ORIGINAL CONTRIBUTION

The Effectiveness of *Cannabis* Flower for Immediate Relief from Symptoms of Depression

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Objective: Scientific research on how consumption of whole, natural *Cannabis* flower affects low mood and behavioral motivations more generally is largely nonexistent, and few studies to date have measured how common and commercially available *Cannabis* flower used *in vivo* may affect the experience of "depression" in real-time. **Methods**: We observed 1,819 people who completed 5,876 cannabis self-administration sessions using the ReleafApp™ between 06/07/2016 and 07/08/2019, with the goal of measuring real-time effects of consuming *Cannabis* flower for treating symptoms of depression. Results: On average, 95.8% of users experienced symptom relief following consumption with an average symptom intensity reduction of –3.76 points on a 0-10 visual analogue scale (SD = 2.64, d = 1.71, p <.001). Symptom relief did not differ by labeled plant phenotypes ("*C. indica*," "*C. sativa*," or "hybrid") or combustion method. Across cannabinoid levels, tetrahydrocannabinol (THC) levels were the strongest independent predictors of symptom relief, while cannabidiol (CBD) levels, instead, were generally unrelated to real-time changes in symptom intensity levels. Cannabis use was associated with some negative side effects that correspond to increased depression (*e.g.* feeling unmotivated) in up to 20% of users, as well as positive side effects that correspond to decreased depression (*e.g.* feeling happy, optimistic, peaceful, or relaxed) in up to 64% of users. **Conclusions**: The findings suggest that, at least in the short term, the vast majority of patients that use cannabis experience antidepressant effects, although the magnitude of the effect and extent of side effect experiences vary with chemotypic properties of the plant.

SIGNIFICANCE

Few studies have measured how the breadth of common and commercially available *Cannabis* flower affects symptoms of depression in real-time. Using a mobile software app for collecting the largest database of individual-level cannabis administration sessions in the United States, we found that *Cannabis* flower is an

effective and fast acting antidepressant medication. Tetrahydrocannabinol (THC) levels are the strongest independent predictors of symptom relief among the product characteristics that are generally available to the public, while cannabidiol (CBD) levels, instead, were generally unrelated to real-time changes in depressive symptom intensity levels. Future research should focus on how THC and CBD interact with other cannabinoids, terpenes, and flavonoids synergistically to alleviate symptoms of depression *in vivo*.

Among the most pressing epidemics faced by Western societies and future generations worldwide [1-3], depression is also a core feature of numerous other health conditions, including cancer, substance use disorders, anxiety disorders, schizophrenia, dementia, diabetes, cardiovascular disease, chronic pain, and other physical disabilities [4-9]. Firstline treatments for depression remain cognitive behavioral therapy and pharmaceuticals with the most commonly prescribed pharmaceutical medications being sedatives (*e.g.* benzodiazepines), antidepressants (*e.g.* monoamine oxidase inhibitors, tricyclics antidepressants, selective serotonin-reuptake inhibitors, selective norepinephrine reuptake inhibitors), antihistamines, and anticonvulsant medicines, with many adolescent and adult suffers also seeking relief through alcohol and illicit drugs [10-12]. However, depression is not a specifically approved condition under any state-regulated medical cannabis program, except as treatment for depression among pediatric patients with terminal illness in Delaware (http://pdaps.org/datasets/medical-marijuana-patient-related-laws-1501600783).

The extant literature has shown mixed finding on the association between cannabis use and symptoms of depression, with unclear conclusions as to the direction of causality [13-16]. For example, while a consistent relationship exists between adolescent cannabis use and greater risk for depression and anxiety in adulthood [17-20], several studies among healthy people and people with psychological diagnoses have shown that current cannabis users are no more likely than non-users to be suicidal [21-23]. Legal access to cannabis is associated with a reduction in suicide rates at the population level [24,25] and a substantial proportion of medical cannabis patients report using cannabis to self-medicate for depression [26,27]. However, several clinical studies using synthetic analogues (*e.g.* tetrahydrocannabinol (THC) agonists) have failed to find antidepressant effects [28-34]. Unfortunately, there remains very little research on the actual effects of common and commercially available cannabis products such as whole, dried natural flower, on mood and behavioral motivations more generally. As a result of federal regulatory barriers to conducting clinical research on potential medicinal applications of the plant in the United States, the extant research has been mostly limited to measurements of synthetic analogue therapies or cannabis-derived formulates neither widely used nor generalizable to the extensive range of cannabis-based products used by millions of people every day [35,36].

