The effectiveness of cannabidiol for anxiety and understanding patterns of and motivations for consumption of cannabidiol products in the UK

Georgina Wallington

DClinPsy Thesis (Volume 1), 2022

University College London

UCL Doctorate in Clinical Psychology

Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

Name: Georgina Wallington

Date: 15.06.2022

Overview

Part one of this project is a systematic review evaluating the effectiveness of cannabidiol (CBD) on anxiety. Included studies evaluate the experience of CBD on anxiety, in varying populations, as well as with individuals who are classified as experiencing anxiety disorders. Measures of anxiety include questionnaires or biomarkers (e.g., heart rate, blood pressure).

Part two, an empirical paper, is an explorative study that involved UK-based participants completing an online survey. The primary aims of the study are to understand consumption patterns of CBD, factors influencing decisions to use CBD-products, attitudes towards health treatments and to also explore the impacts of perceived expectancy and beliefs of CBD-products. The study compares attitudes about CBD and health treatment behaviour amongst CBD users and non-CBD users. Statistical analysis includes mean comparisons and regression analysis.

Part three evaluates and reflects on the process of parts one and two. Common themes emerge when personal beliefs made it uncomfortable completing the research. Furthermore, researcher inexperience led to some difficulties in the completion of all parts of the research.

Impact statement

There has been global exponential growth in availability of over-the-counter cannabidiol (CBD) products. These low-dose products receive remarkable claims about their beneficial effects, marketed as a panacea. However, there are mixed results and research investigating low-dose CBD is lacking. Both the systematic review and empirical paper presented in this report contribute new ideas to CBD research and hold significant clinical relevance.

The systematic review provides an updated summary of clinical studies that investigate the effects of CBD on anxiety (humans only), reviewing subjective and physiological measures of anxiety and/or stress. This systematic review includes randomised and non-randomised controlled trials, including case series which contain invaluable findings of longer-term effects and in non-laboratory settings. Existing systematic reviews often do not include these research designs. Anxiety is consistently reported as a main indication for CBD use. The findings indicate there are clear, inconclusive results on the impacts on anxiety at varying doses and most research focusses on social-based anxiety and induced fear and/or stress. Further studies are required to investigate the effects of CBD on the different experiences of chronic anxiety and to include low-dose CBD, particularly using participants who are using concurrent medications.

The empirical paper, part two, provides valuable data of UK residents who are using CBD products. This survey compares the data to individuals who have not used CBD products, which is not often done in existing CBD-consumer research. This enables hypotheses to be developed regarding CBD preferences. The paper provides insights to the consumption of CBD and the main reasons for CBD use, which reflects findings of similar, existing studies that is relevant to CBD suppliers. This study reveals factors that may influence individuals to use CBD products. For example, the survey investigates the possibility of an expectancy effect

(placebo/meaning response), comparing individuals' perceived hopefulness before using CBD products and their perceived efficacy after CBD use. Very few studies have investigated this effect from CBD. The findings suggest higher hopefulness about CBD, is associated with higher ratings of perceived efficacy. Further research into this area would be helpful to understand potential psychological and physiological changes that may occur from CBD and/or an expectancy effect, which may be of therapeutical value, not a hindrance. The study also demonstrates other factors may increase the likelihood of CBD use, including higher rates of previous treatments and increased hopelessness about other treatments. This suggests that individuals who seek out more health treatments, are more likely to use CBD products and are more sceptical of the pharmaceutical industry. These findings are important for policy making and the healthcare system – many individuals are seeking alternative treatment for a range of health difficulties, predominantly stress, anxiety, problems sleeping, with many experiencing hopelessness of other treatments and distrust of pharmaceuticals.

Efforts will be made to publish the results of the survey and the systematic review. Reports will be created to summarise key findings to researchers in the cannabinoid field, including those who are involved in policy making and for CBD and related advocacy groups.

Table of contents

Appendices

List of tables and figures

Part 1: Literature review

Part 2: Empirical paper

Acknowledgements

I give thanks to my research supervisors who have guided me throughout this process and offered their invaluable expertise, advice and support for this thesis: Professor Valerie Curran, Dr Jon Waldron and Professor Sunjeev Kamboj.

I also give thanks to my course colleagues Amrita Ramanathan and James Adamson who supported me with the systematic review, as well as my other course colleagues, previous supervisor Dr Chandni Hindocha, and experts and researchers in the drug science field who offered advice.

Lastly, I am thankful to all participants of the survey for the empirical paper, and to those who shared the information, who so kindly gave their time and experience.

Part 1: Literature review

Cannabidiol use for anxiety: A systematic review

Abstract

Background: Cannabidiol (CBD) is increasingly being used for a variety of mental and physical health problems. Both clinical and survey-based studies report mixed findings on the benefits of CBD for anxiety and other psychological or physical health difficulties. This systematic review aims to provide an overview of existing clinical studies investigating the effects of CBD on anxiety for individuals aged 18 or over, whilst other disclosed treatments are not being concurrently used.

Methods: The databases MEDLINE, EMBASE, PsycINFO, Web of Science, The Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov were systematically searched using terms related to anxiety and anxiety disorders, for all clinical studies, not limited to Randomised Controlled Trials (RCT's). The searches retrieved 2085 studies with duplicates removed, of which 235 were fully analysed for eligibility. In total, 22 studies were included and described in this review.

Results: Overall, the included studies provide mixed reports of the effects of CBD on anxiety. There is some descriptive evidence for an inverted U-shaped dose response curve. For example, 300 mg appears to provide an anxiolytic effect, with lower efficacy reported with lower and higher doses. CBD at this dose was found to reduce anxiety in single-dose studies, during fear or stress induction procedures, as well as in studies examining long-term use.

Conclusions: The reviewed studies suggest CBD may be effective at reducing fear and anxiety, particularly at the intermediate dose of 300 mg. There are mixed findings for the efficacy for

acute, situational anxiety and for more chronic experiences of anxiety. Further research looking into the effects of anxiety that also describe concurrent treatments, medications and substances would enable a more detailed understanding of the impacts of CBD on anxiety and other emotional states.

Introduction

Cannabidiol

Cannabidiol (CBD) is one of over 100 cannabinoid compounds from the *Cannabis sativa* plant (Crippa et al., 2018). A surge of interest and research on CBD occurred in the 1970's and around the 2000's (Crippa et al., 2018), including online searches in the USA (Narayanan et al., 2020). CBD is the major ingredient of Epidiolex (or Epidyolex) which is approved for the treatment of some forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in 2018 by the US Federal Drug Agency and 2019 by the European Medicines Agency.

For CBD products to be sold legally, THC content must be below 0.2% in Europe (Commission Regulation), 0.3% in Canada and the USA (Grow Hemp, 2018), and 1% in Switzerland. In many countries, CBD oils are sold as food supplements. In the UK, CBD was announced as a 'novel food' in 2019. In the US, CBD was the 12th highest selling herbal supplement in 2017, with a dramatic increase of 303% from the previous year (Williamson et al., 2020). If CBD products are sold for medicinal purposes, additional licenses are typically required and safety/quality standards must be met, potentially reducing the incentive to develop and market it as a treatment for specific disorders. CBD products are also sold in vaping shops, convenience stores and online (White, 2019). There are risks involved with unregulated CBD products. For example, Evans (2020) raises concerns for products being sold in essentially a 'black market', if they are not approved by the appropriate government agency. Some concerns also exist about the potential THC content in CBD products (for example, Merrick et al., 2016). There are also warnings of the unreliability of THC content in CBD, therefore some risks of unintentional 'doping' are present (Lachenmeier & Diel, 2019). Studies which have investigated the actual CBD content of products have found differing levels of what is described, including

within the UK (Liebling et al., 2022), in Europe (Pavlovic et al., 2018) and in the US (Bonn-Miller et al., 2017).

Cannabinoids and medical cannabis research

In recent years, medical cannabis research has also increased significantly. Pain and anxiety are cited as the most common indications for medical cannabis use (DrugScience, 2022). In the USA, in states with cannabis medication laws, self-medication of marijuana/cannabis was higher for mood and anxiety disorders (Sarvet et al., 2018). The authors argue that high quality evidence is needed for individuals who use cannabis for mood and anxiety. A large systematic review and meta-analysis of 83 studies, evaluating impacts of cannabinoids on mental health, found pharmaceutical THC-grade (with or without CBD) was linked with improvements in a variety of conditions including anxiety, chronic non-cancer pain and multiple sclerosis (Black et al., 2019). Naturalistic study designs have found Cannabis-based medicinal products (CBMPs) to be effective for neuropathic pain (Ueberall, Essner & Mueller-Schwefe, 2019).

Reviews of cannabinoids effectiveness found strong evidence for treatment in adults for chronic pain, chemotherapy-induced nausea and vomiting and multiple sclerosis spasticity symptoms (NASEM, 2017). Limited evidence was found for other illnesses. Sarris et al. (2020) found tentative suggestions of improvements in anxiety (attributed mostly to CBD) and schizophrenia.

In the UK, US, and Canada, sellers of CBD are not allowed to make claims about benefits to health, although many ignore this prohibition (Food Standards Agency; Zenone, Snyder & Crooks, 2021). Some authors have raised concerns about researchers' claims of beneficial effects of CBD use. For example, Stuyt and Hilderbrand (2020) raise their concerns on the case study by Elms et al. (2019) reporting improvements of PTSD from CBD. Stuyt and

Hilderbrand (2020) discuss how the authors of the case series did not comment on (or disregarded) the effects of other treatments the individuals received, the CBD dose was not used in standardised doses and other components of cannabinoid treatments were not effectively monitored; collectively, these may be contributing to the 'craze' of CBD being considered as a panacea with minimal supporting evidence. A study completed a content analysis on online data about vape shop products and found many made explicit health claims about CBD, which "are not FDA-approved for recommended uses of CBD" (Leas et al., 2021).

CBD and anxiety

In humans, anxiolytic effects have been studied in laboratory-based studies, observational and clinic-based settings. Survey-based studies report high levels of CBD use for anxiety, with it being one of the most common indications for CBD use (Goodman et al., 2020; Moltke & Hindocha, 2021; Moinas et al., 2020), alongside pain, sleeping problems, low mood and stress. Animal models will not be discussed in detail in this report but there is increasing evidence of anxiolytic effects in animals (e.g., Wright, Di Ciano & Brands, 2020). Some reviews of clinical studies including humans and animals, suggest CBD can be helpful for anxiety, including reduction of fear expression, reduction of fear memory consolidation, and 'enhancing fear extinction' (Lee et al., 2017), particularly for social anxiety (Schier et al., 2012). CBD has been described as being a beneficial adjunctive treatment for anxiety and/or stress (Sharpe et al., 2020). Henson et al. (2021) highlight seven double-blind placebo controlled clinical trials that all showed benefits to the stress response, with studies measuring different sources of anxiety, expression, and stimuli. For example, Appiah-Kusi et al. (2020) investigated 'social stress' in a public speaking situation (Tier Social Stress Test; TSST). Crippa et al. (2004) focussed on subjective anxiety ratings and Regional Cerebral Blood Flow (rCBF) and Das et al. (2013)

investigated the effect of CBD on fear memory extinction and consolidation. More recently, an experimental study investigating the impact of CBD on trauma memory re-living and reconsolidation in individuals with post-traumatic stress disorder (PTSD), found that CBD attenuated cognitive impairments, but not for anxiety mood states and physiological markers of anxiety/stress (Bolsoni et al., 2022). Black et al's (2019) large-scale systematic review concluded the available evidence for the effectiveness of cannabinoids in improving symptoms of anxiety was of very low quality and there have been calls for more systematic reviews evaluating the efficacy of CBD, its effects and safety considerations (D'Souza, 2019).

CBD and treatment of other (non-anxiety) psychological disorders

CBD has also been found to have beneficial effects on other psychological disorders/problems. A systematic review evaluating CBD dose efficacy for a variety of illnesses/symptoms, found positive effects in 66% of the studies evaluated, with doses ranging from <62–3100 mg/d for an adult, for disorders or conditions including: schizophrenia and psychosis, seizures and epilepsy (including drug-resistant), social anxiety, movement disorders, cannabis dependency, anxiety and insomnia (in a one-person case study), and graft-vs-host disease (cell transplantation) (Millar et al., 2019). Researchers have also found potential benefits of CBD in drug-use disorders, such as cannabis use. Freeman et al. (2020) found one month treatment of 400 & 800mg significantly reduced cannabis use for individuals with cannabis use disorder. A single dose of 800 mg CBD also aided response to cigarette cues for dependent cigarette smokers after brief tobacco abstinence (Hindocha et al., 2018). Other systematic reviews, however, suggest there is limited evidence for treatments of other psychological disorders and more research is needed (Black et al., 2019; Bonaccorso et al., 2019). The evidence

of CBD's efficacy is lacking for its use in mood disorders and inflammatory/painful conditions (Williamson et al., 2020).

CBD is also being increasingly used in children, with debates over the sufficiency of evidence regarding risks and benefits (Singer et al., 2020). This review will not focus on the effects of CBD on children, though there is increasing research on the use of CBD for epilepsy (e.g. Sands et al., 2019) and for Autism Spectrum Disorder (ASD; e.g. Barchel et al., 2019).

Current review

This review aims to evaluate and synthesise literature evaluating the effectiveness of CBD on anxiety. Other systematic reviews with a similar aim have focussed on all mental health difficulties (Bonaccorso et al., 2019), randomised control trials only (Millar et al., 2019) and animal studies (Honório Júnior et al., 2021). Many conclusions from animal research are applied to humans, for example, anxiolytic dose-response effects (Campos & Guimarães, 2008; Guimarães et al., 1990). There are, however, differences in how CBD is administered and the blood concentration of CBD between humans and rodents, so caution should be applied when making these comparisons and inferences (Iffland & Grotenhermen, 2017). Blessing et al's (2015) systematic review included pre-clinical and epidemiological studies published up until 1st January 2015, which investigated CBD impacts on anxiety; they also included studies evaluating anxiety symptoms induced by cannabis use. This current review provides an update on research published since this time, until February 2022, and focuses on research on humans aged 18 or over, with no other known treatments or substances (including THC) which may also impact on anxiety, being used at the same time. This systematic review's main research aims are to address:

1. How effective is cannabidiol as a treatment for anxiety and anxiety disorders, in adults, aged 18 and above?

2. What is the quality and risk of bias in the included studies in the systematic review?

Method

Search strategy

The search strategy followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist reporting guidance (Moher et al., 2015). The systematic review protocol was registered with PROSPERO, registration number CRD42021279646.

For this review, only public sources were searched. The following international electronic databases were searched for resources up until 9th February 2022:

- MEDLINE (1946 to February 2022)
- EMBASE (1980 to February 2022)
- PsycINFO (1806 to February 2022)
- Web of Science
- The Cochrane Central Register of Controlled Trials (CENTRAL)
- ClinicalTrials.gov

These databases were chosen as MEDLINE, EMBASE and PsycINFO are reported as important databases (Lefebvre et al., 2022) and Web of Science is a large interdisciplinary database. CENTRAL and ClinicalTrials.gov were searched as additional research can be found with available results, which may not be identified elsewhere. In addition, the reference lists of the included studies were manually searched to identify additional, suitable papers. All searches were conducted by one person, the main author.

In the search strategy, anxiety and cannabidiol were the main concepts searched for. The following keywords were used for cannabidiol:

Cannabidiol OR CBD OR Epidiolex OR Epidyolex

The following keywords were used to capture anxiety disorders and anxiety related difficulties:

Anxiety OR Fear OR Phobia OR Trauma OR PTSD OR OCD OR Obsessive OR Panic

The syntax function * was used to allow for truncation of words when the database allowed this. For example, anxi* would capture anxiety and anxiolytic and phobi* would capture phobia and phobic. The search concepts were combined using the Boolean operator AND.

Other anxiety disorders and presentations of anxiety, which should be identified within the search of 'anxiety', include social anxiety, health anxiety and agoraphobia. Disorders such as Trichotillomania or hoarding would not be captured within this search strategy, however in the databases where subject headings exist, terms were included such as hoarding disorder, trauma and stress disorders, and attachment disorders (in Medline) and anticipatory anxiety and performance anxiety (in Embase). The full search strategies are detailed in Appendix 1.

Eligibility criteria

This review aimed to investigate the effects of cannabidiol on anxiety. Included studies had to assess experiences of anxiety by including either self-report measures, such as questionnaires, or biomarkers of anxiety, such as heart rate and blood pressure. It was not required for participants to have a diagnosis of an anxiety disorder, to increase the available studies that investigate the effects of any experience or definition of anxiety. If studies investigated other psychological outcomes, only the anxiety effects were reported in this review. Only human research was included, and any animal studies were excluded. The minimum age of participants was 18, to focus the analysis on the effects on adults. The amount and dose of CBD needed to be documented and if the percentage of CBD in the product was stated, studies would be excluded if THC content exceeded 0.2%, in line with UK laws. Studies that did not state the

percentage of CBD, but did state the product was CBD, were included. Studies were excluded if other medications, treatments or substances were taken within a time frame that is likely to influence anxiety outcomes.

The types of studies included could be controlled or non-controlled laboratory-based, retrospective case reviews, case studies, case series or observational/naturalistic studies, if they met the above-described criteria. Grey literature could be included if the inclusion criteria was met.

Studies were also excluded if the statistical analysis or results did not infer the effects of anxiety from CBD-only products. For example, if a study investigated varying compound percentages, but the CBD levels were not distinguishable in the data. No limits were applied to publication date.

Comparator groups may include other treatments, as well as a placebo, control group of no treatment or treatment as usual (TAU). Comparator groups may also be other forms of treatment or substances, such as cannabinoids or another anxiolytic treatment.

Study selection and data extraction

Results from the electronic database searches were transported to EndNote 20 citation management software (Clarivate Analytics) and duplicates were removed. Titles and abstracts were screened using the eligibility criteria by the main author and subsequent full text screening was completed independently with two additional reviewers who were not otherwise involved in the review, with any discrepancies discussed and resolved. A standardised template was used for data extraction (Appendix 2) and inclusion decision for each included study (Appendix 3).

Risk of bias assessment

Multiple quality assessment tools were chosen to appropriately evaluate the variety of included study designs. Version 2 of the Cochrane risk-of-bias tool (the RoB 2; Sterne et al., 2019) was used for randomized control trials. It includes five domains of analysis, assessing bias from: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each item is rated, with response options ranging from 'low-risk', 'some concerns' or 'high-risk'. An overall result is then concluded.

The Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I; Sterne et al., 2016) assessment tool was used for non-randomized studies. The tool is used for studies with at least two interventions and is based on the RoB 2. The tool includes seven domains of analysis, bias from: confounding, selection of participants, classification of interventions, missing data, deviations from intended interventions, measurement of outcomes and selection of the reported result. An overall judgement of 'low', 'moderate', 'serious' or 'critical' risk of bias, or 'no information' is provided.

The Canada Institute of Health Economics (IHE) Quality Appraisal Tool for Case Series (IHE, 2014) was used to assess case reports and series. The results of these assessments will inform further critical analysis of the included studies.

Results

The results of the systematic review data extraction process are shown in Figure 1. From the initial searches, 2513 results were retrieved, of which 2085 studies remained after duplicates were removed. Following screening of the titles and abstracts, 262 studies were assessed for

eligibility by the full texts being read. 240 of the studies were excluded as they did not meet the criteria. In total, 22 studies met all inclusion criteria and were included in this review.

Study description

Seventeen randomised controlled trials, two non-randomised trials and three case reports/series were included in this review. Five RCT's used restricted randomisation approaches to balance participant group numbers or prognostic factors. The date of publication ranged from 1982 to 2022, with 20 papers published since 2004, demonstrating the increase of publications investigating CBD effects. Descriptive information of the included studies are detailed in Table 1.

Participant and study characteristics

The average age of the participants across studies was 31.0. Two studies had an older average ag: de Faria et al. (2020) had an average age of 64.1 and Vela et al. (2021) had a median age of 62 (mean not reported). Most other studies' average participant age was in the 20's. Overall, male participants were over-represented, with six studies including only males and eight studies had majority male participants (>70%) and only one study had female majority participants (60% in the CBD and 70% in the placebo group; Vela et al., 2021). It was also common for many studies to include 'healthy' (i.e., non-clinical) participants. Of 19 experimental studies, 11 used only 'healthy' participants, which mostly excluded past or current 'psychiatric history', significant physical health difficulties, current medications. Nine studies included a 'clinical' participant group (e.g., Kimless et al., 2020), with other studies including both a clinical and a comparator 'healthy' participant group (e.g., Bergamaschi et al., 2011). Ethnicity of participants were rarely reported in the included studies.

Figure 1.

PRISMA flow diagram showing the record retrieval and screening process

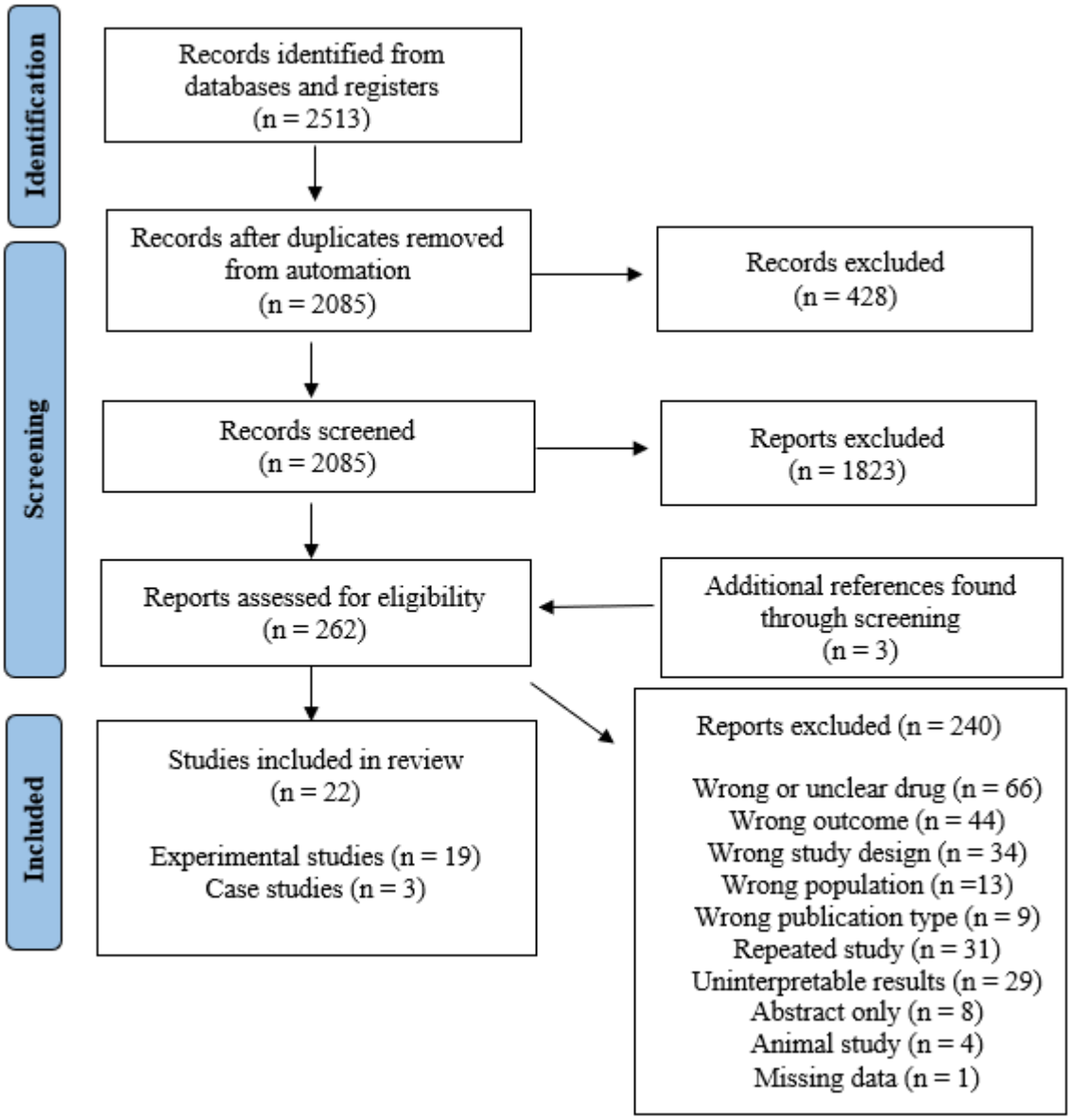


Table 1

Descriptive table of the included studies

Reference	Participant characteristics* (mean age/range; % gender)	Study design	Active and comparator groups (sample size)	Outcome measures	Outcomes	Procedure	Risk of bias rating
Randomised-controlled trials							
Appiah-Kusi et al. (2020)	'Healthy' participants with 'clinical high risk of psychosis' (22.3 ±5.1]; 37.5% female, 'gender matched')	Between groups, laboratory based	600mg CBD capsule, daily for 7 days (n=16) Placebo capsule daily for 7 days (n=16) 'Healthy' control group, no drug administration but completed measures (n=26)	STAI, SSDPS, cortisol levels	CBD reduced anxiety and cortisol levels during the stress test, in comparison to the healthy control group	The Trier Social Stress Test (TSST) - public speaking	High
Bergamaschi et al. (2011)	Experimental group SAD traits in the CBD and placebo group and 'healthy' control participants (24.6 ±3.6; 50% female)	Between groups, laboratory based	1 occasion: 600mg CBD powder in capsule, (n=12) SAD-placebo capsule (n=12) Healthy control group, no drug administration (n=12)	VAMS, SSPS-N, BSS, SC, HR, BP	CBD significantly reduced anxiety, cognitive impairment, discomfort in speech performance, and alertness to anticipatory speech and a reduction of negative self-evaluation during public speaking	SPST - public speaking	Low
Bolsoni et al. (2022)	PTSD diagnosis (33.94 ±11.55; 76% male)	Between groups, laboratory based	1 occasion: 300 mg CBD capsules (n=17) Placebo capsules (corn oil) (n=16)	STAI***, VAMS*** (anxiety factor), PCL-5, BP, HR, SC	The CBD group did not attenuate increases in anxiety, alertness, and discomfort induced by the traumatic memory recall.	Participants audio recorded their trauma memory, which they listened back to 7 days later.	Low

Table 1 continued

Reference	Participant characteristics* (mean age/range; % gender)	Study design	Active and comparator groups (sample size)	Outcome measures	Outcomes	Procedure	Risk of bias rating
Crippa et al. (2004)	'Healthy postgraduate students'** (30, range 25–42 ±5; 100% male)	Within groups, laboratory based	400 mg CBD powder, 1 dose on two occasions separated by 1 week (n=10) Placebo (n) what?	VAMS	CBD significantly decreased subjective anxiety and increased mental sedation, while placebo did not induce significant changes	The anxiety provoking procedure was the SPECT imaging process itself	Some concerns
Crippa et al. (2011)	Experimental group: SAD diagnosis (24.2, range 20-33 ±3.7; 100% males)	Within groups, laboratory based	1 occasion: 400mg CBD capsules (n=10) Placebo capsule (n=10)	VAMS***, brain imaging	In comparison to the placebo group, the CBD group had significantly reduced state anxiety prior to SPECT imaging	The anxiety provoking procedure was the SPECT imaging process itself	Low
de Faria et al. (2020)	Idiopathic Parkinson's Disease (PD) (64.12 ±9.72; 91% male)	Within groups, crossover clinical trial	1 occasion: 300mg CBD capsule (n=24) Placebo capsule (n=24)	VAMS, SSPS, BP, HR	No significant differences between the groups in the VAMS anxiety factor, BP or HR, but statistical difference between time (phase) of baseline to pre-speech in the CBD group	SPST	Low
Linares et al. (2019)	'Healthy participants' (24.2 ±3.08, 24.6 ±2.93, 22.6 ±3.4; 100% male)	Between groups, laboratory based	1 occasion: 150mg CBD capsule (n=15) 300mg CBD capsule (n=15) 600mg CBD capsule (n=12) Placebo capsule (n=15)	VAMS, BP, HR	Significant lower anxiety levels (VAMS) in the CBD 300mg group (intermediate dose) during the public speaking phase compared to placebo (p = 0.042), producing an inverted U-shaped dose-response curve. No significant group effects in BP	SPST	Some concerns

Table 1 continued

Reference	Participant characteristics* (mean age/range; % gender)	Study design	Active and comparator groups (sample size)	Outcome measures	Outcomes	Procedure	Risk of bias rating
Masataka et al. (2019)	SAD diagnosis (18-19 ;70% male in both groups)	Between groups, home-based	300mg CBD, daily for 4 weeks (n=17) Placebo capsule, daily for 4 weeks (n=20)	FNE, LSAS	CBD significantly decreased anxiety in both measures, when comparing pre-treatment and post-treatment scores, in comparison to the placebo groups. Both post-treatment mean scores were lower than the placebo groups. There was not a statistical difference between the two groups on the FNE post-treatment scores.	Participants did not take part in any additional experimental procedures. Outcome measures were completed pre- and post-intervention	Low
Morgan et al. (2013)	Tobacco smokers >10 a day and had an interest in stopping smoking (28 ±4.29; 18-35; 50% female)	Between groups, home-based	CBD 400µg inhaler, ad-hoc for 1 week (n=12) Placebo inhaler, ad-hoc for 1 week (n=12)	MRS, STAI (baseline only)	Both the CBD and placebo groups demonstrated reduced anxiety across the 7 days. There was no main effect of treatment found, however the MRS anxiety factor score decrease was larger in the CBD group	On day 1 participants received brief smoking cessation advice. Participants used the inhaler as needed and reported daily craving, inhaler use and tobacco use.	

