# The Effectiveness of Common *Cannabis* Products for Treatment of Nausea

*Sarah S. Stith, PhD,* Xiaoxue Li, PhD,* Joaquin Orozco, MS,† Victoria Lopez, BS,‡ Franco Brockelman, BS,§ Keenan Keeling, BS,§ Branden Hall,§ and Jacob M. Vigil, PhD†*



**Goals:** We measure for the first time how a wide range of cannabis products affect nausea intensity in actual time.

**Background:** Even though the *Cannabis* plant has been used to treat nausea for millennia, few studies have measured real-time effects of common and commercially available cannabis-based products.

**Study:** Using the Releaf App, 886 people completed 2220 cannabis self-administration sessions intended to treat nausea between June 6, 2016 and July 8, 2019. They recorded the characteristics of self-administered cannabis products and baseline symptom intensity levels before tracking real-time changes in the intensity of their nausea.

**Results:** By 1 hour postconsumption, 96.4% of people had experienced symptom relief with an average symptom intensity reduction of −3.85 points on a 0 to 10 visual analog scale (SD = 2.45, $d = 1.85$, $P < 0.001$). Symptom relief was statistically significant at 5 minutes and increased with time. Among product characteristics, flower and concentrates yielded the strongest, yet similar results; products labeled as *Cannabis indica* underperformed those labeled as *Cannabis sativa* or hybrid; and joints were associated with greater symptom relief than pipes or vaporizers. In sessions using flower, higher tetrahydrocannbinol and lower cannabidiol were generally associated with greater symptom relief (eg, within 5 min).

**Conclusions:** The findings suggest that the vast majority of patients self-selecting into cannabis use for treatment of nausea likely experience relief within a relative short duration of time, but the level of antiemetic effect varies with the characteristics of the cannabis products consumed in vivo. Future research should focus on longer term symptom relief, including nausea-free intervals and dosing frequency; the risks of consumption of medical cannabis, especially among high-risk populations, such as pregnant women and children; and potential interactions between cannabis, conventional antiemetics, other medications, food, tobacco, alcohol, and street drugs among specific patient populations.

**Key Words:** nausea, cannabis, marijuana, antiemetic, cannabidiol, tetrahydrocannabinol, *C. sativa*

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Nausea is a substantial treatment-resistant problem, sometimes described as a "neglected symptom"[1] due in part to the lack of major breakthroughs in nausea treatments in the last 20 years.[2] Common causes of nausea include pregnancy, food poisoning, emotional distress, gastrointestinal disorders, hyperemesis gravidarum, gallbladder disease, HIV, motion sickness, and radiation, and antineoplastic and other medication exposure. Acute, delayed, and anticipatory nausea all involve multiple body systems and organs, and the physiological mechanisms of nausea and their distinction from emesis are not fully understood.[1,3] Although most conventional antiemetics have fairly mild reported side effects, they tend to offer limited relief for treating nausea and are not effective for all patients.[4] Newer medications, such as 5-hydroxy-tryptamine receptor 3 (5-HT3) antagonists (eg, ondansetron and Ramosetron), have also shown modest efficacy, with numbers needed to treat between 6 and 27 for postoperative nausea and vomiting.[5] Alternative therapies such as acupuncture and acupressure similarly show little evidence of dangerous side effects and limited effectiveness.[6–8] While the safety of conventional antiemetics is encouraging, their lack of efficacy for treating nausea demands more optimal solutions. Herbal medications, such as ginger and peppermint, are also commonly used to treat nausea, especially among pregnant women. Ginger has been shown to be effective among pregnant women, but concerns exist with respect to safety.[9] Outside of pregnancy-induced nausea, the literature shows mixed results with respect to effectiveness, with positive effects found for postoperative nausea,[10] but not for chemotherapy-induced nausea.[11] Peppermint has been less-studied than ginger, with no known significant side effects, but mixed results postoperatively,[12,13] potentially greater effectiveness than ginger among chemotherapy patients,[14] and likely less relief experienced among pregnant women.[15]

Humans have been using another herbal medication to treat nausea for millennia, the *Cannabis* plant,[16,17] and considerable research suggests that the endocannabinoid system (ECS) can modulate the expression of nausea.[1,18] In the 1970s, oncologists found that smoked cannabis reduced chemotherapy-induced nausea,[1,19] and some research suggests that cannabis may be particularly effective for nausea management and anticipatory nausea in chemotherapy patients.[20] In a recent study of 2000 Israeli patients with cancer who had government licenses to use medicinal cannabis, 91% ranked nausea and vomiting as the most common symptom improved.[21] Clinical trials have also demonstrated the effectiveness of cannabis-based medicines for treating nausea,[1,20,22,23] and the US Food and Drug Administration has approved a synthetic cannabinoid medication, dronabinol, to treat intractable nausea. However, while the American Cancer Society now acknowledges that cannabis is a potent therapeutic for relieving nausea,[24] and the National Academies of Sciences Engineering and Medicine (NASEM) ranked cannabinoids among the strongest available agents for chemotherapy-induced nausea,[22] the NASEM also acknowledged that most previous clinical studies have been limited to retrospective, synthetic cannabinoid, and animal

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From the Departments of *Economics; †Psychology; ‡College of Pharmacy, University of New Mexico, Albuquerque, NM; and §MoreBetter Ltd, Washington, DC.