This is the largest study to measure how different types of *Cannabis* flower, the most prevalent type of product used in the US, affect depression-related symptoms in actual time, as consumed in the patients' natural environments. We operationalize this research question using the mobile software application, ReleafApp™ (Releaf App, 2019), which was designed to help patients navigate the variable nature of cannabis-based products available to the general public. The app records cannabis usage at the session-level, including product types, routes of administration, labeled phenotypes, and major cannabinoid contents, along with a wide array of symptoms, real-time changes in symptom severity levels, and experienced side effects of the cannabis used, allowing us to analyze at the cannabis-session level, how these *Cannabis* flower product characteristics affected patient depression severity and associated side effects. A recent study using a similar app among a smaller sample of mostly Canadian respondents showed that cannabis users report dramatic (around 50%) reductions in depression symptom intensity [38]. However, the app relied on retrospective (rather than prospective) reporting and used a respondent incentive system that rewards users for repeated engagement with the app, which could lead to confounding motivations for using the app and potentially weaken the validity of the study's findings. The current study, instead, measures how *Cannabis* flower affects depressive symptom intensity levels in real time among respondents with no extrinsic motivations for using the tool other than to obtain feedback on the *Cannabis* they are using therapeutically. Based on widespread anecdotal patient reporting patterns, we hypothesized that THC potency levels will be positively correlated with elevations in users' mood.

METHODS

Study Design

The study design was approved by the Institutional Review Board at the University of New Mexico. Under an investigator confidentiality agreement, de-identified user-level data were provided by the owner of the Releaf App, MoreBetter, Ltd. The Releaf App is a mobile software application designed to help users manage cannabis consumption by facilitating recording of real-time changes in symptom intensity and side effects. In each user-administered session, the patient first specified the symptoms to be treated and recorded a battery of potentially available (*e.g.* labeled) product characteristics. Spe-

cifically, users record product type (flower, concentrate, pill, tincture, topical, and edible), species (*C. sativa*, *C. indica*, or hybrid), combustion method (joint, pipe, and vape), and THC and CBD content. While some of these product characteristics, such as the distinction between "*C. sativa*" and "*C. indica*" plant strains are largely believed to be baseless by the modern scientific community [39], we included them because they still tend to play a major role in patient purchasing decisions. Once the product characteristics are entered the patient is prompted to specify a starting symptom intensity level (on a 0-10 on a visual analogue scale), record any cannabis consumption, update the symptom intensity level, select from a range of side effects (referred to as "feelings" in the user interface), and end the session. The patient could update the symptom intensity level at any time throughout the session. The Releaf App included 47 side effects and a patient can select multiple side effects in the same session. We restricted the study sample to treatment sessions with a depression symptom reported, starting symptom intensity levels greater than 0, and ending symptom intensity levels reported within 4 hours, the estimated range of time that inhaled cannabinoids produce maximum psychotropic effects and are concentrated in the plasma [40-42]. The analyzed sample only included sessions that reported using dried flower product, which is the most common and homogeneous product type. The resulting analysis sample included 5,876 sessions completed by 1,819 users between 06/06/2016 and 07/08/2019.

Study Outcomes

The objective of the study is to estimate changes in symptom intensity (symptom relief) and the prevalence of side effects following *Cannabis* use. We also examined whether these effects varied by product characteristics. The main outcome of interest, symptom relief, is measured as the difference between ending symptom intensity level and the starting symptom intensity level. The resulting variable ranged between -10 (maximum symptom relief) and 9 (maximum symptom exacerbation). In other words, the maximum symptom relief would be experienced by a user with a starting symptom level of 10 and an ending symptom level of 0, while the maximum symptom exacerbation would come from a user with a starting symptom level of 1 and an ending symptom level of 10. On average, 95.8% of users reported symptom relief, 2.1% reported symptom worsening, and 2.1% reported no change in symptom intensity level. We categorized the 47 possible side effects as 17 negative side effects, 19 positive side effects, and 11 context-specific side effects. Context-specific side effects are not unambiguously positive or negative. For example, users can record feeling "high," however, it is unclear whether the user viewed being "high" as a positive or negative side effect. Similarly, increased appetite could be a positive or negative outcome depending on the user's baseline health state (see Supplemental Table S1 in Appendix A). We measured the onset of these side effects using dummy variables as well as continuous variables. For each category of side effects, the dummy variable indicated whether the user reported any of the side effects in the category while the continuous variable measures the proportion of total side effects in that category that the user selected. As shown in Supplemental Table S1, the most commonly reported negative side effects were Dry Mouth (reported in 33% of the user sessions) and feeling Foggy (27%), the most frequent positive side effects were feeling Relaxed (64%) and Peaceful (57%), and the most common context-specific side effects were feeling High (53%) and Tingly (31%).

Statistical Analysis

The change in symptom intensity level from cannabis use was measured using means comparison and fixed effects regression models, controlling for starting symptom level. To estimate the effects of product characteristics on symptom relief and the prevalence of side effects, we used fixed effects models to regress the outcome of interest on different product characteristics recorded by the user. The fixed effects model was estimated by comparing the outcomes of the same user in different sessions, rather than comparing across users. Therefore, fixed effects models are free from the concern that users differ in unobserved time-invariant characteristics that may affect symptom relief, *e.g.* sex or pre-app cannabis use experience. Starting symptom level was included in all regressions because higher starting symptom intensity levels suggested larger possible symptom relief. Standard errors were clustered at the user level to account for heteroscedasticity and user-level arbitrary correlation. Analyses were conducted using Stata 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) and alpha values less than p = .05 were considered significant.

