Local Anesthetic Efficacy in Marijuana Users and Nonusers: A Pilot Study

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Objective: Despite the common clinical impression that patients with a history of drug use are challenging to anesthetize with local anesthesia, literature on this clinical phenomenon is sparse. The objective of this pilot study was to assess if differences in local anesthetic efficacy for dental treatment exist between marijuana users and nonusers.

Methods: Subjects were healthy adult males and females who qualified as either chronic marijuana users or nonusers. All subjects had an asymptomatic, vital maxillary lateral incisor that responded to an electric pulp test (EPT). A standard maxillary infiltration injection technique was employed using 1.7 mL 2% lidocaine with 1:100,000 epinephrine over the test tooth, and the tooth was tested with an EPT at 3-minute intervals.

Results: A total of 88% of nonusers (15/17) and 61% of users (11/18) were successfully anesthetized, defined as anesthesia onset within 10 minutes and lasting at least 15 minutes. The difference in the proportion of anesthetized subjects was not statistically significant ($P = .073$). For subjects with successful anesthesia, there was no significant difference between nonusers and users in the onset or duration of anesthesia.

Conclusion: No significant differences in local anesthetic efficacy with respect to local anesthetic success, onset, or duration of action were found between chronic marijuana users and nonusers. However, larger studies are likely needed to provide more definitive evidence.

Key Words: Marijuana; Cannabis; Local anesthesia; Lidocaine; MDAS; Modified Dental Anxiety Scale.

Achieving profound local anesthesia is essential to providing safe and comfortable dental treatment. There is a common clinical impression in the dental community that patients with a history of recreational drug use are more difficult to anesthetize than patients without such history. Despite this widespread clinical belief, there is a dearth of data on the subject. The published studies vary in study design, drugs of abuse studied, local anesthetic agents utilized, and outcomes measured.[2–6] To our knowledge, there are no published reports investigating the efficacy of local anesthetics related to marijuana use. This is surprising, given the widespread use of marijuana and continually evolving landscape of its legality at the state level within the United States. Marijuana is the most commonly used substance after tobacco and alcohol.[7] In the 2018 National Survey of Drug Abuse and Health, 34.8% of adults ages 18 to 25 and 13.3% of adults ages 26 or older had used marijuana in the past year.[7] Legalization and reduction in stigma may increase the likelihood that patients will report cannabis use to their dentist. Greater transparency between the patient and provider allows for better understanding of a patient's clinical presentation and insight into potential treatment challenges and outcomes.

Although the terms "marijuana" and "cannabis" are often used interchangeably, the 2 are technically distinct. "Marijuana" is utilized in this manuscript as that was the term used when recruiting and communicating with research subjects. However, when referencing other publications, the term used in the citation (ie, marijuana or cannabis) is utilized.

The objective of this pilot study was to assess if differences exist in the efficacy of local anesthesia for dental treatment between marijuana users and nonusers. This study focused on assessing the chronic effects of

Received June 7, 2021; accepted for publication March 7, 2022.

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Anesth Prog 69:15–21 2022 | DOI 10.2344/anpr-69-02-08

marijuana use, rather than acute effects. We hypothesized that marijuana users would have less successful local anesthesia compared with nonusers.

METHODS

The University of Washington Human Subjects Division approved this pilot study (IRB #52559), and all participants provided written informed consent. Participant recruitment targeted adults in the Seattle, Washington metropolitan area. Recruitment strategies included advertisements placed in a local free weekly periodical, online classifieds, and social media, as well as word of mouth by previously enrolled individuals. Those interested were directed to contact the team at the Regional Center for Dental Research Clinic at the University of Washington School of Dentistry by phone.

The phone screening took ~5 to 10 minutes to complete and included a description of the study design and objectives, as well as 10 questions related to the inclusion and exclusion criteria (see below). Interested eligible subjects were then scheduled for a single in-person screening and study session at the Regional Center for Dental Research Clinic. Subjects were instructed during the phone screening and by way of phone or email confirmation to avoid marijuana, alcohol, and all restricted medications (analgesics, anxiolytics, or any psychoactive drug) for at least 24 hours prior to their scheduled appointment.