Table 1 continued

Reference	Participant characteristics* (mean age/range; % gender)	Study design	Active and comparator groups (sample size)	Outcome measures	Outcomes	Procedure	Risk of bias rating
Vela et al. (2021)	Participants with hand osteoarthritis and psoriatic arthritis (Median 62 [IQR 56.25 to 68] ;60%/70% female)	Between groups, home-based	10mg CBD tablets daily, increased to 20 mg daily after 2 weeks. If participants did not experience pain reduction after 4 weeks, then the dose increase to 30mg. Total treatment duration 12 weeks (n=68) Placebo tablets (n=61)	HADS (anxiety)	There were no significant effects on the HADS-anxiety factor for the CBD group	Participants took their medication at home and assessments were complete at baseline and week 12. Monitoring occurred after 2 and 4 weeks.	Low
Zuardi et al. (1993)	'Healthy' participants (22.8 years, 20-30; 80% males)	Within groups, laboratory based	1 occasion: 300 mg CBD, capsules (n=10) Ipsapirone 5 mg, capsules (n=10) Diazepam 10 mg, capsules (n=10) Placebo, capsules (n=10)	VAMS, STAI, HR, BP, BSS	CBD significantly decreased VAMS anxiety ratings after the SPS test compared to placebo, but not at other stages. There were no significant differences of the effects of CBD on the other measures.	Participants completed a one-off Simulated Public Speaking (SPS) test in a laboratory setting	Low
Zuardi et al. (2017)	'Healthy' participants (22.5 ±2.9, 22.6 ±2.9, 23.3 ±2.8, 22.1 ±2.4, 22 ±2.1; 18-35; 52% female)	Between groups, laboratory based	1 occasion: 100 mg CBD capsules (n=12) 300 mg CBD capsules (n=12) 900 mg CBD capsules (n=12) 1mg Clonazepam	VAMS, BP, HR, STAI-trait (baseline only)	300 mg CBD significantly decreased VAMS anxiety compared to the placebo group after the speech. However, not for 100 mg or 900 mg. CBD-300 differed significantly from the CBD-900 group during the speech, and from the CBD-100 group after the speech. There was a	Participants took part in a test of public speaking in a real situation (TPSRS), observed by others	Low

Table 1 continued

			(n=12) Placebo, capsule, corn oil (n=12)		significant difference between CBD-300 and Clonazepam during the speech phase in DBP and SDP, and between CBD-300 and CBD-100, where CBD-300mg was higher.		
Reference	**Participant characteristics* (mean age/range; % gender)**	**Study design**	**Active and comparator groups (sample size)**	**Outcome measures**	**Outcomes**	**Procedure**	**Risk of bias rating**
Randomised-controlled trials with restricted randomisation approaches							
Das et al. (2013)	No history of serious mental or physical health problems, or substance misuse problems (18-35; 50%/ 62.5% males)	Between subjects, laboratory based	1 occasion: 32 mg CBD vapourised (pre-extinction group; n=16) 32 mg CBD vapourised (post-extinction group; n=16) Placebo, vapourised (n=16)	STAI, MRS, BSS, SC	CBD administered both pre- and post-extinction phase (both after the conditioning phase), produced trend level reduction in reinstatement of autonomic measures. No acute effects of CBD were found on extinction phase. No group effects found on subjective mood (including anxiety) reported on the MRS. CBD administered post-extinction led to reduced fearful responding during recall and fear reinstatement 24 hours later.	Participants took part in a Pavlovian fear-paradigm.	Some concerns

Table 1 continued

Reference	Participant characteristics* (mean age/range; % gender)	Study design	Active and comparator groups (sample size)	Outcome measures	Outcomes	Procedure	Risk of bias rating
Fusar-Poli et al. (2009)	'Healthy' participants (26.7; 100% male)	Within subjects, laboratory based	1 occasion: 600mg CBD capsule (n=15) THC (10 mg) (n=15 between groups) Placebo (n=15 between groups)	State-Trait Anxiety Inventory, HR, BP, brain imaging, SC	No significant change in STAI anxiety scores, heart rate or blood pressure during the recall task. No significant change in brain image activation.	Subjective measures were taken at different time points after CBD administration. fMRI scanning whilst viewing fearful faces and completing learning and verbal tasks	Some concerns
Hundal et al. (2017)	Non-clinical, individuals with high traits of paranoia (26 ±9; 50% female)	Between groups, laboratory based	1 occasion: 600mg CBD capsule (n=16) Placebo capsule (n=16)	BAI, UMACL, HR, BP, salivary cortisol	Anxiety (BAI) was not statistically significant and was higher during the VR session, in comparison to placebo. There were no effects between groups on diastolic and systolic blood pressure, heart rate or salivary cortisol. There was also no effect on the paranoia measures or tense arousal (UMACL) measure.	Immersion in a 3D virtual-reality scenario designed to create persecutory ideation and anxiety	Low

Table 1 continued

Reference	Participant characteristics* (mean age/range; % gender)	Study design	Active and comparator groups (sample size)	Outcome measures	Outcomes	Procedure	Risk of bias rating
Hurd et al. (2019)	Abstinent people with heroin use disorder (All groups: *49.8 ±9.2; 83.3% males)	Between groups, laboratory based	400mg CBD oral solution, once daily on 3 consecutive days (n=14) 800mg CBD oral solution, once daily on 3 consecutive days (n=13) Placebo oral solution, once daily on 3 consecutive days (n=15)	VAS-A, salivary cortisol, HR, BP	No significant difference in the anxiety scores between groups, however the placebo group had higher average anxiety scores than both CBD groups.	Heroin-abstinent individuals participated in drug-cue and neutral-cue exercises to induce cravings and to monitor stress, anxiety and craving levels. Cognitive tasks were also complete during this study.	Low
Winton-Brown et al. (2011)	'Healthy' (26.7 ±5.7; 100% male)	Within groups, laboratory based	1 occasion: 600mg CBD capsule (n=14) 10 mg delta-9-THC, (n=14) placebo (flour) (n=14)	VAMS, STAI, BP, HR	No significant changes in ratings of anxiety (STAI) between CBD and the placebo condition, as well as with CBD and the THC condition	Functional MRI imaging was completed, whilst participants completed cognitive tasks. An intravenous line was also inserted	High

Table 1 continued

Reference	Participant characteristics* (mean age/range; % gender)	Study design	Active and comparator groups (sample size)	Outcome measures	Outcomes	Procedure	Risk of bias rating
Non-randomised clinical trial							
Leweke et al. (2020)	'Healthy' participants (29.4, 26 - 35; 100% male)	Within subjects, laboratory based	1 occasion: 200mg CBD capsule + placebo capsule (n=9) 200mg CBD capsule + 1mg Nabilone capsule (n=9) 1mg Nabilone capsule + placebo capsule (n=9)	STAI, SAS	There were no significant effects of CBD, or the other intervention groups, on either anxiety measure	Participants took part in a visual experiment to test binocular depth inversion. Outcome measures were complete prior to, 3 h, and 24 h after administration of the substance	Moderate
Zuardi et al. (1982)	'Healthy' participants (27, 20-38; 75% male)	Between groups, laboratory based	(n=6 for all groups; one occasion for all conditions) 1 mg/kg CBD liquid THC 0.5 mg/kg Mixture (0.5 mg/kg THC + 1 mg/kg CBD) 10mg Diazepam Placebo	STAI, Scale of Bodily Symptoms, pulse rate, interviews and spontaneous reports	No anxiolytic effect was seen in the STAI's, from pre- and post-drug in the CBD group. However, the pulse rate dropped significantly in the CBD group, from pre- and post-drug.	Participants took part in experimental sessions 1 week apart. No anxiety inducing procedure was involved.	Moderate

Table 1 continued

Reference	Participant characteristics* (mean age/range; % gender)	Study design	Active and comparator groups (sample size)	Outcome measures	Outcomes	Procedure	Risk of bias rating
Case series							
Kimless (2020)	People with diabetic neuropathic pain (DNP) (Minimum age 18+, mean not stated; gender ratio not stated)	One group, open label	60mg CBD tablets, for 3 weeks (n=31) No comparator group	SAS	A reduction in average anxiety scores: pre 38.1%, post 12.7%	No details provided	Some concerns
Pacheco et al. (2021)	Healthcare workers who presented to a workplace stress support service (32.5, ±6.9; 53.8% female)	Prospective case series	330 mg CBD oral daily dose for 4 weeks (n=13)	GAD-7	There were significant differences in anxiety levels compared to baseline, measured at all time-points; week 1, 2 and 3, as well as at follow-up at week 6 and 7. There were also significant and sustained improvements in depression, insomnia and emotional exhaustion.	CBD was taken by participants at home, there was no experimental procedure	Some concerns
Pokorski et al. (2017) Cases: 1, 3, 6 and 8	Participants with a diagnosis of cannabis dependence (29.75, 25-37; 100% male - of the included 4 cases, 87.5% male of all the cases)	Open label trial	1: 300 mg on day 1 and 6, 600 mg days 2 - 5 3: 600 mg CBD 6: 600 mg days 1 and 6, 1200 mg days 2-5 8: 1200 mg All received capsules	CWS - anxiety and irritability ratings	1: -10 CWS anxiety score, -10 irritability score 3 -10 anxiety score and -5 irritability score 6: No change in anxiety score, -5 irritability score 8: -6 anxiety, +1 irritability score	Participants were admitted for a 7-day stay at a detoxification centre	Low

Table 1 continued

*Participant characteristics are reported for the CBD group, or for all group data if this was all that was reported.
**When 'healthy' is used to describe the participant group, this generally meant that people with disclosed mental health difficulties or in receipt of a mental health diagnosis were excluded. Often people receiving medication, or who had physical health difficulties or used substances regularly were excluded. For cannabis use, often a lifetime cannabis use was capped, for example, < 15 times.
*** Portuguese version

BAI = Beck's Anxiety Inventory
BP = blood pressure
BSS = The Bodily Symptoms Scale
CWS = Cannabis Withdrawal Scale
FMRI = functional magnetic resonance imaging
FNE = Fear of Negative Evaluation Questionnaire
GAD-7 = Generalised Anxiety Disorder-7 Scale
HADS = Hospital Anxiety and Depression Scale
HR = heart rate
LSAS = Liebowitz Social Anxiety Scale
MRS = Mood Rating Scale (includes 3 subscales, anxiety scale described in this report)
PCL-5 = Posttraumatic Stress Disorder Checklist
PD = Parkinson's disease
POMS = The Profile of Mood States
SAD = Social Anxiety Disorder
SAS = Zung Self-Rating Anxiety Scale
SC = skin conductance
SPECT = Single Photon Emission Computed Tomography
SPSS = the Self-Statements during Public Speaking Scale
SPST = Simulation Public Speaking Test
SSDPS = Self-Statements during Public Speaking Scale
SSPS = The State Social Paranoia Scale
SSPS-N = Negative Self-Statement scale
STAI = State Trait Anxiety Inventory
TPSRS = test of public speaking in a real situation
TSST = The Trier Social Stress Test
UMACL = The University of Wales Mood Adjective Checklist
VAMS = visual analogue mood scale
VAS-A = visual analogue scale for anxiety

Table 2.

Risk of bias individual ratings on RCT's using the Rob 2 tool

Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Outcome measurement	Selection of reported results	Overall bias rating
Appiah-Kusi et al. (2020)						
Bergamaschi et al. (2011)						
Bolsoni et al. (2022)						
Crippa et al. (2004)						
Crippa et al. (2011)						
de Faria et al. (2020)						
Linares et al. (2019)						
Masataka et al. (2019)						
Morgan et al. (2013)						
Vela et al. (2021)						
Zuardi et al. (1993)						
Zuardi et al. (2017)						
Das et al. (2013)						
Fusar-Poli et al. (2009)						
Hundal et al. (2017)						
Hurd et al. (2019)						
Winton-Brown et al. (2011)						

*Colour coding of the risk of bias ratings are as follows: Green = low risk, Amber = some concerns, Red = high risk

Table 3.

Risk of bias individual ratings on non-randomised controlled trials using the ROBINS-I tool

Study	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Outcome measurement	Selection of reported results	Overall bias rating
Leweke et al. (2020)								
Zuardi et al. (1982)								

*Colour coding of the risk of bias ratings are as follows: Green = low risk, Amber = moderate risk of bias.

Higher risk of rating options were serious risk of bias and critical risk of bias.

Table 4.

Risk of bias individual ratings on case series/reports using the (IHE) Quality Appraisal Tool for Case Series

Study	Study objective	Study design	Study population	Intervention and co-intervention	Outcome measure	Statistical analysis	Results and conclusions	Competing interests and sources of support	Overall bias rating
Kimless (2020)									
Pacheco et al. (2021)									
Pokorski et al. (2017)									

*The assessment tool does not have final rating outcomes. Instead, an overall bias rating is interpreted after rating each component, with each question having a response for'yes' which indicates lower risk of bias, 'partial' or 'unclear' which indicates some concerns or 'no' which indicates higher risk.

Risk of bias assessment

Scores ranged from low risk to high risk of bias (see Table 2, 3 and 4 for ratings). In general, many studies had limitations within the domain of 'missing data', often not reporting the extent of incomplete data or reasons for participants' drop-out. The RoB 2 can determine this as a weakness for RCT's and therefore the overall risk of bias rating could be impacted. A systematic review of CBD for a range of disorders found that among the clinical trial records retrieved from ClinicalTrials.gov, only 60% of completed trials had results available, suggesting the occurrence of publication bias (Millar et al., 2019).

Detailed description of studies

The section below is organised according to three study design characteristics: the nature of the control condition (placebo controlled versus other designs), number of doses used (single v multiple) and nature of participants (clinical v non-clinical).

PLACEBO-CONTROLLED TRIALS

Single-dose CBD.

Thirteen studies investigated the effects of single-dose CBD, with three studies finding that the effects of CBD reached statistical significance in attenuation of anxiety, at doses of 300 mg (Linares et al., 2019; Zuardi et al, (2017), 400 mg (Crippa et al., 2011) and 600 mg (Bergamaschi et al., 2011), in comparison to a placebo or healthy control group. Five studies did not find anxiolytic effects (Bolsoni et al., 2022; Fusar-Poli et al., 2009; Hundal et al., 2017; Leweke et al., 2020; Winton-Brown et al., 2011). Four studies found partial effects of: no significant main effect, only one experimental phase experienced anxiolytic effects, or only one CBD intervention group had significant effects (de Faria et al., 2020; Zuardi et al.,

1982, 1993, 2007). Das et al. (2013) found promising, but non-statistically different effects on autonomic arousal between 32 mg CBD vapourised and a placebo group.

Non-clinical participant groups.

One of the earlier Brazilian studies using a Simulation Public Speaking Test, found CBD reduced anxiety once the test started, in comparison to placebo, but this effect was greater (reached statistically significant difference) after the test (Zuardi et al., 1993). Diazepam 10 mg and Ipsapirone 5 mg revealed more anxiolytic effects, with diazepam having quicker effects. No CBD effects were noted on STAI, blood pressure, heart rate, or the BSS.

A later study of a test of 'public speaking in a real situation' (Zuardi et al., 2017) found support for an inverted U-shaped dose-effect curve, whereby 300mg CBD eased anxiety in participants post-speech (stress) phase, but this did not occur for the lower (100 mg) or higher (600 mg) doses. CBD, however, was not found to reduce blood pressure, and Clonazepam 1mg was more sedative and reduced anxiety in the post-stress phase.

Linares et al. (2019) also found an inverted U-shaped dose-response curve, whereby 300mg produced a significant different reduction in Visual Analogue Mood Scale (VAMS) anxiety scores, compared to placebo. Although the 150mg and 600mg did not produce statistically significant differences, all CBD groups had reduced anxiety scores at all phases of the public speaking test. There were no significant group differences in blood pressure. The heart rate analyses were not reported, along with no information on missing data, leading to some risk of bias concerns of data reporting.

Fusar-Poli et al. (2009) revealed no significant changes in subjective or physical anxiety measures following 600 mg CBD, but skin conductance fluctuations, a biomarker of arousal (Williams et al., 2001), significantly decreased during the viewing of intensely fearful, but not mildly fearful or neutral faces whilst participants completed cognitive tasks.

Other linked papers provide additional results (Bhattacharyya et al., 2009; 2010; Borgwardt et al., 2008). Three participants' data were excluded from data analysis as they could not complete the experiment due to psychotic reactions. Notably, one of the primary aims of this research was investigating psychotic effects from CBD and THC, but potential issues of tolerability were not discussed in detail.

Hundal et al. (2018) used non-clinical participants scoring high on trait paranoia. The CBD group had higher average BAI scores than the placebo group during a virtual reality session used to assay persecutory ideation and anxiety, but this may be partly explained by the anxiety provoking situation. Overall, CBD did not provide anxiety reducing effects and there were no differences in the paranoia measure, tense arousal, or biomarkers. The RoB 2 raised concerns of lack of information of missing data.

Das et al. (2013) investigated the effects of short-term fear extinction and consolidation, using a Pavlovian fear-conditioning paradigm. No significant group effects were found in the anxiety-related sub-scales of the Mood Rating Scale (Bond & Lader, 1974), but in all groups there was a reduction in anxiety after inhaling the placebo and vapourised CBD 32 mg, and the CBD group had a reduced fearful responding during recall and fear reinstatement the following day. A limitation is that the STAI and BSS measures were collected, but not reported in this paper. This contributed towards 'some concerns' on the RoB 2, alongside large baseline differences in cannabis and tobacco use amongst participant groups.

Clinical participant groups.

Appiah-Kusi et al. (2020) recruited participants without and with 'clinical high risk of psychosis' (CHR), assigning them to a CBD or placebo group. The participants took part in the Trier Social Stress Test (TSST; Kirschbaum et al., 1993); a public speaking task. In comparison to the non-CHR control group, 600mg CBD daily for 7 days was found to reduce

the anxiety scores and cortisol levels after completing the TSST. However, the CBD group had more of an intermediary effect, with the difference mainly driven by the significant difference between the placebo-CHR group and the control group. The RoB 2 assessment concluded 'high risk of bias', influenced by a lack of information on the randomisation process and multiple analysis completed - the study trial outlined analysis would be complete on day 28, however this report only detailed analysis after day 7.

Bergamaschi et al. (2011) found single-dose 600mg CBD significantly reduced alertness in the anticipatory speech stage and anxiety and discomfort during the speech performance phase of a public speaking test. Negative self-evaluation (using the SSPS-N, negative subscale), was reduced during anticipatory phases after drug administration, and significantly different to the SAD-placebo group. There were no significant differences between groups on physiological markers or the Bodily Symptoms Scale scores, however the scores did increase for the SAD-placebo group. The RoB 2 rating was deemed as low, with thorough details of the randomisation process and descriptions of statistical analysis. A strength of this study is the variety of outcome measurements for anxiety, including subjective and physical ratings (biomarkers).

Bolsoni et al. (2022) recently investigated the effects of 300mg dose on anxiety symptoms during traumatic memory recall for individuals with PTSD. The authors conclude CBD had limited impact on anxiety, alertness, and discomfort induced by the recall. However, cognitive impairment was significantly lower after recall in the CBD group compared to the placebo group, and these effects were sustained at a 1-week follow-up. The researchers used a minimisation randomisation approach, aiming to reduce imbalances in groups.

Crippa et al. (2011) also looked at participants with a Social Anxiety Disorder (SAD) diagnosis. Compared to placebo, VAMS anxiety scores significantly decreased 1 hour after

administration and during the neuro-imaging procedure. CBD 400 mg was also found to have significant effects on functional activity changes in areas of the brain associated with anxiety (limbic and paralimbic cortical areas). Limited information was provided about randomisation, blinding and statistical plans.

de Faria et al. (2020) investigated the effects of single-dose 300mg CBD on individuals performing public speaking tests who were diagnosed with idiopathic Parkinson's Disease. They found statistically significant differences in the VAMS anxiety factor, with lower mean scores in the CBD condition and lowest scores in the pre-stress phase. CBD did not reduce negative self-evaluations during public speaking (using the SSPS-N, negative subscale), in contrast to Bergamaschi et al. (2011) who found this reduced significantly. No significant group differences were found with blood pressure or heart rate. The amplitude of tremors also reduced in the CBD condition. It is hypothesised anxiety may increase tremors. Participants were screened to not be taking benzodiazepines or anti-depressants, however one participant was noted to be taking propranolol (beta-blocker). The type of release and dose were not recorded, but as it was only one person, the paper was included within this systematic review. Although deemed as low risk, the RoB 2 raised concerns of no details of missing data.

Multiple doses of CBD.

Non-clinical participant groups.

Crippa et al. (2004) found CBD 400 mg was associated with significantly decreased anxiety at 60 and 75 minutes after administration, compared to placebo, suggesting CBD aided in reducing anticipatory and responsive anxiety to the neuro-imaging procedure. The quality assessment was rated as 'some concerns', influenced by lack of description of the randomisation process, of any missing data and reduced clarity on the statistical analysis.

Clinical participant groups.

Hurd et al. (2019) found a significant decrease in anxiety scores for both 400 and 800 mg CBD doses, relative to placebo, in heroin-abstinent individuals' responses to drug-cues, after single-dose administration and upon testing seven days following a three daily dose. Of note, several participants were found to have used heroin at follow-up and it is not clear if these results were excluded in analysis. An increase in heart rate and temperature observed in the placebo group during drug-cue was not present in the CBD groups, but there were no significant group effects of heart rate, temperature or blood pressure. There was a significant increase in cortisol levels (a measure of the stress response) in the drug-cue placebo group compared to the 400 mg CBD group, suggesting CBD 400mg (and at trend level for 800mg), relative to placebo, reduced cortisol levels in response to drug-cues. Overall, the researchers found 800mg tended to have strongest effects but there was not a significant difference between the two CBD doses. This study had the best description of the randomisation process and linked their ClinicalTrials.gov registration.

Masataka (2019) found both state measures of anxiety were statistically significantly reduced after 4 weeks of daily 300 mg CBD, compared to placebo, however there were no significant differences in the Fear of Negative Evaluation Questionnaire, post-treatment. The authors described the procedure in detail and allowed for a thorough RoB 2 assessment, however they acknowledged that a more detailed baseline sociodemographic evaluation could have ensured further pre-treatment similarity of the groups and the CBD had a characteristic smell and taste.

Morgan et al. (2013) investigated the effects of regular ad-hoc CBD inhalation for regular tobacco smokers. The dose is therefore variable for all participants. Initial studies suggested a bioavailability of CBD following administration through inhaler of > 65%. The 16-item Mood Rating Scale (anxiety factor) did not reveal a significant main effect, but the

CBD group had overall reduced anxiety scores, compared to placebo. The anxiety factor includes two rating scales that do not explicitly state anxiety.

Vela et al. (2021) provided the longest duration of daily CBD treatment for 12 weeks, however their dose ranging from 10 - 30 mg was significantly lower than multiple-dose studies detailed above. This may reflect the outcome that Hospital Anxiety and Depression Scale-anxiety scores (Zigmond, 1983) did not decrease in their sample of individuals with arthritis. Participants also started with low baseline scores. Like Hurd et al. (2019), the report was very detailed, allowing for a low risk of bias assessment. This study allowed concurrent analgesic treatments.

The majority of studies had restrictions on medication and substance use prior to the study. Hurd et al. (2019) included participants with heroin use disorder and allowed use of certain drugs (nicotine, methadone, buprenorphine, or an opioid antagonist) but otherwise retained strict substance use and psychiatric inclusion requirements.

NON-RANDOMISED CONTROLLED TRIALS

The earliest included study is Zuardi et al. (1982) using a small sample size of eight participants. In this non-anxiety-induction study, the researchers found no effects on state trait anxiety from the CBD dose, compared to THC, THC+CBD, diazepam and placebo, however there was a significant effect on reduction of pulse rate, a known indicator of stress and/or anxiety. The study received moderate risk of bias, due to lack of information on missing data.

Leweke et al. (2000) found no significant effects of either CBD and Nabilone, alone and in combination, on the two anxiety scales. However, participants noted some sedative effects from cannabidiol. The quality assessment indicated risk of bias due to no information on any missing data or adjustments to statistical analysis.

CASE STUDIES

Kimless et al's (2020) open-label trial found daily 60mg CBD for 3 weeks reduced anxiety for people with diabetic neuropathic pain. Although the results weren't deemed as statistically significant, the reduction in anxiety was apparent from the rating scales. There were also significant improvements in pain relief consumption and sleep quality. Pacheco et al. (2021) also found anxiolytic effects, in healthcare workers receiving a much higher dose of 330mg CBD daily for 4 weeks, and these improvements were sustained at 6 and 8-week follow up. As both these reports were only in brief, abstract form, the IHE quality assessment ratings were 'some concerns'.

Pokorski et al. (2017) reported the effects on cannabis withdrawal of an inpatient 7-day treatment, with a 28 day follow up. Four cases out of eight met the systematic review criteria and were included within this study. Participants had consumed cannabis within 24 hours of the beginning of the study, however as the study lasted seven days, the effects of anxiety could be reviewed at the end of treatment measures with minimal possible confounding factors. There is an obvious confounding factor, however, that anxiety levels would be directly impacted by cannabis withdrawal. The results indicate the higher dose of 1200 mg was more effective at alleviating withdrawal symptoms, including anxiety and irritability. There were also promising effects of 600 mg on anxiety, with reductions in the anxiety and irritability factors of the Cannabis Withdrawal Scale (Allsop et al., 2012). This study does not discuss if other treatments or confounding effects were considered, but whilst considering the assessment of anxiety, the quality assessment determined a low risk of bias.

Discussion

This systematic review aimed to analyse the effects of cannabidiol on anxiety in humans. Both clinical and non-clinical studies were reviewed, which included participants

with social anxiety and paranoid traits, and the experimental procedures included the induction of fear, stress and social stress. Several studies demonstrated that CBD reduced state-anxiety in non-clinical participant groups and some effects in clinical populations, however these were limited. Multiple-dose CBD treatment, ranging from two doses separated by one week, to daily treatment of 12 weeks, appeared to produce more consistent anxiolytic effects. Overall, doses of 300 mg and above were found to reduce anxiety from single-dose and multiple-dose /longer-term treatment studies. One study found beneficial effects of a lower dose of 60mg CBD tablets treatment for 3 weeks (Kimless et al., 2020). In contrast, there were also several studies indicating that a range of doses from 10 to 1200 mg were not effective at alleviating anxiety, in the short and long-term. The studies in this review demonstrated minimal side effects, similar to a recent review article that found CBD doses ranging from 300 to 400 mg/day have anxiolytic effects with good safety and tolerability (Crippa et al., 2018).

Many of the studies investigated anxiety in social situations. Bergamaschi et al. (2011) found significantly decreased alertness rating for the CBD group in anticipation of public speaking. Explanatory models of the stress response state that alertness is increased (for example, Qi & Gao, 2020). In line with the cognitive-behavioural model of social anxiety, which suggest individuals can be heavily self-focussed (including body symptom awareness) and focussed on others' reactions (Clark & Wells, 1995), Bergamaschi et al. (2011) found single-dose 600mg CBD significantly reduced anxiety and discomfort during public speaking and negative self-evaluation was reduced during anticipatory phases. There were no significant between-group differences in Bodily Symptoms Scale scores and physiological measures.

Skin conductance levels were reduced following 600 mg CBD administration, (Fusar-Poli et al., 2009). Skin conductance levels are commonly used methods to measure

sympathetic autonomic activity associated with both emotional valence and attention (Laine et al., 2009) and higher skin conductance levels typically indicate increased anxiety and are associated with increased amygdala activity (Williams et al., 2001), providing further support for anxiolytic effects of CBD, at 600 mg.

de Faria et al (2020) provided additional evidence in the area of social anxiety and public speaking, by investigating the effects on individuals with Parkinson's Disease. Although not considered a 'clinical' population from a psychiatric diagnostic perspective, individuals with PD exhibit symptoms of social anxiety (Moriyama et al., 2016) often relating to social evaluative beliefs relating to their tremors.

Other studies provided additional information on neural mechanisms. Brain imaging showed CBD attenuated the amygdala response and other areas in the left medial temporal region, whilst viewing fearful faces, compared to placebo (Fusar-Poli et al., 2009). The amygdala is strongly related to conditioned fear and stress responses (Duvarci & Pare, 2014).

Methodological limitations of the included studies

Anxiety induction.

Six studies in this review used a Simulated Public Speaking Test (SPST), or an alternative (see Table 1), to increase anxiety. Zuardi et al. (2017) suggest the SPST might not have good construct or face validity. It has generally not been found to increase the physiological markers of anxiety, such as heart rate or blood pressure. For example, public speaking in a real-life situation is more effective at increasing physiological markers of anxiety (Turner et al., 1990; Zuardi et al., 2013). A meta-analysis of 11 studies (Zuardi et al., 2013) found the subjective ratings of anxiety overall increased during these public speaking situations, reflecting the anxiogenic nature of the tests, and this current review demonstrates that the public speaking tests increase self-reported anxiety. One argument is that studies

using public speaking tests in an experimental setting may not be generaliseable to more chronic and complex experiences of anxiety.

Eleven studies did not involve an anxiety inducing situation as such, but Crippa et al. (2004) discuss how procedures such as SPECT can be anxiety inducing, particularly before the procedure.

Measurement of anxiety.

Anxiety was broadly defined, referring to different emotional states (e.g. fear, stress), anxiety 'disorders' and biological/physiological expressions of anxiety (Leen-Feldner et al., 2021). There are however differences between these. Fear is often considered a response to the presence, or imminent presence, of aversive stimulus. Anxiety is considered a more prolonged state produced by a sustained expectation or anticipation that an aversive event is likely to occur (Daniel-Watanabe & Fletcher, 2021). There are also inconsistencies within the physiological responses to anxiety and fear, suggesting that their physiology and conceptual definitions cannot be easily differentiated (Daniel-Watanabe & Fletcher, 2021). The included studies used a range of measures of anxiety. State-trait anxiety measures were most common which measure state anxiety and trait anxiety, however more research is needed using longer-term measures of anxiety, such as the Liebowitz Social Anxiety Scale (Liebowitz, 1987) or the Fear of Negative Evaluation Questionnaire (FNE; Watson and Friend, 1969) which were used in Masataka et al. (2019)'s study. Research has found trait anxiety correlates positively to state anxiety in situations of interpersonal threat (such as social situations), but not of physical threat (Leal et al., 2017). This review often-found discrepancies whereby subjective anxiety and physiological markers of anxiety did not concurrently decrease or increase. It may be that the presentations of anxiety differ in different situations. These methodological and conceptual differences can lead to limitations in implications from research.

Participant characteristics.

There are issues with psychological research being conducted in western, educated, industrialized, rich and democratic (WEIRD) societies (Henrich et al., 2010), with outcomes and implications being largely biased towards these populations and significant under-representation of the vast diversity of populations across the world. A large amount of the included studies were conducted in Brazil, however, most of the included studies did not disclose participant characteristics, such as ethnicity, religion or other cultural considerations. Therefore, comments on this are restricted.

Variation in study design.

Nine studies used non-clinical populations. As noted by Arndt and de Wit (2017), using 'non-clinical' participants - those who do not identify as experiencing regular anxiety mood states – or a lack of anxiety inducing stimuli or context, may not be sufficient to detect any anxiolytic effects of CBD.

More research is needed to evaluate the long-term effects of CBD. As Iffland and Grotenhermen (2017) highlight, many human studies which are stated to be investigating 'chronic' CBD use, only last a few weeks. The longest period of CBD consumption evaluated in this review was 12 weeks, but this was unusual. It is also important that future randomised controlled studies are appropriately powered (Iffland & Grotenhermen, 2017). As can be seen from the sample sizes summarised in Table 1, it is likely that the studies were only powered to detect large or very large differences between groups. In this review, the study with the most participants was Vela et al. (2021) with 129 participants which was powered (1-beta=0.8) to detect standardized mean difference between groups of d=0.5.

Risk of bias.

Some of the included studies used a 'minimisation randomisation' approach, which involves matching groups on key indicators to reduce the chances of group imbalances on prognostic factors (Saghaei, 2011). The RoB 2 guidance does not clearly state the acceptability of this approach. This current review regarded this approach as generally acceptable, provided other RoB 2 criteria were well rated. A systematic review of meta-epidemiological studies found that intervention effect estimates may be exaggerated in trials with inadequate/unclear sequence generation and allocation concealment and this tended to be higher in studies using subjective, rather than objective, measurements (Page et al., 2016). The studies within this systematic review tended to use subjective, state trait measurements of anxiety, so may have been affected by this exaggerated estimated effect.

Most studies in this review were regarded as having 'some concerns', mostly due to minimal or no information on statistical analysis plans, missing data and randomisation sequences. The COCHRANE handbook (Lefebvre et al., 2022; section 4.6.3) states that studies should not be excluded solely based on missing data, as it can increase selective outcome reporting bias.

Review Limitations

Methodological limitations.

The database searches were conducted by one author only due to resource availability and course constraints, which is not true to the systematic review process and may influence researcher bias during the study selection process. In this systematic review, studies were excluded when CBD contained more than 0.2% THC or other cannabinoid mixtures. It is possible that several studies were excluded that may indicate potential therapeutic benefits of other cannabinoid compounds which retain high CBD content.

Studies were also excluded if other pharmacologically based anxiolytic treatments were used within the study time frame. For example, a study found important data that suggests CBD used as an adjunct to an anti-depressant in a younger sample, had anxiolytic effects for 5 out of the 6 participants. The study was not included as the results did not distinguish between under 18 and over 18-year-olds (Anderson et al., 2021). By excluding studies like this, it becomes more difficult to examine the effects of CBD on health conditions and populations where people are using other medications.

CBD is classed as a food product, not medication. This review excluded studies when other medications were being used, however participants may have been using other 'food products', complimentary therapies, and other treatments such as mindfulness and meditation, that may be extraneous variables but these were rarely stated in the studies.

Risk of bias.

For the purposes of this publication, time and resource constraints meant that study authors were not contacted for missing information or to clarify information, such as statistical analysis plans. To ensure the risk of bias rating was not unfairly negatively rated from this lack of information, ratings tended to be rated as 'probably' instead of 'no information'. In addition, the use of different risk of bias assessment tools used within this review, make the analysis and outcomes less comparable and valid.

Bias due to missing results may have occurred in this report. This refers to how some published studies may not disclose certain outcomes or statistical analysis if they are, for example, undesirable or not statistically significant (Page, Higgins & Sterne, 2022; section 13.1) and therefore not included in subsequent reviews. This review aimed to minimise publishing bias, by including non-randomised-control trials. Future reviews could further minimise bias by including additional types of sources. Case series tend to be viewed as a weak research design as they lack a control or comparator group (Moga et al., 2012) and

hence receive higher risk of bias ratings. Nevertheless, they can offer important contributions to understanding effects of treatments or interventions.

Review strengths

A systematic review has previously investigated the effects of cannabidiol on anxiety (Blessing et al., 2015), however this included pre-clinical (animal) studies, in addition to human studies. This current systematic review includes human only studies, focussing on adults aged 18 over. This study also only included studies where CBD was the only anxiolytic medication/treatment used at the time of the outcome measurement. Blessing et al's (2015) review retrieved studies up until January 2015, and since this time many relevant papers have been published with an international surge in popularity of CBD as a 'treatment' and research into its effects. Blessing et al's (2015) systematic review also did not clearly describe or critically analyse the methodological designs of the included studies, nor state the age of the participants, which this current review adds to.

Research recommendations

As described throughout this review, there is increasing evidence for higher dose CBD products but minimal research into non-medicinal CBD products which are generally accessible for the public (Freeman et al., 2019) and contain much lower doses of CBD than those used in clinical trials. As suggested by White (2019), CBD use has been recommended for many health issues for which it has not been studied or with limited evidence of therapeutic effects. This is particularly needed in countries such as the UK, where consumption is high, there is a lack of regulations and there are limitations to the transferability of research in other countries. This difficulty in medical science for CBD products remains similar to issues that the prescription of CBMPs faces.

Other cannabinoids, such as cannabinol (CBN), cannabigerol (CBG) and cannabichromene (CBC), are also receiving more interest and have potential beneficial medical effects (Salami et al., 2020) and more research into these would be of value.

Future research.

Whilst completing the screening process and reviewing ClinicalTrials.gov registrations, many prospective study protocols of interest that would likely meet the criteria for this review were identified and some examples are compiled in Appendix 4.

