Letters

RESEARCH LETTER

Labeling Accuracy of Cannabidiol Extracts Sold Online

There is growing consumer demand for cannabidiol (CBD), a constituent of the cannabis plant, due to its purported medicinal benefits for myriad health conditions.1 Viscous plant-derived extracts, suspended in oil, alcohol (tincture), or vaporization liquid, represent most of the retail market for CBD. Discrepancies between federal and state cannabis laws have resulted in inadequate regulation and oversight, leading to inaccurate labeling of some products.2 To maximize sampling and ensure representativeness of available products, we examined the label accuracy of CBD products sold online, including identification of present but unlabeled cannabinoids.

Methods | Internet searches (keywords: CBD, cannabidiol, oil, tincture, vape) were performed between September 12, 2016, and October 15, 2016, to identify CBD products available for online retail purchase that included CBD content on packaging. Products with identical formulation as another product under the same brand were excluded. All unique CBD extracts that met these criteria were purchased. Products were stored according to packaging instructions, or if none were provided, in a cool, dry space. Within 2 weeks of receipt, product labels were replaced with blinded study identifiers and sent to the laboratories at Botanacor Services for analysis of cannabinoid content (cannabidiol, cannabidiolic acid, cannabigerol, cannabinol, Δ-9-tetrahydrocannabinol, Δ-9-tetrahydrocannabibolic acid [THC]) using high-performance liquid chromatography (in triplicate; lower limit of quantification, ≤0.3170% wt/wt). A 10-point method validation procedure was used to determine the appropriate sample preparation and analytical method. Triplicate test results were averaged and reported by product weight. Data were analyzed using SPSS Statistics (IBM), version 23, with descriptive analyses and a 2-tailed χ² (α <.05).

Results | Eighty-four products were purchased and analyzed (from 31 companies). Observed CBD concentration ranged between 0.10 mg/mL and 655.27 mg/mL (median, 9.45 mg/mL). Median labeled concentration was 15.00 mg/mL (range, 1.33-800.00). With respect to CBD, 42.85% (95% CI, 32.82%-53.53%) of products were underlabeled (n = 36), 26.19% (95% CI, 17.98%-36.48%) were overlabeled (n = 22), and 30.95% (95% CI, 22.08%-41.49%) were accurately labeled (n = 26) (Table 1). Accuracy of labeling depended on product type [χ²(1) = 16.75; P = .002], with vaporization liquid most frequently mislabeled (21 mislabeled products; 87.50% [95% CI, 69.00%-95.66%]) and oil most frequently labeled accurately (18 accurately labeled products; 45.00% [95% CI, 30.71%-60.17%]). Concentration of unlabeled cannabinoids was generally low (Table 2); however, THC was detected (up to 6.43 mg/mL) in 18 of the 84 samples tested (21.43% [95% CI, 12.50% [4.34-31.00] mg/mL (mean, 56.15 mg/mL; range, 14.23-98.07 mg/mL). Median concentration was 22.26 mg/mL (range, 2.50-800.00 mg/mL). Table 1. Label Accuracy by Cannabidiol Extract Type

<table>
<thead>
<tr>
<th>Cannabidiol Extract Products</th>
<th>Oil (n = 40)</th>
<th>Tincture (n = 20)</th>
<th>Vaporization Liquid (n = 24)</th>
<th>Total (N = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Label accuracy, No. of products (%) [95% CI]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accurate*</td>
<td>18 (45.00) [30.71-60.17]</td>
<td>5 (25.00) [11.19-46.87]</td>
<td>3 (12.50) [4.34-31.00]</td>
<td>26 (30.95) [22.08-41.49]</td>
</tr>
<tr>
<td>Underb</td>
<td>10 (25.00) [14.19-40.19]</td>
<td>8 (40.00) [21.88-61.34]</td>
<td>18 (75.00) [55.10-88.00]</td>
<td>36 (42.85) [32.82-53.53]</td>
</tr>
<tr>
<td>Overc</td>
<td>12 (30.00) [18.07-45.43]</td>
<td>7 (35.00) [18.12-56.71]</td>
<td>3 (12.50) [4.34-31.00]</td>
<td>22 (26.19) [17.98-36.48]</td>
</tr>
<tr>
<td><strong>Labeled concentration, mg/mL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>56.15 (14.23-98.07)</td>
<td>11.14 (5.60-16.60)</td>
<td>26.15 (12.50-39.74)</td>
<td>36.86 (16.21-57.51)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>22.26 (2.50-800.00)</td>
<td>8.33 (1.33-50.00)</td>
<td>18.33 (2.00-160.00)</td>
<td>15.00 (1.33-800.00)</td>
</tr>
</tbody>
</table>

* Cannabidiol content tested within 10% of labeled value.

b Cannabidiol content exceeded labeled value by more than 10%.

c Cannabidiol content tested more than 10% below labeled value.