We conducted several robustness checks including continuous rather than categorical measures of THC and CBD, maximum symptom relief (minimum symptom level reported, rather than ending symptom level, minus starting symptom level), and symptom relief reported within 1, 2, and 3 hours, rather than 4.

RESULTS

Table 1 presents descriptive statistics for the product characteristics, the starting and ending symptom intensity levels, and the prevalence of side effects. The sample size changes due to non-reporting of product characteristics.

Table 1. Descriptive statistics.

	Proportion of Sessions / Means	Std. Dev.	Minimum	Maximum
Panel A: Labeled Plant Phenotype (5,182 symptom-sessions, 1,662 users)				
Hybrid	50%	0.50	0	1
C. indica	26%	0.44	0	1
C. sativa	24%	0.43	0	1
Panel B: Combustion Method (5,513 symptom-sessions, 1,700 users)				
Joint	15%	0.36	0	1
Pipe	51%	0.50	0	1
Vape	33%	0.47	0	1
Panel C: THC (2,305 symptom-sessions, 748 users)				
THC %	18.61	7.90	0	35
THC < 10%	17%	0.37	0	1
THC 10-19%	35%	0.48	0	1
THC 20-35%	48%	0.50	0	1
Panel D: CBD (1,267 symptom-sessions, 528 users)				
CBD %	6.17	7.03	0	35
CBD < 1%	31%	0.46	0	1
CBD 1-9%	38%	0.49	0	1
CBD 10-35%	31%	0.46	0	1
Panel E: Outcome and Control Variables (5,876 symptom-sessions, 1,819 users)				
Starting Symptom Level	5.85	2.33	1	10
Ending Symptom Level	2.08	2.07	0	10
Symptom Change	-3.76	2.64	-10	9
Panel F: Side Effects (4,493 sessions, 1,482 users)				
Any Negative Side Effect	72%	0.45	0	1
% of Negative Side Effects	13%	0.15	0	1
Any Positive Side Effect	95%	0.22	0	1
% of Positive Side Effects	30%	0.20	0	1
Any Context-Specific Side Effect	86%	0.34	0	1
% of Context-Specific Side Effects	24%	0.19	0	1

Notes: The sample includes sessions treating depression. Nineteen positive, seventeen negative, and eleven context-specific side effects were available for selection. The % of Side Effects represent the average number of side effects experienced out of the total number of possible side effects within each category.

On average, users with depression reported a starting symptom intensity of 5.85 and an ending symptom of 2.08, leading to a decrease in symptom intensity of 3.76 (SD=2.64, d=1.71, p<.001). Table 2 shows the results from regressing the change in symptom intensity level on product characteristics. Each column represents a separate regression with different product characteristics included. In all columns, a higher starting symptom intensity level is associated with greater symptom relief. Column 1 shows the effect of labeled plant phenotype.

Results show no statistical difference in symptom relief between products labeled "*C. indica*," "*C. sativa*," or "Hybrid." Column 2 suggests that symptom relief does not vary with combustion method. Column 3 shows that higher THC levels are associated with greater symptom relief while higher CBD levels are not statistically significant predictors of symptom relief. In column 4, all product characteristics are included in the regression. Results suggest that when labeled plant phenotype and combustion method are controlled for, THC levels are the

[1]Similar findings were obtained if the omitted categories are *C. indica* (instead of Hybrid), Pipe (instead of Joint), and high THC/CBD categories (instead of low THC/CBD categories).

Table 2. Effects of flower characteristics on depression relief.

Outcome = Symptom Change (Ending - Starting Symptom)				
	(1)	(2)	(3)	(4)
Panel A: Labeled Plant Phenotype, omitted category = Hybrid				
C. indica	-0.001			0.213
	(0.071)			(0.187)
C. sativa	-0.040			-0.121
	(0.066)			(0.183)
Panel B: Combustion Method, omitted category = Joint				
Pipe		0.110		-0.069
		(0.149)		(0.283)
Vape		-0.007		-0.091
		(0.187)		(0.328)
Panel C: THC and CBD, omitted categories = THC<10% and CBD<1%				
THC 10-19%			-0.424	-0.325
			(0.220)	(0.208)
THC 20-35%			-0.549*	-0.505*
			(0.272)	(0.250)
CBD 1-9%			0.227	0.155
			(0.157)	(0.178)
CBD 10-35%			0.291	0.364
			(0.211)	(0.234)
Starting Symptom Level	-0.741**	-0.742**	-0.659**	-0.648**
	(0.031)	(0.029)	(0.049)	(0.052)
Constant	0.540**	0.487*	0.350	0.286
	(0.181)	(0.213)	(0.367)	(0.374)
Number of sessions	5,182	5,513	1,020	915
R^2	0.389	0.392	0.373	0.373
Number of users	1,662	1,700	436	387