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Address correspondence to: Jacob M. Vigil, PhD, University of New Mexico, Albuquerque, 87106 NM (e-mail: vigilj@unm.edu).



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studies,[22] largely because of federal prohibitions.[25] No prior study on the effects of cannabis on nausea has controlled for the diversity in commercially available cannabis products or how different product characteristics influence the effectiveness of cannabis for treating nausea, despite 'severe nausea' being one of the most commonly approved conditions for enrollment in state-sanctioned medical cannabis programs across United States.[26]

These potential therapeutic benefits must be disentangled from the side effects of cannabis consumption, both positive and negative. In particular, a summary of the literature indicates that tetrahydrocannabinol (THC) has been associated with euphoria, relaxation and perceptual changes, but also dysphoria, anxiety, and psychotic symptoms.[27,28] Meanwhile, cannabidiol (CBD) is associated with diarrhea, somnolence, and nausea, but also has anxiolytic and antipsychotic effects. Nonmedical cannabis use has been associated with mental health changes, increased motor vehicle accidents, impaired respiratory function, and cardiovascular disease, along with altered psychosocial development among adolescents, and hyperemesis syndrome concomitant with abnormal washing behaviors.[29–31] Because any combination of these side effects could result from cannabis consumption, the net effects of cannabis consumption on, for example, nausea and anxiety, are unclear.

This study uses observational data to assess how a wide range of cannabis products used in vivo affect momentary feelings of nausea in actual time. For measuring cannabis consumption and its effects, we used the largest database of real-time cannabis self-administration sessions in the United States, collected by the mobile software application, Releaf App.[32] The app was designed to help patients monitor the variable effects of cannabis across product types, routes of administration, labeled cannabis subtypes or subspecies, and cannabinoid contents of the products consumed. Users indicate the medical condition(s) for which they are consuming cannabis and real-time symptom intensity levels before and following consumption under otherwise naturalistic conditions. We analyze how labeled and other general product characteristics are associated with changes in nausea intensity feelings in real-time from 5 minutes to 1 hour postconsumption.

## METHODS

### Study Design

The observational study design was deemed 'exempt' by the Institutional Review Board at the University of New Mexico, because of the anonymized nature and limited harm posed by the data analyses. Data used in this study come from user activities recorded in the Releaf App, which was designed for patients to monitor the effects of non-FDA approved cannabis usage. Users voluntarily use the free app to record cannabis product characteristics and real-time changes in symptom intensity levels. De-identified user-level data were collected by the owner of the Releaf App, MoreBetter Ltd., and were provided to the research team under an investigator confidentiality agreement. In each user-administered session, the user is first asked to specify the symptoms being treated, input several product characteristics, which are generally available from product labels, and record a starting symptom intensity level (on a 0 to 10, 11-point visual analog scale) for each specified symptom. The product characteristics include type of product (flower, concentrate, edible, topical, pill, or tincture), the product's labeled plant phenotype *Cannabis sativa*, *Cannabis indica*, or hybrid), combustion method when applicable (use of a joint, pipe or vaporizer), and major cannabinoid potency levels for THC and CBD. We include the labeled plant phenotypes, which, despite being widely criticized by the scientific community,[33] are still commonly used by consumers in their purchasing decisions. After entering the starting symptom level, the user starts a session, recording updates to their symptom intensity level as many times as desired until they enter a final symptom level and close out the session. For this study, we restrict the sample to sessions with a starting symptom intensity level $>0$ and in which "Nausea" was the selected symptom. We further restrict the sample to "active sessions," defined as those with at least 1 symptom update within 1 hour. The resulting analysis sample includes 2220 sessions completed by 886 users between June 6, 2016 and July 8, 2019. Only the recording of product type is mandatory, so regressions controlling for the full range of product characteristics include only 406 sessions. As shown in Table 1, THC and CBD content are the least frequently recorded of the product characteristics, because only users