Study Visit

Subjects were scheduled for a study visit with the principal investigator (MM), a licensed dentist. Subjects were provided with a summary description of the visit and consent forms to review and sign. The subject then completed a written medical history that was reviewed by the dentist, and the subject's blood pressure was measured. All qualifying subjects were in good health as determined by the written medical history and oral interview. Inclusion criteria were as follows: ages 21 to 65 years; American Society of Anesthesiologists Class I or II; and blood pressure reading below 180/110 mm Hg. Exclusion criteria were as follows: medical conditions associated with chronic pain or altered pain perception; regular use of analgesics, anxiolytics, or antidepressants within the past 3 months; consuming more than 15 alcohol drinks per week on average for the past 3 months; allergy to local anesthetics or sulfites; ongoing pregnancy or active breastfeeding; and use of marijuana, alcohol, analgesics, anxiolytics, or other psychoactive drug within 24 hours of the scheduled appointment.

Subjects were asked to answer questions regarding their possible marijuana usage drawn from the Cannabis Use Problems Identification Test (CUPIT).[9] A marijuana user was someone who uses marijuana on average 1 day per week or more for the past 12 months and uses marijuana >3 days per week or more over the past 3 months. A nonuser uses marijuana <1 day per month for the past 12 months and has not used marijuana at all over the past 3 months. Potential subjects whose use-pattern fell between these 2 categories were disqualified from enrolling.

Subjects were also asked to complete the Modified Dental Anxiety Scale (MDAS) questionnaire, as dental anxiety has been shown have a positive relationship with reports of increased dental pain.[10–13] Subjects' responses did not impact their participation eligibility.

Clinical Exam and Testing Protocol

A brief dental exam focusing on the maxillary anterior teeth evaluated for existing restorations and signs of dental disease. Maxillary lateral incisors were selected for use in study and the side was determined by a random number generator. An electric pulp tester (EPT; Elements Diagnostic Unit) was used to evaluate vitality of the test tooth as well as at least 2 other anterior teeth to acclimate the subject to the testing procedure. Subjects were excluded if there were signs of disease at the anticipated site of injection, <50% natural tooth structure of test teeth, and if test teeth failed to respond to EPT at baseline. The contralateral maxillary lateral incisor was tested if the first lateral incisor did not qualify.

Testing procedures commenced immediately following the dental exam if the subject and tooth qualified (Figure 1). Topical anesthetic (0.25 mL of 20% benzocaine) was applied to the buccal mucosa of the assigned tooth for 2 minutes. Local anesthetic (1.7 mL of 2% lidocaine with 1:100,000 epinephrine, Carestream Health, Inc) was administered via conventional buccal infiltration over a period of 1 minute. The test tooth was challenged with EPT every 3 minutes following the injection, starting 3 minutes after completion of the injection. An EPT reading of 80 was considered a negative response. Testing continued for successfully anesthetized teeth until 2 consecutive, positive EPT responses were recorded.

Anesthetic onset was defined as the time of the first of 2 consecutive, negative EPT tests. Anesthetic duration

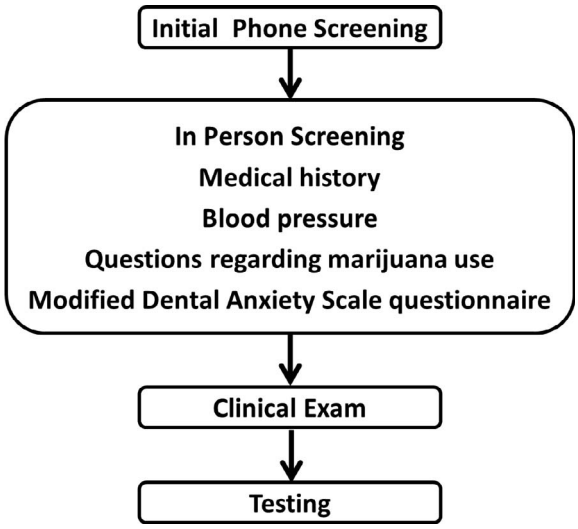

Figure 1. Flowchart of subject screening and testing protocol.

was defined as the difference between the onset time and the time of the first of 2 consecutive, positive EPT responses after having been anesthetized. Anesthetic success was defined by (1) the onset of pulpal anesthesia within 10 minutes after the injection, and (2) a duration of at least 15 minutes.

