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Survey of Patients Employing Cannabigerol-Predominant Cannabis Preparations: Perceived Medical Effects, Adverse Events, and Withdrawal Symptoms

Ethan B. Russo,[1,*,i] Carrie Cuttler,[2,ii] Ziva D. Cooper,[3,iii] Amanda Stueber,[2] Venetia L. Whiteley,[1] and Michelle Sexton[4,iv]

Abstract

Introduction: Cannabigerol (CBG), and its precursor before decarboxylation, cannabigerolic acid is sometimes labeled the "mother of all cannabinoids." The purpose of the present study was to investigate reasons for use and self-reported therapeutic effects in CBG-predominant cannabis users. Usage patterns and adverse effects, including withdrawal symptoms were also explored.

Methods: Cannabidiol-predominant cannabis users were recruited online to complete an online survey assessing CBG use patterns, conditions treated with CBG-predominant cannabis (containing > 50% CBG), perceived efficacy, associated adverse events, and withdrawal symptoms. One hundred twenty-seven eligible participants (U.S. residents ages 21+ who reported using CBG-predominant cannabis in the past 6 months) completed the survey.

Results: Most of the samples ($n = 65$; 51.2%) reported use of CBG-predominant products solely for medical purposes ($n = 46$; 36.2% reported use for medical and recreational purposes; $n = 8$; 6.3% reported recreational use only, and $n = 8$ were missing). The most common conditions the complete sample reported using CBG to treat were anxiety (51.2%), chronic pain (40.9%), depression (33.1%), and insomnia/disturbed sleep (30.7%). Efficacy was highly rated, with the majority reporting their conditions were "very much improved" or "much improved" by CBG. Furthermore, 73.9% claimed superiority of CBG-predominant cannabis over conventional medicines for chronic pain, 80% for depression, 73% for insomnia, and 78.3% for anxiety. Forty-four percent of CBG-predominant cannabis users reported no adverse events, with 16.5% noting dry mouth, 15% sleepiness, 11.8% increased appetite, and 8.7% dry eyes. Around 84.3% reported no withdrawal symptoms, with sleep difficulties representing the most frequently endorsed withdrawal symptom (endorsed by two respondents).

Conclusions: This is the first patient survey of CBG-predominant cannabis use to date, and the first to document self-reported efficacy of CBG-predominant products, particularly for anxiety, chronic pain, depression, and insomnia. Most respondents reported greater efficacy of CBG-predominant cannabis over conventional pharmacotherapy, with a benign adverse event profile and negligible withdrawal symptoms. This study establishes that humans are employing CBG and suggests that CBG-predominant cannabis-based medicines should be studied in randomized controlled trials.

Keywords: anxiety; cancer; cannabigerol; pain; phytocannabinoids; psychopharmacology

[1]CReDO Science, Vashon, Washington, USA.
[2]Washington State University, Pullman, Washington, USA.
[3]University of California, Los Angeles, Los Angeles, California, USA.
[4]University of California, San Diego, San Diego, California, USA.
[i]ORCID ID (https://orcid.org/0000-0003-4715-515X).
[ii]ORCID ID (https://orcid.org/0000-0002-5890-2985).
[iii]ORCID ID (https://orcid.org/0000-0001-8001-2332).
[iv]ORCID ID (https://orcid.org/0000-0002-0443-8355).

*Address correspondence to: Ethan B. Russo, MD, CReDO Science, 20402 81st Avenue SW, Vashon, WA 98070, USA, E-mail: ethanrusso@comcast.net

Introduction: Cannabigerol in Context

Cannabigerol discovery and early history

Cannabigerol (CBG), along with its parent compound cannabigerolic acid (CBGA), is found in raw *Cannabis sativa* before decarboxylation by heat, light, or aging. CBGA is the parent compound precursor to the better-known cannabinoid compounds delta9-tetrahydrocannabinol (THC) and cannabidiol (CBD) and has been referred to as the "mother of all cannabinoids" (Fig. 1). CBG was isolated and structurally characterized in 1964[1] through chromatography of a hexane extract of confiscated Lebanese hashish, and was characterized as the "missing link in the plant synthesis of cannabinoid constituents." Initial tests of its pharmacologic activity followed 5 years later,[2] finding no behavioral changes in dogs after injections of intravenous doses up to 7 mg/kg, in monkeys up to 5 mg/kg intraperitoneally, subcutaneously in mice on a rotarod after doses up to 20 mg/kg, or in rats in a conditioned avoidance test up to 20 mg/kg (route unspecified), suggesting a lack of psychoactivity or intoxication.