**TABLE 1.** Descriptive Statistics for Product Characteristics and Symptom Intensity Measures

| Product Characteristics | % or Mean | SD | Minimum | Maximum |
|---|---|---|---|---|
| Panel A: product type (2220 symptom sessions, 886 users) | | | | |
| Concentrate | 32 | | 0 | 1 |
| Edible | 02 | | 0 | 1 |
| Flower | 61 | | 0 | 1 |
| Pill | 00 | | 0 | 1 |
| Tincture | 04 | | 0 | 1 |
| Topical | 00 | | 0 | 1 |
| Panel B: labeled plant phenotype (1852 symptom sessions, 758 users) | | | | |
| Hybrid | 52 | | 0 | 1 |
| *Cannabis indica* | 30 | | 0 | 1 |
| *Cannabis sativa* | 18 | | 0 | 1 |
| Panel C: combustion method (1976 symptom sessions, 783 users) | | | | |
| Joint | 10 | | 0 | 1 |
| Pipe | 38 | | 0 | 1 |
| Vape | 52 | | 0 | 1 |
| Panel D: THC (900 symptom sessions, 371 users) | | | | |
| % THC | 39.01 | 29.57 | 0 | 98 |
| THC <10% | 14 | | 0 | 1 |
| THC 10%-19% | 22 | | 0 | 1 |
| THC 20%-35% | 26 | | 0 | 1 |
| THC 35%+ | 38 | | 0 | 1 |
| Panel E: CBD (536 symptom sessions, 245 users) | | | | |
| % CBD | 16.26 | 20.47 | 0 | 99 |
| CBD <1% | 18 | | 0 | 1 |
| CBD 1%-9% | 35 | | 0 | 1 |
| CBD 10%-35% | 27 | | 0 | 1 |
| CBD 35%+ | 20 | | 0 | 1 |
| Panel F: symptom relief variables (2220 symptom sessions, 886 users) | | | | |
| Starting symptom level | 5.84 | 2.16 | 1 | 10 |
| Ending symptom level | 1.99 | 2.00 | 0 | 10 |
| Symptom change | −3.85 | 2.45 | −10 | 6 |
| Symptom relief indicator | 96 | | 0 | 1 |

The sample includes sessions with a starting symptom level $>0$ and at least 1 symptom update in 1 hour. All variables are dichotomous except for % THC, % CBD, starting and ending symptom levels, and symptom change.
CBD indicates cannabidiol; THC, tetrahydrocannbinol.

of products from commercial dispensaries are likely to have this information. Combustion method further limits the product characteristics regression sample to only flower and concentrates.

## Study Outcomes

The objective of the study is to explore the effect of cannabis on symptom changes across a relatively short amount of time, from 5 to 60 minutes following consumption. We measure symptom relief by subtracting postadministration symptom intensity levels from starting symptom intensity level. The resulting symptom relief variable ranges between −10 (maximum symptom relief) and 9 (maximum symptom exacerbation). We measure symptom relief at 5, 15, 30, 45, and 60 minutes following cannabis consumption. For sessions that ended within 1 hour, we use the ending symptom level to calculate the symptom relief variables for times after the session ended. For example, if a session ended 35 minutes since cannabis use, the 45-minute relief and 60-minute relief are recorded as the ending symptom level (recorded at 35 min) minus starting symptom. Because we carry forward the starting symptom level for anyone who has not yet updated their symptom level for a given time period, our results are biased away from finding an effect before 1 hour, and especially for the 5-minute and 15-minute reporting windows. Even though 93% of the sessions in our sample used combustion-based consumption methods, which have an immediate effect through lung absorption, in only 38% of sessions was the symptom intensity level updated within 5 minutes. By 15 minutes postconsumption, 63 percent had updated their symptom intensity level. Percentages at 30 and 45 minutes were 84% and 93%, respectively. Because the sample exclusion criteria required that sessions have an ending symptom recorded within 1 hour, the measurements at 1 hour all include at least 1 symptom intensity level update. By 1 hour postconsumption, 96.4% of users reported symptom relief within 1 hour, 1.94% reported symptom worsening, and 1.62% reported no change in symptom intensity level.

## Statistical Analysis

We use paired-samples means comparisons to measure the change in symptom intensity level over time. To examine the effects of product characteristics on symptom relief, we regress the outcomes of interest on different user-reported product characteristics using a mixed effects model, which allows the slopes and intercepts to vary randomly by user. We control for starting symptom level in all regressions, since higher initial symptom intensity is mechanically associated with larger possible symptom relief. Standard errors are clustered at the user level to account for heteroscedasticity and user-level arbitrary correlation. We also conduct analyses focusing only on cannabis flower, in order to evaluate the effects in an arguably more uniform product, or at least a product in which THC and CBD have known ranges. Cannabis flower is also the most widely used cannabis product in our sample.[34] Analyses were conducted using Stata 15.1.

