Utilization of medicinal cannabis for pain by individuals with spinal cord injury

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Abstract
Study design A cross-sectional multi-center study using an on-line survey addressing utilization, knowledge, and perceptions of medicinal cannabis (MC) by people with spinal cord injury (SCI).
Objective To characterize differences between current (CU), past (PU), and never users (NU) of MC with SCI; to determine why people with SCI use MC; to examine reports of MCs’ efficacy and tolerability by individuals with SCI.
Setting Three academic medical centers in the United States.
Methods Comparison of demographic and attitudinal differences between CU, PU, and NU and differences in the groups’ reports of pain, health, and quality of life (QOL). Evaluation of utilization patterns and perceived efficacy of MC among CU and PU and reports of side effects of MC versus prescription medications. Data were analyzed using either Chi Square, distribution-free exact statistics, or t-tests for continuous data.
Results Among a nationwide sample (n = 353) of individuals with SCI, NU were less likely than CU and PU to believe that cannabis ought to be legalized and more likely to endorse risks of use. Current users and PU reported greater pain interference in daily life than did NU, but there were no between group differences in QOL or physical or emotional health. Current users and PU took MC to address pain (65.30%), spasms (63.30%), sleeplessness (32.70%), and anxiety (24.00%), and 63.30% reported it offered “great relief” from symptoms. Participants reported that MC is more effective and carries fewer side effects than prescription medications.
Conclusions Medicinal cannabis is an effective and well-tolerated treatment for a number of SCI-related symptoms.

Introduction
Despite being legal in 31 states, medicinal cannabis (MC) remains relatively understudied. It is known that just over 1% of adult Americans use MC [1] and that the vast majority of them are seeking relief from severe pain or muscle spasms [2, 3]. There is evidence that MC is effective in relieving chronic pain [4, 5], chemotherapy induced nausea [6, 7], and spasticity in Multiple Sclerosis [4, 8, 9]. Several studies have suggested that use of MC is associated with reduced need for narcotic and non-narcotic pain medications [10–12].

Spinal cord injury (SCI) is often attended by pain and spasticity [13–15]. Between 64 and 88% of people with SCI live with chronic pain [16–19], and as pain is associated with poor social functioning, community participation, and overall quality of life, it is frequently listed among the top health concerns of individuals living with SCI [20–22]. While MC might effectively address the pain and spasticity of SCI, its potential uses and benefits have been inadequately studied. Three trials have investigated cannabis’ effects on pain in SCI. Rintala et al. [23] found that MC was ineffective for relief of sub-lesional neuropathic pain,
Wilsey et al. [24] demonstrated efficacy for short-term (not chronic) pain relief, and while Wade et al. [25] showed that MC yields significant improvements in pain, spasticity, and spasms, their subjects had a mix of neurological disorders and there was no sub-group analysis of the 4 participants with SCI.

Several authors have interrogated utilization patterns of recreational and medicinal cannabis among people with SCI. Drossel et al. surveyed 244 community dwelling individuals with SCI, finding that just under one-quarter used cannabis and that many sought relief from pain (70.4%) and spasticity (46.3%) [26]. Andresen et al. reported that among 48 active cannabis users with SCI in Denmark, pain and spasticity were the second and third most cited reasons for use and nearly 60% described their symptom relief as “good” or “very good” [27]. In a survey of 147 individuals with SCI, Cardenas et al. [28] found that just under 20% were current MC users and that while it afforded substantial pain relief, most reported that it lasted just hours. Hawley et al. described common reasons for methods of, and side effects of cannabis use among 27 people living with SCI [29].

While each of these studies has substantively contributed to the literature, all four groups surveyed subjects from limited geographic areas, introducing potential biases based on attitudes toward, legal status of, and availability of cannabis. Further, none of the authors examined how attitudes toward cannabis use may affect individuals’ utilization patterns nor how MC users compare its perceived efficacy to that of prescription medications. These represent important persistent gaps in the literature.