Clinical implications

CBD is being consumed at very high levels, globally and for multiple health reasons. Studies reveal that common reasons for CBD use are anxiety, problems sleeping, stress, and general health and wellbeing, pain, depression, headaches/migraines and PTSD (Goodman et al., 2020; Moltke & Hindocha, 2021). However, as discussed, the research regarding the effects and efficacy are mixed and inconclusive. CBD is mostly sold as non-prescription and seen as 'low dose', in comparison to clinical trials which use much higher doses of CBD (McGregor et al., 2020). Research suggests that CBD can be helpful for anxiety, however this can only be suggested for social-based anxiety and specific fear inducement. Longer-term studies reveal more promising effects, which are not well captured within this review due to the exclusion criteria. It is not clear how CBD may be helpful for more chronic and generalised forms of anxiety, nor on other anxiety conditions, such as health anxiety, obsessive compulsive disorder or post-traumatic stress disorder.

Trials and case reports have been completed amongst children and adolescents which also indicate the therapeutic potential of CBD. (see Berger & Amminger 2020, for a summary of two papers). A systematic review of CBD effects on mental health difficulties in younger people would be helpful for clarity, particularly given the varying doses of CBD and often

concurrent medications or therapies used. For example, Anderson et al's (2021) research on 15–24-year-olds found that CBD could impact drug-drug interactions (DDIs).

There are also calls for stricter regulations around CBD products being sold, particularly considering content analysis demonstrate CBD levels can differ to what the label states (Liebling et al., 2022; Pavlovic et al., 2018).

Conclusion

This systematic review described 22 clinical studies investigating the effects of CBD on anxiety with mixed and often conflicting results. Some studies demonstrate potential beneficial effects on anxiety, in social-anxiety inducing situations and in response to specific stress or fear inducement, following single and multiple-doses of CBD, and in both clinical and non-clinical samples. Studies involving longer-term CBD treatment demonstrated more promising effects on anxiety symptom improvement, yet there were less of these. However, there were also many studies that suggest CBD is not effective at aiding anxiety, with both single and multiple doses. Many of the studies demonstrated promising anxiolytic effects at doses of 300 mg above, however some studies using lower doses also revealed potential anxiolytic effects. Given such high levels of consumption, it is important to understand how and why CBD is used and what the effects are, particularly when individuals are using additional treatments, often for multiple health reasons. Research is needed to understand the effects of this in the general population, in different countries, with different cultures and healthcare settings, with diverse populations.

References

Allsop, D. J., Copeland, J., Norberg, M. M., Fu, S., Molnar, A., Lewis, J., & Budney, A. J. (2012). *Quantifying the clinical significance of cannabis withdrawal*. https://doi.org/10.1371/journal.pone.0044864

Anderson, L. L., Doohan, P. T., Oldfield, L., Kevin, R. C., Arnold, J. C., Berger, M., Amminger, G. P., & McGregor, I. S. (2021). Citalopram and Cannabidiol: In Vitro and In Vivo Evidence of Pharmacokinetic Interactions Relevant to the Treatment of Anxiety Disorders in Young People. *Journal of Clinical Psychopharmacology*, *41*(5), 525-533. https://doi.org/ /10.1097/JCP.0000000000001427

Appiah-Kusi, E., Petros, N., Wilson, R., Colizzi, M., Bossong, M., Valmaggia, L., Mondelli, V., McGuire, P., & Bhattacharyya, S. (2020). Effects of short-term cannabidiol treatment on response to social stress in subjects at clinical high risk of developing psychosis. *Psychopharmacology*, *237*(4), 1121-1130. https://doi.org/http://dx.doi.org/10.1007/s00213-019-05442-6

Arndt, D. L., & de Wit, H. (2017). Cannabidiol Does Not Dampen Responses to Emotional Stimuli in Healthy Adults. *Cannabis and Cannabinoid Research*, *2*(1), 105-113. https://doi.org/https://dx.doi.org/10.1089/can.2017.0014

Barchel, D., Stolar, O., De-Haan, T., Ziv-Baran, T., Saban, N., Fuchs, D. O., Koren, G., & Berkovitch, M. (2019). Oral cannabidiol use in children with autism spectrum disorder to treat related symptoms and Co-morbidities. *Frontiers in Pharmacology*, *9(JAN) (no pagination)*, Article 1521. https://doi.org/http://dx.doi.org/10.3389/fphar.2018.01521

Bergamaschi, M. M., Queiroz, R. H. C., Chagas, M. H. N., De Oliveira, D. C. G., De Martinis, B. S., Kapczinski, F., Quevedo, J., Roesler, R., Schroder, N., Nardi, A. E., Martin-Santos, R., Hallak, J. E. C., Zuardi, A. W., & Crippa, J. A. S. (2011). Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-nave social phobia patients. *Neuropsychopharmacology*, *36(6)*, 1219-1226. https://doi.org/http://dx.doi.org/10.1038/npp.2011.6

Berger, M., Li, E., & Amminger, G. P. (2020). Treatment of social anxiety disorder and attenuated psychotic symptoms with cannabidiol. *BMJ Case Reports*, *13*(10). https://doi.org/10.1136/bcr-2020-235307

Bhattacharyya, S., Fusar-Poli, P., Borgwardt, S., Martin-Santos, R., Nosarti, C., O'Carroll, C., Allen, P., Seal, M. L., Fletcher, P. C., Crippa, J. A., Giampietro, V., Mechelli, A., Atakan, Z., & McGuire, P. (2009). Modulation of mediotemporal and ventrostriatal function in humans by A9-tetrahydrocannabinol a neural basis for the effects of cannabis sativa on learning and psychosis. *Archives of General Psychiatry, 66(4)*, 442-451. https://doi.org/http://dx.doi.org/10.1001/archgenpsychiatry.2009.17

Bhattacharyya, S., Morrison, P. D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., Nosarti, C., O'Carroll, C. M., Seal, M., Allen, P., Mehta, M. A., Stone, J. M., Tunstall, N., Giampietro, V., Kapur, S., Murray, R. M., Zuardi, A. W., Crippa, J. A., Atakan, Z., & McGuire, P. K. (2010). Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology, 35(3)*, 764-774. https://doi.org/10.1038/npp.2009.184

Black, N., Stockings, E., Campbell, G., Tran, L. T., Zagic, D., Hall, W. D., Farrell, M., & Degenhardt, L. (2019). Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. *The Lancet. Psychiatry, 6*(12), 995-1010. https://doi.org/10.1016/S2215-0366(19)30401-8

Blessing, E. M., Steenkamp, M. M., Manzanares, J., & Marmar, C. R. (2015). Cannabidiol as a Potential Treatment for Anxiety Disorders [Review]. *Neurotherapeutics, 12*(4), 825-836. https://doi.org/10.1007/s13311-015-0387-1

Bolsoni, L. M., Crippa, J. A. S., Hallak, J. E. C., Guimaraes, F. S., & Zuardi, A. W. (2022). Effects of cannabidiol on symptoms induced by the recall of traumatic events in patients with

posttraumatic stress disorder. *Psychopharmacology*. https://doi.org/10.1007/s00213-021-06043-y

Bonaccorso, S., Ricciardi, A., Zangani, C., Chiappini, S., & Schifano, F. (2019). Cannabidiol (CBD) use in psychiatric disorders: A systematic review. *Neurotoxicology*, *74*, 282-298. https://doi.org/10.1016/j.neuro.2019.08.002

Bond, A., & Lader, M. (1974). The use of analogue scales in rating subjective feelings. *British Journal of Medical Psychology, 47*(3), 211–218. https://doi.org/10.1111/j.2044-8341.1974.tb02285.x

Bonn-Miller, M. O., Loflin, M. J. E., Thomas, B. F., Marcu, J. P., Hyke, T., & Vandrey, R. (2017). Labeling Accuracy of Cannabidiol Extracts Sold Online. *JAMA*, *318*(17), 1708. https://doi.org/10.1001/jama.2017.11909

Borgwardt, S. J., Allen, P., Bhattacharyya, S., Fusar-Poli, P., Crippa, J. A., Seal, M. L., Fraccaro, V., Atakan, Z., Martin-Santos, R., O'Carroll, C., & et al. (2008). Neural basis of Delta-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition. *Biological Psychiatry*, *64*(11), 966-973. https://doi.org/10.1016/j.biopsych.2008.05.011

Campos, A. C., & Guimaraes, F. S. (2008). Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. *Psychopharmacology, 199*(2), 223-230. https://doi.org/10.1007/s00213-008-1168-x

Casarett, D. J., Beliveau, J. N., & Arbus, M. S. (2019). Benefit of Tetrahydrocannabinol versus Cannabidiol for Common Palliative Care Symptoms. *Journal of Palliative Medicine*, *22*(10), 1180-1184. https://doi.org/10.1089/jpm.2018.0658

Clark, D. M., & Wells, A. (1995). A cognitive model of social phobia. In R. G. Heimberg, M. R. Liebowitz, D. A. Hope, & F. R. Schneier (Eds.), *Social phobia: Diagnosis, assessment, and treatment* (pp. 69–93). The Guilford Press.

Crippa, J. A., Guimaraes, F. S., Campos, A. C., & Zuardi, A. W. (2018). Translational Investigation of the Therapeutic Potential of Cannabidiol (CBD): Toward a New Age. *Frontiers in Immunology*, *9*, 2009. https://doi.org/10.3389/fimmu.2018.02009

Crippa, J. A. D., Zuardi, A. W., Garrido, G. E. J., Wichert-Ana, L., Guarnieri, R., Ferrari, L., Azevedo-Marques, P. M., Hallak, J. E. C., McGuire, P. K., & Busatto, G. F. (2004). Effects of cannabidiol (CBD) on regional cerebral blood flow. *Neuropsychopharmacology*, *29*(2), 417-426. https://doi.org/10.1038/sj.npp.1300340

Crippa, J. A. S., Nogueira Derenusson, G., Borduqui Ferrari, T., Wichert-Ana, L., Duran, F. L. S., Martin-Santos, R., Vinicius Simoes, M., Bhattacharyya, S., Fusar-Poli, P., Atakan, Z., Santos Filho, A., Freitas-Ferrari, M. C., McGuire, P. K., Zuardi, A. W., Busatto, G. F., & Hallak, J. E. C. (2011). Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: A preliminary report. *Journal of Psychopharmacology*, *25(1)*, 121-130. https://doi.org/10.1177/0269881110379283

Daniel-Watanabe, L., & Fletcher, P. C. (2021). Are Fear and Anxiety Truly Distinct? *Biological Psychiatry Global Open Science*. https://doi.org/10.1016/j.bpsgos.2021.09.006

Das, R. K., Kamboj, S. K., Ramadas, M., Yogan, K., Gupta, V., Redman, E., Curran, H. V., & Morgan, C. J. A. (2013). Cannabidiol enhances consolidation of explicit fear extinction in humans. *Psychopharmacology*, *226(4)*, 781-792. https://doi.org/10.1007/s00213-012-2955-y

de Faria, S. M., de Morais Fabricio, D., Tumas, V., Castro, P. C., Ponti, M. A., Hallak, J. E. C., Zuardi, A. W., Crippa, J. A. S., & Chagas, M. H. N. (2020). Effects of acute cannabidiol administration on anxiety and tremors induced by a Simulated Public Speaking Test in patients with Parkinson's disease. *Journal of Psychopharmacology*, *34(2)*, 189-196. https://doi.org/10.1177/0269881119895536

D'Souza, D. C. (2019). Cannabis in psychiatric disorders: the cart before the horse? *The Lancet Psychiatry*, *6*(12), 968–969. https://doi.org/10.1016/S2215-0366(19)30375-X

Duvarci, S., & Pare, D. (2014). Amygdala Microcircuits Controlling Learned Fear. *Neuron*, *82*(5), 966–980. https://doi.org/10.1016/j.neuron.2014.04.042

Elms, L., Shannon, S., Hughes, S., & Lewis, N. (2019). Cannabidiol in the Treatment of Post-Traumatic Stress Disorder: A Case Series. *Journal of Alternative & Complementary Medicine*, *25*(4), 392-397. https://doi.org/10.1089/acm.2018.0437

Evans, D. G. (n.d.). Medical Fraud, Mislabeling, Contamination: All Common in CBD Products. *Missouri Medicine*, *117*(5), 394–399.

Freeman, A. M., Petrilli, K., Lees, R., Hindocha, C., Mokrysz, C., Curran, H. V., Saunders, R., & Freeman, T. P. (2019). How does cannabidiol (CBD) influence the acute effects of delta-9-tetrahydrocannabinol (THC) in humans? A systematic review. *Neuroscience & Biobehavioral Reviews*, *107*, 696-712. https://doi.org/10.1016/j.neubiorev.2019.09.036

Freeman, T. P., Hindocha, C., Baio, G., Shaban, N. D., Thomas, E. M., Astbury, D., Freeman, A. M., Lees, R., Craft, S., Morrison, P. D., Bloomfield, M. A., O'Ryan, D., Kinghorn, J., Morgan, C. J., Mofeez, A., & Curran, H. (2020). Cannabidiol for the treatment of cannabis use disorder: A phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. *The Lancet Psychiatry*, *7*(10), 865-874. https://doi.org/10.1016/S2215-0366%2820%2930290-X

Food Standards Agency. (2020, May 9). *Food Standards Agency sets deadline for the CBD industry and provides safety advice to consumers*. Retrieved May 23, 2020 from https://www.food.gov.uk/news-alerts/news/food-standards-agency-sets-deadline-for-the-cbd-industry-and-provides-safety-advice-to-consumers

Fusar-Poli, P., Crippa, J., Bhattacharyya, S., Borgwardt, S. J., Allen, P., Martin-Santos, R., Seal, M., Surguladze, S. A., O'Carrol, C., Atakan, Z., Zuardi, A. W., & McGuire, P. K. (2009). Distinct effects of A9-Tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. *Archives of General Psychiatry*, *66(1)*, 95-105. https://doi.org/10.1001/archgenpsychiatry.2008.519

Goodman, S., Wadsworth, E., Schauer, G., & Hammond, D. (2020). Use and Perceptions of Cannabidiol Products in Canada and in the United States. *Cannabis and Cannabinoid Research*, *20*, 20. https://doi.org/10.1089/can.2020.0093

Grow hemp. (2018). Canadian Hemp Trade Alliance. http://www.hemptrade.ca/grow-hemp (accessed April 13, 2018).

Guimaraes, F., Chiaretti, T., Graeff, F., & Zuardi, A. (1990). Antianxiety effect of cannabidiol in the elevated plus-maze. *Psychopharmacology*, *100*(4), 558-559. https://doi.org/10.1007/BF02244012

Henson, J. D., Vitetta, L., Quezada, M., & Hall, S. (2021). Enhancing Endocannabinoid Control of Stress with Cannabidiol. *Journal of Clinical Medicine*, *10*(24). https://doi.org/10.3390/jcm10245852

Henrich, J., Heine, S. J., & Norenzayan, A. (2010). The weirdest people in the world? *Behavioral and Brain Sciences*, *33*(2–3), 61–83. https://doi.org/10.1017/S0140525X0999152X

Hindocha, C., Freeman, T. P., Grabski, M., Stroud, J. B., Crudgington, H., Davies, A. C., Das, R. K., Lawn, W., Morgan, C. J. A., & Curran, H. V. (2018). Cannabidiol reverses attentional bias to cigarette cues in a human experimental model of tobacco withdrawal. *Addiction*, *01*, 01. https://doi.org//10.1111/add.14243

Honório Júnior, J. E. R., Barriga, J. R. D. M., Mesquita, D. D. S., & Pinto, J. P. (2021). Anxiolytic and antidepressant effects of cannabidiol: a systematic review. *Journal of Health & Biological Sciences*, *9*(1). https://doi.org/10.12662/2317-3076jhbs.v9i1.3366.p1-7.2021

Hundal, H., Lister, R., Evans, N., Antley, A., Englund, A., Murray, R. M., Freeman, D., & Morrison, P. D. (2018). The effects of cannabidiol on persecutory ideation and anxiety in a high trait paranoid group. *Journal of Psychopharmacology*, *32*(3), 276-282. https://doi.org/10.1177/0269881117737400

Hurd, Y. L., Spriggs, S., Alishayev, J., Winkel, G., Gurgov, K., Kudrich, C., Oprescu, A. M., & Salsitz, E. (2019). Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial. *American Journal of Psychiatry*, *176*(11), 911-922. https://doi.org/10.1176/appi.ajp.2019.18101191

Iffland, K., & Grotenhermen, F. (2017). An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. *Cannabis and Cannabinoid Research*, *2(1)*, 139-154. https://doi.org/10.1089/can.2016.0034

Institute of Health Economics (IHE). (2014). *Quality Appraisal of Case Series Studies Checklist*. Edmonton (AB): Institute of Health Economics. Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about

Kimless, D. (2020). Cannabidiol (CBD) for the treatment of diabetic neuropathic pain [Conference Abstract]. *Journal of the Peripheral Nervous System*, *25(4)*, 441. https://doi.org/10.1111/jns.12416

Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test'–a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology*, *28*(1-2), 76-81. https://doi.org/10.1159/000119004

Lachenmeier, D. W., & Diel, P. (2019). A Warning against the Negligent Use of Cannabidiol in Professional and Amateur Athletes. *Sports*, *7*(12), 14. https://doi.org/10.3390/sports7120251

Laine, C. M., Spitler, K. M., Mosher, C. P., & Gothard, K. M. (2009). Behavioral triggers of skin conductance responses and their neural correlates in the primate amygdala. *Journal of Neurophysiology*, *101*(4), 1749–1754. https://doi.org/10.1152/jn.91110.2008

Leal, P. C., Goes, T. C., da Silva, L. C. F., & Teixeira-Silva, F. (2017). Trait vs. state anxiety in different threatening situations. *Trends in Psychiatry and Psychotherapy*, *39*(3), 147–157. https://doi.org/10.1590/2237-6089-2016-0044

Leas, E. C., Moy, N., McMenamin, S. B., Shi, Y., Benmarhnia, T., Stone, M. D., Trinidad, D. R., & White, M. (2021). Availability and Promotion of Cannabidiol (CBD) Products in Online Vape Shops. *International Journal of Environmental Research & Public Health*, *18*(13), 22. https://doi.org/10.3390/ijerph18136719

Lee, J. L. C., Bertoglio, L. J., Guimaraes, F. S., & Stevenson, C. W. (2017). Cannabidiol regulation of emotion and emotional memory processing: relevance for treating anxiety-related and substance abuse disorders. *British Journal of Pharmacology*, *174*(19), 3242-3256. https://doi.org/10.1111/bph.13724

Leen-Feldner, E. W., Bynion, T.-M., Gournay, R., Bonn-Miller, M. O., & Feldner, M. T. (2021). Practical considerations for testing the effects of cannabidiol on human anxiety. *Journal of Anxiety Disorders*, *82*, 102429. https://doi.org/10.1016/j.janxdis.2021.102429

Lefebvre, C., Glanville, J., Briscoe, S., Featherstone, R., Littlewood, A., Marshall, C., Metzendorf, M-I., Noel-Storr, A., Paynter, R., Rader, T., Thomas, J., Wieland, L. S. (2022). Chapter 4: Searching for and selecting studies. In: Higgins, J. P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., Welch, V. A (editors). *Cochrane Handbook for Systematic Reviews of Interventions version 6.3* (updated February 2022). Available from www.training.cochrane.org/handbook

Leweke, F., Schneider, U., Radwan, M., Schmidt, E., & Emrich, H. M. (2000). Different effects of nabilone and cannabidiol on binocular depth inversion in man. *Pharmacology, Biochemistry and Behavior*, *66*(1), 175-181. https://doi.org/10.1016/S0091-3057%2800%2900201-X

Liebling, J. P., Clarkson, N. J., Gibbs, B. W., Yates, A. S., & O'Sullivan, S. E. (2022). An Analysis of Over-the-Counter Cannabidiol Products in the United Kingdom. *Cannabis and Cannabinoid Research*, *7*(2), 207–213. https://doi.org/10.1089/can.2019.0078

Liebowitz, M. R. (1987). *Social phobia. Modern Problems in Pharmacopsychiatry*. 22, 141–173.

Linares, I. M., Zuardi, A. W., Pereira, L. C., Queiroz, R. H., Mechoulam, R., Guimaraes, F. S., & Crippa, J. A. (2019). Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test. *Revista Brasileira de Psiquiatria*, *41*(1), 9-14. https://doi.org/10.1590/1516-4446-2017-0015

Masataka, N. (2019). Anxiolytic Effects of Repeated Cannabidiol Treatment in Teenagers With Social Anxiety Disorders. *Frontiers in Psychology*, *10*, 2466. https://doi.org/10.3389/fpsyg.2019.02466

Mauzay, D., LaFrance, E. M., & Cuttler, C. (2021). Acute Effects of Cannabis on Symptoms of Obsessive-Compulsive Disorder. *Journal of Affective Disorders*, *279*, 158-163. https://doi.org/10.1016/j.jad.2020.09.124

McGregor, I. S., Cairns, E. A., Abelev, S., Cohen, R., Henderson, M., Couch, D., Arnold, J. C., & Gauld, N. (2020). Access to cannabidiol without a prescription: A cross-country comparison and analysis. *International Journal of Drug Policy*, *85*, 102935. https://doi.org/10.1016/j.drugpo.2020.102935

Merrick, J., Lane, B., Sebree, T., Yaksh, T., O'Neill, C., & Banks, S. L. (2016). Identification of Psychoactive Degradants of Cannabidiol in Simulated Gastric and Physiological Fluid. *Cannabis and Cannabinoid Research*, *1*(1), 102–112. https://doi.org/10.1089/can.2015.0004

Millar, S. A., Stone, N. L., Bellman, Z. D., Yates, A. S., England, T. J., & O'Sullivan, S. E. (2019). A systematic review of cannabidiol dosing in clinical populations. *British Journal of Clinical Pharmacology*, *85*(9), 1888-1900. https://doi.org/10.1111/bcp.14038

Moga, C., Guo, B., Schopflocher, D. P., & Harstall, C. (2012). *Development of a Quality Appraisal Tool for Case Series Studies Using a Modified Delphi Technique: Methodology Paper*. Institute of Health Economics. *Available from: https://www.researchgate.net/publication/281411226_Development_of_a_Quality_Appraisal_Tool_for_Case_Series_Studies_Using_a_Modified_Delphi_Technique*

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., & Stewart, L. A. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews*, *4*(1), 1-9. https://doi.org/10.1186/2046-4053-4-1

Moinas, M., Angerville, B., Naassila, M., & Dervaux, A. (2020). Frequency of anxious and depressive symptoms in a population of cannabidiol users [Meeting Abstract]. *European Neuropsychopharmacology*, *40*, S5-S5. https://doi.org/10.1016/j.euroneuro.2020.09.013

Moltke, J., & Hindocha, C. (2021). Reasons for cannabidiol use: a cross-sectional study of CBD users, focusing on self-perceived stress, anxiety, and sleep problems. *Journal of Cannabis Research*, *3*(1), 5. https://doi.org/10.1186/s42238-021-00061-5

Moriyama, T. S., Chagas, M. H. N., Silveira-Moriyama, L., Tumas, V., Lees, A. J., Crippa, J. A., & Bressan, R. A. (2016). Diagnosing social anxiety in Parkinson's disease: characteristics and frequencies according to two diagnostic criteria. *Archives of Clinical Psychiatry (São Paulo)*, *43*(6), 139–142. https://doi.org/10.1590/0101-60830000000100

Morgan, C. J. A., Das, R. K., Joye, A., Curran, H. V., & Kamboj, S. K. (2013). Cannabidiol reduces cigarette consumption in tobacco smokers: Preliminary findings. *Addictive Behaviors*, *38(9)*, 2433-2436. https://doi.org/10.1016/j.addbeh.2013.03.011

National Academies of Sciences, Engineering, and Medicine (NASEM). (2017). *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*. The National Academies Press.

Narayanan, S., Lazar Neto, F., Tanco, K., Lopez, G., Liu, W., Bruera, E., & Subbiah, V. (2020). Cannabidiol (CBD) Oil, Cancer, and Symptom Management: A Google Trends Analysis of Public Interest. *Journal of Alternative & Complementary Medicine*, *26*(4), 346-348. https://doi.org/10.1089/acm.2019.0428

Pacheco, J. C., Souza, J. D. S., Hallak, J. E. C., Osorio, F. D. L., Campos, A. C., Guimaraes, F. S., Zuardi, A. W., & Crippa, J. A. S. (2021). Cannabidiol as a Treatment for Mental Health Outcomes among Health Care Workers during the Coronavirus Disease Pandemic. *Journal of Clinical Psychopharmacology, 41(3),* 327-329. https://doi.org/10.1097/JCP.0000000000001405

Page, M. J., Higgins, J. P. T., Clayton, G., Sterne, J. A. C., Hróbjartsson, A., & Savović, J. (2016). Empirical Evidence of Study Design Biases in Randomized Trials: Systematic Review of Meta-Epidemiological Studies. *PLOS ONE*, *11*(7), e0159267. https://doi.org/10.1371/journal.pone.0159267

Page, M. J,. Higgins, J. P. T., Sterne, J. A C. (2022). Chapter 13: Assessing risk of bias due to missing results in a synthesis. In: Higgins, J. P. T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., Welch, V. A (editors). *Cochrane Handbook for Systematic Reviews of Interventions version 6.3* (updated February 2022). Available from www.training.cochrane.org/handbook.

Pavlovic, R., Nenna, G., Calvi, L., Panseri, S., Borgonovo, G., Giupponi, L., Cannazza, G., & Giorgi, A. (2018). Quality Traits of "Cannabidiol Oils": Cannabinoids Content, Terpene Fingerprint and Oxidation Stability of European Commercially Available Preparations. *Molecules*, *23*(5), 1230. https://doi.org/10.3390/molecules23051230

Pokorski, I., Clement, N., Phung, N., Weltman, M., Fu, S. L., & Copeland, J. (2017). Cannabidiol in the management of inpatient cannabis withdrawal: clinical case series. *Future Neurology*, *12*(3), 133-140. https://doi.org/10.2217/fnl-2016-0035

Qi, M., & Gao, H. (2020). Acute psychological stress promotes general alertness and attentional control processes: An ERP study. Psychophysiology, 57(4), e13521.

Saghaei, M. (2011). An overview of randomization and minimization programs for randomized clinical trials. *Journal of Medical Signals and Sensors, 1*(1), 55–61.

Salami, S. A., Martinelli, F., Giovino, A., Bachari, A., Arad, N., & Mantri, N. (2020). It Is Our Turn to Get Cannabis High: Put Cannabinoids in Food and Health Baskets. *Molecules, 25*(18), 04. https://doi.org/10.3390/molecules25184036

Sands, T. T., Rahdari, S., Oldham, M. S., Caminha Nunes, E., Tilton, N., & Cilio, M. R. (2019). Long-Term Safety, Tolerability, and Efficacy of Cannabidiol in Children with Refractory Epilepsy: Results from an Expanded Access Program in the US. *CNS Drugs, 33(1),* 47-60. https://doi.org /10.1007/s40263-018-0589-2

Sarris, J., Sinclair, J., Karamacoska, D., Davidson, M., & Firth, J. (2020). Medicinal cannabis for psychiatric disorders: a clinically-focused systematic review. *BMC Psychiatry*, *20*(1), 24. https://doi.org/10.1186/s12888-019-2409-8

Sarvet, A. L., Wall, M. M., Keyes, K. M., Olfson, M., Cerdá, M., & Hasin, D. S. (2018). Self-medication of mood and anxiety disorders with marijuana: Higher in states with medical marijuana laws. *Drug and Alcohol Dependence*, *186*, 10–15. https://doi.org/10.1016/J.DRUGALCDEP.2018.01.009

Schier, A. R. M., Ribeiro, N. P. O., e Silva, A. C. O., Hallak, J. E. C., Crippa, J. A. S., Nardi, A. E., & Zuardi, A. W. (2012). Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug. *Revista Brasileira de Psiquiatria*, *34(SUPP 1),* S104-S110. https://doi.org/10.1016/s1516-4446%2812%2970057-0

Sharpe, L., Sinclair, J., Kramer, A., de Manincor, M., & Sarris, J. (2020). Cannabis, a cause for anxiety? A critical appraisal of the anxiogenic and anxiolytic properties. *Journal of Translational Medicine*, *18*(1), 374. https://doi.org/10.1186/s12967-020-02518-2

Singer, L., Tokish, H., Park, F., Campisi, C., & Milanaik, R. L. (2020). The cannabidiol conundrum: Potential benefits and risks of cannabidiol products for children. *Current Opinion in Pediatrics*, *32(1),* 198-205. https://doi.org/10.1097/MOP.0000000000000861

Sterne, J. A. C., Hernán, M. A., Reeves, B.C., Savović, J., Berkman, N. D., Viswanathan, M., Henry, D., Altman, D. G., Ansari, M. T., Boutron, I., Carpenter, J. R., Chan, A. W., Churchill, R., Deeks, J. J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y. K., Pigott, T. D., … Higgins JPT. (2016). ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. *BMJ*, *355*, i4919. https://doi.org/10.1136/bmj.i4919

Sterne, J. A., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H-Y., Corbett, M. S., Eldridge, S. M., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R, Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., McAleenan, A., Reeves, B.C., Shepperd, S., Shrier, I., Stewart, L. A., Tilling, K., White, I.R., Whiting, P.F & Higgins, J. P. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*, *366*, 14898.

Stuyt, E., & Hilderbrand, R. L. (2020). "Cannabidiol in the treatment of post-traumatic stress disorder: A case series": Comment. *The Journal of Alternative and Complementary Medicine*, *26*(4), 349-350. https://doi.org/10.1089/acm.2019.0380

Turner, J. R., Girdler, S. S., Sherwood, A., & Light, K. C. (1990). Cardiovascular responses to behavioral stressors: Laboratory-field generalization and inter-task consistency. *Journal of Psychosomatic Research*, *34*(5). https://doi.org/10.1016/0022-3999(90)90033-Z

Ueberall, M., Essner, U., & Mueller-Schwefe, G. H. H. (2019). Effectiveness and tolerability of THC:CBD oromucosal spray as add-on measure in patients with severe chronic pain: analysis of 12-week open-label real-world data provided by the German Pain e-Registry. *Journal of Pain Research*, *Volume 12*, 1577–1604. https://doi.org/10.2147/JPR.S192174

Vela, J., Dreyer, L., Petersen, K. K., Lars, A. N., Duch, K. S., & Kristensen, S. (2021). Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind placebo-controlled trial. *Pain*, *27*, 27. https://doi.org/j.pain.0000000000002466

Watson, D., & Friend, R. (1969). Measurement of social-evaluative anxiety. *Journal of Consulting and Clinical Psychology*, *33*(4), 448–457. https://doi.org/10.1037/h0027806

White, C. M. (2019). A Review of Human Studies Assessing Cannabidiol's (CBD) Therapeutic Actions and Potential. *Journal of Clinical Pharmacology*, *59*(7), 923-934. https://doi.org/10.1002/jcph.1387

Williams, L. M., Phillips, M. L., Brammer, M. J., Skerrett, D., Lagopoulos, J., Rennie, C., Bahramali, H., Olivieri, G., David, A, S., Peduto, A., & Gordon, E. (2001). Arousal dissociates amygdala and hippocampal fear responses: evidence from simultaneous fMRI and skin conductance recording. *NeuroImage, 14*(5), 1070-1079. https://doi.org/10.1006/nimg.2001.0904

Williamson, E. M., Liu, X., & Izzo, A. A. (2020). Trends in use, pharmacology, and clinical applications of emerging herbal nutraceuticals. *British Journal of Pharmacology, 177(6),* 1227-1240. https://doi.org/10.1111/bph.14943

Wright, M., Di Ciano, P., & Brands, B. (2020). Use of Cannabidiol for the Treatment of Anxiety: A Short Synthesis of Pre-Clinical and Clinical Evidence. *Cannabis and Cannabinoid Research,* *5*(3), 191-196. https://doi.org/10.1089/can.2019.0052

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta psychiatrica scandinavica*, *67*(6), 361-370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

Zuardi, A. W., Cosme, R. A., Graeff, F. G., & Guimaraes, F. S. (1993). Effects of ipsapirone and cannabidiol on human experimental anxiety. *Journal of Psychopharmacology*, *7*(1 Suppl), 82-88. https://doi.org/10.1177/026988119300700112

Zuardi, A. W., Crippa, J. A. S., Hallak, J. E. C., & Gorayeb, R. (2013). Human experimental anxiety: actual public speaking induces more intense physiological responses than simulated public speaking. *Revista Brasileira de Psiquiatria*, *35*(3), 248-253. https://doi.org/10.1590/1516-4446-2012-0930

Zuardi, A. W., Rodrigues, N. P., Silva, A. L., Bernardo, S. A., Hallak, J. E. C., Guimaraes, F. S., & Crippa, J. A. S. (2017). Inverted U-Shaped Dose-Response Curve of the Anxiolytic Effect of

Cannabidiol during Public Speaking in Real Life. *Frontiers in Pharmacology*, *8*, 259. https://doi.org/10.3389/fphar.2017.00259

Zuardi, A., Shirakawa, I., Finkelfarb, E., & Karniol, I. (1982). Action of cannabidiol on the anxiety and other effects produced by !D-9-THC in normal subjects. *Psychopharmacology*, *76*(3), 245-250. https://doi.org/10.1007/BF00432554

Zung, W. W. (1971). A rating instrument for anxiety disorders. *Psychosomatics: Journal of Consultation and Liaison Psychiatry*, *12*(6), 371–379. https://doi.org/10.1016/S0033-3182(71)71479-0

Part 2: Empirical paper

Understanding patterns of and motivations for consumption of cannabidiol products in the UK: an explorative study

Abstract

Background: In recent years, over-the-counter cannabidiol (CBD) has seen significant increases in availability and demand in the United Kingdom (UK) and globally. Studies, websites and companies claim a vast array of benefits from CBD use. Common reasons for CBD use include anxiety, pain, sleeping problems and general wellbeing, amongst others. However, it is less clear what factors influence CBD consumption over, or in addition to, other treatments and remedies. The reported effects of low dose (over-the-counter) products are also less clear, compared to high-dose products that are not available for general purchase, which research often focusses on.