# RESULTS

Table 1 presents descriptive statistics for the product characteristics and symptom relief variables. On average, users in sessions treating nausea reported a starting symptom intensity of 5.84 and an ending symptom (at the 1-h cutoff point) of 1.99, resulting in an average decrease in symptom intensity of 3.85 points (SD = 2.45, $d = 1.85$, $P < 0.001$). The majority of the sample (61%) used a flower product, followed by sessions in which a concentrate (32%) was used. A small number of sessions involved the use of edibles (2%), pills (0%), tinctures (4%), and topicals (0%). *C. sativa* and *C. indica* "hybrids" were the most common labeled plant phenotypes (52%) and vaping was the most common combustion method (52%). The average THC level was 39.01%, and the average CBD level was 16.26%.

**TABLE 2.** Change in Nausea Symptom Intensity Over Time

| Time Lapse | Symptom Intensity Level | Symptom Relief | *P* | Symptom Relief Relative to Previous Reading | *P* |
|---|---|---|---|---|---|
| Start | 5.84 (2.16) | | | | |
| 5 minutes | 4.49 (2.55) | −1.35 | < 0.001 | −1.35 | < 0.001 |
| 15 minutes | 3.55 (2.55) | −2.30 | < 0.001 | −0.94 | < 0.001 |
| 30 minutes | 2.68 (2.33) | −3.17 | < 0.001 | −0.87 | < 0.001 |
| 45 minutes | 2.24 (2.14) | −3.61 | < 0.001 | −0.44 | < 0.001 |
| 60 minutes | 1.99 (2.00) | −3.85 | < 0.001 | −0.25 | < 0.001 |

The sample includes sessions with a starting symptom level > 0 and at least 1 symptom update in 1 hour.

Standard deviations for symptom intensity level are reported in parentheses.

Table 2 shows the change in average symptom intensity over time. From an average starting symptom intensity of 5.84, recorded symptom intensity levels started to decrease immediately after cannabis consumption, with average intensity levels decreasing to 4.49 after 5 minutes, 3.55 after 15 minutes, 2.69 after 30 minutes, and 1.99 after 1 hour.

Figure 1 plots symptom relief over time by different product characteristics. Adjusted average symptom relief obtained from mixed effects models controlling for starting symptom intensity level and corresponding 95% confidence intervals are presented. Panel A shows the effect across product types. Pills and topical products are omitted because of the small sample sizes. Findings suggest that concentrates and flower products provide faster and greater symptom relief compared with edible or tincture cannabis products. Panel B shows the effects of labeled plant phenotype. Findings suggest no significant differences in symptom relief. Panel C shows the effects of combustion method for inhalable flower and concentrated products only. Use of a vaporizer is generally associated with the significantly less symptom relief as compared with the use of a joint or the use of a pipe. Panels D and E show the effects of THC and CBD levels, respectively. Higher THC potency levels are weakly associated with the greater symptom relief while higher CBD levels are generally associated with less relief from feelings of nausea. While intriguing, these findings should be interpreted with caution because cannabinoid levels and combustion methods are mechanically associated with product types. We therefore, use regression analyses to isolate the effects of product characteristics for cannabis concentrates and flower, and then for flower only, the most common type of product.

Table 3 reports the results regressing symptom relief on product characteristics for concentrates and flower. Each column reports results from a separate regression and compares the effects of each type of characteristic relative to a reference category. Once other product characteristics are controlled for, concentrate products are not associated with significant differences in symptom relief compared with flower products. *C. indica* products are generally associated