CBG was synthesized *de novo* by its discoverers in 1971.[3] Research on the compound languished thereafter for decades, and CBG was passed over for testing in the 1970s in pioneering human bioassay experiments.[4]

Although it is a common misconception that phytocannabinoids occur in Nature solely in the cannabis plant, CBG was previously extracted from *Helichrysum umbraculigerum*[5,6] in 1979. This botanical medicine is known to be used by South African healers,[7,8] with species of the genus employed for headaches, menstrual pain, and wound dressings, even smoked for treatment of pain.[9]

Mechanism of action and pre-clinical investigation

Investigation of the pharmacology of CBG resumed only in the 21st century. CBG is a weak partial agonist of cannabinoid receptors CB_1 (K_i 440–1300 nM) and CB_2 (K_i 337–490 nM)[10,11] with suggestion that it may act as a competitive antagonist at the CB_1 receptor,[12–14] providing insight into reasons for CBG's lack of cannabimimetic effects typically observed with THC.[2,11,15] CBG reduced behavioral despair, a presumed antidepressant effect, in the tail suspension test in mice after intraperitoneal administration.[16] A previous study demonstrated tritiated gamma aminobutyric acid (GABA) uptake inhibition by CBG in rodent cortical synaptosome homogenates (K_i 140 μM),[17] findings which could suggest possible muscle relaxant[18] and antianxiety

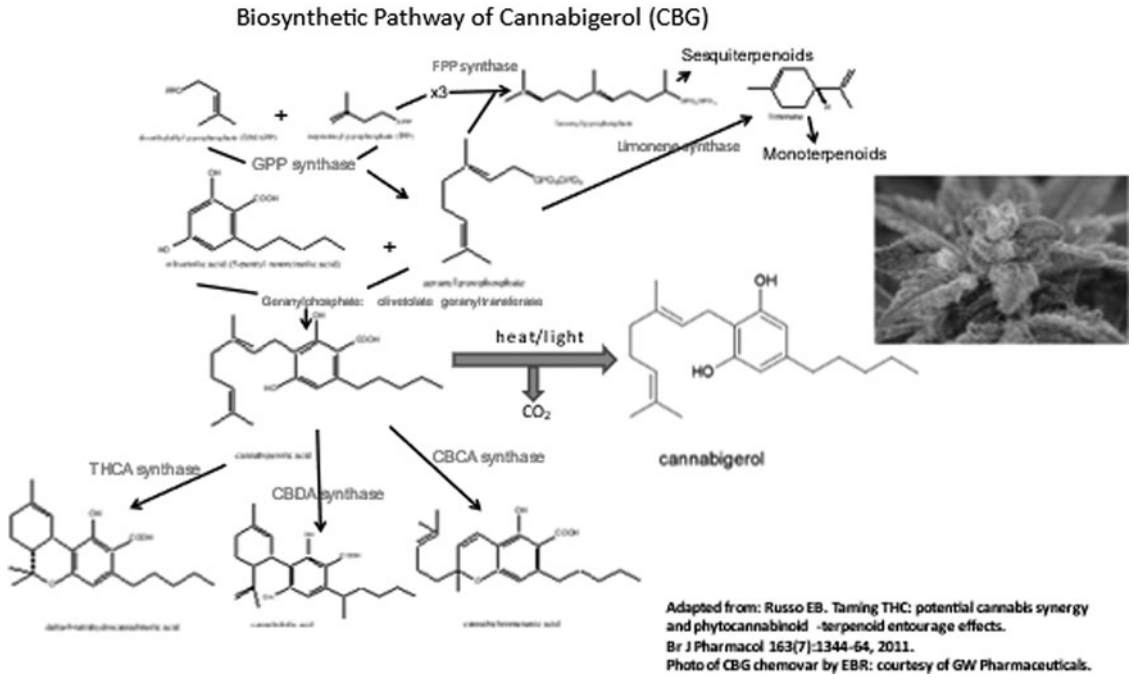

FIG. 1. Biosynthetic pathway of CBG. CBG, cannabigerol.

effects. Potential dose-dependent anxiolytic-like effects observed with CBG[11] may also be ascribed to its effects at the 5-hydroxytryptamine (serotonin) $(5\text{-HT})_{1A}$ receptor, where higher doses may in fact be anxiogenic due to the cannabinoid's actions as a 5-HT_{1A} antagonist.[12,19,20]

In rodents, the antinociceptive effects of CBG in the warm water tail-withdrawal assay have been established.[11] CBG was also shown to be analgesic in inflammatory pain models (writhing test),[21,22] also demonstrating antierythemic and lipoxygenase blocking effects.[23] The pain-relieving properties of CBG are hypothesized to be due to the cannabinoid's effects as a potent alpha-2-adrenoreceptor agonist (mouse brain $EC_{50} = 0.2$ nM, mouse vas deferens $EC_{50} = 72.8$ nM[12,24]), a mechanism of action that was subsequently demonstrated to reduce inflammatory pain in mice after carageenan or formalin injection in both transient and late phases (10 mg/kg ip), in a manner analogous to clonidine. Other potential mechanisms by which CBG may exert pain-relieving properties are through interactions with transient receptor potential (TRP) channels,[25,26] and as an inhibitor of N-arachidonylethanolamine (AEA) reuptake, thereby enhancing endocannabinoid tone.[26] In a study of neuroinflammation, CBG showed neuroprotective effects mediated by PPAR-γ,[27] and in combination with CBD, downregulated TNF-α expression that was elevated in lipopolysaccharide-exposed motor neurons, and increased anti-inflammatory cytokines interleukin (IL)-10 and IL-37. These findings further support the cannabinoid's role in mitigating negative outcomes due to inflammation, including pain.