Method: Both CBD-users and non-CBD users completed an online survey from June to December 2021, that asked about CBD consumption, previous treatments, attitudes towards CBD and the healthcare and pharmaceutical industries. Expectancy attitudes of CBD products, pre- and post-CBD use were also explored. Cross-sectional wellbeing measures and demographic data were collated and compared across both groups.

Results: 309 participants completed the survey. CBD-users scored higher than non-CBD users on psychological wellbeing and pain measures, and they also had higher rates of cannabis use within the last 12 months. The common reasons for CBD use were anxiety (25%), chronic pain (12%) sleeping problems (10%) and stress (9%). CBD users averaged 5.3 doses per day, during 26 weeks of the year and the most common type of product was oil. Prevalent reported benefits were feeling calmer and more relaxed, relaxed muscles/tension, sleep improvements and reduced pain and most participants did not experience side effects. Higher CBD expectancy beliefs and prior hopelessness about other treatments, pre-CBD use, was mildly positively correlated with perceived effectiveness post-use.

Conclusions: Most CBD-users in this sample sought additional or alternative treatment for predominantly mental health and wellbeing reasons. CBD consumers experience a variety of benefits from low-dose CBD products and with minimal side effects. There may be a small expectancy effect on the perceived effectiveness of CBD products, but this is expressed with caution. Further research into understanding other potential factors that influence CBD use and its perceived efficacy is needed.

Introduction

Background

Cannabidiol (CBD) is the most cited and researched cannabinoid after delta-9-tetrahydrocannabinol (THC). Cannabidiol is a psychoactive cannabinoid which, unlike THC, does not produce an intoxicated state. CBD has been reported to have a variety of potential therapeutic effects (e.g., Bonaccorso et al., 2019; Oberbarnscheidt & Miller, 2020)(e.g., Bonaccorso et al., 2019; Oberbarnscheidt & Miller, 2020). Over recent years, the CBD industry has been booming globally. A recent report estimated United Kingdom (UK) CBD sales in 2021 at £690m, which increased from £314m since 2019 (ACI, 2021). Forecasts of the market in the United States of America (USA) reach $23.7 billion by 2023 (Brightfield Group, 2019). Internet analysis of Australian searches of 'CBD oil' found the top twenty ranked websites claimed benefits of cannabis (not limited to CBD) for many mental health and physical health problems, including post-traumatic stress disorder, eating disorders and schizophrenia (Webb & Mansfield, 2021).

Global market, regulations and safety

In the UK, Epidyolex, a prescription CBD medicinal product was approved in 2018 for only three indications: tuberous sclerosis complex and two severe treatment-resistant epilepsies (Lennox-Gastaut syndrome and Dravet syndrome) (NICE, 2019). In 2019, the European Union (EU) and the UK (Food Standards Agency, 2020) classified CBD products as 'novel food' which must contain less than 0.2% THC to be legally sold (Commission Regulation, 2000; White, 2019), and in the US, <0.3%. In Brazil, CBD products are controlled substances, but some CBD medical products can be prescribed. In the UK, daily maximum CBD consumption is not recommended above 70 mg a day (approximately 28 drops of 5% CBD) and CBD products are not advised for individuals who are pregnant,

breastfeeding or taking medications (Food Standards Agency, 2020). In Europe, significant differences have been found in the use, availability, and costs of plant-derived and synthetic cannabinoids across countries (Häuser et al., 2018).

Cannabinoids

Although this current paper does not focus on THC combinations, it is important to note cannabis is being used globally for a variety of physical and mental health difficulties (Hazekamp et al., 2013), often for conditions that pharmaceuticals may typically be prescribed for (Stith et al., 2018).

Reasons for CBD use and patterns of consumption

Researchers have used surveys to explore CBD consumption patterns and reported effects. A recent survey on (predominantly) UK residents found the most common reasons for CBD use were anxiety, sleep problems, stress, and general health and wellbeing (Moltke & Hindocha, 2021). That study also found women had higher odds of using CBD for anxiety, whereas men had higher odds for using it post-exercise. Other surveys completed in the USA and Canada have found most endorsed reasons for CBD use are pain, anxiety, depression, headaches/migraines, problems sleeping and PTSD (Goodman et al., 2020) and in young adults: stress relief, relaxation, sleep improvement, and pain relief (Wheeler et al., 2020). Corroon and Phillips (2018) found CBD was used more frequently for medical conditions and in contrast, THC-dominant cannabis for recreational reasons.

Searches online, bring up a plethora of websites selling CBD and articles discussing many potential benefits from it, see Figure 1 as an example.

Figure 1

An image sourced from an online search of 'CBD benefits'

What is the evidence for the effectiveness of CBD?

Anxiety, mood, sleep and pain.

Evidence from controlled trials suggests CBD, at relatively large doses, has important medical and psychiatric value. Systematic reviews have found some efficacy of CBD for anxiety and/or stress, as an adjunctive treatment (Sharpe et al., 2020), or alternative treatment (Skelley et al., 2020), as well as for panic disorder (Soares & Campos, 2017). Systematic reviews have found mixed and inconclusive findings of the effects of CBD on sleep (Gates et al., 2014; Suraev et al., 2020), and often poor methodology is noted, such as lacking statistical control for confounding factors. Non-controlled studies also provide evidence of the effects of CBD. For example, clinic audits report effectiveness for overall symptoms for non-cancer chronic pain, anxiety and depression (Gulbransen et al., 2020) and pain, insomnia, anxiety, depression and 'overall function' (Roth et al., 2019). A study using app data from individuals, using CBD and/or medicinal cannabis showed higher concentrations of CBD and higher doses predicted larger reductions in obsessive compulsions (Mauzay, LaFrance and Cuttler, 2021). Recent studies have also demonstrated that CBD could have

significant impacts on the experience of stress in frontline health workers (Crippa et al., 2021).

Studies of individuals with fibromyalgia show that high doses of cannabidiol are being used as a substitute for other pain-relieving medications such as opiates and demonstrate improvements in health and pain from CBD (Boehnke et al., 2021).

Other benefits.

CBD has also reported beneficial effects for alleviating psychosis reactions (Leweke et al., 2012; McGuire et al., 2018). There is concern about the effects of THC on psychosis reactions, but it is thought the counterbalancing effect of CBD can aid with such reactions (Freeman et al., 2019). Daily treatment of 300mg CBD has shown improvements in the quality of life for people with Parkinson's disease (Chagas et al., 2014). CBD has also shown promising effects in the treatment of drug use disorders, including for cravings and cue-based anxiety for recovering heroin addiction (Hurd et al., 2019) and cannabis use disorder (Freeman et al., 2020). Single dose 800 mg CBD was found to aid tobacco craving or withdrawal (Hindocha et al., 2018).

However, systematic reviews have not come to firm conclusions about the benefits of CBD products, with some highlighting contradictory and inconclusive results (Black et al., 2019; Bonaccorso et al., 2019; Rong et al., 2017).

Disadvantages of CBD

A thorough review of the safety and side effects of CBD summarised the overall safety and high tolerability of CBD, including at high doses and longer-term use (Bergamaschi et al., 2011). Commonly reported side effects are tiredness, diarrhoea, and changes of appetite/weight (Iffland & Grotenhermen, 2017).

CBD expectancy

Researchers have also discussed the likelihood of a 'larger than normal' placebo effect for cannabis products (Shannon et al., 2019). The placebo effect, or meaning response, refers to improvements from a non-active treatment, often from an expectancy that the product will be helpful (Gertsh, 2018). The placebo effect has been observed in treatments for a variety of difficulties, including anxiety, depression, pain and insomnia (Colloca et al., 2013).

Correlations have been found between positive expectancies and perceived efficacy with cannabis use (Loflin et al., 2017; Winiger et al., 2020). However, expectancy effects have rarely been studied with CBD. A recent randomised crossover study investigated the impact of prior beliefs about CBD, using a CBD placebo (Spinella et al., 2021). The study found an expectancy effect. Following a CBD-expectancy condition, sedation significantly increased, as did biological markers of stress (heart rate variability; HRV). Participants with higher CBD expectancy beliefs, experienced lower levels of anxiety in the CBD-expectancy conditions, and higher levels of anxiety in the CBD-free expectancy condition. In contrast, individuals with lower expectancy beliefs tended to experience less differences in anxiety in the two conditions. This study has its limitations: a non-clinical sample tested in an artificial setting and the possibility of participant demand responses.

Attitudes towards CBD

A survey by Wheeler et al. (2020) with US college students found more than half of CBD-users and non-users were unsure if CBD use would result in a failed drug test and further, CBD-users had significantly higher agreement with the statement that CBD does not have an accepted medical use. CBD users were 4.5 times more likely than non-users to have friends or family that use CBD products. Amongst a sample of people with cancer, the most

common reasons for not using CBD included a lack of knowledge and medical recommendations (Butler et al., 2021).

Alternative treatments

There is a clear perceived therapeutic effect of CBD products amongst a sub-set of the population, however, it remains largely unclear as to why CBD products are preferred to other pharmaceutical products, as described above. CBD is often classed within the 'complementary and alternative medicines' or therapies but there are vast differences between these (Trkulja & Barić, 2020). To date, there is limited research or understanding as to what factors may influence a person to use 'alternative' treatments, including CBD.

Covid-19

With the recent Covid-19 pandemic, there have been claims of CBD's efficacy in treating or preventing Covid-19 despite a lack of credible evidence for these claims (Khalsa et al., 2021). The US Food and Drug Administration issued Warning Letters to companies with 'fraudulent' claims and to companies advertising CBD, for treating Covid-19 (Bramstedt, 2021). There is limited research that explores treatment seeking behaviour or attitude changes since the Covid-19 pandemic.

The current study

There has been a surge in the availability of over-the-counter CBD products in the UK, however, most research on the direct effects of CBD are on 'pure, pharmaceutical grade CBD' at relatively high doses. Research is needed on the effects of low-dose, non-medicinal products which are being widely sold and consumed (Chesney et al., 2020). Questions remain

as to why CBD has increased in popularity so significantly and what factors influence an individual's decision to use CBD, in comparison to other treatments.

The main aims of this research are to explore:

- Patterns of current consumption of CBD-products in the UK, including dose, types and sourcing methods used.
- Factors that may influence CBD use, compared to non-CBD users.
- How attitudes to CBD-products differ between CBD-users and non-CBD users.
- How are perceived expectancy and belief of effectiveness of CBD related to perceived benefits and harms.
- How attitudes towards CBD and other treatments may have changed since the Covid-19 pandemic and how this compares to non-CBD users.

As there is limited research, it is difficult to hypothesise individual reasons for taking CBD (beyond the primary health problem), such as treatment expectancy, hopelessness, or attitudes towards treatments. Therefore, this research is exploratory and minimal hypotheses are drawn out. However, it is hypothesised that CBD users are more likely than non-users to have positive attitudes to CBD, higher beliefs in its efficacy and greater preferences towards more 'natural products' rather than pharmaceuticals.

Method

Design and Participants

A between-groups design was used, with two participant groups: CBD-users (any lifetime use) and CBD non-users. Participants were a self-selected, convenience sample and the study was advertised on social media platforms and by email, with snowball sampling using personal and professional connections. CBD, drug science and health-related forums were identified with the aim of advertisement towards people who were likely to have used CBD

and these efforts were increased when participant numbers were lower in the CBD group, compared to the non-CBD group. The inclusion criteria for participants required a minimum age of 18, the UK as their main country of residence and to have heard of CBD. The study aimed to understand the impact of available treatments in the UK only, as guidelines, regulations, and products differ in other countries.

Ethics

Ethical approval was granted by UCL Research Ethics Committee (REC), Project ID: 19641/001 (Appendix 5). Data was collected anonymously, however participants had the voluntary option of adding their email address to enter a prize draw for retail vouchers. Email addresses were stored separately from the anonymised data and were deleted once the prize draw was complete. Participants could stop completion at any time. The participant information sheet and consent form are detailed in Appendix 6 and 7.

The survey

Participants completed a cross-sectional online survey, hosted on the platform Qualtrics, consisting of approximately 60 to 81 questions, which included the questionnaires). The number of questions varied depending on the participant group and some questions were optional. The survey was split into nine sections. Key questions and measures are detailed in Table 1. The full questionnaire is available in Appendix 8. Participants completed the survey from June to November 2021.

The survey included validated psychological measures: The Depression, Anxiety and Stress Scales (DASS-21; Lovibond & Lovibond, 1995), The Insomnia Severity Index (ISI; Bastien, Vallières & Morin, 2001) to assess sleeping problems, specifically insomnia, and The Brief Pain Inventory (BPI; Cleeland, 2009) to understand pain severity and interference.

Questions were removed from the BPI that are not validated or necessary for subscale score calculations.

Data analysis

The data was analysed using IBM SPSS Statistics for Windows, Version 27.0. Descriptive statistics were used for demographic data, reasons for treatment use, benefits, and side effects. Comparisons of the two groups were carried out using independent t-tests or Mann-Whitney U tests as appropriate, for demographic data, psychological/wellbeing questionnaires, cannabis use, attitudes to CBD, and attitude to treatment since the Covid-19 pandemic. The questions regarding attitudes about CBD, treatment beliefs and attitudes to healthcare since Covid-19, all asked participants to rate their agreement to the statements and used a 5-point Likert Scale, ranging from -2 (strongly disagree), to 2 (strongly agree). All comparisons and analyses were conducted in an explorative fashion, as minimal hypotheses were drawn out due to the novel nature of the research.

To explore the relationship between perceived expectancy and belief of the effectiveness of CBD/treatments to their perceived impacts (perceived effectiveness, benefits and side effects), Spearman's Rho correlational analysis was conducted. To explore the nature of significant correlations, scatterplots were examined. One-tailed Spearman's Rho correlations were conducted, predicting CBD users would have positive correlations between prior belief that CBD could help their problem (pre-belief), prior hopelessness about previously tried medications/treatments and post-use perceived effectiveness of CBD. There were predicted positive correlations between prior beliefs that CBD could help the problem and post-use perceived effectiveness with perceived benefits and side effects.

Logistic regression models were used in an exploratory manner to examine the effects of various factors on the likelihood of using CBD. Three different models were complete, to not have an excessive number of factors in one model at a time.

Several variables were not normally distributed, so non-parametric tests were mostly used, including when variables included Likert Scale response options. The scoring of 3 for 'I don't know' in Likert Scales were not included in the comparison analysis. Data was not transformed. Statistical significance was assessed using a cut-off $\alpha=0.05$. Where degrees of freedom are non-integer values, this reflects the assumption of equal variance was not met, and corrected t value and p values were reported.

Table 1

Online survey sections, variables and example questions

Survey section	Topics covered	Measures / questions
1. Demographics	Age, gender, ethnicity, education, area of residence	
2. Psychological measures and health history	Depression, stress, anxiety	The Depression, Anxiety and Stress Scales (DASS-21; Lovibond & Lovibond, 1995)
		The Insomnia Severity Index (ISI; Bastien, Vallières & Morin, 2001)
	Insomnia	The Brief Pain Inventory (BPI; Cleeland, 2009)**
	Pain (severity and interference)	*'Have you experienced any of the following conditions in the last 12 months?'*
	Health history	
3. Attitudes about CBD	Regulation of CBD	*1. I would only take CBD-products if they were regulated*
	Trust of the pharmaceutical industry	*2. I trust the pharmaceutical industry*
	CBD safety	*3. I think CBD products are safe*
	CBD effectiveness	*4. I think CBD products are effective*
	CBD potency	*5. I think CBD products have enough CBD levels in them*
	Perception of CBD's natural tendency	*6. I think CBD products are more natural*
	CBD acceptability	7. *Scores from statements 3-6 were combined*
4. CBD consumption decider question		'*Have you ever used cannabidiol (CBD) products before*?'
5. Indications for using treatments/medication in the last year	What types of treatment used (both groups) and indications for CBD use (CBD-users only)	

Table 1 continued

Note: **Questions were removed from the BPI that are not validated or necessary for subscale score calculations.

Survey section	Topics covered	Measures / questions
6. Product consumption	Frequency, consumption change in the last year (both groups) and CBD dosing, type, source of purchase, expenditure (CBD group only)	
7. Treatment beliefs	Pre-belief	*1. Before I started using CBD or the treatment/remedy/medication, I believed it could help my problem*
	Post-belief	*2. Since or after using CBD or the treatment/remedy/medication, I believe it has helped my problem*
	Pre-hopelessness	*3. Before using CBD or the treatment/remedy/medication, I was feeling hopeless about previous treatments/medications*
	Post-hopelessness	*4. Since or after using CBD or the treatment/remedy/medication, I am/was feeling hopeless about future treatments/medications*
	'Pre-hopefulness'	*5. Scores from statement 1 and 3 were combined*
	'Post-hopefulness'	*6. Scores from statement 2 and 4 were combined*
8. Perceived effectiveness and impacts of products		*'How much do you agree with the following statement: CBD products have been or were effective in helping me with my main problem'*
9. Attitudes towards healthcare since Covid-19		*'Please answer the following questions, thinking about whether your attitudes to medications or remedies have changed during the Covid-19 pandemic, i.e., since March 2020.'*
	Post-covid natural preference	*1. I am more likely to use herbal or natural remedies or alternative therapies*
	Post-covid prescription preference	*2. I am more likely to take prescribed medications*
	Post-covid pharmaceutical tendency	*3. I am more sceptical of the pharmaceutical industry*

Results

In total, 341 participants began the survey, and 309 participants completed the survey to the main dependent variable 'CBD decider' question, with 132 participants in the CBD-user group and 177 participants in the non-user group. The results are reported for the 309 completers, however, there was some missing data which is reflected in the statistical analysis and/or in the reported degrees of freedom.

DEMOGRAPHICS

The two groups were largely well matched in demographics (Table 2). In total, 71.2% of participants identified as women, 28.2% as men and 0.6% as non-binary. For both groups, the most prevalent ethnicity was 'White'. Only education comparisons reached a statistically significant difference, χ^2 (2, n = 263) = 6.71, p = .035, when comparing Key Stage 4 education, Undergraduate and Postgraduate level of education. Of the non-CBD users, 79% (n=132) had higher education levels (NVQ4 or above) compared to 68.9% (n=84) of CBD users. The most common educational level was Postgraduate degree/qualification. For both groups, the most common area of residence was in a large town/city.

Table 2

Demographics descriptive data and group comparison statistical analysis

	CBD group	Non-user group	Total			
	(*n* =132)	(*n*=175)	(*n*=307)	*df*	U	*p*
Age *n* years (SD; range)	39.7 (15.5; 18 - 87)	39.9 (14.1; 20 - 82)	39.8 (14.7; 18 - 87)		11644.5	.902
	(*n*=132) *n* (%)	(*n*=177) *n* (%)	(*n*=309) *n* (%)	*df*	χ^2	*p*
Gender				1 (*n*=307)	.22	.637
Women	95 (72)	125 (70.6)	220 (71.25)			
Men	35 (26.5)	52 (29.4)	87 (28.2)			
Non-binary[a]	2 (0.6)	0	2 (0.6)			
Ethnicity[b]				2 (*n*=309)	1.14	.95
Asian, Asian British, Pakistani, Chinese	5 (3.8)	8 (4.5)	13 (4.2)			
Black, African Caribbean or Black British, Arab	1 (0.8)	1 (0.6)	2 (0.6)			
Mixed or Multiple ethnic groups[c]	4 (3)	4 (2.3)	8 (2.6)			
'Other' ethnic group[d]	4 (3)	4 (2.3)	8 (2.6)			
Prefer not to choose/state	3 (2.3)	2 (1.1)	5 (1.6)			
White	115 (87.1)	158 (89.3)	273 (88.3)			
Education level[e]				2 (*n*=263)	6.71	.035*
Primary school						
Secondary school - key stage 3	4 (1.3)	1 (0.3)	5 (1.6)			
GCSE / A Level / GNVQs / NVQs 1-3 key stage 4	27 (8.7)	31 (10)	58 (18.8)			
Sub-degree / NVQ4	7 (2.3)	4 (1.3)	11 (3.6)			
Undergraduate degree	27 (8.7)	66 (21.4)	93 (30.1)			
Postgraduate degree / qualification	50 (16.)	62 (20.1)	112 (36.2)			
Doctorate	8 (2.6)	3 (1)	11 (3.6)			
Prefer not to say	7 (2.3)	3 (1)	10 (3.2)			
Other	2 (0.6)	6 (1.9)	8 (2.6)			
None	0	1 (0.3)	1			

Table 2 continued

	CBD group	Non-user group	Total			
	(*n* =132)	(*n*=175)	(*n*=307)	*df*	U	*p*
Area of residence				2 (*n*=307)	4.04	.133
Large town/city	59 (19.1)	99 (32)	158 (51.1)			
Small to mid-sized town	38 (12.3)	47 (15.2)	85 (27.5)			
Rural/ countryside	33 (10.7)	31 (10)	64 (20.7)			
Prefer not to say[f]	2 (0.6)	0	2 (0.6)			

Note. [a] removed for this analysis as *n*=2 violated the minimum expected cell frequency assumption.

[b] Pearson's Chi Squared test analysis complete for ethnicity categories Asian/Asian British, Pakistani/Chinese, and White. The other ethnicity categories were removed for this analysis as they did not meet the cell minimum expectancy count.

[c]includes: Mixed Chinese/White, Mixed White/Asian, Mixed White and Black Caribbean

[d]includes: Arab, English traveller (Gypsy Roma), Jewish, White Other

[e]Pearson's Chi Squared test analysis complete for education categories: Key Stage 4 education, Undergraduate and Postgraduate level of education. The other education categories were removed for this analysis as they did not meet the cell minimum expectancy count.

[f]removed for this analysis as *n*=2 violated the minimum expected cell frequency assumption

[*]Significant at $p < .05$

PSYCHOLOGICAL AND HEALTH OUTCOMES

Independent sample t-tests compared the two user groups on the depression, anxiety, stress, insomnia, and pain questionnaires. There were statistically significant differences between the two user groups on all measures, with higher mean scores in the CBD-user group (Table 3), which indicates higher levels of depression, anxiety, stress, insomnia, and pain within the CBD sample. In terms of clinical outcomes, the non-user group were largely scoring in the 'normal' range and the CBD users in the 'mild' range.

CANNABIS USE

CBD use was associated with cannabis use. A chi-squared test revealed χ^2 (2, n=309) = 57.29, p <.001. As can be seen in Table 4, non-CBD users appear more likely to have never used or not used cannabis in the past 12 months (159 out of 177; 89.8%), whereas CBD users were more likely to have ever used or used cannabis in the past 12 months (75%).

CBD CONSUMPTION BY CBD USERS

The average days CBD products were consumed in the last year was 185.3 days, with an average daily dose of 5.3 mg. The mean estimated monthly spend on CBD products was £83.85, although the mode was £0, which suggests people are most likely to buy products less than monthly. The most common place to purchase CBD products was from health shops (such as Holland & Barrett): 22% (n=29). The second most common was online (open web): 13.1% (n=17). No one purchased CBD products from a pharmacy, a prescriber or online (darknet).

Participants chose all the CBD products they had used in the last 12 months (multiple choice) and the most common was oil for oral use and this remained the most preferred option (Table 5).

Table 3

Psychological and health assessment	CBD user group (n =132)			Non-CBD user group (n=177)			*df*	*t*	*p*
	Mean	**SD**	**Mean score interpretation**	**Mean**	**SD**	**Mean score interpretation**			
Depression (DASS-21)	6.12	5.43	'Mild'	3.81	4.16	'Normal'	307	4.07	<.001**
Anxiety (DASS-21)	4.05	4.12	'Mild'	2.66	2.9	'Normal'	307	3.28	.001**
Stress (DASS-21)	7.11	4.87	'Normal'	5.28	3.75	'Normal'	307	3.58	<.001**
Insomnia (ISI)	10.08	6.64	'Subthreshold insomnia'	8.31	5.62	'Subthreshold insomnia'	307	2.48	.014**
Pain severity (BPI)	8.9	8.69	n/a	5.23	6.09	n/a	307	4.15	<.001**
Pain interference (BPI)	16.12	19.56	n/a	8.62	13.14	n/a	307	3.81	<.001**

Comparison of psychological assessments' scores and independent t-tests

Note. The maximum score for the depression, anxiety and stress scores, individually, is 21. The maximum score for the insomnia measure is 28. The maximum score for pain severity is 40 and 70 for pain interference.

All tests revealed the assumption of homogeneity of variance was violated, so the t-value was reported from the 'equal variances not assumed' row.

*= significant at p<.05

**= significant at $p<.01$

Most respondents (42.4%) said their CBD consumption had not changed in the last year and 25% of participants stopped using CBD, in the last year. For some participants, CBD consumption had increased (18.9%), whilst 12.2% had decreased their CBD consumption (see Figure 2).

Table 4

Cannabis use	**CBD users** ***(n* = 132)** ***n* (%)**	**Non-CBD users** ***(n* = 177)** ***n* (%)**	**Total** ***(n* = 309)** ***n* (%)**
Used in the last 12 months	63 (47.7)	18 (10.2)	81 (26.2)
Used before, but not in the last 12 months	36 (27.3)	65 (36.7)	101 (32.6)
Never used before	33 (25)	94 (53.1)	127 (41.1)

Cannabis use descriptive statistics

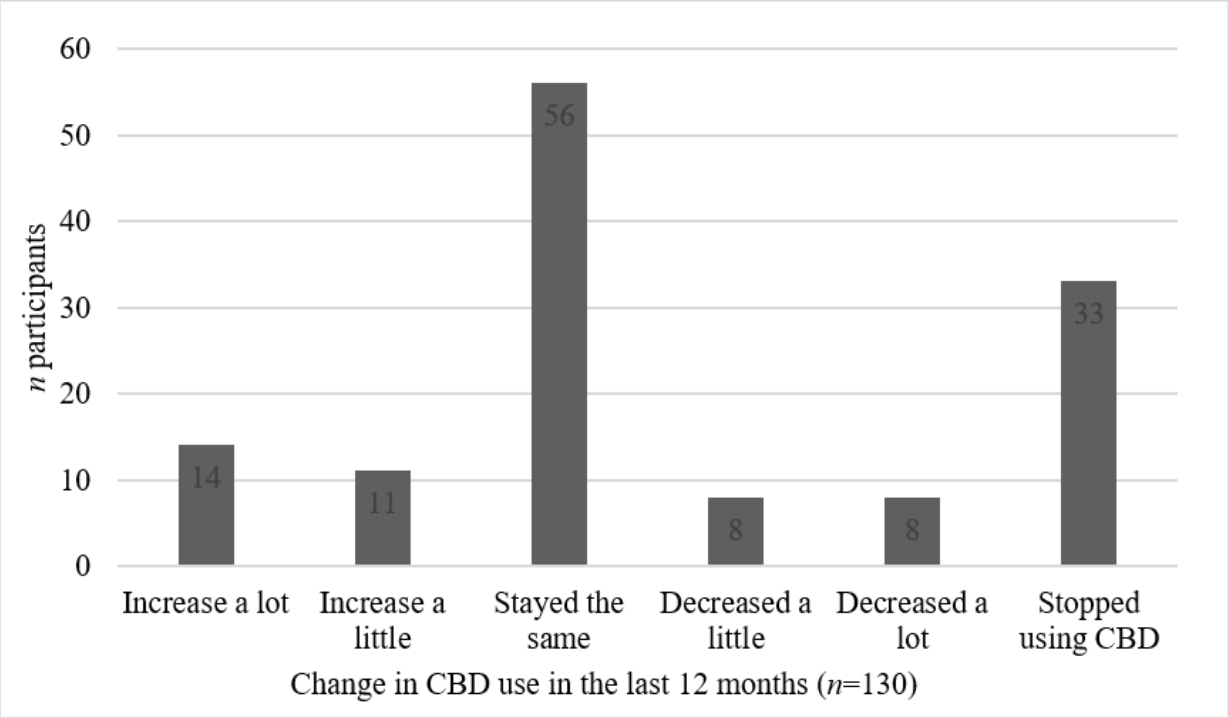
Table 5

CBD-user types of CBD products used and most used products

Type of CBD product	**Type of CBD products used in the last year (*n*=130) (210 responses, multiple choice)** ***n* (%)**	**Most used type of CBD product (*n*=130)** ***n* (%)**
Oil for vaping	17 (8.1)	7 (5.4)
Oil for oral use	70 (33.3)	57 (43.8)
Oil for topical use	20 (9.5)	11 (8.5)
Capsules	23 (11)	11 (8.5)
Edibles (food/drink)	29 (13.8)	14 (10.8)
Spray	10 (4.8)	6 (4.6)
Flower	17 (8.1)	8 (6.1)
Other	13 (6.2)	5 (3.8)
None	11 (5.2)	11 (8.5)

Figure 2

Change in CBD use in the last 12 months for the CBD-user group



REASONS FOR TREATMENT USE

Most CBD users 84.3% (*n*=107) had not had a medical professional recommend CBD products to them, whereas 13.4% (*n*=17) had.

The most common reasons for CBD consumers to use CBD was for stress (*n*=62, 11.9%) followed by anxiety (*n*=56, 10.75%), general wellbeing (*n*=48, 9.21%) and sleeping problems (*n*=45, 8.64%). In comparison, the most common reasons for non-CBD users to seek treatment was occasional pain (*n*=77, 15.52%), anxiety (*n*=50, 10.1%), stress (*n*=47, 9.48%) and low mood (*n*=36, 7.26%). Thirty-two people (6.45%) selected ‘none’ (see Figure 3).

When CBD users were asked to select the most common problem that they used CBD for, a quarter (*n*=29, 25%) selected anxiety. This was followed by chronic pain (12.1%, *n*=14), sleeping problems (10.3%, *n*=12) and stress (8.6%, *n*=10). In comparison, non-users' most common problems for seeking treatment were occasional pain (*n*=34, 23.6%), low mood (*n*=16, 11.1%) and anxiety (*n*=14, 9.7%) (see Figure 4 for all responses).

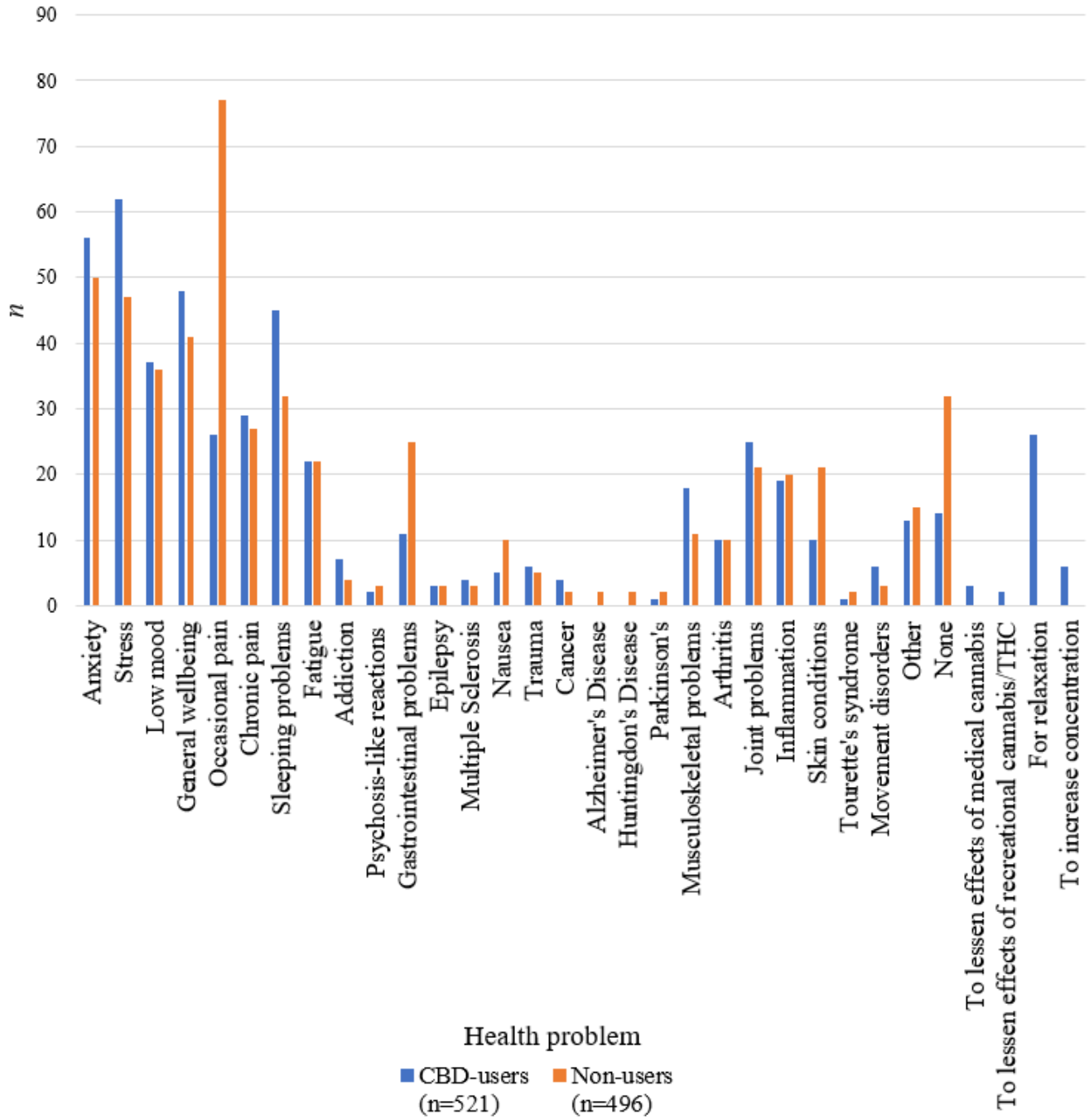
ALTERNATIVE TREATMENTS

CBD users were asked if they had used any other medications, treatments, or remedies for their main problem, in the last 12 months. The most used treatment was mindfulness (*n*=40, 11.3%), followed by healthy eating (*n*=34, 9.6%) and meditation (*n*=33, 9.3%). Shop-bought pain relief was the fourth most used treatment (*n*=27, 7.61%), followed by yoga (*n*=26, 7.3%) and prescribed pain relief (*n*=25, 7%). Other remedies used (*n*=1), respectively, were aromatherapy, psychological therapy and reflexology (see Figure 5).