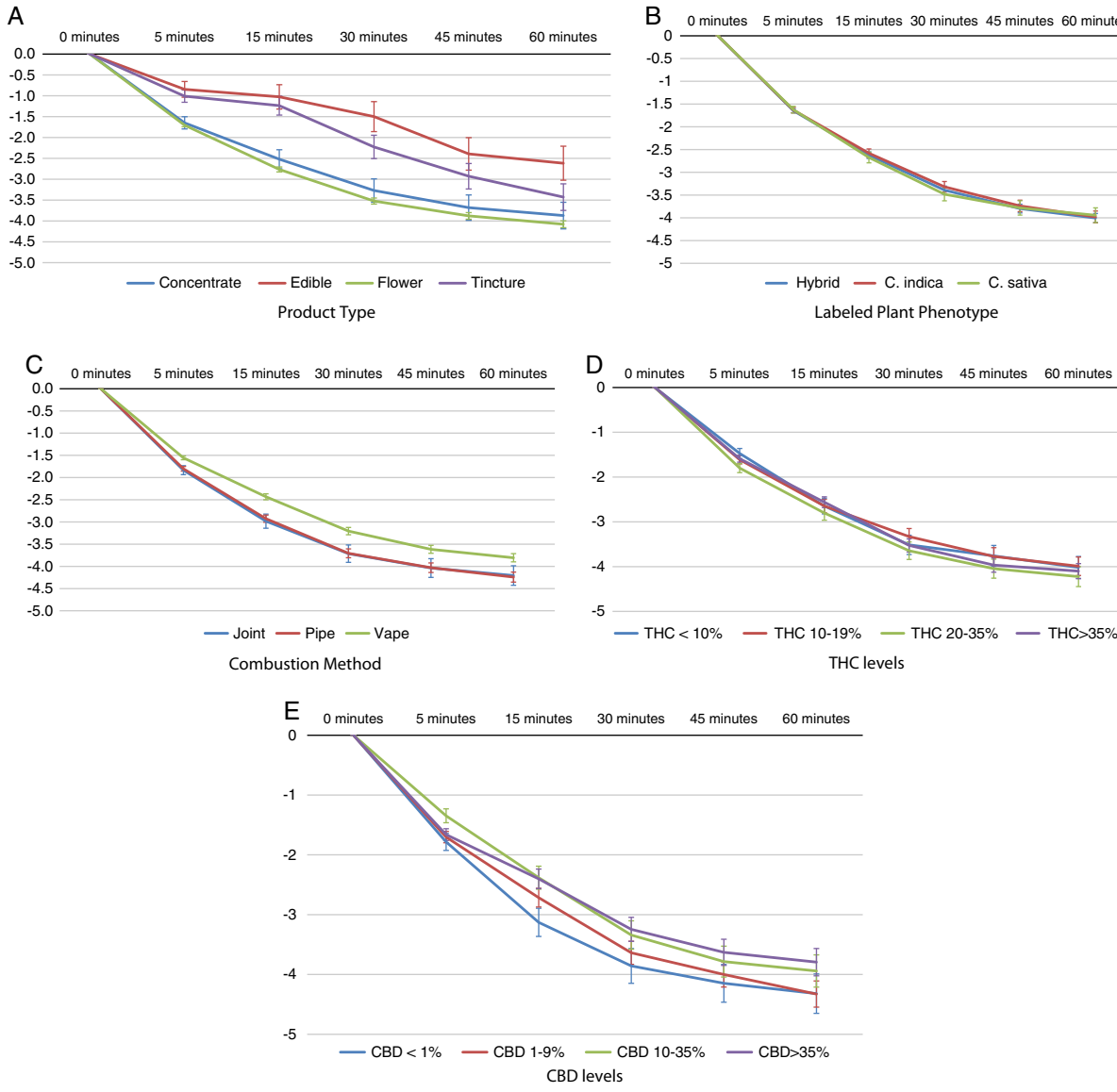


**FIGURE 1.** Nausea symptom relief over time by product characteristics. Each panel presents the adjusted change in symptom intensity level (symptom relief) at 5, 15, 30, 45, and 60 minutes, with their corresponding 95% confidence intervals. The adjusted changes are obtained from mixed effects models regressing symptom relief on product characteristics and starting symptom intensity level. CBD indicates cannabidiol; *C. indica*, *Cannabis indica*; *C. sativa*, *Cannabis sativa*; THC, tetrahydrocannbinol.

with less symptom relief than *C. sativa* or hybrid products. Vaping and pipe use are associated with less immediate symptom relief compared with joints, with the gap narrowing over time. THC levels are generally not a significant predictor of symptom relief after controlling for other product characteristics, both in the short term and longer term. Mid-level CBD potency (1% to 35%) are associated with less symptom relief within 15 minutes after cannabis consumption, but are not a significant predictor of symptom relief in the longer term.

Table 4 reports regression results restricting the sample to sessions using flower products only. Products that labeled *C. indica* are associated with less relief within 15 minutes, but are not significantly different in the longer term. Vaping is associated with less symptom relief in short term and medium term (within 45 min), but is not significantly different in the longer term. High THC levels are likely associated with greater immediate relief, but explain no differences in symptom relief beyond 5 minutes. Products with high CBD levels are generally associated with less symptom relief in the first 30 minutes after cannabis use, but show similar effects compared with products with low CBD at 45 minutes and 1 hour.

## DISCUSSION

By measuring the real-time effects of consuming common and commercially available cannabis-based products, using the largest database of cannabis administration sessions in the United States, we found that cannabis is an



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**TABLE 3.** Effects of Product Characteristics on Symptom Relief Over Time for Cannabis Concentrates and Flower