Other promising potential therapeutic effects of CBG include its activity as an antifungal[28] and impressive antibiotic activity, particularly against Gram-positive bacteria and methicillin-resistant *Staphylococcus aureus* (minimum inhibitory concentration 1 μg/mL).[29] CBG has also demonstrated broad cytotoxicity in cancer cell lines in high concentrations on human epithelioid carcinoma,[30] and was second in potency to CBD in breast cancer cell lines.[31] As mentioned above, CBG has prominent activity on TRP receptors, especially as a TRP ion channel melastatin-type (TRPM8) antagonist ($IC_{50} = 160$ nM), suggesting benefits in prostate cancer,[32] bladder pain, and overactive detrusor activity.[33] Also related to this action at TRPM8, CBG reduced the viability of glioblastoma tumor and stem cells comparably to THC,[34] and its combination with CBD was more efficacious than THC in induction of caspase-dependent apoptosis. CBG mildly lowers blood pressure[35] and intraocular pressure through an increase in aqueous outlflow,[36] suggesting therapeutic use in glaucoma. Its ability to reduce proliferation of keratinocytes[37] also suggests utility to treat psoriasis.

Contemporary cultivation and production of CBG-predominant cannabis and its use

Under normal circumstances, CBGA appears in cannabis inflorescences in very low concentrations, serving as a brief way station before enzymatic activity proceeds to the production of tetrahydrocannabinolic acid (THCA), cannabidiolic acid (CBDA) through codominant genes,[38] and more rarely to cannabichromenic acid (CBCA) through a recessive trait (Fig. 1).[39] However, this situation changed with the development of plants expressing 100% of cannabinoid content as CBGA/CBG through selective mendelian breeding of cannabis to eliminate enzymatic activity beyond CBGA.[40,41] This notwithstanding, CBG has remained a rare commodity in the cannabis trade until recent years, when hundreds of hectares of CBG-predominant plants have been cultivated in the United States Pacific Northwest, particularly in the state of Oregon. It is now recognized that alongside THC and CBD, CBG is an increasingly abundant phytocannabinoid with some cannabis samples reaching nearly 20% CBG content.[42] In addition to cannabis containing high percentages of CBG, CBG-predominant products are emerging on the market with various modes of administration, including topical, oral, and sublingual routes.

Despite the fact that CBG popularity is growing in the marketplace, there is close to no description of its effects in humans. Furthermore, there has been no account providing information regarding CBG use patterns, motives for use, self-perceived efficacy, or its self-reported adverse and withdrawal effects. Therefore, the authors of this study felt it a propitious time to investigate the therapeutic claims of CBG-predominant cannabis users, their usage patterns, reactions, adverse events, and reported withdrawal symptoms. The current study is the first to examine such activity in human subjects and may serve as a prelude and compass to more formal randomized controlled trials.

Methods and Results

The Washington State University Human Research Protection Program determined that this study satisfied criteria for exemption. The study was advertised on various listservs related to cannabis and cannabinoid research as well as on social media. Inclusion criteria were being 21

years of age or older, residing in the United States, and self-reported use of a CBG-predominant cannabis product (containing >50% CBG) in the past 6 months.

Interested candidates were directed to an online Qualtrics survey that was drafted based on a prior survey of cannabis use.[31] After providing informed consent, participants responded to questions designed to assess demographic characteristics, CBG use patterns, medical conditions treated with CBG, perceived efficacy of CBG-predominant products, substitution of conventional medication (prescribed and over-the-counter [OTC]) with CBG-predominant cannabis products, as well as associated adverse events and withdrawal symptoms. The complete survey can be found at cbg-survey.com and required ~15 min to complete. Respondents who provided contact information were entered into a draw for one of two $50 gift cards.

Data were analyzed using descriptive statistics (%, means, ranges, standard deviations [SDs], and/or standard errors [SEs]). Furthermore, percentages were compared using chi-square tests. Descriptive statistics were computed using SPSS version 27 and one-way chi-square tests and follow-up contrasts were computed using SciStat's® online applet: https://www.scistat.com/statisticaltests/chisquared-1way.php.

Participants

One hundred sixty-six individuals initiated the survey. However, 22 participants answered no questions, 2 provided no informed consent, 1 was under the age of 21, 6 resided outside the United States, and 8 had not used a product with >50% CBG in the past 6 months. The final sample comprised 127 participants, was well balanced with respect to gender (44.9% male, 40.2% female, 1.6% transgender/gender nonbinary, 0.8% other/prefer not to say, 12.6% missing) and ranged in age from 21 to 77 with a mean age of 45.45 (SD = 14.06). Only 1.6% reported that they had been diagnosed or treated for cannabis dependency or addiction and only 2.4% had been told they should stop using cannabis for health reasons. Participants from 30 different states responded with heaviest representation in California ($n = 28$; 22%) and Washington State ($n = 20$; 15.7%). Complete demographic characteristics are presented in Table 1.