All subjects who attended the in-person screening were compensated with a $25 Amazon gift card. Those who qualified to participate and received anesthesia regardless of anesthetic success received an additional $75 Amazon gift card. There was no follow-up visit.

Data Analysis

The measured outcomes were anesthetic success, time until anesthesia onset, duration of anesthesia, and the level of dental anxiety (MDAS score). Anesthetic success between groups was compared using Fisher exact test. Anesthetic onset, anesthetic duration, and MDAS scores were compared between groups using a *t* test. The Mann-Whitney rank sum test was used if the data set did not pass a normality test. Statistical significance was set at $P < .05$.

RESULTS

Phone screenings of 174 interested individuals were completed, 98 of which did not qualify. The most common reasons for exclusion during the phone screening were medical history and casual marijuana use that did not meet this study's threshold for a chronic user. A total of 41 people attended an in-person screening, and 6 did not qualify to participate following review of their medical history, marijuana use, and/or clinical exam (Figure 2). A total of 35 subjects ultimately proceeded to clinical testing and received a local anesthetic injection.

Subject demographics are reported in Table 1. Of the 17 nonusers, 8 were male and 9 were female, whereas the 18 marijuana users were evenly divided at 9 male participants and 9 female participants. There were no significant differences in age ($P = .110$) or MDAS score ($P = .749$) between nonusers and users (Table 1).

A total of 88% of nonusers and 61% of marijuana users were successfully anesthetized; however, that difference lacked statistical significance ($P = .073$). Both nonusers who failed to achieve anesthesia were female participants; the users who failed to achieve anesthesia included 3 female participants and 4 male participants. The median onset of anesthesia was 3 minutes for both groups ($P = .432$; Figure 3). The mean duration of anesthesia was 32.8 ± 3.6 minutes for nonusers and 30.8 ± 3.6 minutes for users; however, that difference also lacked statistical significance ($P = .708$; Figure 3; Table 2).

DISCUSSION

This study intended to investigate the differences in the response of chronic marijuana users and nonusers to local anesthetic administered for pulpal anesthesia. This stems from common clinical impression that patients admitting to recreational drug use are more difficult to anesthetize with local anesthesia. Any such differences could pose significant clinical challenges, especially during invasive dental treatment. Despite the dental community's generally accepted belief that patients with

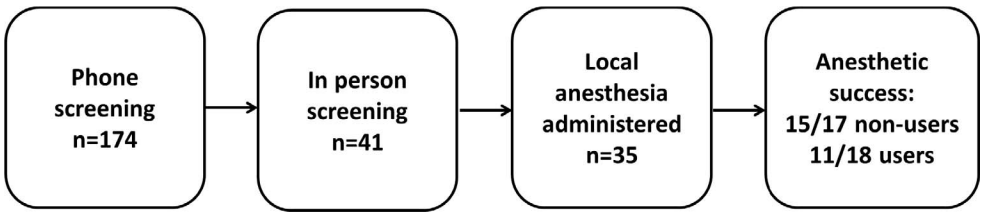

Figure 2. Subject screening and participation results.

Table 1. Subject Demographics*

	Nonusers	*Users*	*P* value
Total subjects	17	18	n/a
Male	8	9	n/a
Female	9	9	n/a
Age	43.1 ± 3.3	36.3 ± 2.6	$P = .110$
MDAS	8	8	$P = .749$

* Age is reported in years (mean ± SEM). MDAS score is reported as a median. MDAS, Modified Dental Anxiety Scale.

Table 2. Anesthesia Characteristics*

	Nonusers	*Users*	*P* value
Success	15/17	11/18	$P = .073$
Onset	3	3	$P = .432$
Duration	32.8 ± 3.6	30.8 ± 3.6	$P = .708$

* Anesthetic success is reported as a proportion. Anesthetic onset and duration are reported in minutes. Onset was not normally distributed and is reported as a median; duration was normally distributed and is reported as a mean ± SEM.

a history of drug use are more difficult to anesthetize, there are few studies in the literature that document this phenomenon.[2–6] Although those studies collectively suggest that local anesthesia may have lower efficacy in patients with a history of drug use, the drugs investigated and outcomes measured varied between studies. Further, none of those previous studies investigated marijuana, so their results are not directly applicable to this study.