| | (1) | (2) | (3) | (4) | (5) |
|---|---|---|---|---|---|
| **Product Characteristics** | **5 Minutes** | **15 Minutes** | **30 Minutes** | **45 Minutes** | **60 Minutes** |
| Concentrate (flower) | 0.223 | 0.039 | −0.385 | 0.095 | −0.296 |
| | (0.221) | (0.459) | (0.422) | (0.408) | (0.351) |
| Hybrid (*Cannabis sativa*) | 0.145 | 0.246 | 0.217 | 0.279 | 0.131 |
| | (0.165) | (0.251) | (0.219) | (0.189) | (0.201) |
| *Cannabis indica* (*Cannabis sativa*) | 0.150 | 0.635* | 0.598* | 0.493* | 0.377 |
| | (0.201) | (0.303) | (0.257) | (0.225) | (0.215) |
| Pipe (joint) | 1.084** | 0.582 | 0.654* | 0.372 | 0.205 |
| | (0.407) | (0.395) | (0.332) | (0.301) | (0.280) |
| Vape (joint) | 1.356** | 1.126** | 1.015** | 0.806* | 0.710* |
| | (0.393) | (0.412) | (0.364) | (0.355) | (0.319) |
| THC 10%-19% (< 10%) | −0.152 | −0.222 | −0.275 | −0.199 | −0.304 |
| | (0.179) | (0.325) | (0.343) | (0.353) | (0.293) |
| THC 20%-35% (< 10%) | −0.306 | 0.013 | −0.311 | −0.221 | −0.262 |
| | (0.241) | (0.321) | (0.363) | (0.360) | (0.310) |
| THC 35%+ (< 10%) | −0.370 | −0.388 | −0.245 | −0.551 | −0.360 |
| | (0.262) | (0.399) | (0.343) | (0.411) | (0.250) |
| CBD 1%-9% (< 1%) | 0.125 | 0.497 | 0.400 | 0.039 | −0.179 |
| | (0.276) | (0.290) | (0.329) | (0.244) | (0.241) |
| CBD 10%-35% (< 1%) | 0.372 | 0.648* | 0.423 | −0.074 | −0.132 |
| | (0.222) | (0.324) | (0.361) | (0.285) | (0.252) |
| CBD 35%+ (< 1%) | −0.290 | 0.323 | 0.325 | −0.102 | 0.055 |
| | (0.292) | (0.413) | (0.389) | (0.320) | (0.295) |
| Starting symptom level | −0.229** | −0.471** | −0.608** | −0.667** | −0.718** |
| | (0.052) | (0.055) | (0.051) | (0.048) | (0.040) |
| Constant | −1.067* | −0.930 | −0.644 | −0.188 | 0.139 |
| | (0.498) | (0.601) | (0.638) | (0.525) | (0.432) |
| Observations | 406 | 406 | 406 | 406 | 406 |
| N users | 189 | 189 | 189 | 189 | 189 |

*$P < 0.05$.
**$P < 0.01$.
Each column represents a separate equation regressing change in symptom intensity level on product characteristics with omitted categories shown in parentheses.
All regressions are estimated using a mixed effects model.
SE, clustered at the individual user level, are shown in parentheses.
CBD indicates cannabidiol; THC, tetrahydrocannbinol.

effective and fast-acting treatment for feelings of nausea. The effects of cannabis on symptom relief increase over the course of a cannabis self-administration session, but at a decreasing rate from 5 to 60 minutes postconsumption. Although symptom relief experienced at 60 minutes post-consumption does not vary with product characteristics other than combustion method, shorter term effects appear to vary with such characteristics. The most effective products for immediate relief appear to be *Cannabis* flower and concentrates, products labeled as *C. sativa* or "hybrid," the use of a joint for combusting *Cannabis* flower, and products with relatively high amounts of THC and relatively low amounts of CBD. Regardless of differences across product types, in the vast majority of sessions, significant antinausea effects were reported within the 60-minute observation window. The current results support prior retrospective and animal studies and help explain why *C. sativa* has been used as an antiemetic medication for hundreds if not thousands of years.[2] The findings are also consistent with observations of decreased sales of prescription and over-the-counter gastrointestinal medications such as antacids following relaxation of cannabis prohibition laws.[35,36]

Widespread use of cannabis-based products for nausea-related symptoms and the immediate effects documented herein reveal its relative effectiveness with respect to easily obtained conventional over-the-counter and prescription medications. This apparent effectiveness is not without caveat; although prior studies suggest short-term side effects are minimal,[27] abuse and dependence are well-documented. Furthermore, certain populations, specifically pregnant women, children and teenagers, and people with mental illness may be at greater risk of negative consequences from cannabis.[37,38] Research suggests cannabis use has been increasing among pregnant women[39] and likely among children as well, given its widespread availability. Perhaps further encouraging use among pregnant women and children, the US Food and Drug Administration recently approved a cannabis-derived medication, Epidiolex (CBD), for treatment of epilepsy in children. Evidence also exists that pregnant women are seeking and obtaining medical advice through cannabis dispensaries. For example, Dickson et al[40] conducted a cross-state study in which a confederate caller described herself as 8 weeks pregnant and experiencing morning sickness and requested advice about cannabis use. Nearly 70% of the local commercial dispensaries recommended that the caller experiment with cannabis to treat her nausea, with only 19% encouraging the caller to first discuss cannabis usage with a health care provider.[40] These data points raise concern, because it appears that the ineffectiveness of conventional approaches