Non-CBD users were asked the same question (multiple-choice; Figure 5), and the common treatments for the main selected problem were shop-bought pain relief (*n*=65, 14.3%), followed by healthy eating (*n*=59, 13%), mindfulness (*n*=40, 8.8%) and yoga (*n*=37, 8.1%). When selecting the most used treatment (see Figure 6), shop-bought pain relief remained most used (*n*=33, 25%), followed by anti-depressant medication (*n*=19, 14.4%), 'other' (*n*=16, 12.1%) and healthy eating (*n*=13, 9.8%).

Figure 3

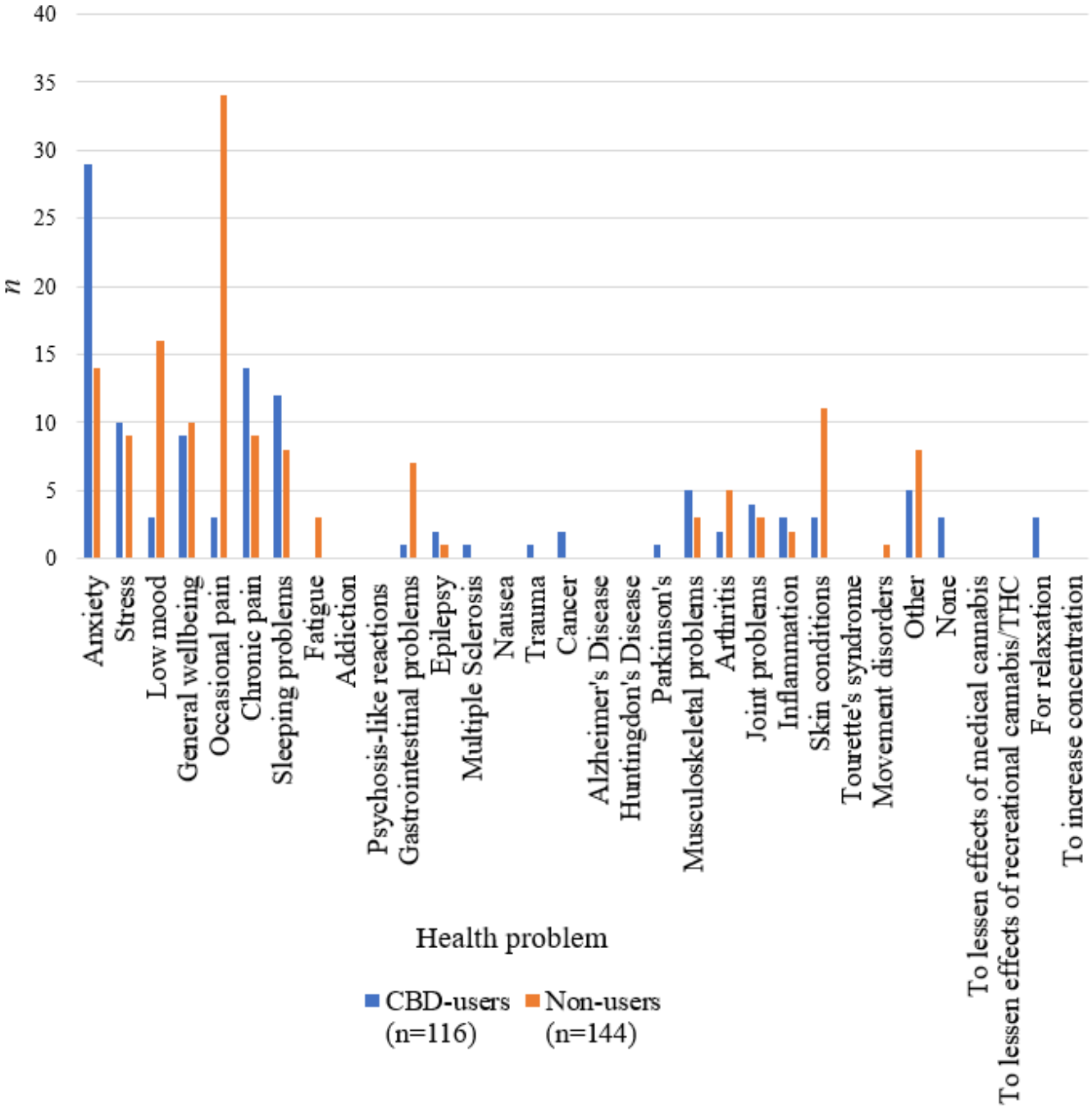
CBD-users' and non-users' problems that CBD or other treatments were used for



Note. Non-users were not provided the option of the last four responses.

Figure 4

CBD-users' and non-users' most common problem that CBD or other treatments were used for



Note. Non-users were not provided the option of the last four responses.

Figure 5

CBD-users' and non-users' treatments that were used for the main selected problem

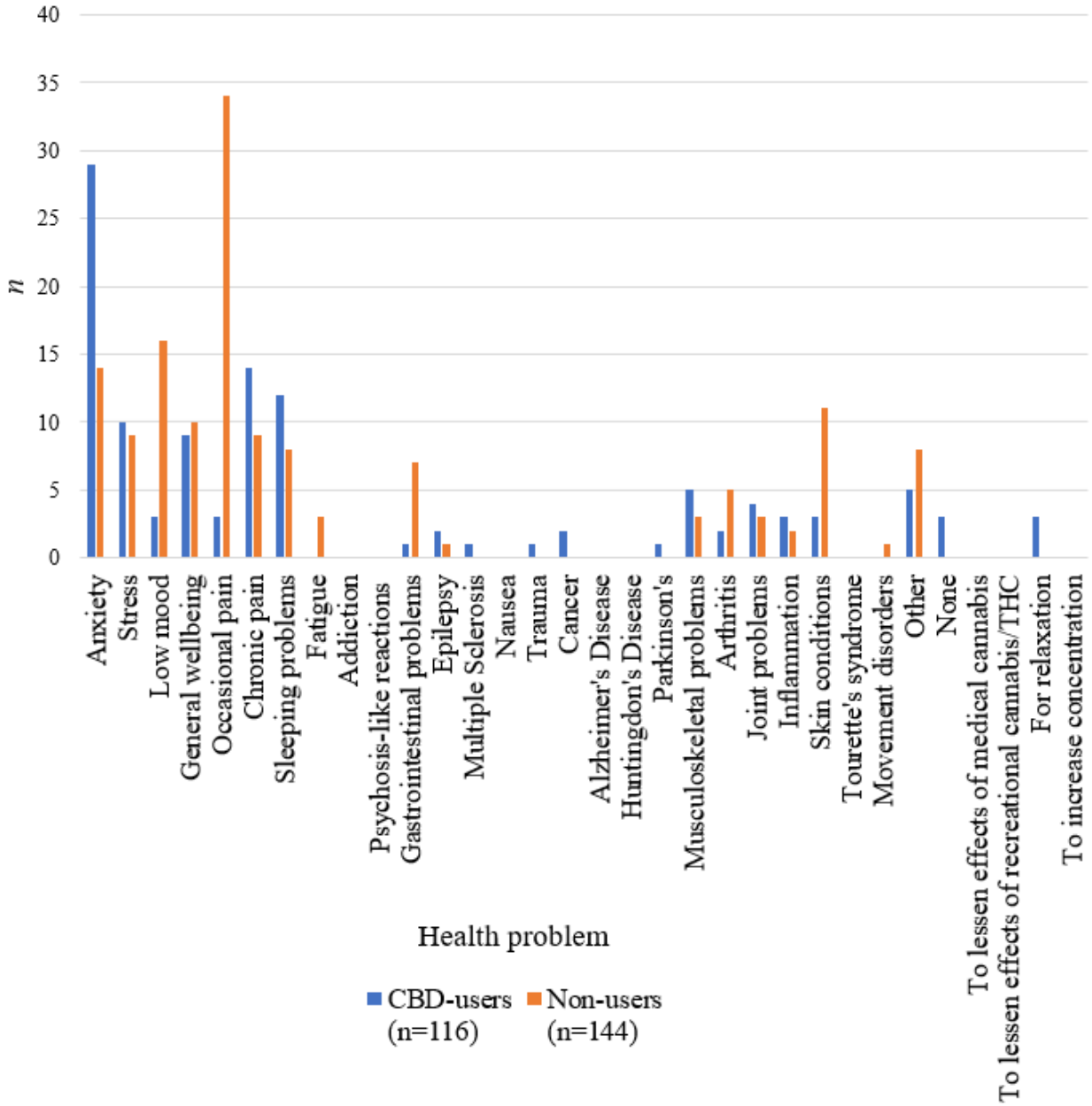
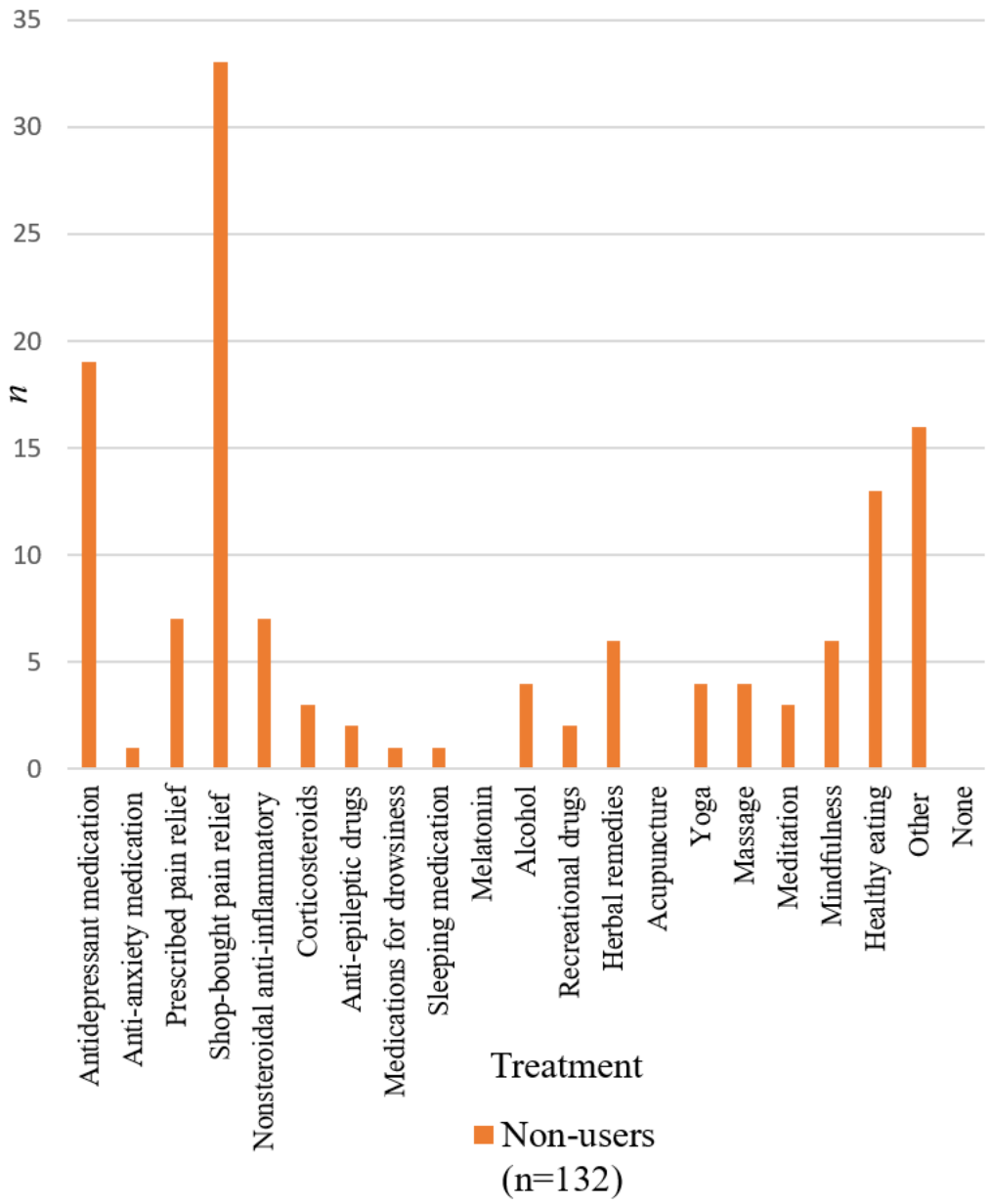


Figure 6

Non-CBD users' most used treatment for their main selected problem

Figure 6

Non-CBD users' most used treatment for their main selected problem



THE EXPERIENCE OF USING CBD

CBD benefits and side effects.

The most common benefits observed from using CBD products were 'feeling more calm and relaxed' (*n*=52), 'less pain' (*n*=42), 'relaxed muscles and/or less tension' (*n*=40) and 'improved sleep (*n*=40). See Figure 7.

The most common CBD side effect was 'none', with 101 out of 126 reporting this. After this, the most common side effects reported were a dry mouth (n=7) and fatigue (n=5). Five people scored 'other' resulting in five different responses. See Figure 8.

ATTITUDES TO CBD

The majority (45.5%; *n*=60) of CBD users said they would discontinue the product if they found out their main CBD preparation contained significantly different amounts of CBD than advertised, whereas 18.2% (*n*=24) would not stop using the product and 34.8% (*n*=46) were not sure what they would do.

Differences between CBD users and non-users on the attitudes to CBD.

To identify any differences between the two user groups and their attitudes to CBD products, independent sample t-tests were conducted for those who selected an agreement rating (see Table 6). These variables are formed of ordinal data, 5-point Likert Scales, however t-tests were still used as studies have found similar power and Type 1 error rates amongst t-tests and Mann-Whitney-Wilcoxon tests (de Winter & Dodou, 2010).

Figure 7

CBD-users' reported benefits

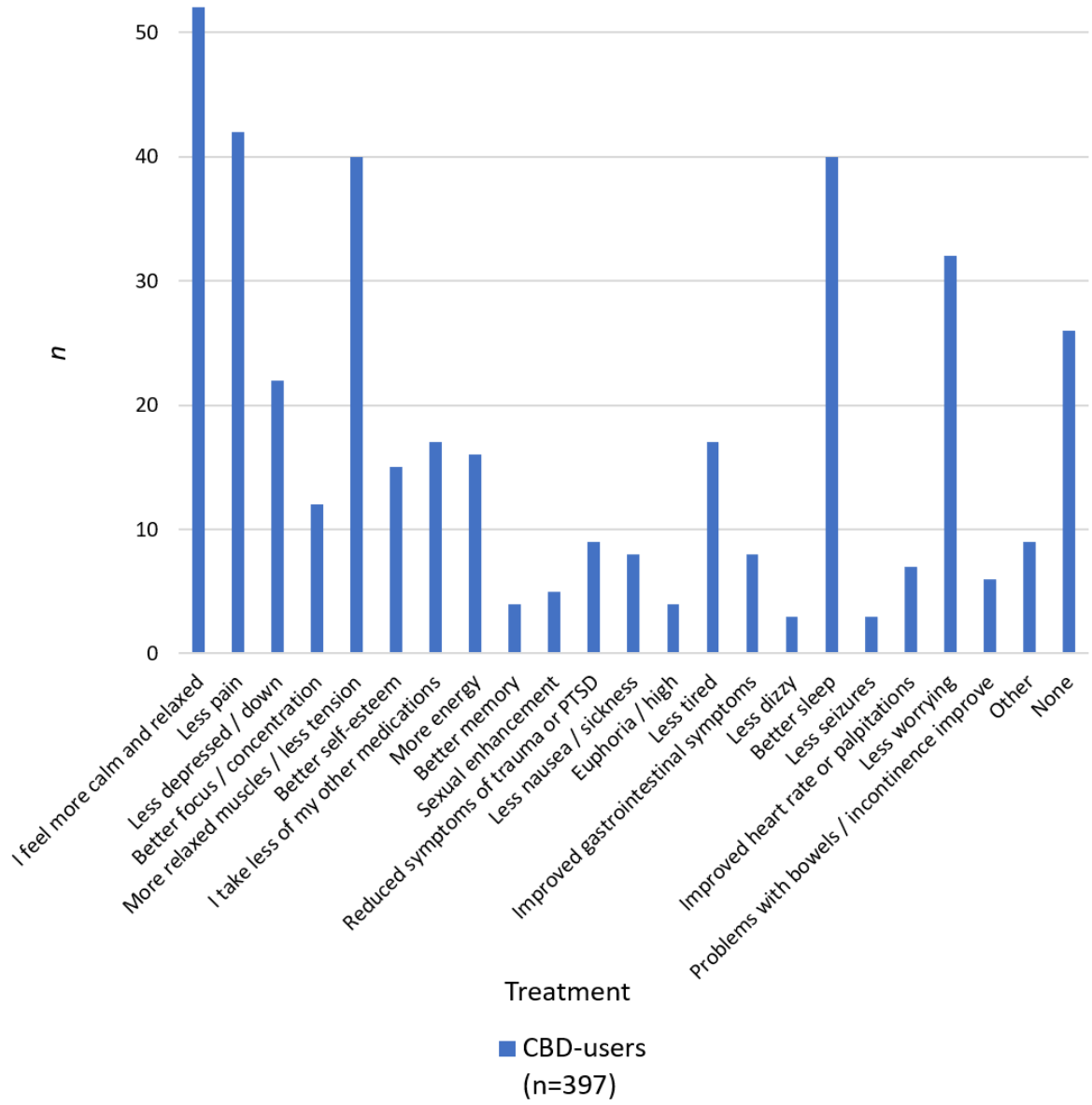


Figure 8

CBD-users' reported side effects

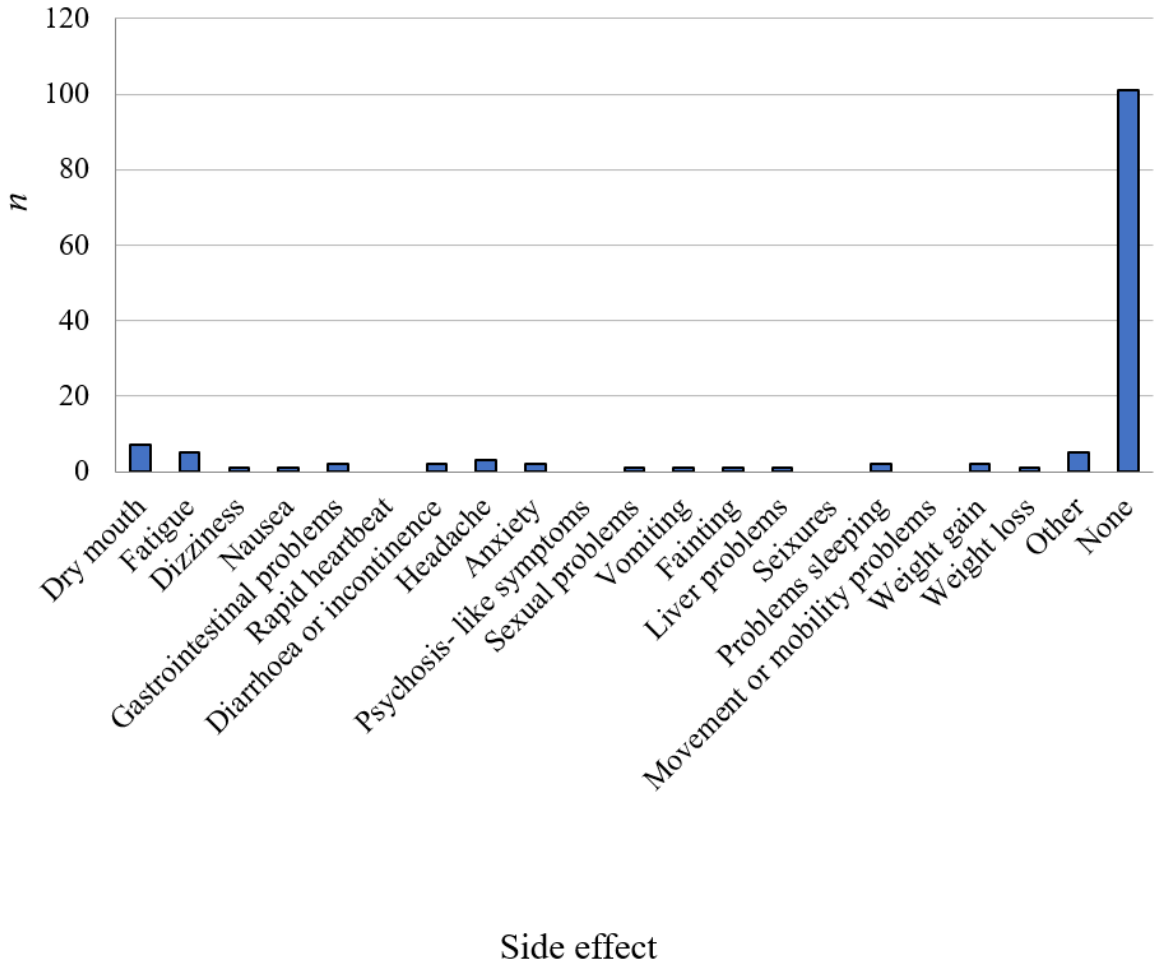


Table 6

T-test results of group comparisons between attitudes to CBD products

Variable and description	CBD user group			Non-CBD user group			*df*	*t*	*p*
	Mean	SD	Mean score interpretation	Mean	SD	Mean score interpretation			
1. CBD regulated - Attitudes to CBD needing to be regulated	0.24	0.09	Neither agree nor disagree - somewhat agree	0.073	1.12	Neither agree nor disagree	228.4	-3.09	.002*
2. Pharmaceutical trust - Trust of the pharmaceutical industry	-0.35	1.33	Somewhat disagree	0.025	1.18	Neither agree nor disagree	255.1	-4.07	<.001*
3. CBD safe - Perception of the safety of CBD products	1.54	0.75	Somewhat agree	0.072	0.91	Neither agree nor disagree	260.5	8.04	<.001*
4. CBD effective - The perception of the effectiveness of CBD	1.08	1.02	Somewhat agree	0.58	0.87	Neither agree nor disagree	248	4.14	<.001*
5. CBD enough - The perception that CBD has enough potency	-0.04	1.16	Neither agree nor disagree - Somewhat agree	-0.01	0.85	Neither agree nor disagree	201.6	-.17	.86
6. CBD natural - CBD is natural	1.02	1	Somewhat agree	0.43	0.95	Neither agree nor disagree	262	4.92	<.001*
7. CBD acceptability	14.9	3.67	n/a	9.48	5.66	n/a	301.6	10.21	<.001*

Note. The Likert Scale ranged from -2 (strongly disagree) to 2 (strongly agree), with 0 reflecting 'neither agree nor disagree'.

*= significant at p<.01

Comparing attitudes about CBD needing to be regulated between both groups, there was a significant difference in scores with non-CBD users having an overall higher score to the statement. This suggests that CBD-users are less inclined than non-users to think that CBD products need to be regulated.

There was a significant difference in scores for trust of the pharmaceutical industry, with CBD-users more often disagreeing with the statement and non-CBD users more often agreeing with the statement. This suggests that CBD-users are less likely to be trusting of the pharmaceutical industry than non-CBD users.

When comparing perceptions regarding the safety of CBD products, there was a significant difference in scores with CBD users having a higher agreement with the statement 'I think CBD products are safe' than non-users.

Comparing agreement to the statement 'I think CBD-products are effective', there was a significant difference in scores and CBD-users on average had higher agreement scores to the statement, suggesting stronger perceptions of CBD's efficacy than non-users.

There was no significant difference in scores on perception of CBD having enough potency.

With regards to the perception of CBD being more natural, there was a significant difference in scores with CBD-users tending to have a higher agreement score to the statement. This suggests CBD-users are more likely to view CBD as a natural product, more than non-users.

Overall, apart from the perception of CBD products being more 'natural', both groups had similar agreement direction (e.g., agree or disagree) on the statements of CBD acceptability. There was a significant difference in scores for overall views of acceptability of CBD products for CBD users (M = 14.9, SD = 3.67) and non-CBD users (M = 9.48, SD = 5.66); t (301.6) = 10.21, p <.001, with CBD users scoring more highly than non-CBD users

on the overall acceptability questions. This suggests that CBD users perceive CBD more favourably (safe, effective, containing enough CBD levels and more natural) than non-CBD users.

Qualitative responses from participants.

Additional comments about the CBD acceptability questions were gathered for both user groups (see Appendix 9 for examples). Several people commented how they believed more research is needed and more regulation on CBD products. Distrust and frustration were described regarding a lack of regulation impacting the availability of products, a lack of trust of what is being sold and the impact on the industry becoming a 'fad'. There were also comments from people explaining how helpful CBD has been for some ailments and for quality of life.

Participants were asked 'What reason(s) influence you taking CBD, rather than other medications, treatments or remedies?'. The most common responses were regarding CBD products being more natural, non-chemical and having lower risks and/or side effects than other medications, such as pain relief. Others commented on it being accessible, not being on medical records and it was recommended to them.

PERCEIVED EFFECTIVENESS

A variable was created to combine the users and non-users perceived effectiveness of the treatment (CBD or the main treatment).

A one-way ANOVA was completed and reveals that the non-user group's mean score (1.04) of perceived effectiveness was significantly higher than CBD-users (.62) $f = 8.24$, p=.004. In response to the agreement rating to the following statement: "CBD products/chosen treatment have been or were effective in helping me with my main problem", a score of 0 represents 'neutral' and 1 represents 'agree a bit'.

The relationships between perceived expectancy of products and the impacts.

The relationship between CBD users' prior beliefs and hope about treatment, with perceived effectiveness.

A Spearman's Rho correlation (one-tailed) was conducted to examine the relationship between CBD users' prior belief that CBD could help their problem, prior hopelessness about previously tried medications/treatments, and post-use perceived effectiveness of CBD. One score was missing for the perceived effectiveness question. Prior belief about CBD was significantly, mildly positively associated with perceived effectiveness $\rho(124) = .24$, $p = .004$, and prior hopelessness about other treatments used, was also significantly, mildly positively associated with perceived effectiveness $\rho(124) = .16$, $p=.033$. Previous hopelessness was significantly, mildly, positively associated with prior belief about CBD products $\rho(125) = .21$, $p=.009$. These findings indicate that the higher belief in CBD products before taking them that someone has and the more hopeless they feel about previously tried treatments, then the more they may view CBD as being effective, after using the CBD product. The more hopeless someone feels about previously tried treatments was also related to their prior belief in CBD products, or vice versa. Regardless of the p-value, these correlations are very small, with generally negligible associations between the variables.

The relationship between CBD users' prior beliefs and perceived effectiveness, with perceived benefits and side effects.

As hypothesised, there was a significant, strong, positive linear relationship between the perceived effectiveness of CBD after use, with the total amount of benefits observed $\rho(124) = .63$, $p = .000$.

For the CBD user group, there was not a linear relationship between the pre-belief of the CBD and the total amount of benefits or side effects. There also was not a linear

relationship between the total amount of benefits and the total amount of side effects noticed, suggesting there is not a correlation between the two - a negative correlation was hypothesised.

Correlation analysis was not conducted on these variables using the non-CBD user groups, as this group includes data on a wide group of treatments/medications and the *n*-values would be small when the categories of treatments were broken down.

FACTORS PREDICTING CBD USE

Model 1.

A logistic regression model was used to assess the effects of gender, age, cannabis use, CBD acceptability attitudes, the number of health problems in the last year, and the number of treatments previously used over a year ago, on the likelihood of CBD use, with all independent variables held constant. The model was statistically significant when compared to the null model ($x^2(7) = 130.804$, $p<.001$), explained 47% of the variance of CBD use, and correctly predicted 78.4% of cases. Age ($p=.277$), gender ($p=.442$), and the number of health problems in the last year ($p=.219$) were not statistically significant, but cannabis use ($p<.001$), CBD acceptability attitudes ($p<.001$) and the total previous treatment in the previous year ($p=.016$) were. An increase of 1 in CBD acceptability attitude, leads to an increase in the odds of CBD use (OR 1.284 [95% CI 1.19 - 1.39]).

Those who used cannabis use in the last year were .62 more likely to have used CBD, whereas those who had used CBD over a year ago were 3.671 times more likely, in comparison to those who had never used cannabis before. An increase in 1 of the number of treatments previously used (over 1 year ago), increased the odds of CBD use (OR 1.184 [95% CI 1.03 - 1.17]). Females were .771 times more likely to have used CBD, in comparison to males.

Model 2.

A logistic regression model was used to assess the effects of scores on the depression, anxiety, stress, pain, and insomnia scales, on the likelihood of CBD use, with all independent variables held constant. The model was statistically significant when compared to the null model ($x^2(6) = 27.691$, $p<.001$), explained only 12% of the variance of CBD use, and correctly predicted 64.4% of cases. Only pain severity was a significant predictor of CBD use ($p=.045$), and depression ($p=.230$), anxiety ($p=.721$), stress ($p=.414$), insomnia ($p=.368$), and pain interference ($p=.814$) were not statistically significant predictors. An increase of 1 in pain severity, leads to an increase in the odds of CBD use (OR 1.054 [95% CI 1.00 - 1.11]).

Model 3.

Another logistic regression model was used to assess the effects of scores on trust of the pharmaceutical industry and hopeless of treatments prior to using treatment in the last year, on the likelihood of CBD use, with all independent variables held constant. The two variables were re-coded from a Likert scale of -2 to 2, to a 0-5 scale, with a higher score suggesting higher agreement to the statements. The pharmaceutical trust variable was not included in the overall CBD acceptability variable. The model was statistically significant when compared to the null model ($x^2(2) = 16.094$, $p<.001$), explained only 8% of the variance of CBD use, and correctly predicted 62.5% of cases. Both trust of the pharmaceutical industry ($p=.003$) and pre-treatment hopelessness were statistically significant ($p=.044$). An increase of 1 (from a scale of 0 - 5) in trust of the pharmaceutical industry, leads to a decrease in the odds of CBD use (OR .733 [95% CI .599 - .897]). An increase of 1 in the hopelessness of previous treatments agreement rating (from a scale of 0 - 5), leads to an increase in the odds of CBD use (OR 1.238 [95% CI 1.006 - .1.525).

ATTITUDE CHANGE SINCE COVID-19

All participants were asked three questions regarding their preferences or tendencies about healthcare treatment or remedies (Table 7). Mann-Whitney tests were conducted to compare the two user groups on their ratings. When comparing post-covid natural preferences, there was a statistically significant difference (U = 8660.5, p = .003). The CBD group had a higher average mean of .37 compared to the non-CBD group of -.05 but had equal medians. The CBD group were more likely to slightly agree with the statement and the non-CBD group were more likely to slightly disagree with the statement.

When comparing the user groups post-covid likelihood of using prescription medication, there was a statistically significant difference (U = 12579, p = .004). The CBD group had a lower average mean of -0.27 compared to the non-CBD group of 0.07 but equal medians. This means the CBD group were more likely to slightly disagree with the statement and the non-CBD group were more likely to slightly agree with the statement.

When comparing the user groups scepticism of the pharmaceutical industry, there was a statistically significant difference (U = 8445.5, p = .001). The CBD group had a higher average mean of 0.26 compared to the non-CBD group of -0.16 but equal medians. This means the CBD group were more likely to slightly agree with the statement, whereas the non-CBD group were more likely to slightly disagree.

Additional comments from both user-groups to the qualitative questions are detailed in Appendix 9.