Table 1. Sample Demographics

Ethnicity	%	Income	%
White	69.3	<$20K	11
Black	2.4	$20–40K	18.1
Hispanic/Latino	5.5	$40–60K	13.4
Asian	2.4	$60–80K	10.2
American Indian/Alaska Native	0.8	$80–100K	17.9
Other	3.9	>100K	19.7
Missing	15.7	Missing	19.7
Education	**%**	**Working status**	**%**
High school or less	15	Full time	50.4
Technical school	7.1	Part time	7.1
Associates	11	Student	1.6
Bachelors	33.1	Retired	17.3
Masters	11.8	Unemployed	7.9
Doctorate	7.1	Missing	15.7
Missing	15		

CBG use patterns

Participants were asked about their CBG-predominant use patterns, including duration, quantity, frequency, reason (medical, recreational, both), whether they prefer CBG-predominant cannabis to other types, methods of administration (multiple methods could be endorsed), preferred percentage of CBG, source(s) (multiple sources could be endorsed), and where they first learned about CBG. Respondents also reported the cannabinoid and terpenoid composition in the CBG-predominant cannabis products they used most often.

Participants reported using CBG-predominant products (containing >50% CBG) for an average of 9.29 months (SD = 10.71, range = 0–71 months). Participants reported using an average of 3.46 g of CBG-predominant flower per week (SD = 2.99, range = 0.25–12, $n = 37$) and 1.09 g of CBG-predominant cannabis concentrates per week (SD = 1.43, range = 0.01–5.25, $n = 16$).

The majority (51.2%, $n = 65$) reported using CBG-predominant cannabis products for medical purposes only, 6.3% ($n = 8$) reported using for recreational purposes only, and 36.2% ($n = 16$) reported using for both medical and recreational purposes (6.3%, $n = 8$ missing). Around 37.8% ($n = 48$) of the complete sample reported preferring CBG-predominant cannabis, whereas 43.3% ($n = 55$) preferred other types (18.9%, $n = 24$ missing). The remaining details of the CBG use patterns of the complete sample are reported in Table 2, including how often they use CBG-predominant products, the percentage of CBG they typically seek when purchasing cannabis, methods of administering CBG-predominant cannabis, where they purchase CBG-predominant products, where they first learned about CBG-predominant products, and the percentage of respondents who indicated which constituents are in the CBG-predominant products they most often use. Values in the table reflect the percentage of participants who endorsed each response.

Table 2. Cannabigerol Use Patterns ($N = 127$)

Frequency of CBG use %		Source of CBG %		Composition of products %	
Once a month or less	6.3	Online	55.9	CBG	73.2
Once a week	15.0	Dispensary	22.8	CBD	45.7
2–4 times a week	26.0	Friend	16.5	THC	29.1
Daily	40.9	Grow Myself	8.7	CBN	11.8
More than once daily	11.0	Other	12.6	Beta-caryophyllene	11.8
Missing	0.8			Limonene	11.8
Preferred % of CBG	%	First learned about CBG %		Myrcene	11.8
100% pure	25.2	Online article	18.1	Linalool	7.1
50%–99%	26.0	Friend	17.3	Pinene	6.3
25%–49%	11.8	Dispensary	9.4	Humulene	6.3
Any	26.8	Doctor	8.7	CBDV	5.5
Do not seek CBG	7.9	Nurse or other health	5.5	THCV	4.7
Missing	2.4	Care professional		Terpinolene	2.4
Administration method %		Journal article	6.3	Terpineol	1.6
Oral	76.4	Lecture	3.9	Other	14.2
Smoke	30.7	Podcast	3.1		
Vape	22.8	Other	26.8		
Topical	15.7	Missing	0.8		
Other	5.5				

Numbers reflect the % of the total sample ($N = 127$) who endorsed each response.

"Frequency of CBG Use" refers to how often they use CBG-predominant products, "Preferred % of CBG" refers to the percentage of CBG they typically seek when purchasing cannabis, "Administration Method" refers to methods participants use to administer CBG-predominant cannabis, "Source of CBG" refers to where they purchase CBG-predominant products, "First Learned About CBG" refers to where they first learned about CBG-predominant products, and "Composition of Products" refers to the constituents that are in the CBG-predominant products they most often use.

CBD, cannabidiol; CBDV, cannabidivarin; CBG, cannabigerol; CBN, cannabinol; THC, tetrahydrocannabinol; THCV, tetrahydrocannabivarin.

Medicinal use of CBG-predominant cannabis

Participants indicated the conditions for which they used CBG-predominant cannabis (Table 3). Most commonly reported were anxiety, chronic pain, depression, and insomnia/disturbed sleep. Furthermore, 33.9% of the sample reported using CBG-predominant cannabis for general wellness and 4.7% indicated use to enhance sexual experiences.

Participants rated the degree to which CBG-predominant cannabis improves or worsens each symptom on a scale ranging from 1 (very much improves) to 7 (very much worsens). As shown in Table 3 CBG-predominant cannabis was perceived as very much improving (1), much improving (2), or slightly improving (3) most conditions, with the highest mean self-reported efficacy ratings for endometriosis ($M = 1.67$; $n = 3$), Crohn's/ulcerative colitis ($M = 1.75$; $n = 4$), and irritable bowel syndrome ($M = 1.88$; $n = 17$). Only anxiety had a range extending to 5, indicating that while most individuals found it improved anxiety, 2 of the 62 participants who responded to this item reported that it slightly worsened their anxiety. CBG-predominant cannabis was not reported to worsen any other condition.