Anesthetic success in this study was defined as pulpal anesthesia obtained within 10 minutes of the injection and having a minimum duration of 15 minutes. We chose this as a clinically relevant definition of success that would reflect the anecdotal observations about local anesthetic failure that clinicians report. Clinical failure of local anesthesia can result from either a failure to obtain adequate anesthesia or failure to maintain anesthesia for the duration of a procedure. It is unlikely experienced clinicians would wait >10 minutes after an initial maxillary infiltration injection if anesthesia was not achieved before attempting additional injection techniques. Prior studies have also used 10 minutes as a cut-off time for anesthetic success.[14–20] Further, 15 minutes of effective anesthesia would be a minimum amount of time for an experienced clinician to perform a brief procedure requiring profound pulpal anesthesia, like pulpectomy of the maxillary lateral incisor. The anesthetic success rates for nonusers and users were 88% and 61%, respectively. The incidence of successful anesthesia in our nonuser group was similar to that observed using similar techniques in a recent study with a large sample size of 163 subjects.[15]

We observed no statistically significant difference in anesthetic onset between groups for those subjects who were successfully anesthetized. For these subjects, 85% achieved anesthesia by 3 minutes. EPT testing started 3 minutes following anesthetic injection. Spacing the first EPT tests by 3 minutes may have restricted our ability to evaluate differences in onset in the first minutes after delivery. However, any such variation during this time likely lacks clinical relevance. There was also no statistically significant difference in anesthetic duration between groups. The mean durations of 32.8 and 30.8 minutes for nonusers and users are on the low end of the ranges previously reported for an injection of 1.8 mL 2% lidocaine with 1:100,000 epinephrine by buccal infiltration over a maxillary lateral incisor.[14–20]

The 2 questions asked to categorize potential subjects into nonusers and users in this study were drawn from the CUPIT survey.[9] The thresholds between each group were chosen after reviewing that survey and literature that made use of other cannabis consumption surveys.[21–23] The thresholds were intended to discriminate between those subjects who use marijuana occasionally and those who use regularly over a long period. The CUPIT evaluates cannabis use in the past 3 and 12 months as well as cannabis-induced problems and risks of harm and dependence. Only those questions regarding cannabis use were utilized, and not those directed toward subjects' perceptions of cannabis or behavioral

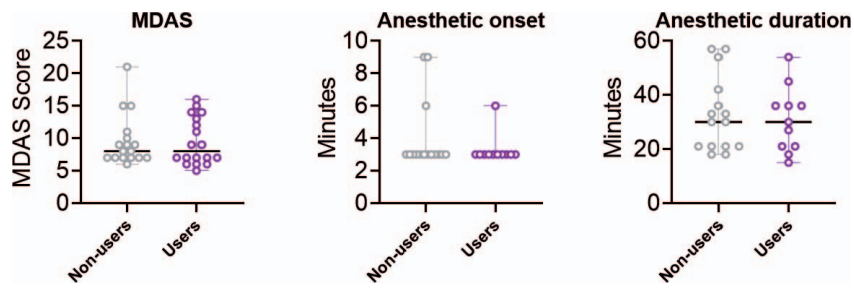

Figure 3. Individual data points, median, and range for dental anxiety, anesthetic onset, and anesthetic duration. There were no significant differences between the groups for Modified Dental Anxiety Scale (MDAS) scores ($P = .749$), anesthetic onset ($P = .432$), or anesthetic duration ($P = .708$).

implications, to focus on the physiological rather than psychological consequences of chronic use in the present study.

There remains to be a consensus for the most effective method of categorizing subjects based on cannabis use for research purposes. Questionnaires are easy to administer, require no additional clinical or laboratory set-up, and have been shown to be reliable and valid measures of an individual's consumption.[9,24,25] The Recreational Cannabis Use Questionnaire, published after the start of this study, provides a more exhaustive determination of the frequency, intensity, quality, and method of cannabis-related product consumption.[26,27] Further, sampling techniques to evaluate the concentrations and composite of exogenous cannabinoids in blood, hair, or urine may be used in some research.[28–30]

The use of an EPT as a stimulus to assess local anesthetic efficacy is a validated method used in dental research.[31,32] The maxillary lateral incisor as a test tooth has frequently been utilized.[14–20] Other studies used the inferior alveolar nerve block, and it is possible that local anesthetics may have different efficacies with maxillary infiltration versus a block injection.

