients with chronic pain admitted to a single inpatient clinical research center and excluded patients with severe coronary artery disease, uncontrolled hypertension, cardiac ventricular conduction abnormalities, orthostatic mean blood pressure drop of greater than 24 mmHg, severe chronic obstructive pulmonary disease, history of renal or hepatic failure, evidence of clinically significant hepatic or renal dysfunction based on judgment of physician, active substance abuse, neurological dysfunction or psychiatric disorder severe enough to interfere with assessment of pain, current use of smoked tobacco products or a confirmed cotinine level, pregnant or breast-feeding women, or not practicing adequate birth control. Three studies [Ballas; Curtiss; Wilson][25-26,28] were retrospective and the remaining two were cross-sectional [Curtiss and Brandow; Howard][24,27], therefore did not report the follow-up time. (Table 1). Sample sizes ranged from 50 (18) to 37307 (20) participants (Table 1).

In Abrams, 2020 the control group received vaporized placebo cannabis from which the cannabinoids had been extracted and the intervention group received cannabis plant material containing 4.4% THC and 4.9% CBD, which were vaporized in a vaporizer. Patients continued their outpatient analgesic regimen with additional inpatient analgesics prescribed as needed for increased pain (Table 2).

Risk of bias in individual studies

Randomized Controlled Trial

Abrams 2020 was the only RCT included in this review, and although risk of bias issues deriving from conflict of interest could arise, the results from this RCT did not favor the spon-

sors. Thus the overall risk of bias was considered low (Table 3).

Table 1. Characteristics of included studies according to population and setting.

Author year	Country	Number of included participants	Mean age per studied group	Sex (male, n)	Inclusion criteria	Exclusion criteria	Follow-up (weeks)
Abrams 2020	USA	23	C-P: 41,7 P-C: 33,8	C-P: 4, 11 P-C: 5, 12	Adults with Hb SS and chronic SCD-related pain receiving opioid analgesic therapy.	Patients with severe CAD, uncontrolled hypertension, cardiac ventricular conduction abnormalities, orthostatic mean blood pressure drop of greater than 24 mm Hg, severe COPD, history of renal or hepatic failure, evidence of clinically significant hepatic or renal dysfunction based on judgment of physician, active substance abuse, neurological dysfunction or psychiatric disorder severe enough to interfere with assessment of pain, current use of smoked tobacco products or a confirmed nicotinine level, pregnant or breast- feeding women, or not practicing adequate birth control.	2 periods of 5 days
Howards 2005	UK	86	Users:29 Non-users:30	Users: 13, 31 Non-users: 18, 55 (cross-over study)	Adults with SCD attending hospital.	Not reported.	Cross-sectional
Ballas 2017	USA	72	Positive: 32.1 Negative: 36.0	Not reported	Adult African Americans with SCD that were followed–up in our sickle cell center.	Not reported.	1994-2009
Curtis 2020a	USA	75	OC: 30.9 ± 7.6 DOC: 34.4 ± 13.1 DRC: 36.3 ± 12.8	OC: 59% DOC: 38% DRC: 36%	Patients seen in a academic medical center with an adult sickle cell program	History of psychosis or controlled substance diversion.	2016-2018
Curtis 2020b	USA	49	DU: 34.3 – 14.7 O: 31.8 – 8.2	DU: 50% O: 40%	Subjects enrolled were adults with a diagnosis of SCD (HbSS, HbSC, HbSb+ , or HbSb0) who presented for regular scheduled clinic visits during the enrollment period.	Patients were excluded if they had any complaint of acute pain or illness, were pregnant, or were unable to offer informed consent.	Cross-sectional
Wilson 2020	USA	291	<25: Not reported >25: Not reported	<25: 47.9% >25: 45.5%	Patients recruited in the waiting rooms of outpatient adult and pediatric hematology clinics, had	Not reported.	Cross-sectional

(continued) Wilson 2020					to be 15 years of age or older at time of enrollment, diagnosed with a sickle cell hemoglobinopathy, report no plans to relocate in three years, and report willingness to adhere to study procedure.		

C-P: Cannabis-Placebo; P-C: Placebo-Cannabis; OC: Obtained certification; DOC: Did not obtain certification; DRC: Did not request certification; DU: Daily Users; O: Other users; <25: younger than 25 years old; >25: older than 25 years old; Hb: hemoglobin; CAD: Coronary Artery Disease; COPD: chronic obstructive pulmonary disease.

Table 2. Study Characteristics related to description of intervention and comparator, and outcomes.