Participants were also asked to indicate whether CBG-predominant cannabis or conventional medication produced better outcomes, or whether the two were equally effective (Table 4). Significantly more people preferred CBG-predominant cannabis to conventional medications for chronic pain, acute pain, insomnia/sleep disturbances, migraine/headache, nausea, irritable bowel syndrome, autoimmune disease, other inflammation, anxiety, and depression. Differences in efficacy of CBG-predominant cannabis and conventional medications claimed for migraine/headache and autoimmune disorders were not statistically significant. For none of the conditions was conventional medication reported more effective than CBG-predominant cannabis.

Medication use and discontinuation related to CBG-predominant cannabis

Participants were asked to indicate whether or not they were currently taking or recently discontinued taking (within the past 3 months) 13 prescription and OTC medications. Respondents were further asked to indicate whether or not they had discontinued medication use because of cannabis (yes, no, N/A = still taking medication) (Table 5). Results revealed no evidence that participants substituted conventional medications for CBG-predominant cannabis. Specifically, a significantly higher percentage of respondents indicated

Table 3. Medical Conditions Managed with Cannabigerol-Predominant Cannabis and Perceived Efficacy ($N=127$)

Medical condition	% endorsed	*n*	Range	Mean	Standard error
Anxiety	51.2	62	1–5	2.02	0.11
Chronic pain	40.9	48	1–4	2.15	0.11
Depression	33.1	40	1–4	2.13	0.14
Insomnia/disturbed sleep	30.7	37	1–4	2.22	0.15
Migraine/headache	18.1	22	1–4	2.23	0.20
Other inflammatory problems	18.1	22	1–3	2.14	0.17
Acute pain	16.5	20	1–4	2.25	0.18
Nausea	14.2	17	1–3	2.06	0.20
Irritable bowel syndrome	13.4	17	1–3	1.88	0.21
Cancer treatment	7.1	9	1–4	2.11	0.42
Autoimmune disease	7.1	9	1–4	2.89	0.31
Bacterial infection/antibiotic	6.3	7	1–4	2.14	0.40
High blood pressure	6.3	8	1–4	2.50	0.46
Osteoarthritis	5.5	6	2–3	2.50	0.22
Menstrual cramps	4.7	6	1–3	2.33	0.33
Premenstrual syndrome	3.9	5	2–3	2.40	0.24
Crohn's/ulcerative colitis	3.1	4	1–3	1.75	0.48
Glaucoma	3.1	3	1–4	2.67	0.88
Fibromyalgia	5.5	7	1–3	2.14	0.34
Cancer treatment-related symptoms	2.4	3	2–2	2.00	0.00
Menopausal symptoms	2.4	3	2–3	2.67	0.33
Seizures/epilepsy	2.4	2	1–4	2.33	0.88
Endometriosis	2.4	3	1–3	1.67	0.67
Rheumatoid arthritis	3.1	3	2–3	2.33	0.33
Multiple sclerosis	0.8	1	2–2	2.00	0.00
Premenstrual dysphoric disorder	0.8	1	3–3	3.00	0.00
Huntington's disease	0.0				
Other	9.4				

% endorsed refers to the percentage of the total sample ($N=127$) who reported use for each medical condition. *n* refers to the total number of participants who provided efficacy ratings. Efficacy scale ranged from 1 (very much improved) to 7 (very much worsens). Conditions are listed in order of the % who endorsed use for the condition.

that they had not discontinued use of nonopioid pain relievers than those who reported that they had discontinued use due to cannabis. Furthermore, a higher percentage of participants continued antidepressants and protein pump inhibitors than those who reported either discontinuing use because of cannabis or not discontinuing use of these medications because of cannabis.

Adverse events associated with CBG-predominant cannabis

Participants were also asked to assess 16 adverse events they may have experienced when using CBG-predominant cannabis as well as to list others (Table 6). Forty-four percent ($n=56$) of the complete sample reported no adverse events from CBG-predominant cannabis. Most commonly noted were dry mouth, sleepiness, increased appetite, and dry eyes. Nearly 10% reported experiencing "other" changes, which included increased clarity/focus ($n=2$), change in time perception ($n=2$), headache/sinus pain ($n=2$), brain fog ($n=1$) dissociation ($n=1$), headrush ($n=1$), and vivid dreams ($n=1$). For each endorsed side effect, participants were further asked to indicate the percentage of CBG-predominant cannabis use exposures during which it was experienced, with descriptive statistics reported in Table 6. Only one participant reported hot flashes, with high frequency.

Withdrawal symptoms from CBG-predominant cannabis versus other cannabis products

Participants assessed a series of nine withdrawal symptoms in relation to cessation of CBG-predominant cannabis as well as cannabis that was not predominantly CBG. The overwhelming majority (84.3%; $n=107$) never experienced withdrawal symptoms upon cessation of CBG-predominant cannabis. Only 1.6% reported experienced any withdrawal symptoms (14.2% were missing). Consistent with this, as shown in Table 7, endorsement of the nine specific withdrawal symptoms were extremely low, with sleep difficulties cited most often (endorsed by 1.6% [$n=2$] of the total sample).