Local anesthesia is affected by many variables, in addition to the type of injection. Most significantly, pulpal inflammation decreases the efficacy of local anesthesia, as multiple studies have demonstrated that teeth with irreversible pulpitis ("hot" teeth) are more difficult to anesthetize than teeth with a vital, normal pulp.[33] In the present study, we only investigated asymptomatic teeth that had no clinically detectable caries and at least 50% of the crown present as intact tooth structure, thus minimizing the likelihood of pulpal inflammation. Although it is impossible to rule out any pulpal inflammation on a histological level, we assumed that any significant inflammation would result in sensitivity or symptoms for the subject. Other potential variables that may affect local anesthetic efficacy include clinician error, needle deflection, cross-innervation, accessory innervation, the core theory, and anatomic variations; however, the effects of these variables are largely mitigated because we used a local infiltration injection rather than an inferior alveolar nerve block.

We found no difference in reported dental anxiety between marijuana users and nonusers. Overall, there was a low level of dental anxiety among subjects, with a median MDAS score of 8 for both groups. This result is not surprising, as individuals with high levels of dental anxiety would be unlikely to pursue participation in this study involving a voluntary dental injection. This may have obscured any actual differences in anxiety between marijuana users and nonusers.

The relationship between cannabis, the endocannabinoid system, and anxiety has been widely studied in animal models.[34] However, literature on the association between cannabis use and anxiety in humans is conflicting. Cross-sectional studies do not consider causality; that is, if cannabis use precedes anxiety symptoms, or if anxious patients tend to use cannabis due to the desirable effects of the drug. A meta-analysis of prospective longitudinal studies investigated the impact of baseline cannabis use on the later development of anxiety in the general population, and it was concluded that cannabis use was at most a minor risk factor for the development of anxiety.[35] The acute effects of cannabis on anxiety may also be complex. Cannabis is typically associated with a feeling of mild euphoria and mood relaxation.[36] Short-term effects may include a feeling of well-being and drowsiness but also anxiety and paranoia.[36] For example, 22% of cannabis users ages 18 to 35 reported acute anxiety or panic attacks after cannabis use.[37] The literature lacks information about the acute or chronic effects of cannabis use specifically on dental anxiety.

There are specific limitations of the current study. A single dentist completed the in-person screening, local anesthetic administration, and pulpal anesthesia testing. This precluded the researcher from being blinded to the subjects' marijuana usage status. This is somewhat mitigated by the fact that the subjects themselves were unaware of how they should respond relative to other subjects, and therefore could answer "yes/no" following an EPT challenge without consideration. Future studies ideally should employ a blinded design. A second limitation is the low number of subjects included. As a pilot study, this research was intended to gather preliminary data upon which more robust studies could be designed. We intentionally sought healthy subjects with medical histories that would not be expected to impact local anesthesia efficacy. We also sought subjects who used marijuana chronically, rather than casual users. Thus, it is remarkable that only 20% (35/174) of subjects originally phone-screened were eligible to receive an injection based on inclusion and exclusion criteria. This points to the challenges of enrolling interested and qualified subjects for such a study. The inclusion and exclusion criteria were developed to be rigorous enough to eliminate subjects that might skew the data due to confounding variables or dilute the significance of no use versus chronic cannabis use. It is possible that by increasing the number of subjects, the trend toward a difference in anesthetic failure between marijuana users and nonusers may reach statistical significance. Expansion in recruitment strategies and lengthening the period for recruitment would be necessary for future studies that carried greater statistical power.

It is important to note the intentional constraints of the type of subjects enrolled. This study offers a snapshot of the potential effect of chronic marijuana use. Users were asked to abstain from marijuana use for at least 24 hours before their scheduled appointment. The effect of acute marijuana use on local anesthetic efficacy remains to be investigated. Even amongst chronic users, there is tremendous variation in the potency, composition, and manner of consumption of cannabis products used. Recruitment of recreational users does not offer the consistency of a regimented clinical investigation. These subjects also presented under nonemergent, asymptomatic conditions. The potential changes in expression across the endocannabinoid system caused by chronic cannabis use may not be manifest at times of homeostasis. Results could vary for chronic users who present with acute dental pain. These are all areas of future research.