We developed an on-line survey addressing adults living with SCI’s use and knowledge of MC and their perceptions of its risks and benefits (Appendix A). It contained 88 questions, the majority of which were multiple choice, 19 of which invited free-text responses, and 6 of which utilized a 10-point Likert Scale. The first paper to have been published from this data set interrogated attitudes toward recreational and medicinal cannabis among individuals living with SCI [30]. Most respondents felt that cannabis is safe for use, has potential therapeutic benefits, and ought to be legalized, however substantial pluralities expressed concerns about health-related and social risks of use, and a majority thought cannabis use was attended by legal risks. In this paper, we sought to answer three main questions: (a) which characteristics among individuals with SCI are associated with being a never user (NU), a past user (PU), or a current user (CU) of MC; (b) why and for which conditions do people with SCI choose to use MC, and; (c) how do current and past MC users with SCI describe its efficacy. In attempting to understand what motivates or dissuades people with SCI from using MC and whether cannabis offers people with SCI substantial relief from bothersome symptoms, we hoped to provide a foundation for further efficacy research and advocacy work.

**Methods**

**Survey development**

This study utilized a cross sectional multi-center survey methodology that has been described in our prior publication [30]. The authors reviewed existing surveys and manuscripts [1, 3, 26, 27, 31] addressing perceived risks and benefits of MC use, utilization patterns among MC users, and primary reasons for use of MC. We also used established pain and quality of life questionnaires taken from the International Spinal Cord Injury Pain and Quality of Life Basic Data Sets [32, 33]. We then received input from experts in the areas of neuropathic pain, MC use, and spinal cord injury medicine seeking to understand how MC users obtain and administer the agent, their risk of attendant substance abuse, and the evolution of attitudes toward MC use. Based on this preliminary work, we developed a survey with four primary foci: (a) participants’ attitudes toward and utilization of recreational and MC; (b) their experiences with other controlled and illicit substances; (c) their perceptions of the risks and benefits of MC use, and; (d) their knowledge of recreational and MC. We solicited feedback on the survey’s content and usability from Thomas Jefferson University’s SCI Consumer Ethics Advisory Board—a group composed exclusively of individuals living with SCI —then submitted the instrument for IRB approval. For the purposes of the survey, “medicinal cannabis” was defined as cannabis used to treat a medical condition or symptom, regardless of how it was obtained or who had recommended it.

Of note, this manuscript, while drawing upon the same dataset used in a previous publication, sought to answer an entirely different and unique set of questions. The authors were cautious not to present redundant data.

**Survey distribution**

The survey was administered electronically (SurveyMonkey Inc, San Mateo, CA, www.surveymonkey.com) and no identifying data were collected. We distributed the survey to SCI consumer mailing lists maintained by Thomas Jefferson University, University of Washington at Seattle, and University of Alabama at Birmingham. This effort yielded 246 responses. A second “reminder” email was sent 4 weeks after the first and yielded an additional 107 responses for a total “n” of 353. The final subject pool included participants from 39 states in the United States. Inclusion criteria included being an adult with SCI and being able to access...
and complete an internet-based survey. There were no stated exclusion criteria. Consent to participate was obtained by having potential subjects read an explanation of the study—including express permission to stop at any point—then click a link to access it. The three institutions’ email lists included 2315 potential respondents. Given our final “n” of 353, our formal response rate was 15.25%.

Data analysis

Survey responses were reviewed for completeness and each section’s results were analyzed based on number of responses. For purposes of analysis, participants’ data were grouped into three user categories of current MC user (CU), past MC user (PU), or never used MC (NU). For certain analyses—particularly when attempting to delineate factors associated with never use of cannabis—responses from current and past users were combined and defined as “present or past user of MC.” For other analyses, the three groups were treated separately. Individual survey items were evaluated for which test would be appropriate. The three choices were Chi Square, distribution-free exact statistics, or t-tests for continuous data.

Results

A total of 353 people with SCI responded to the survey and 274 (77.60%) were completed in their entirety. All answers from incomplete surveys were included in analyses, hence, the “n” for certain responses was less than 353 and are provided, where appropriate. The mean age of respondents was 52.74 years (Table 1), average age at injury was 35.25 years, 62.50% identified as male (36.50% as female and 1.0% as transgender), and the majority (60.20%) had a college or advanced degree. A sizable minority (37.20%) of participants reported “working for pay,” 43.60% were retired, 74.20% lived in either a suburban or an urban area, and with 11 (3.1%) exceptions, all respondents reported living in a private residence.