Notes: Columns 1-4 represent separate equations regressing change in symptom intensity level on different types of product characteristics, comparing each product type to an omitted category. All regressions are estimated using a fixed effects model. Unstandardized coefficients are shown with standard errors, clustered at the individual user level, in parentheses. ** $p<0.01$, * $p<0.05$

strongest independent predictor of symptom relief while CBD levels are not statistically significant predictors[1]. Figure 1 presents adjusted symptom relief by THC and CBD level.

Table 3 provides regressions of side effect outcomes on product characteristics, including all product characteristics. Labeled plant phenotype is not associated with the prevalence of side effects. Relative to joint, vaping is associated with less reporting of positive and context-specific side effects. Higher THC levels are associated with decreased reporting of positive side effects.

Table 4 presents results from our robustness checks. In column 1, THC and CBD levels are coded as continuous variables, confirming that higher THC levels are the strongest independent predictor of symptom relief. In column 2, maximum symptom relief during the session is used as the outcome, rather than ending minus starting symptom level, and the same pattern of results exists with increased statistical significance. As in the main results, higher THC levels are associated with greater symptom relief, but unlike in the main results, maximum symptom relief is lower for sessions involving products labeled as "*C. indica*" rather than "Hybrid." Columns 3-5 restrict the analysis samples to sessions that ended within 1-3 hours. Results are generally similar to the main results, except that higher CBD levels are weakly associated with less symptom relief among users who ended sessions within 1 or 2 hours.
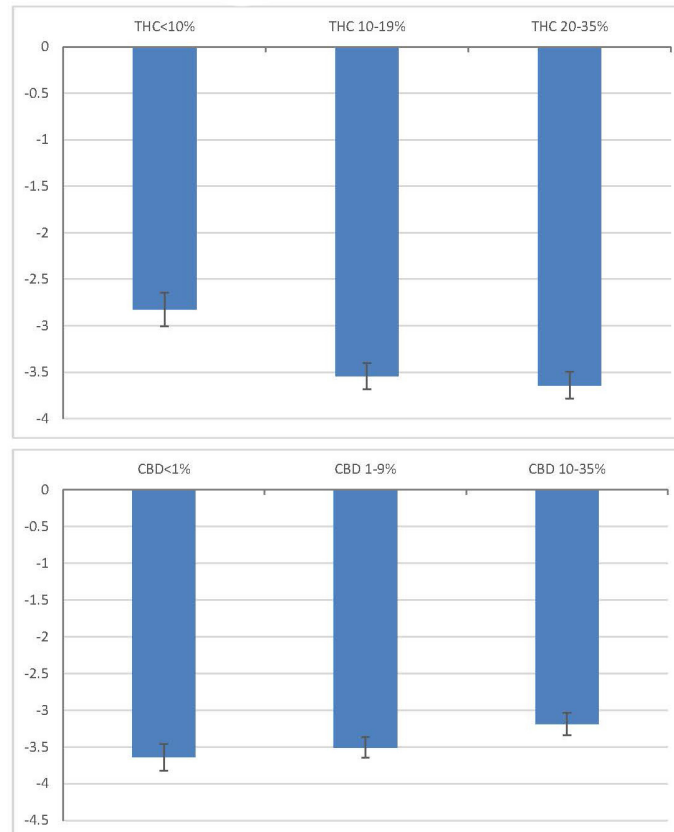
Figure 1. Adjusted symptom relief by THC and CBD levels.

Notes: Adjusted symptom relief refers to covariate-adjusted change in symptom intensity level, obtained from a fixed effects model controlling for labeled plant phenotype, combustion method, and starting symptom level. CBD levels are controlled for in the THC figure while THC levels are controlled for in the CBD figure. 95% confidence intervals are plotted.

DISCUSSION

The current study supports and expands upon the recent work by Cuttler *et al*. (2018) [38] by measuring which types of *Cannabis* flower characteristics among common product alternatives are associated with relief from depression. Rather than including a wide range of cannabis products (*e.g.* topical and edibles) and treating THC and CBD potency levels as continuous measures, we focused exclusively on *Cannabis* flower and allowed the effects of THC and CBD to vary nonlinearly, comparing across ordinal categories (*e.g.* low, medium, and high) to best represent the restricted range of potency levels in which *Cannabis* flower "strains" are typically marketed and to reflect recent findings in the literature that suggest that the increasing THC can have opposite effects depending on the baseline level [43] or that the effect may plateau at high levels, at least for pain conditions [44]. Both the current study and Cuttler *et al*. (2018) [38] showed that common and commercially available *Cannabis* products used by millions of people every day