CONCLUSION

This study provided insight into the potential differences in local anesthetic efficacy between marijuana users and nonusers, and the preliminary results demonstrated no significant differences in anesthetic success, onset, or duration of action. However, larger studies are likely needed to provide more definitive evidence. The impact of marijuana use on dental patients warrants further investigation to best provide safe, comfortable, and effective dental treatment for patients who use marijuana.

ACKNOWLEDGMENTS

The authors acknowledge the support of Mary K. Hagstrom and Marilynn Rothen with the Regional Clinical Dental Research Center, and Dr Tina Olsson for early input into the research.

This project was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number NIH UL1TR000423. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Funding also provided by the Dr Douglass L. Morell Dentistry Research Fund.

REFERENCES

1. Drum M, Reader A, Nusstein J, Fowler S. Successful pulpal anesthesia for symptomatic irreversible pulpitis. *J Am Dent Assoc*. 2017;148:267–271.

2. Kimbrough HM, Jr. Local anesthetic and the addictive patient. *Tex Dent J*. 1975;93:7–9.

3. Scheutz F. Drug addicts and local analgesia–effectivity and general side effects. *Scand J Dent Res*. 1982;90:299–305.

4. Fiset L, Leroux B, Rothen M, Prall C, Zhu C, Ramsay DS. Pain control in recovering alcoholics: effects of local anesthesia. *J Stud Alcohol*. 1997;58:291–296.

5. Dabbagh A, Dahi-Taleghani M, Elyasi H, et al. Duration of spinal anesthesia with bupivacaine in chronic opium abusers undergoing lower extremity orthopedic surgery. *Arch Iran Med*. 2007;10:316–320.

6. Vosoughian M, Dabbagh A, Rajaei S, Maftuh H. The duration of spinal anesthesia with 5% lidocaine in chronic opium abusers compared with nonabusers. *Anesth Analg*. 2007;105:531–533.

7. 2018 National survey on drug use and health: detailed tables. 2019. Substance Abuse and Mental Health Services Administration. Accessed May 3, 2021. https://www.samhsa.gov/data/report/2018-nsduh-detailed-tables.

8. Marijuana drug facts. 2019. National Institute on Drug Abuse. Accessed May 3, 2021. https://www.drugabuse.gov/publications/drugfacts/marijuana.

9. Bashford J, Flett R, Copeland J. The Cannabis Use Problems Identification Test (CUPIT): development, reliability, concurrent and predictive validity among adolescents and adults. *Addiction*. 2010;105:615–625.

10. Humphris GM, Dyer TA, Robinson PG. The modified dental anxiety scale: UK general public population norms in 2008 with further psychometrics and effects of age. *BMC Oral Health*. 2009;9:20.

11. Humphris GM, Freeman R, Campbell J, Tuutti H, D'Souza V. Further evidence for the reliability and validity of the Modified Dental Anxiety Scale. *Int Dent J*. 2000;50:367–370.

12. Humphris GM, Morrison T, Lindsay SJ. The Modified Dental Anxiety Scale: validation and United Kingdom norms. *Community Dent Health*. 1995;12:143–150.

13. Lin CS, Wu SY, Yi CA. Association between anxiety and pain in dental treatment: a systematic review and meta-analysis. *J Dent Res*. 2017;96:153–162.

14. Evans G, Nusstein J, Drum M, Reader A, Beck M. A prospective, randomized, double-blind comparison of articaine and lidocaine for maxillary infiltrations. *J Endod*. 2008;34:389–393.

15. Fowler S, Drum M, Reader A, Nusstein J, Beck M. Pulpal anesthesia of adjacent teeth following infiltration of 2% lidocaine with 1:100,000 epinephrine in the maxillary lateral incisor and first molar. *Anesth Prog*. 2019;66:14–19.

16. Gross R, McCartney M, Reader A, Beck M. A prospective, randomized, double-blind comparison of bupivacaine and lidocaine for maxillary infiltrations. *J Endod*. 2007;33:1021–1024.

17. Katz S, Drum M, Reader A, Nusstein J, Beck M. A prospective, randomized, double-blind comparison of 2% lidocaine with 1:100,000 epinephrine, 4% prilocaine with 1:200,000 epinephrine, and 4% prilocaine for maxillary infiltrations. *Anesth Prog*. 2010;57:45–51.