The majority (85.10%) identified trauma (sports, assault, motor vehicle crash, fall, or “birth injury or other traumatic cause”) as the etiology of their spinal cord injury or dysfunction, 4.10% required ongoing or “as needed” ventilatory assistance, and just over half (52%) had cervical level injuries. While 18% reported having American Spinal Injury Association (ASIA) Impairment Scale (AIS) A injuries, most respondents (53.60%) were unable to classify their injuries.

One hundred eight participants (30.40%) reported currently using MC, 42 (11.80%) reported past use, and 130 (36.60%) had never used MC. Seventy-five individuals (21.10%) did not answer the question and were excluded from related analyses. Current and past users were no more
### Table 2: Attitudes towards cannabis as medicine

| Attitudes                                                                 | Current cannabis user and past cannabis user agree (%) | Significance $\chi^2 (p)$ | Never Used cannabis, agree (%) | Significance $\chi^2 (p)$ |
|---------------------------------------------------------------------------|--------------------------------------------------------|---------------------------|--------------------------------|---------------------------|
| Cannabis should be legalized.                                             | N = 129 4 (3.1%), 126 (96.9%)                          | 1.35 (0.339) NS           | N = 150 3 (2.0%), 147 (98.0%)  | 1.35 (0.339) NS           |
| Cannabis smokers are prone to violence.                                   | N = 129 4 (3.1%), 126 (96.9%)                          | 1.35 (0.339) NS           |                                |                           |
| Cannabis is a gateway drug.                                               | N = 129 4 (3.1%), 126 (96.9%)                          | 1.35 (0.339) NS           |                                |                           |
| It is possible that cannabis could have medicinal effects.                | N = 129 4 (3.1%), 126 (96.9%)                          | 1.35 (0.339) NS           |                                |                           |
| It is safer to take prescription painkillers than to use cannabis.        | N = 129 4 (3.1%), 126 (96.9%)                          | 1.35 (0.339) NS           |                                |                           |

Likely than never users to have family members that have struggled with addiction (CU + PU = 61.90%; NU = 65.10%; $\chi^2 = 0.31, p = 0.618$), to have family members who have had legal troubles due to alcohol or drug use (CU + PU = 37.70%; NU = 35.20%; $\chi^2 = 0.19, p = 0.707$), or to have abused drugs or alcohol in the past (CU + PU = 35.80%; NU = 38.30%; $\chi^2 = 0.18, p = 0.708$). Never users were less likely than current and past users to agree that cannabis should be legalized (CU + PU = 98.00%; NU = 88.10%; $\chi^2 = 10.92, p = .001$) (Table 2) and more likely to believe that cannabis is a “gateway drug” (CU + PU = 7.40%; NU = 22.50%; $\chi^2 = 12.80, p = 0.00$), a “very dangerous” drug (CU + PU = 1.30%; NU = 7.00%; $\chi^2 = 5.90, p = 0.026$), and that it is safer to take prescription painkillers than to use MC (CU + PU = 4.00%; NU = 11.80%; $\chi^2 = 5.91, p = 0.021$). There was widespread agreement among participants that cannabis could have medicinal effects (CU + PU = 96.00%; NU = 95.30%; $\chi^2 = 0.07, p = 1.00$) and that its use carries either no or only slight health risks (CU + PU = 91.20%; NU = 83.60%; $\chi^2 = 3.61, p = 0.067$). There were no significant differences in perceptions of social or legal risks between the user groups.

To assess subjects’ reports of pain, health, and quality of life, we utilized a 10-point Likert scale, grouping answers 0-3 as “low interference,” 4-6 as “some interference,” and 7-10 as “extreme interference.” In comparing responses of current and past MC users (combined $n = 124$) with those of never users ($n = 117$), there were no significant differences in pain’s interference with day-to-day activities ($\chi^2 = 6.76, p = 0.034$), mood ($\chi^2 = 2.14, p = 0.344$), or ability to sleep ($\chi^2 = 0.70, p = 0.704$), in assessments of life satisfaction ($\chi^2 = 2.576, p = 0.276$) or in satisfaction with physical ($\chi^2 = 0.32, p = 0.854$) or emotional health ($\chi^2 = 0.26, p = 0.880$) (Table 3).