**TABLE 4.** Effects of Product Characteristics on Symptom Relief Over Time for Cannabis Flower

| | (1) | (2) | (3) | (4) | (5) |
|---|---|---|---|---|---|
| **Product Characteristics** | **5 Minutes** | **15 Minutes** | **30 Minutes** | **45 Minutes** | **60 Minutes** |
| Hybrid (*Cannabis sativa*) | −0.047 | −0.025 | −0.052 | 0.177 | 0.230 |
| | (0.188) | (0.285) | (0.235) | (0.242) | (0.249) |
| *Cannabis indica* (*Cannabis sativa*) | 0.192 | 0.746* | 0.520 | 0.419 | 0.351 |
| | (0.253) | (0.330) | (0.347) | (0.316) | (0.296) |
| Pipe (joint) | 0.599 | 0.597 | 0.688* | 0.405 | 0.244 |
| | (0.415) | (0.379) | (0.325) | (0.292) | (0.285) |
| Vape (joint) | 1.032* | 1.168** | 1.099** | 0.799* | 0.482 |
| | (0.417) | (0.417) | (0.372) | (0.372) | (0.368) |
| THC 10%-19% (< 10%) | −0.255 | −0.374 | −0.353 | −0.120 | −0.497 |
| | (0.218) | (0.376) | (0.493) | (0.479) | (0.385) |
| THC 20%-35% (< 10%) | −0.665* | −0.295 | −0.524 | −0.167 | −0.355 |
| | (0.332) | (0.426) | (0.502) | (0.495) | (0.420) |
| CBD 1%-9% (< 1%) | 0.463 | 0.708* | 0.478 | 0.104 | −0.175 |
| | (0.290) | (0.325) | (0.302) | (0.321) | (0.339) |
| CBD 10%-35% (< 1%) | 0.397 | 0.851 | 0.767* | 0.226 | 0.069 |
| | (0.266) | (0.444) | (0.384) | (0.307) | (0.293) |
| Starting symptom level | −0.168** | −0.472** | −0.546** | −0.623** | −0.701** |
| | (0.056) | (0.070) | (0.060) | (0.058) | (0.055) |
| Constant | −0.999* | −1.048 | −1.120 | −0.665 | 0.203 |
| | (0.501) | (0.777) | (0.760) | (0.680) | (0.599) |
| Observations | 216 | 216 | 216 | 216 | 216 |
| N users | 117 | 117 | 117 | 117 | 117 |

*$P < 0.05$.
**$P < 0.01$.
Each column represents a separate equation regressing change in symptom intensity level on product characteristics with omitted categories shown in parentheses.
All regressions are estimated using a mixed effects model.
SE, clustered at the individual user level, are shown in parentheses.
CBD indicates cannabidiol; THC, tetrahydrocannbinol.

to treating nausea may be causing pregnant women and parents to opt for the potentially greater effectiveness of cannabis without conclusive scientific research on the long-term effects from its use.

In addition to potential risks to vulnerable populations, there remains significant concern over the potential for some cannabis products to cause hyperemesis. Although research has shown that feelings of nausea are among the least common side effects of using whole natural *Cannabis* flower,[41] case studies and surveys have documented cannabinoid hyperemesis syndrome (CHS), a putative new, yet poorly understood gastrointestinal disorder.[30,31] Extrapolations from survey data suggest CHS could potentially affect as many as 2.75 million Americans.[30] CHS causes recurrent intractable nausea, vomiting, and abdominal pain, partially relieved by hot showers.[30] These effects have been theorized to result from an over-activation of the cannabinoid receptor type 1 and dysregulation of the ECS overall.[31] However, there is considerable controversy about how CHS is defined,[30] and the current diagnostic criteria used is vague and inconsistent, with little existing laboratory or radiographic tests available.[30,42,43] Furthermore, the exact underlying pathophysiological mechanism of CHS is unknown,[31] and there remains contention among clinicians whether CHS is a genuine medical condition or misdiagnosis of cyclic vomiting syndrome.[30,43] Several other root causes, not related to cannabinoid overuse, have also been proposed.[44]

Other clinicians have speculated that CHS's etiology stems from contaminants within the cannabis cultivation and production processes.[45] The most investigated contaminant is the pesticide azadirachtin, derived from neem oil, which is potentially toxic.[46–48] Some clinicians are advising pregnant women to avoid oral consumption of neem oil, as it has been found to be efficacious in pregnancy termination in both rodents and primates.[49] In addition, the producers of azadirachtin characterize the oil as a major irritant to the gut.[50] Despite the absence of reliable clinical trial data, azadirachtin is commonly utilized within the cannabis industry. No epidemiologic studies have been conducted to evaluate whether azadirachtin is safe to inhale. Azadirachtin toxicity and CHS may exhibit similar symptomology, such as the association with vomiting, cardiac conditions, and renal complications.[30,46,47] Interestingly, it has been reported that 2 long-term cannabis users diagnosed with CHS had their symptoms resolve after substituting their brands of cannabis products.[43] It is imperative that future research identify the root causes and pathophysiological mechanisms of CHS in order to better protect medical cannabis patients and evaluate the potential need for more complete contaminant testing in cannabis products.