Table 7

Attitude changes to the healthcare and pharmaceutical industry since Covid-19

	CBD group Mean Median; interquartile range	**Non-user group** Mean Median; interquartile range	**Total**		
	(*n* =125)	**(*n*=171)**	**(*n*=296)**	**U**	***p***
Post-covid natural preference	.37 0; Q1: 0 - Q3: 1	-.05 0; Q1: 0 - Q3: 0		8660.5	.003*
Post-covid prescription preference	-.27 0; Q1: -1 - Q3: 0	.07 0; Q1: -1 - Q3: 0		12579	.004*
Post-covid pharmaceutical tendency	.26 0; Q1: 0 - Q3: 1	-.16 0; Q1: 0 - Q3: 0		8445.5	.001*

*Significant at p<.01

Discussion

Demographics

The CBD using and non-using groups were similar in age, gender, ethnicity, and area of residence. Overall level of education was higher in the non-user group, reaching a statistical difference when comparing Key Stage 4 education and above. The average age of participants was 39.7, with an age range up to 87. One survey found medical cannabis use is increasing in older adults and 45% of the sample used CBD-only products (Brown et al., 2020). Other studies report mixed demographic patterns in their samples. Dunbar et al. (2022)'s survey of US community populations, found CBD-only users and CBD-cannabis users were more likely than non-users to identify as non-Hispanic White, speak only English at home and less likely to identify as heterosexual and Asian. CBD users were more likely to be female. Wheeler et al. (2020) found within their study sample, people of white ethnicity were more likely to use CBD products in comparison to other ethnicities. A survey on US cannabis dispensing staff found they were more likely to be Caucasian (85%) and had a mean age of 33.4 years (Haug et al., 2017). Although this is focussing on dispensing staff, the similarities of ethnicity and average age of dispensing staff is still of relevance.

Wellbeing

CBD-users scored higher (indicating greater distress) on all the psychological measures (depression, anxiety, stress, and insomnia) and pain intensity and interference. However, using the accepted clinical cut-offs, the CBD group's mean anxiety and depression scores were within the 'mild' range; their mean stress scores in the 'normal' range and mean insomnia/sleeping problems scores were in the 'subthreshold' range. These findings are in line with those from another survey with French CBD consumers, which reported higher

anxiety and depression scores for CBD users than control participants (Moinas et al., 2020). Other studies have commonly reported anxiety and low mood as a common reason for CBD, yet few have used validated psychological measures.

Cannabis use

One significant difference between the two groups was in prior use of cannabis. CBD users were more likely to have used cannabis in the last 12 months than the non-CBD users. Over half of the non-user group had not used cannabis before, compared with a quarter of the CBD group. Although this study did not ask further about cannabis use and ratio's, it can be assumed CBD users are more likely to also have experience of using cannabinoid mixtures both recreationally and therapeutically. Additional comments in this study indicate some CBD users are using cannabis for medicinal purposes and refer to the political and legal difficulties of other cannabinoid mixtures. For example, "*perhaps if cannabis or just CBD in isolation were properly decriminalised and regulated by government, people would benefit*" and "*on the contrary cannabis flower does help*". McFadden and Malone (2021)'s survey found less than half of CBD and THC consumers used them as medication substitutes. Of the CBD consumers who used it as a medication replacement, most replaced over-the-counter medication, an anti-anxiety prescription, or an opioid prescription. Similar rates were seen with THC. CBD was consumed more than THC to reduce pain. A clinical survey of over 2,600 patients found that chronic pain and anxiety disorders were the main reason for using medicinal cannabis by 50% and 33%, respectively (Drug Science, 2022).

Reasons for use

Most participants (84%) had not been recommended CBD products by a medical professional. CBD consumers' most prevalent reasons for using CBD were for anxiety (25%), chronic pain (12%) sleeping problems (10%) and stress (9%). In comparison, non-

users' most common reason for seeking treatment were for occasional pain, followed by similar reasons to CBD-users: anxiety, stress and low mood. It is an important finding that many individuals are using CBD to aid their emotional wellbeing rather than for physical health reasons. Our findings are similar to findings from comparable surveys (Goodman et al, 2020; Moltke & Hindocha, 2021; Wheeler et al, 2020). Goodman et al. (2020) found the third most common mental health endorsement was PTSD. Our study did not include PTSD as a response option, which is a limitation and an oversight, but it is possible that trauma-related treatment seeking was captured within other categories, such as anxiety and sleeping problems.

Most used additional treatments used by the CBD group were mindfulness, healthy eating, meditation and shop-bought pain-relief. Commonly used treatments for the non-user group were shop-bought pain relief, anti-depressant medication and healthy eating. This difference suggests CBD users may be more likely to seek more meditative practices than non-CBD users, who may seek more pharmaceutical and physical health focussed treatments.

Cannabidiol consumption patterns

The average daily applications of CBD was 5.3, however this was not a measure of mg, but rather how many drops or applications of the product were used in a day, which all have varying potency. The current study did not ask about mg of products as there are labelling and quantification issues, but this information would have been helpful for comparisons. Published research studies and randomised controlled trials (RCT's) also vary in their doses, with a common single dose ranging from 300 mg, 600 mg and 900 mg. For example Linares et al. (2019) used 150 mg – 600 mg and Zuardi et al. (2017) used 900 mg in their single-dose studies. A case series which reports on CBD for four weeks, used a daily oral dose of 330 mg (Pachecho et al, 2021). Studies which report on user consumption, demonstrate people use significantly lower levels than RCT's do. For example, Moltke and

Hindocha (2021) found 54% reported using less than 50 mg CBD daily, A systematic review of cannabidiol dosing in clinical populations reported helpful doses ranging from <62–3100 mg/d for an adult, a vastly broad range (Millar et al., 2019). One study analysed non-prescription CBD sellers online across a variety of countries, and found that apart from one website, CBD dose recommendations were below 150 mg (McGregor et al., 2020). As highlighted by Rong et al. (2017), there is a need to further explore, specify and compare cannabidiol products and doses. However, doses and nature of products vary and there are limitations with comparisons of effects (Gates, 2014; Rong, 2017). Other studies have been conducted on lower dose CBD with some effect on other health conditions, however these are not described in this report. See a review by McGregor et al. (2020) for further details.

On average, participants used CBD for about 26 weeks of the year in this survey. The most used method of CBD consumption was oil for oral use which is like Corroon and Phillips (2018) findings, and includes sprays, drops, and tinctures. Consuming CBD via vaping, flower and 'other methods' were the least common methods, which are also less commonly referred to in experimental studies investigating CBD effects. The average monthly spend on CBD products was £83.85, however the mode option was £0. It is likely that for many CBD consumers, they spend money on products which last them several months, or longer. Nevertheless, it appears that CBD products are still expensive in comparison to for example, over-the-counter pain relief.

Benefits and side effects

Common reported benefits from using CBD products were 'feeling more calm and relaxed', relaxed muscles/tension, sleep improvements and reduced pain. Participant comments support the beneficial claims, such as '*If I stop taking CBD I am in unbearable pain*' and others commented on the benefits noticed only when using compounds with THC. Several others reported how they did not notice benefits from CBD. Nevertheless, this

study's findings uphold similar results found by clinical Randomised control trials and demonstrate many benefits from using CBD.

Most participants (~80%) reported having no CBD side effects, with less than 10% and 5% reporting a dry mouth and fatigue, respectively. Our study findings support the view of CBD being well tolerated with a good safety profile and has "better side effect outcomes than other drugs" (Bergamaschi et al., 2011; Iffland & Grotenhermen, 2017). Other survey-based studies found more people reported no CBD side effects, compared to those who did (Corroon and Phillips, 2018; Moltke & Hindocha, 2021). However, detailed reviews on the safety and efficacy of CBD conclude that most human studies still require larger participant numbers and more longer-term studies, to fully understand the potential long-term effects of CBD (Iffland & Grotenhermen, 2017). Social media content analysis of the platform Pinterest in 2018 found 91.6% of 'pins' portrayed positive health claims of CBD and 98.2% did not address potential side effects or recommend dosage (Merten et al., 2020). This indicates information on side effects is lacking in many forums.

Perceived efficacy and expectancy

CBD-users had higher average perceived effectiveness ratings of CBD, in comparison to non-users' ratings of their 'main treatment'. As the non-users group includes many treatments, this comparison is limited. Our study found that higher CBD expectancy beliefs prior to using CBD were mildly positively correlated with perceived effectiveness post-use. Prior hopelessness about other previously used treatments was also significantly, mildly positively associated with perceived effectiveness of CBD (post-use) and prior belief about CBD products, which suggests a possible link between these factors. These findings provide support for an expectancy (placebo) effect, although a mild one, that higher prior expectancy beliefs in CBD products correlate with increased efficacy claims (Altman et al., 2021; Shannon et al., 2019; Spinella et al., 2021). Our study adds that increased hopelessness about

other previous treatments may also influence perceived CBD effectiveness. Another recent study found overall positive expectancies of the effects of CBD for anxiety, which tended to be higher for those experiencing higher levels of anxiety, in a community sample (Altman et al., 2021). However, the researchers did not find that CBD expectancy was a predictor of CBD use, and there were no significant correlations between anxiety and CBD use.

Attitudes

Compared to the non-user group, CBD users were less likely to agree that CBD needs to be regulated, less likely to be trusting of the pharmaceutical industry, have higher belief in the safety and the efficacy of CBD and that it is a more natural product. As predicted, CBD users perceive CBD more favourably than non-CBD users.

Predictive factors

Cannabis use, CBD acceptability attitudes and the total previous treatment in the previous year were all found to increase the odds of CBD use. Out of the health questionnaires, only pain severity was a significant predictor of CBD use. Females were more likely than males to use CBD. Trust of the pharmaceutical industry was found to lead to a decrease in the odds of CBD use and increased hopelessness of previous treatments lead to an increase in the odds of CBD use. These findings suggest that individuals who feel distrustful of typically prescribed medications and have required more medical treatment, are more likely to consume CBD. As indicated from this study, the preference for more 'natural' and accessible products with less side effects are desired for many who have used CBD products. An online survey investigated CBD use, compared to individuals who used cannabis as well (Vilches, Taylor & Filbey, 2021). The study found several factors accounted for variance: "indication of CBD use for medical ailments, use of CBD for more than once a day for longer than 2 years, applying CBD topically or consuming it via vaping or edibles, being female,

and, having lower educational attainment*”.* Although less research exists on factors influencing CBD consumption, research has found factors influencing medical cannabis use may include: younger age, living in a larger city, and more legal knowledge of legal and clinic aspects (in a Parkinson's Disease population in Germany; Yenilmez et al, 2021).

Attitudes since Covid-19

CBD-users were found to have higher levels of preferences for natural treatments, since the Covid-19 pandemic. Correlating with this, non-CBD users had higher preference for using prescription medication. CBD-users were also found to be more sceptical of the pharmaceutical industry, which correlates with the earlier finding in this study that CBD users are less trusting of the pharmaceutical industry.

Strengths and limitations

Our study provides new and insightful findings to how attitudes towards CBD, pharmaceuticals and the idea of CBD products being more 'natural', may influence CBD consumption. To the authors knowledge, there is no other research which investigates this. The study provides opportunities to compare CBD-users experiences to those who have not used CBD before and provides insight into other potential factors which may drive CBD use.

In terms of demographics, the two groups were well matched, however, a significant percentage of individuals were of White ethnicity (88.3%), and only .6% of participants were of Black, African, Caribbean or Black British ethnicity. There were also considerably more females (71.3%) across both groups. The authors own demographics and the use of snowballing effect for some of the recruitment, likely influenced the demographics of participants significantly. The significant bias and over-representation of White, Educated, Industrialized, Rich, and Democratic (WEIRD) individuals in research is a significant problem (Henrich, Heine & Norenzayan, 2010), which unfortunately our study contributes to.

One major limitation is the non-user group data. The scope of this research did not allow for further comparison analysis of subcategories for the differing problems and treatments; however, this information would be very insightful. The psychological and health measures (DASS, ISI and BPI) provide insights into clinical presentations and allow for comparisons between the two groups, however as they were only completed at one time-point, their use has limitations as many other factors can influence scoring on these measures.

Implications

The evidence base for CBD is still developing at a pace that is hugely outstripped by the actual uptake of CBD (Compton & Einstein, 2020; Leas et al., 2021). The need for increased education and modification of the knowledge on cannabis medicines and compounds has been highlighted by many, such as in the field of rheumatology and pain (Sarzi-Puttini et al., 2019) and for older adult populations (Calderon & Sayre, 2020), citing mislabelling, standardization issues, and drug interactions as major concerns from lack of education and knowledge. In one study, half of the participants (healthcare professionals in the USA) thought CBD was a good treatment option, however 95.9% did not receive education about CBD and 81.6% reported they informed themselves via lay-media (Schilling et al., 2019). In a public survey, the most common identified barrier to using hemp oil–based CBD for CBD-naive individuals, was not having enough information (Gicewicz et al., 2021). A US survey which found overall positive attitudes about CBD products, found over half the participants reported they would feel more comfortable if their physician could prescribe CBD and almost half of participants preferred to purchase CBD products from their doctor, rather than other sources (Moeller-Bertram et al., 2019). A study which investigated online search terms relating to cannabis, found 80% of the top CBD websites contained misleading information about CBD (Webb & Mansfield, 2021). In contrast, information about cannabis contained correct information.

The role of the placebo has been described as a "nuisance variable to be controlled for" but the placebo effect is now more acknowledged as a contributor to health research, rather than a hindrance (Colagiuri et al., 2015). Further research would be worthwhile to explore the placebo effect in CBD, including understanding potential beneficial therapeutic effects.

Randomised control trials have been the 'gold standard' of research, however other naturalistic research designs can provide helpful and important evidence for treatments and medications (Schlag et al., 2021), including research on more complex multimorbid patients in community settings that may have more rapid impact on clinical, public health and policy (Kessler & Glasgow, 2011). In recent years, the use of social media surveillance has increased, which provides further insight into real-life experiences. For example, recent research evaluating comments on the social media side Reddit, found that anxiety and pain were the most discussed causes for CBD use (Tran & Kavuluru, 2020). More qualitative research and online forum analysis could provide further information to understand other factors that influence treatment seeking behaviour and attitudes towards treatments, including expectancy beliefs and perceived hopelessness/hopefulness.

Even though research into the effects of CBD, and other cannabinoids is increasing, concerns are still raised of the unknown and unaddressed longer-term impacts on individuals, especially in vulnerable groups such as children, older populations, and people with chronic illnesses (Hazekamp, 2018).

Conclusions

This research aimed to understand the patterns of CBD consumption in the UK and potential factors that may influence decisions for CBD use and its perceived efficacy. The findings of CBD consumption patterns and health indications match that of other similar studies. The research contributes new findings to understand CBD consumer attitudes

towards CBD, other healthcare treatments and attitude changes since the Covid-19 pandemic, compared to non-users. Other factors that may increase the likelihood of CBD use are previous cannabis use, high CBD acceptability, more previous treatment in the previous year, increased hopelessness about other treatments and being female. More research into individual factors driving CBD consumption and regarding low-dose CBD efficacy is needed.

References

ACI (Association for the Cannabinoid Industry). (2021). *Green shoots: Sowing the seeds of the new UK cannabinoid market.* https://theaci.co.uk/wp-content/uploads/2021/05/Green-shoots-Sowing-the-seeds-of-the-new-UK-cannabis-market-ACI-_-CMC-report.pdf

Altman, B. R., Mian, M. N., Ueno, L. F., & Earleywine, M. (2021). Expectancies about the effects of cannabidiol products on anxiety symptoms. *Journal of Substance Use*. https://doi.org/10.1080/14659891.2021.2006341

Bastien, C. H., Vallières, A., & Morin, C. M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep medicine*, *2*(4), 297-307. https://doi.org/10.1016/S1389-9457(00)00065-4

Bergamaschi, M. M., Queiroz, R. H. C., Zuardi, A. W., & Crippa, J. A. S. (2011). Safety and side effects of cannabidiol, a Cannabis sativa constituent. *Current Drug Safety*, *6(4)*, 237-249. https://doi.org/10.2174/157488611798280924

Black, N., Stockings, E., Campbell, G., Tran, L. T., Zagic, D., Hall, W. D., Farrell, M., & Degenhardt, L. (2019). Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. *The Lancet. Psychiatry*, *6*(12), 995-1010. https://doi.org/10.1016/S2215-0366(19)30401-8

Boehnke, K. F., Gagnier, J. J., Matallana, L., & Williams, D. A. (2021). Substituting Cannabidiol for Opioids and Pain Medications Among Individuals With

Fibromyalgia: A Large Online Survey. *Journal of Pain*, *13*, 13. https://doi.org/10.1016/j.jpain.2021.04.011

Bonaccorso, S., Ricciardi, A., Zangani, C., Chiappini, S., & Schifano, F. (2019). Cannabidiol (CBD) use in psychiatric disorders: A systematic review. *Neurotoxicology*, *74*, 282-298. https://doi.org/10.1016/j.neuro.2019.08.002

Bramstedt, K. A. (2021). Unicorn Poo and Blessed Waters: COVID-19 Quackery and FDA Warning Letters. *Therapeutic Innovation and Regulatory Science*, *55(1)*, 239-244. https://doi.org/10.1007/s43441-020-00224-1

Brightfield Group. (2019). *From farm to aisle: US CBD Market*. https://global-uploads.webflow.com/596691afde3c5856d866ae50/5d25fbbc528d2e6c4abf56a3_US%20CBD%20Market%20Report_July2019.pdf.

Brown, J. D., Costales, B., van Boemmel-Wegmann, S., Goodin, A. J., Segal, R., & Winterstein, A. G. (2020). Characteristics of Older Adults Who Were Early Adopters of Medical Cannabis in the Florida Medical Marijuana Use Registry. *Journal of Clinical Medicine*, *9*(4), 18. https://doi.org/10.3390/jcm9041166

Butler, T. W., Hande, K., Ryan, M., Raman, R., McDowell, M. R., Cones, B., Jackson, H. J., Cortez, M., & Murphy, B. A. (2021). Cannabidiol: Knowledge, Beliefs, and Experiences of Patients With Cancer. *Clinical Journal of Oncology Nursing*, *25*(4), 405-412. https://doi.org/10.1188/21.CJON.405-412

Calderon, B., & Sayre, T. J. (2020). Cannabidiol use in older adults. *U.S, Pharmacist. 45(3)*, 34-38. https://cdn.coverstand.com/22400/652270/85ba5a7b50a126fff2dab2b842ca7336960f683a.1.pdf

Chagas, M. H. N., Zuardi, A. W., Tumas, V., Pena-Pereira, M. A., Sobreira, E. T., Bergamaschi, M. M., dos Santos, A. C., Teixeira, A. L., Hallak, J. E., & Crippa, J. A.

S. (2014). Effects of cannabidiol in the treatment of patients with Parkinson's disease: An exploratory double-blind trial. *Journal of Psychopharmacology*, *28*(11). https://doi.org/10.1177/0269881114550355

Chesney, E., McGuire, P., Freeman, T. P., Strang, J., & Englund, A. (2020). Lack of evidence for the effectiveness or safety of over-the-counter cannabidiol products [Review]. *Therapeutic Advances in Psychopharmacology*, *10*(no pagination). https://doi.org/10.1177/2045125320954992

Cleeland, C. S. (2009). *The Brief Pain Inventory User Guide*. https://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/BPI_UserGuide.pdf.

Colagiuri, B., Schenk, L. A., Kessler, M. D., Dorsey, S. G., & Colloca, L. (2015). The placebo effect: From concepts to genes. *Neuroscience*, *307*, 171–190. https://doi.org/10.1016/j.neuroscience.2015.08.017

Colloca, L. , Flaten, M. A., & Meissner, K. (2013). *Placebo and pain: from bench to bedside.*

Commission Regulation (EC) No 2860/2000 of 27 December 2000 amending Regulation (EC) No 2316/1999 laying down detailed rules for the application of Council Regulation (EC) No 1251/1999 establishing a support system for producers of certain arable crops, to include flax and hemp grown for fibre, specifying the rules on set-aside areas and amending the base areas for Greece and Portugal. (2000). *Official Journal*, L 332, 63-75. CELEX: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32000R2860

Compton, W. M., & Einstein, E. B. (2020). The Need for Evidence Regarding Cannabidiol. *JAMA Network Open, 3(10) (no pagination),* Article 21067. https://doi.org/10.1001/jamanetworkopen.2020.21067

Corroon, J., & Phillips, J. A. (2018). A Cross-Sectional Study of Cannabidiol Users. *Cannabis and Cannabinoid Research*, *3*(1), 152-161. https://doi.org/10.1089/can.2018.0006

Crippa, J. A., Guimaraes, F. S., Campos, A. C., & Zuardi, A. W. (2018). Translational Investigation of the Therapeutic Potential of Cannabidiol (CBD): Toward a New Age. *Frontiers in Immunology*, *9*, 2009. https://doi.org/10.3389/fimmu.2018.02009

Crippa, J. A. S., Zuardi, A. W., Guimaraes, F. S., Campos, A. C., Osorio, F. D., Loureiro, S. R., Dos Santos, R. G., Souza, J. D. S., Ushirohira, J. M., Pacheco, J. C., Ferreira, R. R., Costa, K. C. M., Scomparin, D. S., Scarante, F. F., Pires-Dos-Santos, I., Mechoulam, R., Kapczinski, F., Fonseca, B. A. L., Esposito, D. L. A., . . . Hallak, J, E, C. (2021). Efficacy and Safety of Cannabidiol Plus Standard Care vs Standard Care Alone for the Treatment of Emotional Exhaustion and Burnout Among Frontline Health Care Workers During the COVID-19 Pandemic A Randomized Clinical Trial. *JAMA Network Open*, *4*(8). https://doi.org/10.1001/jamanetworkopen.2021.20603

de Winter, J., & Dodou D. (2010). Five-point Likert items: t test versus Mann-Whitney-Wilcoxon (Addendum added October 2012). *Practical Assessment, Research & Evaluation*, *15*, 1–12. https://doi.org/10.7275/bj1p-ts64

DrugScience. (2022). *Project Twenty21 - May Update*. https://www.drugscience.org.uk/project-twenty21-may-update-2022/

Dunbar, M. S., Seelam, R., Tucker, J. S., Firth, C. L., Pedersen, E. R., Klein, D. J., Rodriguez, A., & D'Amico, E. J. (2022). Patterns and correlates of cannabidiol product and marijuana co-use in a sample of U.S. Young adults. *Addictive Behaviors*, *126*. https://doi.org/10.1016/j.addbeh.2021.107185

Food Standards Agency. (2020, May 9). *Food Standards Agency sets deadline for the CBD industry and provides safety advice to consumers*. https://www.food.gov.uk/news-

alerts/news/food-standards-agency-sets-deadline-for-the-cbd-industry-and-provides-safety-advice-to-consumers

Freeman, A. M., Petrilli, K., Lees, R., Hindocha, C., Mokrysz, C., Curran, H. V., Saunders, R., & Freeman, T. P. (2019). How does cannabidiol (CBD) influence the acute effects of delta-9-tetrahydrocannabinol (THC) in humans? A systematic review. *Neuroscience & Biobehavioral Reviews*, *107*, 696-712. https://doi.org/10.1016/j.neubiorev.2019.09.036

Freeman, T. P., Hindocha, C., Baio, G., Shaban, N. D., Thomas, E. M., Astbury, D., Freeman, A. M., Lees, R., Craft, S., Morrison, P. D., Bloomfield, M. A., O'Ryan, D., Kinghorn, J., Morgan, C. J., Mofeez, A., & Curran, H. (2020). Cannabidiol for the treatment of cannabis use disorder: A phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. *The Lancet Psychiatry*, *7*(10), 865-874. https://doi.org/ 10.1016/S2215-0366%2820%2930290-X

Gates, P. J., Albertella, L., & Copeland, J. (2014). The effects of cannabinoid administration on sleep: A systematic review of human studies. *Sleep Medicine Reviews, 18*(6), 477–487. https://doi.org/10.1016/j.smrv.2014.02.005

Gertsch, J. (2018). The Intricate Influence of the Placebo Effect on Medical Cannabis and Cannabinoids. *Medical Cannabis and Cannabinoids, 1*(1), 60–64. https://doi.org/10.1159/000489291

Gicewicz, E., Gatewood, S. S., Kaefer, T. N., Nadpara, P., & Goode, J. R. (2021). Assessment of hemp oil-based cannabidiol use in a community-based pharmacy setting. *Journal of the American Pharmacists Association: JAPhA*, *61*(4S), S49-S56. https://doi.org/10.1016/j.japh.2021.02.012

Goodman, S., Wadsworth, E., Schauer, G., & Hammond, D. (2020). Use and Perceptions of Cannabidiol Products in Canada and in the United States. *Cannabis and Cannabinoid Research*, *20*, 20. https://doi.org/10.1089/can.2020.0093

Gulbransen, G., Xu, W., & Arroll, B. (2020). Cannabidiol prescription in clinical practice: an audit on the first 400 patients in New Zealand. *BJGP Open*, *4*(1). https://doi.org/10.3399/bjgpopen20X101010

Haug, N. A., Kieschnick, D., Sottile, J. E., Vandrey, R., Babson, K., & Bonn-Miller, M. O. (2017). Attitudes and practices of cannabis dispensary staff [Conference Abstract]. *Drug and Alcohol Dependence*, *171*, e85. https://doi.org/10.1016/j.drugalcdep.2016.08.240

Häuser, W., Finn, D. P., Kalso, E., Krcevski-Skvarc, N., Kress, H.-G., Morlion, B., Perrot, S., Schäfer, M., Wells, C., & Brill, S. (2018). European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. *European Journal of Pain*, *22*(9). https://doi.org/10.1002/ejp.1297

Hazekamp, A. (2018). The trouble with CBD oil. *Medical cannabis and cannabinoids, 1*(1), 65-72. https://doi.org/10.1159/000489287

Hazekamp, A., Ware, M. A., Muller-Vahl, K. R., Abrams, D., & Grotenhermen, F. (2013). The Medicinal Use of Cannabis and Cannabinoids-An International Cross-Sectional Survey on Administration Forms. *Journal of Psychoactive Drugs*, *45(3)*, 199-210. https://doi.org/10.1080/02791072.2013.805976

Henrich, J., Heine, S. J., & Norenzayan, A. (2010). The weirdest people in the world? *Behavioral and Brain Sciences*, *33*(2–3), 61–83. https://doi.org/10.1017/S0140525X0999152X

Hindocha, C., Freeman, T. P., Grabski, M., Stroud, J. B., Crudgington, H., Davies, A. C., Das, R. K., Lawn, W., Morgan, C. J. A., & Curran, H. V. (2018). Cannabidiol reverses attentional bias to cigarette cues in a human experimental model of tobacco withdrawal. *Addiction*, *01*, 01. https://doi.org/10.1111/add.14243

Hurd, Y. L., Spriggs, S., Alishayev, J., Winkel, G., Gurgov, K., Kudrich, C., Oprescu, A. M., & Salsitz, E. (2019). Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial. *American Journal of Psychiatry*, *176*(11), 911-922. https://doi.org/10.1176/appi.ajp.2019.18101191

Iffland, K., & Grotenhermen, F. (2017). An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies [Review]. *Cannabis and Cannabinoid Research*, *2(1)*, 139-154. https://doi.org/10.1089/can.2016.0034

Kessler, R., & Glasgow, R. E. (2011). A Proposal to Speed Translation of Healthcare Research Into Practice. *American Journal of Preventive Medicine*, *40*(6), 637–644. https://doi.org/10.1016/j.amepre.2011.02.023

Khalsa, J. H., Bunt, G., Maggirwar, S. B., & Kottilil, S. (2021). COVID-19 and Cannabidiol (CBD). *Journal of Addiction Medicine*, *15*(5), 355-356. https://doi.org/10.1097/ADM.0000000000000771

Leas, E. C., Moy, N., McMenamin, S. B., Shi, Y. Y., Benmarhnia, T., Stone, M. D., Trinidad, D. R., & White, M. (2021). Availability and Promotion of Cannabidiol (CBD) Products in Online Vape Shops. *International Journal of Environmental Research and Public Health*, *18*(13), 9, Article 6719. https://doi.org/10.3390/ijerph18136719

Leweke, F. M., Piomelli, D., Pahlisch, F., Muhl, D., Gerth, C. W., Hoyer, C., Klosterkötter, J., Hellmich, M., & Koethe, D. (2012). Cannabidiol enhances anandamide signaling

and alleviates psychotic symptoms of schizophrenia. *Translational Psychiatry*, *2*(3), e94–e94. https://doi.org/10.1038/tp.2012.15

Linares, I. M., Zuardi, A. W., Pereira, L. C., Queiroz, R. H., Mechoulam, R., Guimaraes, F. S., & Crippa, J. A. (2019). Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test. *Revista Brasileira de Psiquiatria*, *41*(1), 9-14. https://doi.org/https://dx.doi.org/10.1590/1516-4446-2017-0015

Loflin, M. J. E., Earleywine, M., Farmer, S., Slavin, M., Luba, R., & Bonn-Miller, M. (2017). Placebo Effects of Edible Cannabis: Reported Intoxication Effects at a 30-Minute Delay. *Journal of Psychoactive Drugs*, *49*(5), 393–397. https://doi.org/10.1080/02791072.2017.1354409

Lovibond, S.H. & Lovibond, P.F. (1995). *Manual for the Depression Anxiety & Stress Scales. (2 Ed.)* Psychology Foundation. http://www2.psy.unsw.edu.au/dass/down.htm

Mauzay, D., LaFrance, E. M., & Cuttler, C. (2021). Acute Effects of Cannabis on Symptoms of Obsessive-Compulsive Disorder. *Journal of Affective Disorders*, *279*, 158-163. https://doi.org/10.1016/j.jad.2020.09.124

McCartney, D., Benson, M. J., Desbrow, B., Irwin, C., Suraev, A., & McGregor, I. S. (2020). Cannabidiol and Sports Performance: a Narrative Review of Relevant Evidence and Recommendations for Future Research. *Sports Medicine - Open*, *6*(1), 27. https://doi.org/ 10.1186/s40798-020-00251-0

McGregor, I. S., Cairns, E. A., Abelev, S., Cohen, R., Henderson, M., Couch, D., Arnold, J. C., & Gauld, N. (2020). Access to cannabidiol without a prescription: A cross-country comparison and analysis. International Journal of Drug Policy, 85, 102935. https://doi.org/10.1016/j.drugpo.2020.102935

McFadden, B. R., & Malone, T. (2021). Homegrown perceptions about the medical use and potential abuse of CBD and THC. *Addictive Behaviors*, *115*, 106799. https://doi.org/10.1016/j.addbeh.2020.106799

McGuire, P., Robson, P., Cubala, W. J., Vasile, D., Morrison, P. D., Barron, R., Taylor, A., & Wright, S. (2018). Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial. *American Journal of Psychiatry*, *175*(3), 225–231. https://doi.org/10.1176/appi.ajp.2017.17030325

Merten, J. W., Gordon, B. T., King, J. L., & Pappas, C. (2020). Cannabidiol (CBD): Perspectives from Pinterest. *Substance Use & Misuse*, *55*(13), 2213-2220. https://doi.org/10.1080/10826084.2020.1797808

Millar, S. A., Stone, N. L., Bellman, Z. D., Yates, A. S., England, T. J., & O'Sullivan, S. E. (2019). A systematic review of cannabidiol dosing in clinical populations. British Journal of Clinical Pharmacology, 85(9), 1888-1900. https://doi.org/https://dx.doi.org/10.1111/bcp.14038

Moeller-Bertram, T. A., Schilling, J. M., Hughes, C. G., Wallace, M. S., Sexton, M., & Backonja, M. (2019). How do you feel about Cannabidiol? Lessons from a survey in a pain clinic environment [Conference Abstract]. *Pain Medicine (United States)_2*, *20(3)*, E2. https://doi.org/10.1093/pm/pnz042

Moinas, M., Angerville, B., Naassila, M., & Dervaux, A. (2020). P.007 Frequency of anxious and depressive symptoms in a population of cannabidiol users [Conference Abstract]. *European Neuropsychopharmacology*, *40(Supplement 1)*, S5. https://doi.org/10.1016/j.euroneuro.2020.09.013

Moltke, J., & Hindocha, C. (2021). Reasons for cannabidiol use: a cross-sectional study of CBD users, focusing on self-perceived stress, anxiety, and sleep problems. *Journal of Cannabis Research*, *3*(1), 5. https://doi.org/10.1186/s42238-021-00061-5

Pacheco, J. C., Souza, J. D. S., Hallak, J. E. C., Osorio, F. D. L., Campos, A. C., Guimaraes, F. S., Zuardi, A. W., & Crippa, J. A. S. (2021). Cannabidiol as a Treatment for Mental Health Outcomes among Health Care Workers during the Coronavirus Disease Pandemic. Journal of Clinical Psychopharmacology, 41(3), 327-329. https://doi.org/10.1097/JCP.0000000000001405Rojas-Valverde, D. (2021). Potential Role of Cannabidiol on Sports Recovery: A Narrative Review. *Frontiers in Physiology*, *12*, 722550. https://doi.org/10.3389/fphys.2021.722550