Among current ($n = 92$) and past users ($n = 27$), mean age of first MC use was 43.12 years. A large majority (65.50%) of current and past users reported using or having used MC at least 3–5 days per week (29.40% reported “several times a day”), and while 64.3% have or had used MC for 5 years or fewer (30.20% <1 year), 10.9% have or had used it for greater than 20 years. There were no demographic or injury-specific differences between current and past MC users and never MC users.

Most current ($n = 99$) and past users ($n = 30$) inhaled MC (CU = 63.60%; PU = 53.30%) or used sprays or tinctures (CU = 11.10%; PU = 23.30%). Sixty-four percent use or used MC because it “helps with [their] condition,” 48% in hopes that MC would help reduce their use of other prescription medications, 34% because prescription medications had failed. 22.7% because it had been recommended by a physician, and 22.7% because it had been recommended by a friend. Current and past users reported using MC to address pain (65.30%), spasms (63.30%), sleeplessness (32.70%), and anxiety (24.00%). When asked...
whether their dose of MC had changed over the duration of treatment, 37.20% responded that it had not, 30.20% answered that their use had changed depending on their condition, and 10.90% reported a need for an initial dose escalation followed by dose stabilization.

When asked if MC affects or had affected their overall condition or symptoms (99 CU and 30 PU), 63.60% reported that it offers or had offered “great relief” and 30.20% that it offers or had offered “a little relief.” Only 6.30% of subjects reported that MC use had either made no difference in their condition or symptoms or made them worse ($\chi^2 = 13.70, p = 0.001$). Over 60% of respondents reported that using MC had allowed them to reduce or discontinue use of other medications (61.20% total; CU = 66.70%; PU = 43.30%; $\chi^2 = 5.28, p = 0.032$) and only 35.20% answered that they had symptoms or conditions that had not been helped at all by MC (CU = 31.60%; PU = 46.70%; $\chi^2 = 2.28, p = 0.19$). When asked to describe effects of MC versus those of prescription medications, 37.20% reported that prescription medications had produced “much worse” effects than MC (CU = 42.40%; PU = 20.00%; $\chi^2 = 4.96, p = 0.031$) and an additional 18.60% reported that other medications’ effects had been “somewhat worse” than MCs’ (CU = 20.20%; PU = 13.3%; $\chi^2 = 0.72, p = 0.593$). Just over 34% reported having suffered no undesirable effects from MC (CU = 32.30%; PU = 40.00%).

When subjects were asked to identify MCs’ and prescription medications’ positive or desirable effects, the top five for each were identical (Table 4). However, a higher percentage of respondents noted beneficial effects of MC than noted beneficial effects of prescription medications. Subjects were also asked to list negative side effects of MC and prescription medications. Their rank orders were different, and higher percentages of respondents listed negative effects of prescription medications than listed negative effects of MC (Table 5). Subjects were asked to select from a list of 33 possible effects that could be ascribed to MC and/or prescription medications and that could be considered either positive, negative, or neutral. On average, MC was assigned 7.6 positive effects while prescription medications were assigned 5.35 ($t = 3.9, df = 234; p = .000$). Medicinal cannabis was assigned an average of 6.0 negative effects while prescription medications were assigned 9.9 ($t = -3.76, df = 203; p = .001$).

When asked to compare the relative efficacy of MC with that of other medications in providing symptom relief (98 CU and 30 PU), 63.3% reported that cannabis works better than prescription medications, 17.20% reported the opposite, and 10.80% answered that only cannabis offered them relief ($\chi^2 = 7.93, p = 0.047$). When asked if they suffer or had suffered from symptoms or conditions that had not been helped by MC, 35.20% replied “yes” (CU = 31.60%; PU = 46.70%; NS) and 64.80% replied “no” (CU = 68.40%; PU = 53.30%; NS).