affect self-reported depression intensity. Also similar, while some user sessions resulted in the manifestation of experiences that contribute to depression and low mood (*e.g.* feeling unmotivated), both studies showed the vast majority of people reported an overall symptom intensity reduction (over 95% in the current study), with an average reduction of three to four points on a standard 0 to 10 scale. The mobile software technology helps solve the challenge of measuring and informing the patient as to the pharmacodynamic effects of an inherently variable ethnomedicinal product that was once alive and that, even across cloned batches, can show chemotypic differences. Not only does plant heterogeneity limit the value of randomized controlled trials using a specific cannabis formulate, but it also forces patients to constantly experiment with fundamentally new products. By enabling prospective, real-time recording of cannabis administration sessions across the vast range of commonly available and chemotypically distinct products and consumption methods used by the general population, the current study made it possible to measure whether consumption of

Table 3. Effects of product characteristics on side effects.

	(1)	(2)	(3)	(4)	(5)	(6)
	Negative	% of Negative	Positive	% of Positive	Context-Specific	% of Context-Specific
C. indica	0.039	0.001	0.007	-0.011	-0.043	-0.002
	(0.068)	(0.014)	(0.021)	(0.017)	(0.045)	(0.016)
C. sativa	0.088	0.011	-0.012	0.005	-0.006	-0.001
	(0.089)	(0.012)	(0.022)	(0.021)	(0.051)	(0.021)
Pipe	-0.119	0.009	-0.050	-0.001	-0.114	-0.032
	(0.092)	(0.026)	(0.031)	(0.027)	(0.076)	(0.031)
Vape	-0.025	0.005	-0.102*	-0.014	-0.214**	-0.040
	(0.123)	(0.026)	(0.046)	(0.028)	(0.079)	(0.031)
THC 10-19%	0.067	0.025	-0.059*	0.013	0.082	0.030
	(0.088)	(0.018)	(0.029)	(0.018)	(0.054)	(0.021)
THC 20-35%	0.001	0.014	-0.056*	0.009	0.079	0.029
	(0.077)	(0.019)	(0.023)	(0.020)	(0.051)	(0.021)
CBD 1-9%	-0.047	0.003	-0.030	-0.022	-0.170*	-0.012
	(0.099)	(0.015)	(0.030)	(0.027)	(0.073)	(0.021)
CBD 10-35%	-0.116	0.005	-0.077	-0.049	-0.174*	-0.020
	(0.077)	(0.015)	(0.040)	(0.030)	(0.087)	(0.024)
Starting Symptom Level	0.019	0.005	-0.002	-0.012**	-0.001	0.002
	(0.013)	(0.004)	(0.005)	(0.004)	(0.011)	(0.004)
Constant	0.631**	0.057	1.120**	0.371**	1.083**	0.213**
	(0.161)	(0.041)	(0.056)	(0.046)	(0.121)	(0.044)
Number of sessions	757	757	757	757	757	757
R^2	0.023	0.015	0.028	0.032	0.047	0.014
Number of users	318	318	318	318	318	318

Notes: All regressions are estimated using a fixed effects model. *C. indica* and *C. sativa* are relative to Hybrid, THC categories are relative to THC between 0 and 10%, and CBD categories are relative to 0% CBD, and Pipe and Vape are relative to Joint. Unstandardized coefficients are shown with standard errors, clustered at the individual user level, in parentheses. ** $p<0.01$, * $p<0.05$.

Cannabis flower products immediately affected changes in depression symptom intensity levels and which types of common product characteristics are associated with the strongest effects. The findings suggest benefits from patient-directed, cannabis therapy as an antidepressant treatment; however, effectiveness and side effect manifestation vary across different types of *Cannabis* flower with different cannabinoid potency levels.

In addition to the similarity across studies in the apparent general clinical effectiveness of using *Cannabis* flower for reducing feelings of depression, differences existed in the associations between the product characteristics and the extent of symptom relief. Although Cuttler *et al*. (2018) [38] reported that cannabis products with high CBD / low THC values statistically predicted the greatest improvements in feelings of depression, it is

unclear which types of products (*e.g.* topicals vs edibles) such values would apply. Instead, we found that *Cannabis* flower with relatively higher THC potency levels emerged as the strongest independent predictor of symptom relief and experienced side effects, but that the benefit of higher THC appears to plateau to some extent such that products with THC ranges of 10-19% and 20-35% offer greater relief than products with THC less than 10%, but increasing from 10-19% to 20-35% does not convey additional benefits in terms of symptom relief. In contrast, flower with CBD potency levels greater than 1.0% were generally not predictive of changes in depressive symptom levels and may even reduce depression symptom relief reported within short treatment windows, *e.g.* less than 2 hours to ending effect. Understanding these effects is challenging given the complexity of the etiology of depression which

Table 4. Robustness checks.