The mechanisms behind the effectiveness of cannabis for treating nausea remain incompletely understood, but likely arise from how cannabis affects CB1 receptor responses to other stimuli. Previous human and animal studies have identified the insular cortex (IC) as a region involved in nausea processing.[20,51–53] In humans, IC activity is associated with nausea response activation,[51] nauseainduced autonomic modulation[52] and interoception, a conscious awareness of internal bodily states.[54,55] In rats, conditioned gaping was shown to be minimized by decreased neural activity in the visceral IC through endocannabinoid, 2-arachidonoylglycerol

stimulation of CB1 receptors.[56] Sticht et al[56] also demonstrated regulation of nausea in the IC involved increased levels of 2-arachidonoylglycerol stimulating CB1 receptors. These studies demonstrate the IC's role in nausea perception and physiological responses, and how the ECS may be involved in nausea reduction through the IC's effects on CB1 receptors. In addition to the IC, the ECS has been shown to modulate nausea in the area postrema (AP).[57] However, the mechanism in which the ECS relates to the AP differs from its relationship to the IC. Rock et al[57] suggest administration of systemic fatty acid amide hydrolase inhibitors decrease anticipatory nausea through CB1 receptor activation in the AP and reduce acute nausea through peroxisome proliferator-activated receptor α activation. Despite limited information on nausea physiology, our findings and the above studies suggest that cannabinoids have potential to alleviate nausea through ECS regulation within the IC and AP. The subtle variations we observed in symptom relief across product characteristics may also be indicative of multiple mechanisms at play, including the involvement of yet unstudied other cannabinoid receptors beyond CB1 and CB2, such as GPR55, a recently discovered cannabinoid receptor found in the human colon.[18]

Although this study contributes to the literature on the effects of cannabis by including immediate precannabis and postcannabis consumption measurements of symptom severity and product characteristics, the most prominent limitation of the current study is the observational nature of the data in our study, which did not include conventional experimental controls (eg, randomization, standardized dosing and use of a placebo). Likewise, the current dataset did not include individuals who do not use cannabis to treat their nausea or users who did not use the app to track their consumption, potentially resulting in selection bias, though the effects of such bias are unclear. For example, users may consist of people who have most benefited by cannabis, inflating the magnitude and direction of the observed effects. In contrast, users may discontinue use of the app after experiencing effective cannabis-based treatment solutions resulting in underestimations of cannabis' effectiveness. Other limitations of the study include the lack of information on individual differences in user demographics, medication histories and current regimen, etiology of nausea, health care provider oversight, and other characteristics of both cannabis use and nausea, including the context and setting. The etiology of a patient's nausea is likely a particularly important factor for measuring cannabis' effects. Although we find that almost all patients report improvements in their nausea symptoms, we do not know the distribution of the causes of nausea in our sample, as well as the risks that may vary with each cause, for example, chemotherapy, anesthesia, and pregnancy. A lack of geographic information also may be skewing the results because of regulatory limitations on product availability across states, including reduced product availability arising from illegality, restrictions to only medical use or nonsmokable products, limits on THC and CBD levels, approval of only a limited number of producers, and medical and recreational user constraints such as doctor referral processes, purchase limits, and restrictions on home cultivation. Although our study extended the literature by incorporating a wide variety of common and commercially available cannabis products, a more comprehensive measurement of phytochemicals in the plant, including terpenes, will be necessary to better understand how the natural compounds in the cannabis plant may be operating additively or interactively to affect feelings of nausea.

This study has important clinical implications. Cannabis may be a highly promising tool for treating nausea, especially treatment-resistant nausea in low-risk patient populations or in acute contexts when immediate relief is required. The effectiveness of cannabis for treating nausea is not without caveat, as it may induce individuals at high risk of adverse consequences to consume cannabis as well, for example, pregnant women, children, or individuals with a history of substance abuse or CHS. The lack of research on longer term effects relative to those of other antiemetics and the potential for dependence also suggest clinicians should regularly monitor their medical cannabis patients through the duration of treatment. In conclusion, this study is consistent with retrospective and animal studies showing promising clinical applications of cannabinoid-based medicines in the treatment of nausea. While cannabis has well-established clinical drawbacks, including the potential for dependence and addiction and increased risk of behavioral impairment, the current study suggests that the vast majority of users experience relief from feelings of nausea in a relatively short amount of time, and cannabis product characteristics can influence the magnitude and speed of relief from nausea.

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