In contrast, 75.6% ($n=96$) of the complete sample reported they have never experienced withdrawal symptoms related to the cessation of cannabis that was not predominant in CBG, while 11.8% ($n=15$) reported experiencing such withdrawal symptoms (12.6%; $n=16$ were missing). Chi-square comparisons of the percentages of participants revealed that sleep difficulties, anxiety/nervousness, irritability/aggression, nightmares/vivid dreams, and diminished appetite/weight loss were significantly more likely to be reported following cessation of non-CBG-predominant cannabis than CBG-predominant cannabis (see Table 7).

Discussion

This survey of CBG-predominant cannabis (containing >50% CBG) use represents the first report of perceived potential therapeutic effects of this chemotype. Consistent with findings of other surveys of cannabis use,[43–47] anxiety, pain, depression, and insomnia were among the most frequently reported conditions for which participants endorsed CBG use. Furthermore, CBG was indicated to have greater effectiveness than conventional medications for chronic pain, acute pain, insomnia/sleep, nausea, irritable bowel syndrome, other inflammation, depression, and anxiety. As shown in Table 6, adverse events were reported by a minority of participants with feeling high, difficulty concentrating,

Table 4. Comparison of Whether Cannabigerol-Predominant Cannabis or Conventional Medications Are Reported More Effective or Equally Effective

Medical condition	*n*	CBG,%	Conventional medication, %	Equivalent, %	Chi-square value	*p*
Anxiety	60	78.3[a]	11.7[b]	10.0[b]	54.70	<0.001
Chronic pain	46	73.9[a]	13.0[b]	13.0[b]	34.09	<0.001
Depression	40	80.0[a]	20.0[b]	20.0[b]	39.20	<0.001
Insomnia/disturbed sleep	37	73.0[a]	10.8[b]	16.2[b]	26.32	<0.001
Migraine/headache	22	59.1[a]	13.6[b]	27.3[ab]	7.18	0.03
Other inflammatory problems	22	86.4[a]	4.5[b]	9.1[b]	27.91	<0.001
Acute pain	19	68.4[a]	15.8[b]	15.8[b]	10.53	0.005
Nausea	17	76.55[a]	5.9[b]	17.6[b]	14.59	<0.001
Irritable bowel syndrome	17	82.4[a]	11.8[b]	5.9[b]	18.47	<0.001
Cancer treatment	7	57.1	14.3	28.6	2.00	0.37
Autoimmune disease	9	77.8[a]	0[b]	22.2[ab]	8.67	0.01
Bacterial infection/antibiotic	7	57.1	14.3	28.6	2.00	0.37
High blood pressure	8	50.0	0	50.0	4.00	0.14
Osteoarthritis	6	16.7[a]	16.7[a]	66.7[b]	13.00	0.002
Menstrual cramps	6	33.3	16.7	50.0	1.00	0.61
Premenstrual syndrome	5	80.0	0	20.0	5.20	0.07
Crohn's/ulcerative colitis	4	75.0	0	25.0	3.50	0.17
Glaucoma	3	33.3	0	66.7	2.00	0.37
Fibromyalgia	7	85.7	0	14.3	8.86	0.01
Cancer treatment-related symptoms	3	66.7	33.3	0	2.00	0.37
Menopausal symptoms	3	66.7	0	33.3	2.00	0.37
Seizures/epilepsy	3	66.7	0	33.3	2.00	0.37
Endometriosis	3	66.7	33.3	0	2.00	0.37
Rheumatoid arthritis	3	66.7	0	33.3	2.00	0.37
Multiple sclerosis	1	100	0	0		
Premenstrual dysphoric disorder	1	100	0	0		

Percentages that share a superscript are not significantly different, while those that have different superscript letters are significantly different at $p < 0.05$.

sleepiness, dry mouth, and increased appetite representing the most frequently reported adverse events. Overall, compared with non-CBG-predominant cannabis, most of the common withdrawal symptoms were reported significantly less.[43,48]

Use patterns are mostly consistent with prior reports of medical cannabis users,[43] with daily use common, but favoring oral products (76.4%) compared with previous surveys where smoking/inhaling was the predominant form of administration (84–95%).[43,46,49,50]

Table 5. Medication Use and Discontinuation of Medication for Cannabis

Medication	*n*	No,%	Yes,%	N/A (still taking), %	Chi-square value	*p*
Opioids	7	42.9	42.9	0.8	1.14	0.56
Nonopioid pain Reliever	6	83.3[a]	0[b]	16.7[ab]	7.00	0.03
NSAID	13	38.5	38.5	23.1	6.20	0.74
Antidepressant	19	15.8[a]	21.1[a]	63.2[b]	7.68	0.02
Antianxiety	9	33.3	22.2	44.4	0.67	0.72
Sleeping aid	4	0	50	50	2.00	0.37
Muscle relaxant	4	50	50	0	2.00	0.37
Antiemetic	3	33.3	0	66.7	1.00	0.61
Protein pump inhibitor	5	0	0	100	10.00	0.007
Anticonvulsant	2	0	0	100		
Antimigraine	2	0	0	100		
Sedatives/hypnotics	0					
Antipsychotics	0					

Numbers under "No" indicate the percentage of respondents (*n*) who indicated they have not discontinued medication use for cannabis, while those under "Yes" indicate the percentage of respondents (*n*) who indicated they have discontinued medication use for cannabis. Numbers under "N/A" refer to the percentage of respondents who are still taking that medication.