© 2017 American Medical Association. All rights reserved.
14.01%-31.35%), cannabidiolic acid (up to 55.73 mg/mL) in 13 of the 84 samples tested (15.48% [95% CI, 9.28%-24.70%]), and cannabigerol (up to 4.67 mg/mL) in 2 of the 84 samples tested (2.38% [95% CI, 0.65%-8.27%]).

Discussion | Among CBD products purchased online, a wide range of CBD concentrations was found, consistent with the lack of an accepted dose. Of tested products, 26% contained less CBD than labeled, which could negate any potential clinical response. The overlabeling of CBD products in this study is similar in magnitude to levels that triggered warning letters to 14 businesses in 2015-2016 from the US Food and Drug Administration (eg, actual CBD content was negligible or less than 1% of the labeled content), suggesting that there is a continued need for federal and state regulatory agencies to take steps to ensure label accuracy of these consumer products. Underlabeling is less concerning as CBD appears to neither have abuse liability nor serious adverse consequences at high doses; however, the THC content observed may be sufficient to produce intoxication by cannabidiol-enriched cannabis extract in two children with refractory epilepsy.

Marcel O. Bonn-Miller, PhD
Mallory J. E. Loflin, PhD
Brian F. Thomas, PhD
Jahan P. Marcu, PhD
Travis Hyke, MS
Ryan Vandrey, PhD

Author Affiliations: University of Pennsylvania Perelman School of Medicine, Philadelphia (Bonn-Miller); Veterans Affairs San Diego Health Care System, San Diego, California (Loflin); RTI International, Research Triangle Park, North Carolina (Thomas); Americans for Safe Access, Washington DC (Marcu); Palo Alto University, Palo Alto, California (Hyke); Johns Hopkins University School of Medicine, Baltimore, Maryland (Vandrey).

Accepted for Publication: August 7, 2017.

Corresponding Author: Marcel O. Bonn-Miller, PhD, University of Pennsylvania Perelman School of Medicine, 3440 Market St, Ste 370, Philadelphia, PA 19104 (mbonn@pennmedicine.upenn.edu).

Author Contributions: Dr Bonn-Miller had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Bonn-Miller, Loflin, Thomas, Vandrey.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Bonn-Miller, Loflin, Marcu, Vandrey.

Critical revision of the manuscript for important intellectual content: Bonn-Miller, Loflin, Thomas, Hyke, Vandrey.

Statistical analysis: Loflin, Marcu.

Obtained funding: Bonn-Miller.

Administrative, technical, or material support: Bonn-Miller, Loflin, Thomas, Hyke, Vandrey.

Supervision: Bonn-Miller.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Bonn-Miller, Thomas, and Vandrey reported serving as unpaid board members of the Institute for Research on Cannabinoids. Dr Bonn-Miller reported receiving personal fees from Zynerba Pharmaceuticals, the Lambert Center for the Study of Medicinal Cannabis and Hemp, the Realm of Caring Foundation, Tilray, CW Botanicals, Insys Therapeutics, International Cannabis and Cannabinoids Institute, the Medical Cannabis Institute, and Aphria. Dr Vandrey reported receiving personal fees from Zynerba Pharmaceuticals, CW Hemp, Battelle Memorial Institute, and Insys Pharmaceuticals. No other disclosures were reported.


Association of Trial Registration With Reporting of Primary Outcomes in Protocols and Publications

A major aim of trial registration is to help identify and deter the selective reporting of outcomes based on the results.1,2 However, it is unclear whether registered outcomes accurately reflect the trial protocol and whether registration improves the reporting of primary outcomes in publications. We evaluated adherence to trial registration and its association with subsequent publication and reporting of primary outcomes.

Methods | We conducted a cohort study of all initiated clinical trial protocols approved in 2007 by the research ethics committee for the region of Helsinki and Uusimaa, Finland. Registry records and articles published up to February 2017 were identified using keywords to search trial registries, PubMed, EMBASE, Cochrane Central, Finnish databases (Medic, ARTO, TUHAT), and Google. Trial characteristics and outcomes were extracted in duplicate from each protocol (including amendments), registry record, and publication.

Using descriptive statistics and multivariable logistic regression adjusting for characteristics in Table 1, we determined...