Rong, C., Lee, Y., Carmona, N. E., Cha, D. S., Ragguett, R. M., Rosenblat, J. D., Mansur, R. B., Ho, R. C., & McIntyre, R. S. (2017). Cannabidiol in medical marijuana: Research vistas and potential opportunities. *Pharmacological Research*, *121*, 213-218. https://doi.org/10.1016/j.phrs.2017.05.005

Roth, D., Alonzo, R., Ailinani, H., Straub, T., & Henriksen, B. (2019). Cannabidiol: A retrospective review of patient outcomes for pain, sleep, anxiety, depression and function [Conference Abstract]. *Pain Physician*, *22(4)*, E387. https://www.painphysicianjournal.com/current/pdf?article=NjQyNg%3D%3D&journal=121

Sarzi-Puttini, P., Batticciotto, A., Atzeni, F., Bazzichi, L., Di Franco, M., Salaffi, F., Marotto, D., Ceribelli, A., Ablin, J. N., & Hauser, W. (2019). Medical cannabis and cannabinoids in rheumatology: where are we now?. *Expert Review of Clinical Immunology*, *15(10)*, 1019-1032. https://doi.org/10.1080/1744666X.2019.1665997

Schilling, J. M., Hughes, C. G., Leon, B. N., Parkinson, J. E., Backonja, M., & Moeller-Bertram, T. (2019). A Call for diligent Cannabidiol Research: Discrepancies between Knowledge and Beliefs of Healthcare Professionals [Conference Abstract]. *Postgraduate Medicine*, *131(SUPPL 1)*, 69-70. https://doi.org/10.1080/00325481.2019.1655695

Schlag, A. K., O'Sullivan, S. E., Zafar, R. R., & Nutt, D. J. (2021). Current controversies in medical cannabis: Recent developments in human clinical applications and potential therapeutics. *Neuropharmacology*, *191*, 108586. https://doi.org/10.1016/j.neuropharm.2021.108586

Sharpe, L., Sinclair, J., Kramer, A., de Manincor, M., & Sarris, J. (2020). Cannabis, a cause for anxiety? A critical appraisal of the anxiogenic and anxiolytic properties. *Journal of Translational Medicine*, *18*(1), 374. https://doi.org/10.1186/s12967-020-02518-2

Simpson, A. C., Bradley, C. W., & Schissler, J. R. (2020). Probable cutaneous adverse drug reaction due to a cannabidiol-containing hemp oil product in a dog. *Veterinary Dermatology*, *31(5)*, 404-e108. https://doi.org/10.1111/vde.12876

Skelley, J. W., Deas, C. M., Curren, Z., & Ennis, J. (2020). Use of cannabidiol in anxiety and anxiety-related disorders. *Journal of the American Pharmacists Association: JAPhA*, *60*(1), 253-261. https://doi.org/10.1016/j.japh.2019.11.008

Soares, V. P., & Campos, A. C. (2017). Evidences for the Anti-panic Actions of Cannabidiol. *Current Neuropharmacology*, *15*(2), 291-299. https://doi.org/10.2174/1570159X14666160509123955

Spinella, T. C., Stewart, S. H., Naugler, J., Yakovenko, I., & Barrett, S. P. (2021). Evaluating cannabidiol (CBD) expectancy effects on acute stress and anxiety in healthy adults: a randomized crossover study. *Psychopharmacology*, *238*(7), 1965-1977. https://doi.org/10.1007/s00213-021-05823-w

Stith, S. S., Vigil, J. M., Brockelman, F., Keeling, K., & Hall, B. (2018). Patient-Reported Symptom Relief Following Medical Cannabis Consumption. *Frontiers in Pharmacology*, *9*. https://doi.org/10.3389/fphar.2018.00916

Suraev, A. S., Marshall, N. S., Vandrey, R., McCartney, D., Benson, M. J., McGregor, I. S., ... & Hoyos, C. M. (2020). Cannabinoid therapies in the management of sleep

disorders: a systematic review of preclinical and clinical studies. *Sleep Medicine Reviews, 53,* 101339. https://doi.org/10.1016/j.smrv.2020.101339

Tran, T., & Kavuluru, R. (2020). Social media surveillance for perceived therapeutic effects of cannabidiol (CBD) products. *International Journal of Drug Policy*, *77,* 102688. https://doi.org/10.1016/j.drugpo.2020.102688

Trkulja, V., & Barić, H. (2020). *Current Research on Complementary and Alternative Medicine (CAM) in the Treatment of Anxiety Disorders: An Evidence-Based Review.* (pp. 415–449). https://doi.org/10.1007/978-981-32-9705-0_22

Vilches, J. R., Taylor, M. B., & Filbey, F. M. (2020). A Multiple Correspondence Analysis of Patterns of CBD Use in Hemp and Marijuana Users. *Frontiers in Psychiatry, 11 (no pagination),* Article 624012. https://doi.org/10.3389/fpsyt.2020.624012

Webb, M., & Mansfield, K. (2021). Public perception of medicinal and recreational cannabis and its effect on mental health: a survey of a regional Australian town. *Australasian Psychiatry, 29*(2), 124-128. https://doi.org/10.1177/1039856220970047

Wheeler, M., Merten, J. W., Gordon, B. T., & Hamadi, H. (2020). CBD (Cannabidiol) Product Attitudes, Knowledge, and Use Among Young Adults. *Substance Use & Misuse*, *55*(7), 1138-1145. https://doi.org/10.1080/10826084.2020.1729201

White, C. M. (2019). A Review of Human Studies Assessing Cannabidiol's (CBD) Therapeutic Actions and Potential. *Journal of Clinical Pharmacology*, *59*(7), 923-934. https://doi.org/ 10.1002/jcph.1387

Winiger, E. A., Hitchcock, L. N., Bryan, A. D., & Cinnamon Bidwell, L. (2021). Cannabis use and sleep: Expectations, outcomes, and the role of age. *Addictive Behaviors,112,* 106642. https://doi.org/10.1016/j.addbeh.2020.106642

Yenilmez, F., Frundt, O., Hidding, U., & Buhmann, C. (2021). Cannabis in Parkinson's Disease: The Patients' View. *Journal of Parkinsons Disease Print*, *11*(1), 309-321. https://doi.org/10.3233/JPD-202260

Yu, C. H. J., & Rupasinghe, H. P. V. (2021). Cannabidiol-based natural health products for companion animals: Recent advances in the management of anxiety, pain, and inflammation. *Research in Veterinary Science*, *140*, 38-46. https://doi.org/10.1016/j.rvsc.2021.08.001

Zuardi, A. W., Rodrigues, N. P., Silva, A. L., Bernardo, S. A., Hallak, J. E. C., Guimaraes, F. S., & Crippa, J. A. S. (2017). Inverted U-Shaped Dose-Response Curve of the Anxiolytic Effect of Cannabidiol during Public Speaking in Real Life. *Frontiers in Pharmacology*, *8*, 259. https://doi.org/10.3389/fphar.2017.00259

Part 3: Critical Appraisal

Introduction

This critical appraisal reflects on the process of completing parts one and two of the major research project and themes that occurred across both parts. I reflect on the methodological issues that emerged whilst completing the research, as well as difficulties that arose from personal and professional beliefs.

Reflections on Part 1: Systematic review

Novice naivety.

Completing a systematic review requires significant amounts of planning, time and effort to gather, synthesise and analyse the data. I soon learnt that this process does deserve the 'systematic' label. Whilst completing the abstract screening phase of 2085 papers, I became more aware of differences between many study designs that exist. My limited research experience meant I was less strict when determining if the inclusion criteria were met. I was more lenient whilst completing the abstract screening to reduce the risk of studies being incorrectly excluded. It also took more time to read the full text of studies such as case series, to determine if the data analysis provided sufficient information on CBD-only groups and the impact on anxiety. Following discussion with colleagues, post-hoc decisions were made to be more allowing with the age criteria. If the study did not state the minimum age of 18, but this was implied (such as no parental consent required), then the study was included. Such decisions can be made, as long as it is not based on the findings of the included studies (Chapter 3, Cochrane Training Handbook; McKenzie et al., 2022).

Screening over 2000 papers was a laborious, yet highly interesting process. I initially underestimated how helpful it would be to develop a rich source of information and references for all parts of the research project. I became frustrated that the process took much

longer than expected, but this process was incredibly helpful, as I wrote approximately 3000 (draft) words from papers I screened and subsequently read.

At the beginning of the systematic review process when I was completing preliminary searches and reviewing existing systematic reviews of CBD or cannabinoids, I found that the number of final included papers typically appeared 'reasonable'. For example, a systematic review focussing on cannabidiol in psychiatric disorders (Pavel, Paun & Matei, 2021) retrieved 226 studies, and only nine were deemed suitable for full-text screening. My systematic review investigated anxiety disorders and although it was broad, I expected it to be 'narrower' as it was researching one area only of psychiatric disorders. The number of studies I retrieved was significantly higher than this example. I speculate that the search terms I used or databases I searched were comprehensive and therefore retrieved higher numbers of papers. For example, Pavel et al's (2021) search phrases included MESH terms (cannabidiol AND psychiatry and psychology category), however they only searched three databases: PubMed, ClinicalTrials.gov, Web of Science.

Hopes to reduce bias.

I tried to reduce bias by widening the exclusion criteria of study designs and allowing case studies, case series and non-randomised controlled study designs. However, I found that bias was introduced in other ways and is inevitable. To keep a systematic review with a 'reasonable' number of included studies, exclusion criteria need to be set. My criteria meant that studies needed to state the dose of CBD participants took and no other anxiolytic medication or substances were to be used within the time frame of the study. Survey designs and naturalistic research designs provide rich and meaningful data of how individuals experience and use CBD. Studies that allow other medications enable a better understanding of how CBD may help people with multiple health conditions or complaints, for example,

chronic pain or health conditions that require additional medication. My systematic review does not capture the experience of such individuals or the effects of CBD in addition to other treatments and remedies.

Quality assessment.

I completed risk of bias assessments for the systematic review. I received mixed opinions from supervisors and colleagues as to how necessary this was. Others also consider them as biased in themselves if they are not done comprehensively and/or with multiple authors. Due to the time constraints of the DClinPsy, I was of the understanding it was not required for an additional author to complete the risk of bias assessment. As this was another new area for me, I also think that my lack of knowledge and confidence resulted in this taking a lot longer than I initially expected to decide on the appropriate assessments and to complete them. I was reassured when I read: "*There is currently no universally accepted standard or consensus about the best approach for assessing risk of bias in observational study designs. This can make both systematic reviews and public health guidelines difficult to interpret and evaluate because they use different methods.*" (Bero et al., 2018). I certainly found it difficult to find detailed risk of bias assessments and a consensus within published systematic reviews.

Ambiguity of anxiety.

Anxiety is a term that describes a broad range of experiences, definitions and understanding of similar emotions. It was the main outcome evaluated in the systematic review. Anxiety is an emotion and also often referred to as a type of 'disorder', e.g. to refer to someone who has generalised anxiety or Generalised Anxiety Disorder. Anxiety tends to refer to the experience of fear and apprehension, involving physical reactions and some behavioural reactions, whereas worry typically refers to the cognitive process of future-based concern (Zebb & Beck, 1998). Fear refers to a response to current or imminent threat or

aversive events (Daniel-Watanabe & Fletcher, 2021). Stress is also an emotion or term which is often used interchangeably with anxiety, which I did in the systematic review, however stress typically refers to an excess in demands on an individual. As I progressed with the systematic review and read many studies in detail, I understood that many studies investigated the effects of situation-specific anxiety, or induced fear. A lot of my clinical work has centered around more chronic experiences of anxiety and anxiety 'disorders'. In my professional practice, I often explain the similarities and differences between stress, anxiety and fear. I often describe the emotion of anxiety as like being on a spectrum, which everyone may experience differently. Typically, someone may describe worry as being towards the bottom of the spectrum (despite this being a cognitive process), and fear and panic towards the top. I have often used the Cognitive Behavioural model with clients and in this theoretical framework, anxiety is described as an emotional state that can be acute or chronic.

My search terms on the database searching did not include fear or stress, which was an over-sight and in retrospect, should have been included. In addition, my inclusion criteria for the anxiety measures were quite vague and biomarkers of anxiety were allowed, for example, heart rate variability and cortisol levels. Heart rate variability is considered a good measurement of stress, for example, Kim et al. (2018) conducted a review of human studies which used heart rate variability to measure stress. However, this interpretation could be ambiguous in the included studies and it led my interpretations to be quite vague at times.

Prevalent researchers.

Completing the systematic review, a lot of papers by a Brazilian research team were identified and they are highly cited in the cannabinoid research area. They have a lot of papers that were identified throughout the screening process of the systematic review. I also came across multiple published papers that used the same dataset, with overlapping reports of the outcomes. For example, Fusar-Poli et al. (2009) had 4 associated papers retrieved in the

full-text screening process. A review paper by the Brazilian research team (Crippa et al., 2018) conducted a non-systematic review, and stated they focussed particularly on CBD studies by Brazilian researchers. Collectively, this often made me question the power and influence this team have on CBD research, healthcare and the market. For example, many papers cite the beneficial effects that CBD can have on anxiety and they cite the few papers that use the public speaking tests.

Anxiety, amongst many other areas, is under-researched in parts of the world, such as in the Arab world (Bener et al., 2013). Additional research is needed in the field of cannabinoids in under-researched populations and to encompass cultural and societal differences.

Reflections on Part 2: Empirical paper

Ethnicity.

Whilst creating the survey for the empirical paper, I wanted the ethnicity question within the demographics section to be more inclusive in comparison to common methods. From conversations I have had personally and professionally, I have become more aware of the limitations of ethnicity classifications used in most systems. Ethnicity classification systems are typically limited to a few categories, often in line with centralised recording systems. In England, this is based on the NHS ethnic category codes (NHS Data Model and Dictionary, 2001). This means that many people's ethnic and cultural identity are not included in these classification systems, resulting in many people ticking an 'other' box for multiple registration forms throughout their life.

In my professional career, I felt part of this problem when completing initial assessments with new clients. I would need to go through a registration form, asking all the 'expected' demographics questions. Often, I would hear the disappointment, frustration or

despondence in people's voices. As a White, British person my understanding of this experience is limited as my identity has always been visible, often the first check box on forms. I initially aimed to create a very long ethnicity list, taking the categories from other more inclusive lists I found. Unfortunately, I found creating this list on the Qualtrics system difficult and not user friendly, particularly when trying to do comparison analyses. I contributed to this ongoing problem and used the common categorical list. Instead, in the survey I first asked the question 'How would you describe your ethnicity?', with a free-text comment box before the ethnicity categories. I then tried to incorporate these into the data reporting on part 2. On reflection, I could have put more effort into creating a more inclusive, expansive, category list. I believe that we should all make changes to systemic issues and I was disappointed I did not do this.

Biased demographics.

Overall, the sample in the survey is biased towards White, post-graduate educated females, within the age range of 20-30's. My own demographics and the use of snowball sampling methods from professional and personal contacts likely influenced this and reflects the over-representation in these demographics and under-representation of others, such as other ethnicities and other age ranges. Considerable effort was put in to extending the survey advertisement beyond my personal connections, however this over-representation is still clear.

Discomfort in asking questions.

Within the survey, there were additional questions I felt uncomfortable asking. In earlier designs of the survey, the main aims were to focus on anxiety, mood, pain and sleep. Consequently, we considered the role of specific measures for these constructs to consider the mental health and wellbeing of the sample. As the survey was cross-sectional (one-time point

only), there are limitations to their utility. I felt uncomfortable including these questions in the survey due to the length of the questionnaires and knowing that people I knew would be completing these personal questions. This is despite that I have worked in mental health for ten years and am well exposed to discussing highly sensitive and emotional content with others. I wondered if this was because the survey was going beyond the context of my professional world and merging into my personal word.

Power analysis.

An initial power analysis resulted in a recommendation of an 'absolute minimum' of 350 participants, with 175 in each group. I was heavily focussed on this minimum expectation and the importance of this when intending to publish research. Even though I knew this is a very difficult process, I spent a lot of time worrying about the completion numbers.

Ethics of research.

Since completing my undergraduate degree, I have been sceptical and critical of the research field. One of my main concerns is that copious amounts of research are conducted globally, such as for people completing courses, but unfortunately these may only serve the purpose of gaining the researcher a degree or certification if they are unpublished. Research often involves participants disclosing personal information and requires their time and effort. This, along with my concern of the completion rates, contributed to my concerns that I was asking many people to complete my survey and their efforts would not be worthy.

Social media.

I researched different 'CBD' groups on social media throughout this research project. I often felt very surprised by people's stories on social media of how CBD has transformed

their lives, and how people offered such detailed and confident advice on dose, type, method, time of administration of CBD, etc. I also felt upset when reading people's stories of pain and suffering, and often reading terrible stories of disappointment and frustration of inadequate healthcare and/or treatment for their health conditions and wellbeing. I also experienced this when reading through some comments on the survey. For example, when people described not being able to live a life without pain without the use of CBD, or other treatments. I was also saddened to see the amount of 'problems' that some people ticked on the survey.

Reflections across both parts 1 and 2

Lack of real-life perspectives.

Completing both parts of this research, I believe that I lost the 'patient' perspective and voice. Resulting from the nature of the systematic review, papers that I read in more detail, including the included studies, were clinical trials. These papers are often focussed on statistical analysis and 'average' findings, all using quantitative statistics. I did not come across qualitative analysis or more meaning-focussed research. The nature of writing a research paper also meant that I focussed heavily on published papers, with much less focus on patient forums, advocacy groups and other online methods, as these are regarded as less 'scientific'. Through social media, I have seen many strong opinions and varied perspectives on CBD, including how it has transformed people's quality of life and experiences with chronic mental and physical health. Yet, I feel these have not come across in either paper.

Animals.

Medically and clinically, research completed on animals is extensive, predominantly on rodents, and this is also the case for research investigating drug effects. My systematic review excluded animal studies, however, the database searching revealed plenty of animal

studies. It was also important for me to read and understand some of the animal studies, to understand theoretical frameworks and clinical implications of animal research on CBD and cannabinoids. My personal beliefs and activism against animal cruelty made it uncomfortable for me to read about some animal studies, particularly in studies where harm was induced. For example, one study visually exposed mice to a wild snake to induce anxiety (Twardowschy et al., 2013). Another study investigated whether "exposing lobster to cannabis smoke reduces anxiety and pain during the cooking process" (Gutierrez et al., 2021). My initial thoughts centered around questioning why humans would go to this extent to understand this, whilst they acknowledge the pain and distress for the animal(s).

Reading online forums, I also often read comments from people who used CBD for their pets. One paper reviewed research on 'companion' animals, including dogs and cats (Yu & Rupasinghe, 2021). In addition, I often found many research articles would be discrete about their research being on animals. It felt almost like they were trying to disguise this fact. For example, the animal(s) not being mentioned in the title or abstract and rarely being mentioned in the paper, such as with (Gomes et al., 2013).

Conversely, I also understand the importance of many scientific and medication discoveries that have occurred from animal testing.

Interesting research.

On the other hand, I was often surprised and intrigued by the different contexts in which CBD has been studied, often disguised within cannabis research. For example, research on 'acoustic trauma-induced tinnitus' in rats (Zheng, Reid & Smith, 2015), epidermolysis bullosa (Chelliah et al., 2018) and Rapid Eye Movement Sleep Behavior Disorder (de Almeida et al., 2021).

Time management.

Completing a large project in which I lacked confidence impacted my time-management skills, as discussed previously. During the processes of the full-text screening for the systematic review and the statistical analysis of the survey, I procrastinated in the form of increased research, double-checking and difficulty making decisions.

If I were to do it again.

If I were to complete this process again, I would include more exclusion phrases in the search strategy to enable quicker and more confident decisions. The survey design also contributed to limitations in the statistical analysis and interpretation. Likert scales were commonly used, resulting in ordinal data and non-parametric tests being used throughout the analysis. Non-parametric tests are typically thought to be less powerful and less desirable. The two groups were unequal, with more non-users than CBD-users which is less than ideal, given the research aim towards CBD users. However, it is also a strength of our study that comparisons can be drawn between the groups.

As a therapist and Trainee Clinical Psychologist, I was disappointed with how little I had included 'therapy/psychological' treatment options within the survey. This survey focussed initially on understanding substances people can consume. It then expanded to include additional types of therapies. Mindfulness and meditation sat within this, but they are spiritual practices, that can also be delivered in psychological therapy. It was a major oversight to not include psychological therapy. There are also difficulties in determining the differences between types of therapies, a hugely vast area when often therapies cannot be compared directly.

Commonly occurring papers that resulted from the systematic review searches with the term CBD were 'common bile duct', 'compulsive buying disorder' and 'corticobasal

degeneration'. The appearance of these studies made the process a bit more interesting, but it did add extra work and something I had not anticipated or thought to try and eliminate within the search strategy.

Conclusions

Completing the major research project has been a demanding process. It challenged me to be out of my comfort zone in both research skills and the clinical areas that I am familiar with. On the contrary, it has been an incredibly rewarding process and I have learnt many skills. The challenge of learning new skills and lacking confidence provided opportunities for pride and satisfaction once the challenges were overcome. However, research within pharmaceutical science also highlighted various contradictions and clashes in personal and professional beliefs.

References

Bener, A., Al-Kazaz, M., Ftouni, D., Al-Harthy, M., & Dafeeah, E. E. (2013). Diagnostic overlap of depressive, anxiety, stress and somatoform disorders in primary care. *Asia-Pacific Psychiatry, 5*(1), E29–E38. https://doi.org/10.1111/j.1758-5872.2012.00215.x

Bero, L., Chartres, N., Diong, J., Fabbri, A., Ghersi, D., Lam, J., Lau, A., McDonald, S., Mintzes, B., Sutton, P., Turton, J. L., & Woodruff, T. J. (2018). The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures. *Systematic Reviews, 7*(1). https://doi.org/10.1186/s13643-018-0915-2

Chelliah, M. P., Zinn, Z., Khuu, P., & Teng, J. M. (2018). Self-initiated use of topical cannabidiol oil for epidermolysis bullosa. *Pediatric dermatology, 35*(4), e224-e227. https://doi.org/10.1111/pde.13545

Crippa, J. A., Guimaraes, F. S., Campos, A. C., & Zuardi, A. W. (2018). Translational Investigation of the Therapeutic Potential of Cannabidiol (CBD): Toward a New Age. *Frontiers in Immunology*, *9*, 2009. https://doi.org/10.3389/fimmu.2018.02009

Daniel-Watanabe, L., & Fletcher, P. C. (2021). Are Fear and Anxiety Truly Distinct? *Biological Psychiatry Global Open Science*. https://doi.org/10.1016/j.bpsgos.2021.09.006

de Almeida, C. M. O., Brito, M. M. C., Bosaipo, N. B., Pimentel, A. V., Tumas, V., Zuardi, A. W., Crippa, J. A. S., Hallak, J. E. C., & Eckeli, A. L. (2021). Cannabidiol for Rapid Eye Movement Sleep Behavior Disorder. *Movement Disorders*, *36*(7), 1711-1715 https://doi.org/10.1002/mds.28577

Fusar-Poli, P., Crippa, J., Bhattacharyya, S., Borgwardt, S. J., Allen, P., Martin-Santos, R., Seal, M., Surguladze, S. A., O'Carrol, C., Atakan, Z., Zuardi, A. W., & McGuire, P. K. (2009). Distinct effects of A9-Tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. *Archives of General Psychiatry*, *66(1)*, 95-105. https://doi.org/10.1001/archgenpsychiatry.2008.519

Gomes, F. V., Alves, F. H. F., Guimaraes, F. S., Correa, F. M. A., Resstel, L. B. M., & Crestani, C. C. (2013). Cannabidiol administration into the bed nucleus of the stria terminalis alters cardiovascular responses induced by acute restraint stress through 5-HT1A receptor. *European Neuropsychopharmacology*, *23*(9), 1096-1104. https://doi.org/10.1016/j.euroneuro.2012.09.007

Gutierrez, A., Creehan, K. M., Turner, M. L., Tran, R. N., Kerr, T. M., Nguyen, J. D., & Taffe, M. A. (2021). Vapor exposure to Delta 9-tetrahydrocannabinol (THC) slows locomotion of the Maine lobster (Homarus americanus). *Pharmacology Biochemistry and Behavior*, *207*, 8, Article 173222. https://doi.org/10.1016/j.pbb.2021.173222

Kim, H.-G., Cheon, E.-J., Bai, D.-S., Lee, Y. H., & Koo, B.-H. (2018). Stress and Heart Rate Variability: A Meta-Analysis and Review of the Literature. *Psychiatry Investigation*, *15*(3), 235–245. https://doi.org/10.30773/pi.2017.08.17

McKenzie, J. E., Brennan, S. E., Ryan, R. E., Thomson, H. J., Johnston, R. V., Thomas, J. (2022). Chapter 3: Defining the criteria for including studies and how they will be grouped for the synthesis. In: Higgins, J, P, T., Thomas, J., Chandler, J., Cumpston, M., Li. T., Page. M, J., Welch, V. A. (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Available from www.training.cochrane.org/handbook.

Nazario, L. R., Antonioli, R., Capiotti, K. M., Hallak, J. E., Zuardi, A. W., Crippa, J. A., Bonan, C. D., da Silva, R. S. (2015). Caffeine protects against memory loss induced by high and non-anxiolytic dose of cannabidiol in adult zebrafish (danio rerio). *Pharmacology, Biochemistry & Behavior*, *135*, 210-6. https://dx.doi.org/10.1016/j.pbb.2015.06.008

NHS Data Model and Dictionary. (2001). https://www.datadictionary.nhs.uk/attributes/ethnic_category_code_2001.html

Pavel, A. N., Paun, R., & Matei, V. P. (2021). The Use of Cannabidiol in Treating Psychiatric Disorders: A Systematic Review. *Psychiatry and Clinical Psychopharmacology*, *31*(2), 226-232. https://doi.org/10.5152/pcp.2021.21743

Twardowschy, A., Castiblanco-Urbina, M. A., Uribe-Marino, A., Biagioni, A. F., Salgado-Rohner, C. J., Crippa, J. A. D., & Coimbra, N. C. (2013). The role of 5-HT1A receptors in the anti-aversive effects of cannabidiol on panic attack-like behaviors evoked in the presence of the wild snake Epicrates cenchria crassus (Reptilia, Boidae). *Journal of Psychopharmacology*, *27*(12), 1149-1159. https://doi.org/10.1177/0269881113493363

Yu, C. H. J., & Rupasinghe, H. P. V. (2021). Cannabidiol-based natural health products for companion animals: Recent advances in the management of anxiety, pain, and inflammation. *Research in Veterinary Science*, *140*, 38-46. https://doi.org/10.1016/j.rvsc.2021.08.001

Zebb, B. J., & Beck, J. G. (1998). Worry Versus Anxiety. *Behavior Modification*, *22*(1), 45–61. https://doi.org/10.1177/01454455980221003

Zheng, Y. W., Reid, P., & Smith, P. E. (2015). Cannabinoid CB1 receptor agonists do not decrease, but may increase acoustic trauma-induced tinnitus in rats. *Frontiers in Neurology*, *6*, 9, Article 60. https://doi.org/10.3389/fneur.2015.00060

Appendices

Appendix 1: Search strategy and search terms

Search terms

Search concept	Search terms	Subject headings
Medline		
Cannabidiol	Cannabidiol CBD Epidiolex Epidyolex	Cannabidiol
Anxiety	Anxi* Fear Phobi* Trauma PTSD OCD Obsessive Panic	anxiety disorders agoraphobia anxiety, separation neurocirculatory asthenia obsessive-compulsive disorder hoarding disorder panic disorder phobic disorders phobia, social exp "trauma and stressor related disorders" exp anxiety exp fear
Humans	exp animals/ not humans.sh. CBD and anxiety search terms were combined NOT animals	
Embase		
Cannabidiol	Cannabidiol CBD Epidiolex Epidyolex	Cannabidiol
Anxiety	Anxi* Fear Phobi* Trauma PTSD OCD Obsessive Panic	"mixed anxiety and depression" test anxiety performance anxiety anxiety disorder anxiety anticipatory anxiety separation anxiety generalized anxiety disorder fear panic obsessive compulsive disorder agoraphobia hypochondriasis social phobia
Humans	exp animal experiment/ not (human experiment/ or human/) CBD and anxiety search terms were combined NOT animals	

Search concept	Search terms	Subject headings
APA PsycInfo		
Cannabidiol	Cannabidiol CBD Epidiolex Epidyolex	Cannabidiol
Anxiety	Anxi* Fear Phobi* Trauma PTSD OCD Obsessive Panic	Separation Anxiety Disorder exp Health Anxiety exp Anxiety Management exp Anxiety Disorders exp Anxiety exp Castration Anxiety exp Speech Anxiety exp Generalized Anxiety Disorder exp Anxiety Sensitivity exp Performance Anxiety exp Social Anxiety exp Test Anxiety exp Mathematics Anxiety exp Computer Anxiety exp Separation Anxiety exp Death Anxiety exp Panic Attack exp Panic exp Panic Disorder exp Health Anxiety/ exp Posttraumatic Stress Disorder exp Social Anxiety exp Obsessive Compulsive Disorder exp Compulsions exp Emotional Trauma exp Birth Trauma exp Trauma exp "Stress and Trauma Related Disorders"
Humans	((animals not "Animals") and "Humans"). CBD and anxiety search terms were combined NOT animals	

Search concept	Search terms	Subject headings
Web of Science		
Cannabidiol	Cannabidiol	n/a
	CBD	
	Epidiolex	
	Epidyolex	
Anxiety	Anxi*	n/a
	Fear	
	Phobi*	
	Trauma	
	PTSD	
	OCD	
	Obsessive	
	Panic	
CENTRAL		
Cannabidiol	Cannabidiol	n/a
Anxiety	Anxiety	n/a
ClinicalTrials.gov		
Cannabidiol	Cannabidiol	n/a
Anxiety	Anxiety	n/a

Search strategy

Medline

1. Cannabidiol/

2. (Cannabidiol or CBD or Epidiolex or Epidyolex).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3. 1 or 2 [cbd terms]

4. anxiety disorders/ or agoraphobia/ or anxiety, separation/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or hoarding disorder/ or panic disorder/ or phobic disorders/ or phobia, social/ or exp "trauma and stressor related disorders"/

5. exp anxiety/ or exp fear/

6. (Anxi* or Fear or Phobi* or Trauma or PTSD or OCD or Obsessive or Panic).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

7. 4 or 5 or 6 [anxiety terms]

8. 3 and 7 [cbd and anxiety]

9. exp animals/ not humans.sh.

10. 8 not 9 [cbd and anxiety not animals]

Embase

1. exp cannabidiol/

2. (Cannabidiol or CBD or Epidiolex or Epidyolex).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

3. 1 or 2

4. "mixed anxiety and depression"/ or test anxiety/ or performance anxiety/ or anxiety disorder/ or anxiety/ or anticipatory anxiety/ or separation anxiety/ or generalized anxiety disorder/ or fear/ or panic/ or obsessive compulsive disorder/ or agoraphobia/ or hypochondriasis/ or social phobia/

5. (Anxi* or Fear or Phobi* or Trauma or PTSD or OCD or Obsessive or Panic).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

6. 4 or 5

7. exp animal experiment/ not (human experiment/ or human/)

8. 3 and 6

9. 8 not 7

APA PsycInfo

1. (Cannabidiol or CBD or Epidiolex or Epidyolex).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

2. exp Separation Anxiety Disorder/ or exp Health Anxiety/ or exp Anxiety Management/ or exp Anxiety Disorders/ or exp Anxiety/ or exp Castration Anxiety/ or exp Speech Anxiety/ or exp Generalized Anxiety Disorder/ or exp Anxiety Sensitivity/ or exp Performance Anxiety/ or exp Social Anxiety/ or exp Test Anxiety/ or exp Mathematics Anxiety/ or exp Computer Anxiety/ or exp Separation Anxiety/ or exp Death Anxiety/ or exp Panic Attack/ or exp Panic/ or exp Panic Disorder/ or exp Health Anxiety/

3. exp Posttraumatic Stress Disorder/ or exp Social Anxiety/ or exp Obsessive Compulsive Disorder/ or exp Compulsions/

4. exp Emotional Trauma/ or exp Birth Trauma/ or exp Trauma/ or exp "Stress and Trauma Related Disorders"/

5. (Anxi* or Fear or Phobi* or Trauma or PTSD or OCD or Obsessive or Panic).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

6. 2 or 3 or 4 or 5 [anxiety terms]

7. 1 and 6

8. ((animals not "Animals") and "Humans").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

9. 7 not 8

Web of science

1. Cannabidiol or CBD or Epidiolex or Epidyolex
2. AND Anxi* or Fear or Phobi* or Trauma or PTSD or OCD or Obsessive or Panic

CENTRAL

Searched under ‘trials’ - ‘cannabidiol’ and ‘anxiety’, both in the ‘all text’ fields

CLINICALTRIALS.GOV

Searched ‘anxiety’ under ‘condition or disease’ search field, ‘cannabidiol’ and ‘cbd’ under ‘other terms’ search field

Appendix 2: Data extraction template

Title	Year	Authors	Decision	18+	Humans	CBD only	CBD dose is stated
			Yes/No/Maybe	Yes/No	Yes/No	Yes/No	Yes/No
Clinical study	**Measures anxiety**	**Interpretation of the CBD effect on anxiety**	**Data is available and interpretable**	**Exclude reason**	**Label**	**Notes**	
Yes/No	Yes/No	Yes/No	Yes/No				

Appendix 3: Study inclusion decision template

Title	Year	Authors	Study design	Participant group	n participants in groups	Age	Gender
CBD type	**CBD dose**	**Comparator groups**	**Outcome measures**	**Outcomes / effects**	**Procedure**	**Notes**	

Appendix 4: Prospective study registrations

ClinicalTrials.gov registration number	Study authors/ contact	Study title	Study design and aims
NCT05023759	Formula30A LLC	Anxiety Symptoms in Relation to Use of Hemp-derived, Full Spectrum Cannabidiol (CBD)	Open-label, cohort study examining the effects of 25 mg capsules for eight weeks on adults diagnosed with Generalised Anxiety Disorder using the Generalized Anxiety Disorder 7-Item Scale (GAD7).
NCT05015439	Johns Hopkins University	Cannabidiol (CBD) in Adults With ASD	Participants will receive 100 mg twice daily for 3 weeks, increased to 200 mg twice daily by week 3 – week 6. Then participants will receive no drug/placebo for 2 weeks, then a 6 week period of placebo drug. Participants will have a diagnosis of Autism Spectrum Disorder and several outcome measures will be used, including the Hamilton Anxiety Rating Scale.
NCT04550377	NYU Langone Health	Cannabidiol as a Treatment for PTSD and PTSD Comorbid With TBI	A randomised controlled trial, with 120 participants, half of which will have comorbid mild traumatic brain injury (TBI). There will be three study arms, each with 40 subjects: 1) Oral CBD 400 mg daily; 2) Oral CBD 800 mg daily, and 3) Placebo daily. Treatment duration will be 8 weeks and the primary outcome measured with the Clinician-Administered PTSD Scale.