NSAID, non-steroidal anti-inflammatory drug.

Table 6. Endorsed Side Effects of Cannabigerol-Predominant Cannabis and Percentage of Sessions for Which Side Effects Were Experienced (*N* = 127)

Medical condition	% endorsed	*N*	Range	Mean, %	Standard error
Dry mouth	16.5	21	9–100	52.71	5.66
Sleepiness	15	18	11–90	52.89	5.75
Increased appetite	11.8	14	9–90	51.14	6.42
Dry eyes	8.7	11	25–90	49.82	6.77
Nervousness/anxiety	6.3	8	5–58	26.25	6.04
Difficulty concentrating	6.3	6	30–100	59.18	10.44
Headrush/lightheaded/dizzy	6.3	7	2–74	28.57	11.49
Headache/migraine	5.5	7	2–60	21.57	7.91
More high	4.7	6	10–100	60.3	12.33
Heart palpitations/racing heart	3.1	3	30–51	40.33	6.06
Off-balance/unsteady	2.4	2	46–50	48	2
Paranoia	1.6	2	14–30	22	8
Hot flashes	0.8	1	91–91	91	0
Coughing fit	0				
Hallucinations	0				
Vomiting	0				
Other	9.4	11	10–100	46.55	10.57

Table 7. Comparison of Reported Withdrawal Symptoms Associated with Cannabigerol-Predominant and Non-CBG-Dominant Cannabis ($N = 127$)

Withdrawal symptom	% endorsed for CBG-predominant cannabis	% endorsed for non-CBG-predominant cannabis	Chi-square value	*p*
Sleep difficulties	1.6	9.4	7.40	0.007
Anxiety/nervousness	0.8	7.1	6.62	0.01
Irritability/aggression	0.8	6.3	5.59	0.02
Restlessness	0.8	4.7	3.60	0.06
Depressed mood	0.8	3.9	2.65	0.10
Nightmares/vivid Dreams	0	3.1	3.98	0.046
Nausea	0	1.6	2.04	0.15
Lower appetite/ weight loss	0	3.1	3.98	0.046
Panic	0	0.8	1.02	0.31

This may reflect the lack of availability of CBG-predominant flower for inhalation, but an increased availability of extracted forms for ingestion. This sample was primarily purchasing "online" suggesting that respondents may not have had local access.

It appears from market trends that the next cannabinoid marketing push in the United States is toward CBG.[51] Following a phenomenon similar to that of breeding for CBD dominance, CBG production[40] is proliferating despite the fact that CBG is among the least studied of the cannabinoids. The known pharmacodyamics suggest unique action intermediate to those of CBD and THC,[52] more toward THC but without the intoxicating effects. Relatively weak binding affinities to the CB_1 receptor have been measured ($K_i = 440–1045$ nM),[52] and this could explain the reduced side-effect profiles and withdrawal effects reported by this sample.[12,13,53,54]

Anxiety was the treatment condition endorsed most often by participants as well as the only one for which there was any reported worsening of symptoms. This is consistent with at least one other survey of cannabis use that reported similar findings.[43] Anxiogenesis could be explained by the presence of THC, known to have a narrow therapeutic window,[55] as 29% of respondents indicated the presence of THC in available materials. While anxiety and panic attacks are associated consequences of cannabis use,[56] reduction in anxiety is also clearly a motivation for cannabis use.[43,44–47,57] This paradox may be explained by the biphasic effects of THC on anxiety.[58] Dose-dependent effects of CBG on anxiety may also be due to its *in vitro* and *in vivo* actions as a 5-HT_{1A} receptor antagonist at higher doses.[12,19,20] CBG is also likely to produce anxiolytic effects through the α-2 adrenoreceptor (α-2AR), a member of an autoregulatory family that mediates catecholamine signaling (particularly overflow of epinephrine), thereby reducing sympathetic nervous activity.[12,59,60] The ability to dampen hyperarousal without sedation, metabolic side effects, or addiction risk could be beneficial for post-traumatic stress disorder or other states of hypervigilance associated with elevated noradrenergic tone (panic disorder and attention-deficit hyperactivity disorder).