18. Mason R, Drum M, Reader A, Nusstein J, Beck M. A prospective, randomized, double-blind comparison of 2%

lidocaine with 1:100,000 and 1:50,000 epinephrine and 3% mepivacaine for maxillary infiltrations. *J Endod*. 2009;35: 1173–1177.

19. Mikesell A, Drum M, Reader A, Beck M. Anesthetic efficacy of 1.8 mL and 3.6 mL of 2% lidocaine with 1:100,000 epinephrine for maxillary infiltrations. *J Endod*. 2008;34:121–125.

20. Scott J, Drum M, Reader A, Nusstein J, Beck M. The efficacy of a repeated infiltration in prolonging duration of pulpal anesthesia in maxillary lateral incisors. *J Am Dent Assoc*. 2009;140:318–324.

21. Asmaro D, Carolan PL, Liotti M. Electrophysiological evidence of early attentional bias to drug-related pictures in chronic cannabis users. *Addict Behav*. 2013;39:114–121.

22. Cousijn J, Wiers RW, Ridderinkhof KR, van den Brink W, Veltman DJ, Goudriaan AE. Grey matter alterations associated with cannabis use: results of a VBM study in heavy cannabis users and healthy controls. *Neuroimage*. 2012;59: 3845–3851.

23. Edwards CR, Skosnik PD, Steinmetz AB, Vollmer JM, O'Donnell BF, Hetrick WP. Assessment of forebrain-dependent trace eyeblink conditioning in chronic cannabis users. *Neurosci Lett*. 2008;439:264–268.

24. Adamson SJ, Kay-Lambkin FJ, Baker AL, et al. An improved brief measure of cannabis misuse: the Cannabis Use Disorders Identification Test-Revised (CUDIT-R). *Drug Alcohol Depend*. 2010;110:137–143.

25. Del Boca FK, Darkes J. The validity of self-reports of alcohol consumption: state of the science and challenges for research. *Addiction*. 2003;98(suppl 2):1–12.

26. Troup LJ, Andrzejewski JA, Braunwalder JT, Torrence RD. The relationship between cannabis use and measures of anxiety and depression in a sample of college campus cannabis users and non-users post state legalization in Colorado. *PeerJ*. 2016;4:e2782.

27. Troup LJ, Bastidas S, Nguyen MT, Andrzejewski JA, Bowers M, Nomi JS. An event-related potential study on the effects of cannabis on emotion processing. *PLoS One*. 2016;11: e0149764.

28. Karschner EL, Swortwood MJ, Hirvonen J, et al. Extended plasma cannabinoid excretion in chronic frequent cannabis smokers during sustained abstinence and correlation with psychomotor performance. *Drug Test Anal*. 2016;8:682–689.

29. Moosmann B, Roth N, Auwarter V. Finding cannabinoids in hair does not prove cannabis consumption. *Sci Rep*. 2015;5:14906.

30. Schwilke EW, Gullberg RG, Darwin WD, et al. Differentiating new cannabis use from residual urinary cannabinoid excretion in chronic, daily cannabis users. *Addiction*. 2011;106:499–506.

31. Certosimo AJ, Archer RD. A clinical evaluation of the electric pulp tester as an indicator of local anesthesia. *Oper Dent*. 1996;21:25–30.

32. Dreven LJ, Reader A, Beck M, Meyers WJ, Weaver J. An evaluation of an electric pulp tester as a measure of analgesia in human vital teeth. *J Endod*. 1987;13:233–238.

33. Reader A. Taking the pain out of restorative dentistry and endodontics: current thoughts and treatment options to help patients achieve profound anesthesia. *Endodontics: Colleagues for Excellence*. 2009:1–8.

34. Lisboa SF, Gomes FV, Terzian AL, et al. The endocannabinoid system and anxiety. *Vitam Horm*. 2017;103: 193–279.

35. Twomey CD. Association of cannabis use with the development of elevated anxiety symptoms in the general population: a meta-analysis. *J Epidemiol Community Health*. 2017;71:811–816.

36. What is cannabis. 2012. Alcohol and Drug Abuse Institute. Accessed November 1, 2017. http://learnabout marijuanawa.org/factsheets/whatiscannabis.htm.

37. Thomas H. A community survey of adverse effects of cannabis use. *Drug Alcohol Depend*. 1996;42:201–207.