	(1)	(2)	(3)	(4)	(5)
	THC & CBD continuous	Max symptom relief	1 hour relief	2 hours relief	3 hours relief
C. indica	0.194	0.318*	0.356	0.343	0.223
	(0.189)	(0.141)	(0.200)	(0.210)	(0.185)
C. sativa	-0.108	0.046	0.111	0.075	-0.077
	(0.184)	(0.164)	(0.208)	(0.237)	(0.190)
Pipe	-0.082	-0.068	-0.070	-0.090	-0.082
	(0.287)	(0.328)	(0.282)	(0.269)	(0.281)
Vape	-0.094	-0.114	-0.141	0.018	-0.028
	(0.318)	(0.340)	(0.338)	(0.285)	(0.323)
THC 10-19%		-0.202	-0.484	-0.428	-0.312
		(0.156)	(0.259)	(0.232)	(0.208)
THC 20-35%		-0.324	-0.604*	-0.592*	-0.516*
		(0.186)	(0.294)	(0.293)	(0.253)
CBD 1-9%		0.189	0.352	0.352	0.133
		(0.182)	(0.213)	(0.202)	(0.169)
CBD 10-35%		0.313	0.522	0.524*	0.324
		(0.236)	(0.277)	(0.245)	(0.221)
THC %	-0.025				
	(0.013)				
CBD %	0.009				
	(0.011)				
Starting Symptom Level	-0.646**	-0.690**	-0.637**	-0.687**	-0.648**
	(0.052)	(0.048)	(0.053)	(0.051)	(0.052)
Constant	0.503	0.160	0.261	0.382	0.305
	(0.418)	(0.337)	(0.386)	(0.389)	(0.380)
Number of sessions	915	915	849	897	914
R^2	0.369	0.432	0.379	0.409	0.379
Number of users	387	387	378	384	387

Notes: All regressions are estimated using a fixed effects model. *C. indica* and *C. sativa* are relative to Hybrid, and Pipe and Vape are relative to Joint. In column 1, continuous THC and CBD levels are used. In columns 2-5, THC categories are relative to THC between 0 and 10%, and CBD categories are relative to 0% CBD. Unstandardized coefficients are shown with standard errors, clustered at the individual user level, in parentheses. ** $p<0.01$, * $p<0.05$.

involves much more than a mere neurochemical imbalance. Dysregulation of the hypothalamic-pituitary-arenal (HPA) axis, cancer, pathogens, gut dysbiosis (microbial imbalance), nutritional deficiencies, degenerative neurological conditions, endocannabinoid system disruption, immune system dysregulation, chronic pain, substance abuse, prescription medications, abuse, social isolation, conflict, death, trauma, family history, and chronic stress may all be contributing factors of depression [45,46].

Early antidepressants, primarily monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants, target-ed dopamine receptors in the brain, and were effective for reducing depressive symptoms, but only after several weeks to effect and with potentially severe negative side effects, including sedation, substantial weight gain, and deadly food interactions [47]. Selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs), which target serotonin and norepinephrine generation rather than dopamine levels, can also carry intolerable side effects (*e.g.* sedation, agitation, anxiety, suicidal ideation, anorgasmia, and demotivation) and also have times-to-effect of as many as 5 to 6

weeks, making them of little use in the short run to many dangerously ill individuals at risk of harming themselves or others [48]. More recent research has furthermore documented significant withdrawal symptoms associated with cessation of SSRI use [49]. As a result, individuals who are nonresponsive to or who cannot tolerate selective SSRIs and SNRIs are frequently prescribed older or modified versions of the older antidepressants that enhance dopamine neurotransmission (*e.g.* MAOIs, dopamine receptor agonists) [50]. Newer versions of some products, *e.g.* EMSAM, a transdermal version of the monoamine oxidase inhibitor selegiline, carry lower risks including reduced food interactions, but still involve significant risks and relatively long times-to-effect, when they are effective, which appear to vary by person and with medication-specific tolerances [51,52]. When comparing these drawbacks to the relatively minor negative side effects and quick acting effects reported by the *Cannabis* users in the current study, it is understandable why some patients might choose to replace or augment their conventional pharmaceutical antidepressant treatment with medical *Cannabis* when given the legal opportunity to do so.

