

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 χ^2 ($\alpha < .05$). Consistent with other herbal products in the US Pharmacopeia and emerging standards from medicinal cannabis industry leaders, a ±10% allowable variance was used for product labeling (ie, accurately labeled = 90%-110% labeled value, underlabeled >110% labeled value, and overlabeled <90% labeled value).

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 [$\chi^2(1) = 16.75$; $P = .002$], 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,

Table 1. Label Accuracy by Cannabidiol Extract Type

	Cannabidiol Extract Products			
	Oil (n = 40)	Tincture (n = 20)	Vaporization Liquid (n = 24)	Total (N = 84)
Label accuracy, No. of products (%) [95% CI]				
Accurate ^a	18 (45.00) [30.71-60.17]	5 (25.00) [11.19-46.87]	3 (12.50) [4.34-31.00]	26 (30.95) [22.08-41.49]
Under ^b	10 (25.00) [14.19-40.19]	8 (40.00) [21.88-61.34]	18 (75.00) [55.10-88.00]	36 (42.85) [32.82-53.53]
Over ^c	12 (30.00) [18.07-45.43]	7 (35.00) [18.12-56.71]	3 (12.50) [4.34-31.00]	22 (26.19) [17.98-36.48]
Labeled concentration, mg/mL				
Mean (95% CI)	56.15 (14.23-98.07)	11.14 (5.60-16.60)	26.15 (12.50-39.74)	36.86 (16.21-57.51)
Median (range)	22.26 (2.50-800.00)	8.33 (1.33-50.00)	18.33 (2.00-160.00)	15.00 (1.33-800.00)
Deviation of labeled content from tested value, mg/mL				
Mean (95% CI) [% of deviation]	10.34 (4.95-15.74) [29.01]	3.94 (2.74-5.14) [220.62]	11.52 (8.10-14.94) [1098.70]	9.16 (4.96-13.36) [380.26]
Median (range) [% of deviation]	2.76 (0.13-144.73) [12.11]	1.48 (0.01-22.30) [19.12]	4.62 (0.14-66.07) [67.34]	3.17 (0.10-144.73) [20.42]

^a 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.

Table 2. Observed Cannabinoid Concentration of 84 Tested Extract Products Sold Online

Cannabinoid	Average Observed Concentration Across Tests, mg/mL	
	Mean (SD)	Median (Range)
Cannabidiol ^a	30.96 (80.86)	9.45 (0.10-655.27)
Cannabidiolic acid	1.35 (6.74)	0 (0-55.73)
Cannabigerol	0.08 (0.55)	0 (0-4.67)
Cannabinol	0	0
Δ-9-Tetrahydrocannabinol	0.45 (1.18)	0 (0-6.43)
Δ-9-Tetrahydrocannabinolic acid	0	0

^a The mean labeled concentration for cannabidiol was 36.86 mg/mL (SD, 96.56) and the median was 15.00 mg/mL (range, 1.33-800.0).

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 Administration³ (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^{4,5}; however, the THC content observed may be sufficient to produce intoxication or impairment, especially among children.⁶ Although the exclusive procurement of products online is a study limitation given the frequently changing online marketplace, these products represent the most readily available to US consumers. Additional monitoring should be conducted to determine changes in this marketplace over time and to compare internet products with those sold in dispensaries. These findings highlight the need for manufacturing and testing standards, and oversight of medicinal cannabis products.

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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.

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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