### Table 3: Interference of pain and satisfaction

| Table 3: Interference of pain and satisfaction | Current cannabis user and past cannabis user | Never used cannabis |
|-----------------------------------------------|--------------------------------------------|---------------------|
| Significance | Low interference | High interference | Low interference | High interference | Low interference | High interference |
| $\chi^2 (p)$ | $n$ (%) | $n$ (%) | $n$ (%) | $n$ (%) | $n$ (%) | $n$ (%) |
| How much has pain interfered with your day-to-day activities in the last week? | 44 (35.5%) | 52 (41.9%) | 28 (22.6%) | 48 (41.4%) | 38 (32.8%) | 30 (25.9%) |
| How much has pain interfered with your overall mood in the last week? | 43 (34.7%) | 49 (39.5%) | 32 (25.8%) | 51 (43.6%) | 38 (39.5%) | 28 (23.9%) |
| How much has pain interfered with your ability to get a good night’s sleep in the last week? | 54 (43.5%) | 30 (24.2%) | 40 (32.3%) | 28 (24.3%) | 44 (38.3%) | 38 (32.5%) |
| How satisfied are you with your life as a whole in the past four weeks? | 20 (16.4%) | 27 (22.1%) | 43 (35.2%) | 37 (30.1%) | 66 (53.7%) | 20 (17.1%) |
| How satisfied are you with your physical health in the past four weeks? | 33 (27.0%) | 54 (41.5%) | 33 (26.5%) | 46 (37.7%) | 66 (53.7%) | 20 (17.1%) |
| How satisfied are you with your psychological state, emotions and mood in the past four weeks? | 20 (16.3%) | 43 (34.7%) | 37 (30.1%) | 66 (53.7%) | 20 (17.1%) | 66 (53.7%) |

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Past MC users were asked why they had stopped. A minority of respondents (16.70%) said it had never controlled their symptoms, but none answered that it had lost effect, that side effects were limiting, that it was unaffordable, that it was difficult to ensure a supply, or that its use was illegal. In free text responses, past MC users cited fear of physician repercussions, drops in blood pressure, variability in effect, social stigma, loss of employment, and risk of losing federally funded housing as reasons for having stopped.

Discussion

This study is the first to examine how personal beliefs influence MC use and to compare its perceived efficacy and tolerability to that of prescription medications. A number of our findings are notable.

First, there seem to be demonstrable differences between current and past MC users and those who have never used MC. In contrast to Drossel et al., in which subjects who used MC were more likely to report pain interference with life than were non-MC users [26], our groups did not differ in pain interference or in self-assessments of emotional or physical health. However, current and past users were less concerned than never users with a number of perceived risks of cannabis use, notably that it is a “gateway” or a “very dangerous” drug. Clinicians in states with legal MC must understand that some patients who may find it beneficial may hold both solid (legal risks) and less well established (safety relative to that of other medications) fears about its use, and that those concerns may make them less likely to consider treatment with MC.

Second, our data seem to indicate that MC has variable efficacy. Past users were less likely than CUs to report having been able to reduce use of other medications while they were taking MC and to endorse that prescription medications’ side effects were worse than MCs’. Further, fully 16% of them stopped using MC because they found it ineffective. There was no requirement in this survey that MC be purchased from a medical distributor, and there is variable efficacy of cannabis products taken from the same plant. Therefore, it is expected that there would be considerable variation in the quality, potency, and chemical components of the cannabis our subjects utilized. Even so, these data suggest that there may simply be people who are more or less likely to respond to and benefit from MC therapy, and that ongoing monitoring and evaluation by clinicians is essential to effective prescribing. Future work may also focus on which individuals with SCI are more or less likely to respond to MC therapy.

Third, while other studies have documented MCs’ usefulness in reducing use of other medications and in treating chronic pain, this is the first study to compare perceived effectiveness of MC to prescription medications in treating SCI-related symptoms. While Drossel et al., Andresen et al., and Hawley et al. documented reasons for MC among individuals with SCI [26, 27, 29], only Cardenas et al. [28] and Andresen interrogated its perceived efficacy of cannabis products taken from the same plant. Therefore, it is expected that there would be considerable variation in the quality, potency, and chemical components of the cannabis our subjects utilized. Even so, these data suggest that there may simply be people who are more or less likely to respond to and benefit from MC therapy, and that ongoing monitoring and evaluation by clinicians is essential to effective prescribing. Future work may also focus on which individuals with SCI are more or less likely to respond to MC therapy.