Our results indicate that THC in particular is positively correlated with an immediate reduction in the intensity of depressive feelings. Animal studies have shown that, like conventional antidepressants, THC affects dopamine, serotonin, and norepinephrine generation [53,54]. The differences in time-to-effect and relative side effect prevalence across products and users could arise from other antidepressant and synergistic compounds in the plant beyond THC or CBD, and prior research suggests there may be several thousand cannabis chemotypes, each with its own unique symphony of compounds [55]. In addition to the mood-elevating effects of THC, several terpenoids are known to exhibit antidepressant properties independent from cannabinoids. At least 200 terpenoids are reported to be present within *Cannabis*, and while their yield is usually less than 1% in dried flower, they may constitute as much as 10% of the total trichome content [56]. Only limited research exists on the effects of specific terpenoids. The terpenoid, D-limonene, in particular, appears likely to have antidepressant effects in humans and typically composes more than 50% of commercially available citrus oils [57]. One study found that citrus oil-based fragrance either eliminated the need for or substantially reduced the required dosage of antidepressants [58]. A later study using mice found that, when compared to the SSRI fluoxetine, 400 mg/kg of lemon essential oil was shown to reduce immobility time in mice that were subjected to a tail suspension test (TST). The dose was shown to significantly increase the levels of serotonin, norepinephrine, and dopamine in the mouse prefrontal cortex (PFC), striatum, and hippocampus. The results also indicated no evidence of negative side effects across all dosage levels received by the mice [59].

The relative predominance of specific cannabinoids, flavonoids, and terpenoids can also vary considerably from one plant to another according to combustion method. For example, vaporizing *Cannabis* flower differs from other forms of combustion by allowing the user to select the precise temperature required to target the desired compounds, while pipe use and joints require full combustion of the plant material. In addition to preserving cannabinoid, flavonoid, and terpenoid contents that evaporate at lower temperatures than THC and CBD, vaporizing rather than combusting the plant material could preserve THC levels as well. Although some research has shown that THC rate of delivery is comparable between vaporization and combustion, the process of combustion may destroy as much as 20-30% of the THC [60,61]. Combustion can also result in the pyrolytic degradation of hundreds of therapeutic terpenoids and phenolic compounds, such as flavonoids [62,63], which are conventionally believed to contribute to the enhanced "entourage" effect of whole flower rather than what is experienced from using THC or CBD isolates. Compounds found in the *Cannabis* plant have demonstrable anti-microbial, anti-oxidant, analgesic, neuroprotective, anxiolytic, and anti-inflammatory effects [64]. Certain combinations of both cannabinoid and noncannabinoid components, therefore, may increase the therapeutic effects of THC and reduce unwanted side effects, making vaporization a more optimized delivery mechanism as compared to combustion using pipes and joints [55,65]. Likewise, because vaporization permits lower consumption temperatures than is possible with pipes and joints, vaporization also should be a safer method of administration. The normal process of combustion generates substantially more carbon monoxide, ammonia, nitric oxide, hydrogen cyanide, polynuclear aromatic hydrocarbons (PAHs), and carcinogens such that vaporization may be an attractive delivery option in terms of harm reduction [62,63]. The lack of a difference by combustion methods in our results suggests that either users were vaping at temperatures comparable to those required for full combustion, that some terpenoids are still sufficiently present at higher temperatures to elicit antidepressant effects, or that terpenoid effects are not required for cannabis to have an antidepressant effect, controlling for THC and CBD levels. Future research would benefit from tracking vaping temperatures along with overall product heating method, as well as the direct examination of the effects of terpenes found in the *Cannabis* plant on depression in humans.

The current study does have limitations. Importantly, this study did not include a control placebo group, that is, individuals who did not use *Cannabis* to treat their depression or any *Cannabis* consumption sessions not tracked in the app, potentially resulting in selection bias.

People who choose to use *Cannabis* to treat their depression may be those most likely to benefit from it or those for whom conventional treatments are less effective. The direction of the bias for app use is not as clear. Not using the app could be simply a matter of no knowing about the app or a dislike of app-based technologies, which would introduce noise into our analysis, or it could arise from an intolerance or dissatisfaction with *Cannabis*, making our results an overestimate of expected population effects. Alternatively, not using the app or stopping app use could arise from satisfaction with existing cannabis use and the lack of a need to explore other product options. Although our study extended the literature by incorporating a wider range of product characteristics than had been previously examined, we still were not able to include the full range of characteristics of products available (*e.g.* terpene profiles, vaping temperatures) and did not include non-flower cannabis products. We also did not account for factors beyond those time-invariant characteristics captured by the user fixed effects, including time-varying user demographics, cannabis experience, whether or not respondents had a diagnosis of depression, or the concomitant use of medications other than *Cannabis*. The current cannabis industry in the US is also wrought with product mislabeling [66,67], and black market products without labels may result in people guessing the product characteristics rendering the need for further product validation in future studies. Lastly, because we are focused on short-term effects and do not have every single *Cannabis* use session of the patients documented in our data, we do not know the long-term effects of *Cannabis* use. For example, Cuttler *et al*. (2018) [38] found a correlation between repeated use of their data recording system and increased baseline depression levels, however, it is unclear whether this may be a function of the effects of using *Cannabis* or a sample selection bias among respondents that used the system repeatedly, for example, people using the app to experiment with unfamiliar products, which could be less effective than the treatment approach the patient typically uses.