Author year	No. of randomized patients in intervention and control	Description of intervention	Dose	Description of control	Measured outcomes
Abrams 2020	I:12 C:1	Participants were admitted for 2 inpatient stays of 5 days and 4 nights in the clinical research center that were separated by at least 30 days. During 1 stay, participants inhaled vaporized cannabis 3 times daily. During the other stay, they inhaled vaporized placebo cannabis (from which the cannabinoids had been extracted).	Dose: Plant Material containing 4.4% THC and 4.9% CBD.	Plant material from which cannabinoids had been extracted.	Opioid use, pain intensity (VAS) and adverse effects (anxiety, sedation, disorientation, paranoia, confusion, dizziness, nausea).

Non-randomized studies

1. Bias due to confounding was considered critical in two studies [Curtis and Lew 2020; Howard 2005][24,26]. And considered to be serious in one study [Ballas 2017][25] because they did not correct the groups for confounding factors (Table 4).
2. Bias in selection of participants was considered to be serious in one study [Howard 2005][24] because selection was offered, and not encompassing all the patients (Table 4).
3. Bias in classification of exposures was considered moderate in three studies [Curtis and Brandow 2020; Wilson 2020; Howard 2005][24,27-28] because information was self reported (Table 4).

4. Bias due to missing data was considered serious in all studies [ref] due to the design of the studies (Table 4).

Table 3. Risk of Bias of Randomized Controlled Trials.

Author **year**	**Abrams** **2020**
Was the randomization sequence adequately generated?	Probably yes
Was allocation adequately concealed?	Definetely yes
Was there blinding of participants?	Definetely yes
Was there blinding of caregivers?	Definetely yes
Was there blinding of data collectors?	Definetely yes
Was there blinding of staticians?	Probably yes
Was there blinding of outcome assessors?	Definetely yes
Was loss to follow-up (missing outcome data) infrequent?*	Probably yes
Are reports of the study free of suggestion of selective outcome reporting?	Definetely yes
Was the study apparently free of other problems that could put it at a risk of bias?	Probably yes

Effectiveness of interventions

Randomized Controlled Trial

Not statistically significant results

Pain

Results from one RCT[24] including 90 participants suggested a NON- significant reduction of pain with the use of vaporized cannabis compared to standard of care on day 1 [(MD −5.3 y 1: 0.27 [0.35]; day 5: −1.0 [0.5]), walking (day 1: 0.14 [0.73]; day 5: −0.87 [0.63]), sleep (P= .12)] OIS:09, on day 3 [(MD −16.5 SD(9.2) (P = .07)] OIS:07, on day 4 [(MD −8.9 SD(6.7) SD(8.1) (P = .51)]. Optimal Information Size (OIS): 84, on day 2 [(MD−10.9 SD(7.0)

Opioid Use

There was no statistically significant difference between cannabis and standard of care on opioid use (2.05 [0.21] vs 2.09 [0.22]; P = .20)[24].

Quality of Life

There was for interference in general activities (day 1: 0.59 [0.74]; day 5: −1.3 [0.8]), and joyment (day 1: 0.23 [0.69]; day 5: −0.91 [0.48])[24]. (P = .19)] OIS:12, and on day 5 [(MD −8.2 SD(8.1) p= 0.32] OIS: 21.

Table 4. Risk of bias of non-randomized studies.

Author year	**Ballas 2017**	**Curtis and Brandow 2020**	**Curtis and Lew 2020**	**Howard 2005**	**Wilson 2020**
Was control for confounding adequate?	Serious bias	Low bias	Critical bias	Critical bias	Low bias
Was selection of participants adequate?	Low bias	Low bias	Low bias	Serious bias	Low bias
Was exposure adequate (certainty)?	Low bias	Moderate bias	Low bias	Moderate bias	Moderate bias
Was the study free from departures from intended exposures?	Low bias	Low bias	Low bias	Low bias	Low bias
Was the study free from missing data bias (follow-up)?	Serious bias	Serious bias	Serious bias	Serious bias	Serious bias
Was the study free from outcome measure bias?	Low bias	Low bias	Low bias	Low bias	Low bias
Was the study free from selective reporting?	Low bias	Low bias	Low bias	Low bias	Low bias

Non-Randomized Studies

Not statistically significant results

Pain

From the 5 NRS included in this review[25-29], Curtis and Brandow (2020)[27] found no association between cannabis use and pain severity or visits to the emergency room (ER). Ballas(2017)[25] found no association between cannabis use and its impact on pain. Wilson (2020)[28] found an increased number of visits to the ER amongst the youngster cohort using cannabis.

Curtiss (2020)[27] found reduction of visits to the ER among those using cannabis. Howard (2005)[24] found no difference pain scores between cannabis users and non-users.