Table 4 Positive effects of medications on symptoms following SCI

| Positive effects               | Type of medication | Cannabis* | Prescription** |
|--------------------------------|--------------------|-----------|----------------|
| Muscle relaxation              | Rank               | Count     | Percentage     |
| 1st                            | 112                | 90.3%     | 85             | 72.6%         |
| Promotes sleep                 | 2nd                | 101       | 83.5%          | 58             | 51.3%         |
| A feeling of well being        | 3rd                | 89        | 75.4%          | 52             | 46.0%         |
| Decreased anxiety              | 4th                | 83        | 69.7%          | 50             | 43.5%         |
| Increased appetite             | 5th                | 64        | 53.3%          | 28             | 25.2%         |

* = n = 128
** = n = 126

Table 5 Negative effects of medications on symptoms following SCI

| Negative Effects               | Type of medication | Cannabis* | Prescription** |
|--------------------------------|--------------------|-----------|----------------|
| Dry mouth                      | Rank               | Count     | Percentage     |
| 1st                            | 66                 | 54.5%     | 62             | 51.7%         |
| Residual bad taste in mouth    | 2nd                | 34        | 29.6%          | 33             | 29.5%         |
| Dehydration                    | 3rd                | 33        | 28.7%          | 50             | 42.4%         |
| Memory loss                    | 4th                | 31        | 27.2%          | 35             | 32.1%         |
| Lethargy/lack of energy        | 5th                | 30        | 26.3%          | 52             | 46.4%         |
| Drowsiness                     | 9th                | 25        | 21.7%          | 56             | 49.1%         |
| Constipation                   | 14th               | 20        | 17.2%          | 53             | 46.3%         |

* = n = 128
** = n = 126

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a need for expedited clinical trials evaluating efficacy of MC in chronic SCI, and no justification for cannabis’ continued classification as a Schedule 1 drug, a designation indicating that it has no accepted medical use.

Finally, we were taken by former users’ stated reasons for having discontinued using MC. While some of them seem to have found MC less effective than did current users, very few of them reported having stopped using it due to lack of effect. Rather, they relayed stories of fear of continued use, of variable and unpredictable effects (potentially addressed through regulation), of stigma, and of loss of employment and government-subsidized housing. It seems, then, that some individuals with SCI-related symptoms may benefit from MC treatment but are dissuaded from using it by their fears of facing potentially drastic repercussions.

**Study limitations**

This study has several important limitations. First, we did not ask participants which medications they had taken in the past and/or currently take. As a result, it is difficult to assess the adequacy of attempts to control subjects’ symptoms (particularly pain and spasticity) before they initiated MC use, and to determine whether they are using MC as adjuvant or monotherapy. Second, we did not assess how much MC participants used. While a majority of CU and PU reported using MC several times each week, it is unclear how much they took with each administration. Hence, it is impossible to use this work to estimate appropriate or effective dosing of MC. Third, our distribution method certainly introduced biases into our subject pool. While we did not inquire about annual family income or ethnicity, we know that over 60% of our participants had college or advanced degrees. Depending on duration of injury, between 10.90 and 43.70% of individuals with SCI have completed a college degree [40]. It is certainly possible that people who have completed more school have different attitudes toward cannabis use, though we were unable to find literature to substantiate this. Further, the very topic of this survey may have attracted participants with a history of or a strong interest in using MC. While 30.40% of our subjects were CU of MC, just under 10% of adult Americans report having using cannabis in the past year [41]. Finally, our low response rate is a clear limitation, as only 15.25% of individuals to whom the survey was emailed responded, and under one-third of them were active MC users. This being said, this study provides evidence that some individuals with SCI and associated symptoms find relief with MC, that they find MCs’ side effects largely tolerable and less onerous than those of prescription medications, and that some people with SCI may avoid using or discontinue use of MC not because it is ineffective, but, rather, due to perceived and real repercussions of continued use.

**Data archiving**

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

**Author contributions** MS was responsible for researching and developing the survey, submitting the project to the IRB, coordinating survey distribution, and drafting the manuscript. MC assisted with survey development, was primarily responsible for data analysis, and helped draft the manuscript. MM was responsible for researching and developing the survey, building the on-line survey, and drafting the manuscript. TR was responsible for researching and developing the survey, helping analyze the data, and drafting the manuscript. KG was responsible for researching and developing the survey, helping analyze the data, and drafting the manuscript. DG was responsible for researching and developing the survey, helping analyze the data, and drafting the manuscript.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Statement of ethics** This study was reviewed by the Thomas Jefferson University Institutional Review Board and deemed exempt. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were following during the course of this research.

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