In conclusion, almost all patients in our sample experienced symptom relief from using *Cannabis* to treat depression and with minimal evidence of serious side effects in the short run. However, use of *Cannabis* does have well-established clinical drawbacks, including the potential for dependence and addiction, alterations in judgment, and an increased risk of behavioral accidents [68,69]. In addition, there is a well-established association between adolescent use of *Cannabis* and increased risk of depression in adulthood [20,70], but directionality of this relationship remains elusive. Likewise, the positive effects found in this paper along with the negative long-term associations documented in the prior literature support the importance of supplementing our analysis of short-term *Cannabis* symptom relief with causal studies of the longer term benefits and risks from using commercially available *Cannabis.*

One of the most clinically relevant findings from this study was the widely experienced relief from depression within 2 hours or less. Because traditional antidepressants have times-to-effect in weeks, short-term *Cannabis* use might be a solution to these delays in treatment or could be used to treat acute episodes associated with suicidal behavior and other forms of violence. Such short-term or acute episode treatment approaches would fill an important gap in existing clinical methods while avoiding the addiction and dependence risks of long-term *Cannabis* use. Given the significant costs to our society from depression, the research herein offers hope for new avenues of treatment. Future research on *Cannabis* and depression is needed, directly comparing the short- and long-term treatment effectiveness and side effect severity of *Cannabis* use with conventional antidepressant treatment, in conjunction with conventional treatment approaches, and in the presence of clinically discouraged behaviors, such as alcohol consumption.

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Appendix A: Supplementary Materials

Data Availability: The data that support the findings of this study are available from MoreBetter Ltd.

but restrictions apply to the availability of these data, which were used under license for the current

study, and so are not publicly available. Data are however available from the authors upon

reasonable request and with permission of MoreBetter Ltd.

Supplemental Table 1: Descriptive statistics for side effects.

Side Effect	% Sessions Reporting	Symptom Relief	p-value	Category
Anxious	11%	-3.21	<0.001	Negative
Clumsy	8%	-4.33	<0.001	Negative
Confused	7%	-3.99	<0.001	Negative
Coughing	15%	-4.00	<0.001	Negative
Dizzy	11%	-4.20	<0.001	Negative
Dry Mouth	33%	-3.83	<0.001	Negative
Foggy	27%	-3.64	<0.001	Negative
Forgetful	16%	-4.00	<0.001	Negative
Headache	7%	-3.25	<0.001	Negative
Irritable	7%	-3.11	<0.001	Negative
Nausea	3%	-3.44	<0.001	Negative
Paranoid	5%	-4.18	<0.001	Negative
Rapid Pulse	6%	-4.55	<0.001	Negative
Red Eyes	20%	-3.87	<0.001	Negative
Restless	12%	-3.43	<0.001	Negative
Scattered	21%	-3.62	<0.001	Negative
Unmotivated	20%	-3.71	<0.001	Negative
Active	9%	-3.95	<0.001	Positive
Chill	54%	-3.67	<0.001	Positive
Clear	23%	-3.86	<0.001	Positive
Comfy	41%	-3.99	<0.001	Positive
Creative	17%	-4.41	<0.001	Positive

Dreamy	39%	-3.83	<0.001	Positive
Energetic	14%	-4.10	<0.001	Positive
Focused	24%	-3.91	<0.001	Positive
Frisky	12%	-4.36	<0.001	Positive
Grateful	25%	-4.07	<0.001	Positive
Great	22%	-4.45	<0.001	Positive
Happy	32%	-4.21	<0.001	Positive
Light	29%	-4.10	<0.001	Positive
Optimistic	27%	-4.15	<0.001	Positive
Peaceful	57%	-3.87	<0.001	Positive
Productive	15%	-4.04	<0.001	Positive
Reflective	32%	-3.83	<0.001	Positive
Relaxed	64%	-3.76	<0.001	Positive
Tuned	26%	-4.19	<0.001	Positive
Couchlocked	22%	-3.91	<0.001	Context-Specific
Distracted	19%	-3.74	<0.001	Context-Specific
High	53%	-3.78	<0.001	Context-Specific
Hungry	23%	-4.05	<0.001	Context-Specific
Silly	17%	-4.55	<0.001	Context-Specific
Sleepy	23%	-3.95	<0.001	Context-Specific
Talkative	13%	-4.59	<0.001	Context-Specific
Thinky	25%	-3.81	<0.001	Context-Specific
Thirsty	30%	-4.01	<0.001	Context-Specific
Tingly	31%	-3.96	<0.001	Context-Specific
Visuals	6%	-5.18	<0.001	Context-Specific

Notes: Side effects are categorized according to their visceral descriptions under varying circumstances. The average symptom relief among users that indicated each side effect and the associated p-value of symptom intensity changes for individuals that indicated each side effect are reported.