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Opioid Use

From the 5 NRS included in this review[25-29], one study found no difference in opioids dispensation between certified patients for medical marijuana use and those who were not certified[27]. In another study, Curtis found that daily cannabis users had similar amounts of dispensed opioids in comparison with infrequent users or non-users [Daily opioid use, OME median: Daily users 21.9 (1.8/492.6) vs Others 5.6 (0.5/119.0][28]. Other three studies did not report this outcome.

Hospital Visits or Admissions

All the 5 NRS included in this review[25-29], reported hospital visits or admissions as outcomes. Ballas et. al reported 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 ($p > 0.05$) [26]. However, priapism (seven in the positive group, eight in the negative group), mortality (six patients in each group), and other complications of SCD were not significantly different ($p> 0.05$) in both cohorts.

Curtis et al reported that patients who obtained medical marijuana showed a reduction in median 6-month hospital admissions compared with the patients who were certified but did not obtain medical marijuana[27]. There were no differences in emergency department (ED) or infusion center visits, total health care utilization.

In another paper, Curtis and colleagues showed that daily cannabis users had similar rates of annual hospital admissions, annual emergency room (ER) visits, and length of stay in days. Daily cannabis users had fewer annual admissions and annual ER visits when propensity matched with others by variables with effects on pain outcomes[28].

A comparison between cannabis users younger than 25 years old and those older than 25 years old showed that the younger cohort who reported marijuana use were more likely to have admissions to the hospital for pain compared to those who did not report marijuana use ($\beta = 0.87(0.43)$, $p = 0.0.047$)[29]. In contrast, among the older cohort who reported regular marijuana use, there were more days when they treated their pain at home ($\beta = 0.44$ (0.21),$p = 0.035$; $F = 3.67$), but they had had no difference in resulting ER visits ($\beta = 0.23$ (0.20), $p = 0.252$) or hospitalizations ($\beta = -0.01$ (0.18), $p = 0.968$) compared to those who did not use marijuana.

Mood

From the 5 NRS included in this review[25-29], no study reported mood-related outcomes.

Adverse Outcomes

From the 05 NRS included in this review[25-29], no study reported mood-related outcomes.

Quality of Life

From the 5 NRS included in this review, just Curtiss and Brandow[27] studied this outcome and found no clinical difference between cannabis users and non-users on quality of life.

DISCUSSION

Main findings

This is the scope review with systematic search aimed to analyze the effectiveness and safety of cannabis for the treatment to the treatment of pain originating from Sickle Cell Disease.

The results indicate that there is an association between cannabis use and the frequency of visits to the ER. We must look at this data with caution and remember that these data derive from non-randomized studies, thus association does not mean that cannabis increases adverse side effects or increases pain. Specially because a great deal of these patients use cannabis purchased illegally and without medical advice nor prescription.

We are unable at this point to tell whether these patients are using cannabis appropriately, and since studies did not establish a baseline pain nor were randomized, we cannot tell whether those patients are using cannabis because they suffer from more severe pain or not

and if they are going to the ER more frequently just because they suffer from the consequences of a poorly controlled SCD.

This scope review reveals the lack of information regarding the use of cannabis for SCD. Outcomes such as adverse outcomes, and quality of life should be investigated to unveil us new therapeutic possibilities for cannabis by evaluating a wide range of measured outcomes

Strengths and limitations

Our study has a number of strengths including the completion of a comprehensive literature search and we used a systematic approach to assess eligibility, risk of bias and to abstract data, with each step completed independently and in duplicate.

The primary limitation of our review is the high risk of bias across both included studies. The main risk of bias included inadequate control for confoundings and inadequate follow-up.

Finally, another limitation of this review is the fact that given the limited number of included studies providing data for analysis, it was not possible to assess publication bias. It was also not possible to perform any of the quantitative analyses planed due to the lack of data available.

CONCLUSIONS

In conducting this review, we have attempted to answer the following clinical questions: Is cannabis more effective and safer than standard care for pain treatment in SCD patients?

We found no clear answer to this question in the literature.

Based on the lack of research evaluating the impact of cannabis use among SCD patients on quality of life and on the controversial association between cannabis use and an increase in ER visits we recommend that large RCTs comparing the use of prescribed cannabis to the traditional approaches should be carried on

in order to shed light upon new therapeutic possibilities on this matter.

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No

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Authors' contributions:

JEGP: conception, study design, data acquisition, interpretation of data, analysis, drafting article, revision and final approval; CP: conception, study design, interpretation of data, analysis, drafting article, revision and final approval; IPS: conception, study design, data acquisition, interpretation of data, analysis, drafting article, revision and final approval; CDAB: conception, study design, interpretation of data, analysis, drafting article, revision and final approval; TA: drafting article, revision and final approval, HAA: conception, study design, interpretation of data, analysis, drafting article, revision and final approval.

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Competing interests:

The authors declare that they have no competing interests.

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