Pain is one of the best-studied and highly endorsed benefits for medical cannabis.[61] Consistent with this, chronic pain was the second most endorsed condition for CBG use, with efficacy ratings indicating much improvement. Nociceptive effects could be attributed in part to the reported potent agonism at the α-2AR, which reduces transmission of pain effector molecules glutamate and substance P at the level of the dorsal horn[62] and inhibition of calcium channels.[63] The ability to facilitate pain relief with minimal side effects is a highly sought alternative to current pain strategies. Future studies will reveal whether α-2AR stimulation by CBG carries any of the same side effects as other drugs at this target.[64]

5-HT is the target of selective serotonin reuptake inhibitor antidepressants. Table 5 shows that participants reported using antidepressants more frequently than any other drug class represented in the survey, with a higher percentage of participants indicating that they have not substituted these drugs with CBG. CBG has been shown to have moderate neutral antagonism at the 5-HT_{1A} receptor (1 μM).[12] The 5-HT_{1A} receptor is vital for mediating anxiety and acts as an autoreceptor (key component of a negative feedback loop) to inhibit further release of serotonin.[65] It may seem counterintuitive for antagonism of this receptor to support antidepressant properties, but desensitization to autoregulatory control would essentially increase serotonin concentration at the synapse.[66,67] This could potentially explain results of these subjects' report of continued antidepressant use, while also endorsing antidepressant effects of CBG-predominant cannabis. This finding supports pre-clinical evidence that CBG may be acting as an adjunct, by potentiating the antidepressants already in use. Further research is needed to understand this potential mechanism in humans.

Around 16.5% of these survey responders reported using CBG-dominant cannabis for irritable bowel syndrome or Crohn's/colitis, endorsing CBG as significantly more effective than conventional medications

(82.4% and 75%, respectively). CBG has been studied as a potential therapeutic in cell culture and animal models of gastrointestinal disease.[68] Beneficial effects could be mediated through CB_2 receptor (K_i 153 nM)[10] or PPAR-γ activation ($K_i = 11.7\ \mu M$)[69] or antagonizing TRPM8 ($IC_{50} = 160$ nM),[25] thereby mediating inflammation and providing protection from carcinogenesis in these disorders.[13] Around 18.1% of responders endorsed CBG-predominant cannabis for "other inflammation," with 86.4% reporting greater efficacy of CBG over conventional medications, further supporting the anti-inflammatory properties of CBG.

Sleep disorders and insomnia occur with high prevalence across the population.[70] Aside from nabiximols,[71] cannabinoids have been understudied for sleep disorders in randomized controlled trials, with the most likely benefits produced by THC,[72] supported by evidence that the endocannabinoid system is involved in circadian cycling.[73] Sleep disorders are difficult to treat, and existing pharmacotherapies leave much to be desired due to their side effects and long-term risks, particularly dependency.[74,75] This cohort reported that CBG-predominant cannabis was more effective than conventional sleep medications, however, only half discontinued such use due to CBG. It is unclear whether the THC component of products used by this cohort may have impacted their sleep, but the antisympathetic action of CBG may also contribute to this perceived effect. Notably, significantly fewer participants reported sleep difficulties upon cessation of CBG-predominant cannabis relative to non-CBG-predominant cannabis, consistent with previous findings of sleep difficulties following THC discontinuation.[76] There is a need to improve current strategies for treating sleep disorder, as it is a known contributor to progression of dementia and Alzheimer's disease.[77,78]

Limitations of this study include that there was insufficient information regarding the doses of each cannabinoid being used and thus it is difficult to specifically attribute CBG for the reported effects rather than other cannabinoids present in preparations or to estimate approximate doses that may be safe and effective for the indications reported. Therefore, the possibility that cannabinoids other than CBG are responsible for the reported effects cannot be ruled out. There is also limited information about specific administration methods and frequency of use for each product. Other limitations include selection bias, self-reporting, exaggeration of perceived efficacy, placebo effects, and recall bias. The sample is largely limited to people who access the internet and are skilled in the use of online tools.

Conclusions

This is the first patient survey of CBG use to document self-reported efficacy of CBG-predominant cannabis, particularly for anxiety, chronic pain, depression, and insomnia. Most respondents claimed greater efficacy of CBG over conventional pharmacotherapy for 10 conditions and reported a very benign adverse event profile and negligible withdrawal. Due to the variety of chemotypes represented in the survey, and the likelihood that other cannabinoids or the synergistic effects of multiple compounds could be responsible for some of the effects reported in this study, firm conclusions about the effects of CBG in humans cannot yet be drawn. However, this study demonstrates that CBG-predominant cannabis and related products are available and being used by cannabis consumers and demonstrates the urgent need for randomized controlled trials of CBG-predominant cannabis-based medicines to be studied rigorously to assess safety and efficacy as a function of dose, mode of administration, and specific therapeutic indications.

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Abbreviations Used

2-AG = 2-arachidonylglycerol
α-2AR = α-2 adrenoreceptor
5-HT = 5-hydroxytryptamine (serotonin)
AEA = arachidonoyl ethanolamide (anandamide)
CB = cannabinoid
CB_1/CB_2 = cannabinoid receptor 1 or 2
CBCA = cannabichromenic acid
CBD = cannabidiol
CBDA = cannabidiolic acid
CBDV = cannabidivarin
CBG = cannabigerol
CBN = cannabinol
GABA = gamma aminobutyric acid
IL = interleukin
NSAID = non-steroidal anti-inflammatory drug
OTC = over-the-counter
PPAR-γ = peroxisome proliferator-activated receptor-gamma
THC = tetrahydrocannabinol
THCA = tetrahydrocannabinolic acid
THCV = tetrahydrocannabivarin
TNF-α = tumor necrosis factor-alpha
TRP = transient receptor potential
TRPM8 = transient receptor potential melastatin type 8