ClinicalTrials.gov registration number	Study authors/ contact	Study title	Study design and aims
NCT04978428	University of Chicago	Epidiolex in Obsessive Compulsive Disorder	An open label study with 15 participants with OCD receiving a two-week treatment of Epidiolex (2.5 mg/kg twice daily for one week followed by 5mg/kg twice daily). Various outcome measures will be used, including the Yale Brown Obsessive Compulsive Scale and the Hamilton Anxiety Rating Scale.
NCT02548559	Staci Gruber, Ph.D., Mclean Hospital	Sublingual Cannabidiol for Anxiety	An open label study with estimated 97 participants using sublingual CBD (10 mg/ml) or placebo three times daily for four weeks in addition to their normal treatment regimen. Outcome measures used will be the Beck Anxiety Inventory, the Overall Anxiety Severity and Impairment Scale and the State-Trait Anxiety Inventory.
NCT04729244	Anuradha Anand, Advanced Pain and Rehab Specialists	The Study of Hemp Oil CBD for Evaluation of Efficacy and Safety in Treatment of Pain, Anxiety and Insomnia Management	A cohort pilot study with estimated 30 participants experiencing chronic pain. Half participants will receive 500mg CBD/30ml (50mg/dose) once daily and half will receive CBD cream 2000mg/1oz (50mg/dose) once daily, for 4 weeks. Various outcome measures will be used, including the Hamilton Anxiety Rating Scale.

Appendix 5: Ethical approval letter

UCL RESEARCH ETHICS COMMITTEE
OFFICE FOR THE VICE PROVOST RESEARCH

18th March 2021

Professor Valerie Curran
Research Department of Clinical, Educational and Health Psychology,
UCL

Cc: Georgina Wallington and Jon Waldron

Dear Professor Curran

Notification of Ethics Approval with Provisos
Project ID/Title: 19641/001: Understanding patterns of and motivations for consumption of cannabidiol (CBD) products in the UK: an explorative study

Further to your satisfactory responses to the Committee's comments, I am pleased to confirm in my capacity as Chair of the UCL Research Ethics Committee (REC) that your study has been ethically approved by the REC until **18th March 2022.**

Approval is granted on condition that you provide in due course written evidence of Facebook group moderators approval, where required, to advertise the study for our records.

Approval is also subject to the following conditions:

Notification of Amendments to the Research
You must seek Chair's approval for proposed amendments (to include extensions to the duration of the project) to the research for which this approval has been given. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing an 'Amendment Approval Request Form'
http://ethics.grad.ucl.ac.uk/responsibilities.php

Adverse Event Reporting – Serious and Non-Serious
It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator (ethics@ucl.ac.uk) immediately the incident occurs. Where the adverse incident is unexpected and serious, the Joint Chairs will decide whether the study should be terminated pending the opinion of an independent expert. For non-serious adverse events the Joint Chairs of the Ethics Committee should again be notified via the Ethics Committee Administrator within ten days of the incident occurring and provide a full written report that should include any amendments to the participant information

Office of the Vice Provost Research, 2 Taviton Street
University College London
Tel: +44 (0)20 7679 8717
Email: ethics@ucl.ac.uk
http://ethics.grad.ucl.ac.uk/

sheet and study protocol. The Joint Chairs will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

Final Report

At the end of the data collection element of your research we ask that you submit a very brief report (1-2 paragraphs will suffice) which includes in particular issues relating to the ethical implications of the research i.e. issues obtaining consent, participants withdrawing from the research, confidentiality, protection of participants from physical and mental harm etc.

In addition, please:

- ensure that you follow all relevant guidance as laid out in UCL's Code of Conduct for Research: https://www.ucl.ac.uk/srs/file/579
- note that you are required to adhere to all research data/records management and storage procedures agreed as part of your application. This will be expected even after completion of the study.

With best wishes for the research.

Yours sincerely

[redacted]

Professor Michael Heinrich
Joint Chair, UCL Research Ethics Committee

Appendix 6: Participant information sheet

Participant Information Sheet

UCL Research Ethics Committee Approval ID Number: 19641/001

Title of Study: Understanding patterns of and motivations for consumption of cannabidiol (CBD) products in the UK: an explorative study

Department: Clinical, Education and Health Psychology, University College London

Name and Contact Details of the Researcher(s):
Georgina Wallington ; georgina.wallington.19@ucl.ac.uk
Dr Jon Waldron ; jonathan.waldron.15@ucl.ac.uk

Name and Contact Details of the Principal Researcher:
Professor H. Valerie Curran ; v.curran@ucl.ac.uk
Address: Room 537, 1-19 Torrington Place, London, WC1E 7HB

1. **About the study**

   You are being invited to take part in a study which involves the completion of an online survey. Participation is entirely voluntary and you can stop completing it at any time.
   Please read this information sheet and consent form before deciding to take part. You can contact the research team by email if you have any further questions.

   This study is being conducted as part of one of the researcher's completion of a Doctorate in Clinical Psychology.

   This research aims to understand more about why people in the UK may or may not choose to use cannabidiol (CBD) products, for different physical health or emotional health reasons. We hope to learn more about what, and how, factors may influence decisions to use CBD products and other medications, remedies or health treatments. We also hope to understand how people find using these products, including any perceived effects, benefits or harm.

   It is hoped this research will contribute to a deeper understanding of why and how individuals use CBD products.

2. **Why have I been chosen?**

   Advertisement of this study aims to capture different people's experiences. Posts have been shared with different online groups, but individuals are also encouraged to share this with others who may not see the post.

3. **Inclusion and exclusion criteria**

   Participants are required to have the UK as their main residence and to base their answers on products available in the UK.
   Participants are required to be age 18 or over and to have heard of CBD before.

4. **Do I have to take part?**

It is entirely up to you to decide whether to take part in our study. If you decide to take part, you can download this information sheet on this page and will be required to consent to take part, on the next page, before completing the survey.

You can request the withdrawal of your data, without giving a reason, until the survey closes for responses and data is analysed. This will be up to approximately October 2021. At the end of the survey, you will be provided with a randomly assigned ID number. Please take note of this and quote this via email to any of the researchers above, if you request deletion of your data responses.

5. What will happen if I take part?

You will be asked to provide consent for your data to be used in our research.
You will then be asked to complete an online survey which should take approximately 15 - 20 minutes.
You will also be given the opportunity to provide an email address to be entered into the prize draw for participation (see below). We will only ask for your email address and not for your name, address, or any other contact details. Your email address will be stored separately from your survey responses. Provision of an email address to enter the prize draw is entirely voluntary.

6. What are the possible disadvantages and risks of taking part?

There are no foreseeable risks of participating in the study. Your responses will be stored anonymously and will not be linked to your email address (if you choose to provide this to us). We do not collect your IP address and you can withdraw your participation up until the end of the survey data collection, as detailed in point 4.

Some questions may ask you to think about your own physical and psychological distress. If you find these questions uncomfortable or distressing, participation can be stopped at any time. Sources of support are listed below, under point 14.

7. What are the possible benefits of taking part?

At the end of the survey, you will have the chance to opt into a prize draw for £10 multi-retail e-vouchers. Opting into the prize draw is entirely voluntary. If you decide to opt-in, you will be asked to provide an email address which we will use to contact the winners.
It is also hoped that this work will contribute to scientific knowledge and understanding of individuals' experiences of treatments or remedies for physical and emotional difficulties.
The research will subsequently be made available on the UCL Theses Discovery website. Efforts will be made to publish the results in peer-reviewed journals and public broadcasting.

8. What if something goes wrong?

Whilst we do not foresee any risks in participating in this survey, should you have a complaint or concern, please contact the Principal Researcher (Valerie Curran – v.curran@ucl.ac.uk), or any member of the research team.

You may also contact the Chair of the UCL Research Ethics Committee, who have provided ethical approval for this study – ethics@ucl.ac.uk, if you feel your concern is inadequately addressed by the research team and wish to raise a complaint.

9. Will my taking part in this project be kept confidential?

All the information you provide will remain anonymous and strictly confidential. You will not be able to be identified in any ensuing reports or publications.

The General Data Protection Regulation (GDPR) will apply to all information collected and stored during this study. Survey responses and email addresses will be stored on physically separate servers. Data will be stored within encrypted digital computer files and cloud-based servers, all located within the EU. Only members of the research team will have access to the data you provide. The survey is hosted by Qualtrics, which ensures secure and encrypted data capture and storage.

10. Limits to confidentiality

Confidentiality will be respected unless there are compelling and legitimate reasons for this to be breached. If this was the case, we would inform you of any decisions that might limit your confidentiality.

11. What will happen to the results of the research project?

Efforts will be made to publish reports on the results of the research project, to contribute to the understanding of scientific, psychological and social natures of consumption of CBD products. The results will be presented in the Clinical Psychology Doctoral Thesis for Georgina Wallington. If you are interested in learning about the main findings once the study is complete, please email the research team who will reply to you when findings are available.

12. Local Data Protection Privacy Notice

Notice:
The controller for this project will be University College London (UCL). The UCL Data Protection Officer provides oversight of UCL activities involving the processing of personal data, and can be contacted at data-protection@ucl.ac.uk

This 'local' privacy notice sets out the information that applies to this study. Further information on how UCL uses participant information can be found in our 'general' privacy notice - https://www.ucl.ac.uk/legal-services/privacy/ucl-general-privacy-notice-participants-and-researchers-health-and-care-research-studies

The information that is required to be provided to participants under data protection legislation (GDPR and DPA 2018) is provided across both the 'local' and 'general' privacy notices.

The categories of personal data used will be as follows: age, ethnicity, preferred gender, country of residence, location type, education level, psychological wellbeing, physical health and wellbeing, use of and attitudes towards treatments for physical and psychological health.

The lawful basis that will be used to process your personal data are: 'Public task' for personal data and' Research purposes' for special category data.

Your personal data will be processed so long as it is required for the research project. This will all be deleted after 10 years. Your data will be pseudo-anonymised and efforts have been made to minimise the processing of personal data wherever possible.

If you are concerned about how your personal data is being processed, or if you would like to contact us about your rights, please contact UCL in the first instance at data-protection@ucl.ac.uk.

13. Who is organising and funding the research?

The research is led by researchers at University College London (UCL). UCL is sponsoring the research.

14. Contact for further information

If you have any further questions, please contact the researchers whose contact details are at the top of this page.

15. Further support

Should you become distressed by completing this survey and wish to seek additional support, please consider the options below.

- Your GP or a health professional
- Someone you feel you can speak to, such as a close friend or family member
- A support line or charity, such as:
  MIND - https://www.mind.org.uk/
  The Samaritans – 24 hour telephone line, call **116 123** or visit https://www.samaritans.org/

Thank you for reading this information sheet and for considering taking part in this research study.

Appendix 7: Participant consent form

CONSENT FORM

Please complete this form after you have read the Information Sheet.

Title of Study: Understanding patterns of and motivations for consumption of cannabidiol (CBD) products in the UK: an explorative study

Department: Clinical, Education and Health Psychology, University College London
Name and Contact Details of the Researcher(s):
Georgina Wallington ; georgina.wallington.19@ucl.ac.uk
Dr Jon Waldron ; jonathan.waldron.15@ucl.ac.uk

Name and Contact Details of the Principal Researcher:
Professor H. Valerie Curran ; v.curran@ucl.ac.uk

Name and Contact Details of the UCL Data Protection Officer:
Alexandra Potts- data-protection@ucl.ac.uk

This study has been approved by the UCL Research Ethics Committee, Project ID number: **19641/001**

Thank you for considering taking part in this research. If you have any questions, please ask the researcher before you complete the survey.

I confirm I understand that by selecting each box below, I am consenting to this element of the study.

I understand that by not giving consent for any one element that I may be deemed ineligible for the study and unable to continue.

Yes	No
○	○

I confirm that I have read and understood the Information Sheet for the above study. I have had an opportunity to consider the information and what will be expected of me.

I have also had the opportunity to ask questions which have been answered to my satisfaction.

Yes	No
○	○

I consent to participate in the study. I understand that my personal information will be used for the purposes explained to me. This includes: age, ethnicity, preferred gender, country of residence, psychological wellbeing, physical health and wellbeing, use of and attitudes towards treatments for physical and psychological health.

I understand that according to data protection legislation, ‘public task’ will be the lawful basis for processing and ‘research purposes’ will be the lawful basis for processing special category data.

Yes No

I understand that all personal information will remain confidential and that all efforts will be made to ensure I cannot be identified.

I understand that my data gathered in this study will be stored pseudo-anonymously and securely. It will not be possible to identify me in any publications.

Yes No

I understand my information may be subject to review by responsible individuals from the University for monitoring and audit purposes.

Yes No

I understand my participation is voluntary and that I am free to stop participating in the survey at any time and I can request the withdrawal of my data until approximately October 2021, without giving a reason.
I understand that if I decide to withdraw, any personal data I have provided up to that point will be deleted unless I agree otherwise.

Yes No

I understand the potential risks of participating and the support that will be available to me should I become distressed during the course of the research.

Yes No

I understand I will not benefit financially from this study, or from any possible outcome it may result in in the future, unless if I enter and win a voucher from the prize draw.

Yes No

I agree that my pseudo-anonymised research data may be used by others for future research. No one will be able to identify you if this data is shared.

Yes No

I am aware of who I should contact if I wish to make a complaint - v.curran@ucl.ac.uk or ethics@ucl.ac.uk

Yes No

I understand that my data gathered in this study will be stored anonymously and securely for up to 10 years after study completion. This does not include email addresses, which will be deleted once the winners of the prize draw have been announced. It will not be possible to identify me in any publications.

Yes No

Appendix 8: The online survey

Q1 How old are you?

Q2 How would you describe your gender identity?

- o Woman (1)
- o Man (2)
- o Non-binary (3)
- o Other (4) _____
- o Prefer not to say (5)

Q3 How would you describe your ethnicity?

Q4 Which category do you identify with?

- o Asian or Asian British (1)
- o Black, African, Caribbean or Black British (2)
- o Mixed or Multiple ethnic groups (3)
- o Other ethnic group (4) _____
- o White (5)
- o Prefer not to say (6)

Q5 Where do you currently live?

- o Large town / city (1)
- o Small to mid-sized town (2)
- o Rural/ countryside (3)
- o Prefer not to say (4)

Q6 What is the highest educational level you have attained?

- o Primary school (1)
- o Secondary school - key stage 3 (2)
- o GCSE / A Level / GNVQs / NVQs 1-3 – key stage 4 (3)
- o Sub-degree / NVQ4 (4)
- o Undergraduate degree (5)
- o Postgraduate degree / qualification (6)
- o Doctorate (7)
- o Prefer not to say (8)

o Other (9) _____

o None (10)

Q7 Have you experienced any of the following during the last 12 months?

▢ Anxiety (1)

▢ Stress (2)

▢ Low mood (3)

▢ Problems with my general wellbeing (4)

▢ Occasional pain (5)

▢ Chronic pain (6)

▢ Sleeping problems (7)

▢ Fatigue (8)

▢ Addiction (9)

▢ Psychosis-like symptoms (e.g. hearing voices, unusual experiences) (10)

▢ Gastrointestinal problems (e.g. IBS, an upset stomach) (11)

▢ Epilepsy (12)

▢ Multiple Sclerosis (13)

▢ Nausea (14)

▢ Trauma (15)

▢ Cancer (16)

▢ Alzheimer's Disease (17)

▢ Huntingdon's Disease (18)

▢ Parkinson's (19)

▢ Musculoskeletal problems (20)

▢ Arthritis (21)

▢ Joint problems (22)

▢ Inflammation (23)

▢ Skin conditions (24)

▢ Tourette's syndrome (25)

▢ Movement disorders (26)

▢ None (0)

▢ Other - please state (27) _____

Q8 – 19 were the measures: DASS, ISI and BPI, which have been removed for publication.

Q20 Have you ever tried any of the following medications, treatments or remedies for any physical or mental health problems?

Scoring: Yes in the last 12 months (1) Yes but not in the last 12 months (2) No (0)

Antidepressant medication (1)

Anti-anxiety medication (anxiolytics) (2)

Prescribed pain relief (3)

Shop-bought pain relief (over-the-counter) (4)

Nonsteroidal anti-inflammatory drugs (typically over-the-counter) (5)

Corticosteroids (6)

Anti-epileptic drugs (7)

Medications for drowsiness e.g. anti-histamines (8)

Sleeping medication (9)

Melatonin (10)

Herbal remedies (11)

Acupuncture (12)

Yoga (13)

Massage (14)

Meditation (15)

Mindfulness (16)

Healthy eating (17)

Other - please state (click no if not applicable) (18)

Q21 Have you ever used cannabis?

o Yes in the last 12 months (1)

o Yes but not in the last 12 months (2)

o No (0)

Start of Block: Section 3. General attitudes towards CBD products - both groups

Q22 Cannabidiol (CBD) products refers to products marketed for the sole use of CBD, such as: CBD oil, CBD capsules or CBD spray.

How much do you agree with the following statements?

Scoring: Strongly agree (2) Somewhat agree (1) Neither agree nor disagree (0) Somewhat disagree (-1) Strongly disagree (-2) Don't know (3)

I think CBD-products are safe (1)

I would only take CBD-products if they were regulated (2)

I think CBD-products are effective (3)

I think CBD-products have enough CBD levels in them (4)

I trust the pharmaceutical industry (5)

I think CBD products are more natural (6)

Q23 If you have any other comments on the above questions, please state them here

_____

Start of Block: Section 4.CBD consumption - decider question

Q24 Have you ever used cannabidiol (CBD) products before?

o Yes (1)

o No (2)

Start of Block: Non group Section 5B. Reasons for using medication

Q25 Which of the following problems have you used any treatment or remedies to help with, in the last 12 months?

▢ Anxiety (1)

▢ Stress (2)

▢ Low mood (3)

▢ General wellbeing (4)

▢ Occasional pain (5)

▢ Chronic pain (6)

▢ Sleeping problems (7)

▢ Fatigue (8)

▢ Addiction (9)

▢ Psychosis-like reactions (e.g. hearing voices, unusual experiences) (10)

▢ Gastrointestinal problems (e.g. IBS, an upset stomach) (11)

▢ Epilepsy (12)

▢ Multiple Sclerosis (13)

▢ Nausea (14)

▢ Trauma (15)

▢ Cancer (16)

▢ Alzheimer's Disease (17)

▢ Huntingdon's Disease (18)

▢ Parkinson's (19)

▢ Musculoskeletal problems (20)

▢ Arthritis (21)

▢ Joint problems (22)

- ▢ Inflammation (23)
- ▢ Skin conditions (24)
- ▢ Tourette's syndrome (25)
- ▢ Movement disorders (26)
- ▢ Other (please state) (27) _____
- ▢ None (0)

Skip To: End of Block If Which of the following problems have you used any treatment or remedies to help with, in the last... = None

Carry Forward Selected Choices from "Which of the following problems have you used any treatment or remedies to help with, in the last 12 months?"

Q26 Which of the following problems would you say is the most common one you have used treatment to help with in the last 12 months?

- o Anxiety (1)
- o Stress (2)
- o Low mood (3)
- o General wellbeing (4)
- o Occasional pain (5)
- o Chronic pain (6)
- o Sleeping problems (7)
- o Fatigue (8)
- o Addiction (9)
- o Psychosis-like reactions (e.g. hearing voices, unusual experiences) (10)
- o Gastrointestinal problems (e.g. IBS, an upset stomach) (11)
- o Epilepsy (12)
- o Multiple Sclerosis (13)
- o Nausea (14)
- o Trauma (15)
- o Cancer (16)
- o Alzheimer’s Disease (17)
- o Huntingdon’s Disease (18)
- o Parkinson’s (19)
- o Musculoskeletal problems (20)
- o Arthritis (21)
- o Joint problems (22)
- o Inflammation (23)
- o Skin conditions (24)

o Tourette's syndrome (25)

o Movement disorders (26)

o Other (please state) (27) _____

o None (0)

Q27 Have you used any of the following medications, treatments or remedies for your ${Q60/ChoiceGroup/SelectedChoicesTextEntry} in the last 12 months?

▢ Antidepressant medication (1)

▢ Anti-anxiety medication (anxiolytics) (2)

▢ Prescribed pain relief (3)

▢ Shop-bought pain relief (over-the-counter) (4)

▢ Nonsteroidal anti-inflammatory drugs (typically over-the-counter) (5)

▢ Corticosteroids (6)

▢ Anti-epileptic drugs (7)

▢ Medications for drowsiness e.g. anti-histamines (8)

▢ Sleeping medication (9)

▢ Melatonin (10)

▢ Alcohol (11)

▢ Recreational drugs (12)

▢ Herbal remedies (13)

▢ Acupuncture (14)

▢ Yoga (15)

▢ Massage (16)

▢ Meditation (17)

▢ Mindfulness (18)

▢ Healthy eating (19)

▢ None (0)

▢ Other (please state) (20) _____

Skip To: End of Block If Have you used any of the following medications, treatments or remedies for your selected problem, in = None

Carry Forward Selected Choices from "Have you used any of the following medications, treatments or remedies for your ${q://QID67/ChoiceGroup/SelectedChoicesTextEntry} in the last 12 months?"

Q28 Please select the medication, treatment or remedy you have used most often for ${Q60/ChoiceGroup/SelectedChoicesTextEntry}, in the last 12 months

o Antidepressant medication (1)

o Anti-anxiety medication (anxiolytics) (2)

o Prescribed pain relief (3)

o Shop-bought pain relief (over-the-counter) (4)

o Nonsteroidal anti-inflammatory drugs (typically over-the-counter) (5)

o Corticosteroids (6)

o Anti-epileptic drugs (7)

o Medications for drowsiness e.g. anti-histamines (8)

o Sleeping medication (9)

o Melatonin (10)

o Alcohol (11)

o Recreational drugs (12)

o Herbal remedies (13)

o Acupuncture (14)

o Yoga (15)

o Massage (16)

o Meditation (17)

o Mindfulness (18)

o Healthy eating (19)

o None (0)

o Other (please state) (20) _____

Q29 What reason(s) influence you taking this treatment, rather than other medications, treatments or remedies?

_____

Q30 If you have any other comments on the above questions please state them here (Optional)

_____

Start of Block: Non group Section 6B. Product consumption

Display This Question:

If Which of the following problems have you used any treatment or remedies to help with, in the last... != None

Q31 How many days in an average year would you use ${Q62/ChoiceGroup/SelectedChoicesTextEntry}?

For example: Daily=365, Twice weekly = 104, Weekly = 52, Monthly = 12

_____

Display This Question:

If Which of the following problems have you used any treatment or remedies to help with, in the last... != None

Q32 Have you changed your use of ${Q62/ChoiceGroup/SelectedChoices} in the last 12 months?

o Yes – I have increased it a lot (2)

o Yes – I have increased it a little (1)

o No – it has stayed the same (0)

o Yes – it has decreased a little (-1)

o Yes – it has decreased a lot (-2)

o Yes – I stopped using it (-3)

Start of Block: Section 7B. Beliefs about products - non CBD group

Display This Question:

If Which of the following problems have you used any treatment or remedies to help with, in the last... != None

Q33 You will now be asked some questions about your thoughts and attitudes about ${Q62/ChoiceGroup/SelectedChoices} . Please answer the questions based on the main problem or problems you hoped it would help you with.

Scoring: Strongly disagree (-2) Somewhat disagree (-1) Neutral (0) Somewhat agree (1) Strongly agree (2)

Before I started using the treatment/remedy/medication, I believed it could help my problem (1)

Since or after using the treatment/remedy/medication, I believe it has helped my problem (2)

Before using the treatment/remedy/medication, I was feeling hopeless about previous treatments/medications (3)

Since or after using the treatment/remedy/medication, I am/was feeling hopeless about future treatments/medications (4)

Display This Question:

If Which of the following problems have you used any treatment or remedies to help with, in the last... != None

Q34 If you have any other comments on the above questions, please state them here

_____

Start of Block: Section 8B. Perceived effectiveness and impacts of products - non-CBD group

Display This Question:

If Which of the following problems have you used any treatment or remedies to help with, in the last... != None

Q35 How much do you agree with the following statement: ${Q62/ChoiceGroup/SelectedChoices} has been or was effective in helping me with my main problem

o Strongly disagree (-2)

o Disagree a bit (-1)

o Neutral (0)

o Agree a bit (1)

o Strongly agree (2)

Display This Question:

If Which of the following problems have you used any treatment or remedies to help with, in the last... != None

Q36 What benefits have you noticed, or did you notice, from using ${Q62/ChoiceGroup/SelectedChoices}?

- ▢ I feel more calm and/or relaxed (1)
- ▢ Less pain (2)
- ▢ Less depressed / down (3)
- ▢ Better focus / concentration (4)
- ▢ More relaxed muscles / less tension (5)
- ▢ Better self-esteem (6)
- ▢ I take less of my other medications (7)
- ▢ More energy (8)
- ▢ Better memory (9)
- ▢ Sexual enhancement (10)
- ▢ Reduced symptoms of trauma or PTSD (post-traumatic stress disorder) (11)
- ▢ Less nausea / sickness (12)
- ▢ Euphoria / high (13)
- ▢ Less tired (14)
- ▢ Improved gastrointestinal symptoms (15)
- ▢ Less dizzy (16)
- ▢ Better sleep (17)
- ▢ Less seizures (18)
- ▢ Improved heart rate or palpitations (19)
- ▢ Less worrying (20)
- ▢ Problems with bowels / incontinence improve (21)
- ▢ None (0)
- ▢ Other (please specify) (22) _____

Display This Question:

If Which of the following problems have you used any treatment or remedies to help with, in the last... != None

Q37 What side effects have you noticed, or did you notice, from using ${Q62/ChoiceGroup/SelectedChoices}?

- ▢ Dry mouth (1)
- ▢ Fatigue (2)
- ▢ Dizziness (3)
- ▢ Nausea (4)
- ▢ Gastrointestinal problems e.g. an upset stomach (5)
- ▢ Rapid heartbeat (6)
- ▢ Diarrhoea or incontinence (7)

- ▢ Headache (8)
- ▢ Anxiety (9)
- ▢ Psychotic symptoms (e.g. hearing, seeing, smelling or feeling unusual experiences) (10)
- ▢ Sexual problems (11)
- ▢ Vomiting (12)
- ▢ Fainting (13)
- ▢ Liver problems (14)
- ▢ Seizures (15)
- ▢ Problems sleeping (16)
- ▢ Movement or mobility problems (17)
- ▢ Weight gain (18)
- ▢ Weight loss (19)
- ▢ None (0)
- ▢ Other (please specify) (20) _____

_____

Start of Block: Section 9B. Covid-19 - non CBD group

Q38 Please answer the following questions, thinking about whether your attitudes to medications or remedies have changed during the Covid-19 pandemic, i.e. since March 2020.

	Strongly disagree (-2)	Disagree a little (-1)	My attitudes haven't changed (0)	Agree a little (1)	Strongly agree (2)
I am more likely to use herbal or 'natural' remedies or alternative therapies (1)					
I am more likely to take prescribed medications (2)					
I am more sceptical of the pharmaceutical industry (3)					

Q39 If you have any other comments on the above questions please state them here

_____

Start of Block: CBD group Section 6A. Product (CBD) consumption

Q40 When was the last time you consumed CBD products?

- o Over 10 years ago (6)
- o 5 - 10 years ago (5)
- o 2 - 4 years ago (4)
- o 1 - 2 years ago (3)
- o 6 months - 1 year ago (2)
- o Less than 6 months ago (1)

Q41 How many days in an average year (of using CBD products), would you consume CBD products?

For example: Daily=365, Twice weekly = 104, Weekly = 52, Monthly = 12

Q42 Where have you bought CBD products from before?

- ☐ Health food shops like Holland and Barrett (in the shop or online) (1)
- ☐ CBD specific websites (2)
- ☐ From someone selling them in person (3)
- ☐ Pharmacy (4)
- ☐ Prescriber (5)
- ☐ On-line (open web) (6)
- ☐ On-line (darknet) (7)
- ☐ Social media distributor (8)
- ☐ Other (please state) (9) _____

Q43 If you were to find out that your main CBD preparation contained significantly different amounts of CBD than advertised, would you stop taking the product?

- o Yes (1)
- o No (2)
- o Unsure (3)

Q44 On a typical day that you use CBD products, on average how many single doses do you use?

_____

Q45 Which of the following CBD products have you used in the last 12 months?

- ☐ Oil for vaping (1)
- ☐ Oil for oral use (2)
- ☐ Oil for topical use (on skin surface) (3)
- ☐ Capsules (4)
- ☐ Edibles (food/drink) (5)
- ☐ Spray (6)
- ☐ Flower (7)
- ☐ None (0)
- ☐ Other (please specify) (8) _____

Q46 What is the most common CBD product you have used in the last 12 months? Choose one only

- o Oil for vaping (1)
- o Oil for oral use (2)
- o Oil for topical use (3)
- o Capsules (4)

o Edibles (food/drink) (5)

o Spray (6)

o Flower (7)

o None (8)

o Other (please specify) (9)

Q47 What is the approximate CBD content (mg) in a single dose of the product you typically use, in the last 12 months?

o Amount of CBD (1) _____

o I don't know (2)

Q48 Have you changed your CBD use in the last 12 months?

o Yes – It has increased a lot (2)

o Yes – It has increased a little (1)

o No – It has stayed the same (0)

o Yes – It has decreased a little (-1)

o Yes – It has decreased a lot (-2)

o Yes – I stopped using CBD (-3)

Q49 How much would you estimate you have spent (in £), per month on CBD products over the last 12 months?

_____

Start of Block: CBD group Section 5A. Reasons for using CBD

Q50 Has a medical professional recommended CBD products to you before?

o Yes (1)

o No (2)

o Unsure (3)

Q51 Which of the following problems have you used CBD to help with in the last 12 months?

▢ Anxiety (1)

▢ Stress (2)

▢ Low mood (3)

▢ General wellbeing (4)

▢ Occasional pain (5)

▢ Chronic pain (6)

▢ Sleeping problems (7)

▢ Fatigue (8)

- ▢ Addiction (9)
- ▢ Psychosis-like symptoms (e.g. hearing voices, unusual experiences) (10)
- ▢ Gastrointestinal problems (e.g. IBS, an upset stomach) (11)
- ▢ Epilepsy (12)
- ▢ Multiple Sclerosis (13)
- ▢ Nausea (14)
- ▢ Trauma (15)
- ▢ Cancer (16)
- ▢ Alzheimer's Disease (17)
- ▢ Huntingdon's Disease (18)
- ▢ Parkinson's (19)
- ▢ Musculoskeletal problems (20)
- ▢ Arthritis (21)
- ▢ Joint problems (22)
- ▢ Inflammation (23)
- ▢ Skin conditions (24)
- ▢ Tourette's syndrome (25)
- ▢ Movement disorders (26)
- ▢ To lessen the effects of medical cannabis (28)
- ▢ To lessen the effects of cannabis or THC used recreationally (29)
- ▢ For relaxation (30)
- ▢ To increase concentration (31)
- ▢ None (0)
- ▢ Other (please state) (27) _____

Skip To: End of Block If Which of the following problems have you used CBD to help with in the last 12 months? = None

Carry Forward Selected Choices - Entered Text from "Which of the following problems have you used CBD to help with in the last 12 months?"

Q52 Which of the following problems would you say is the most common one you have used CBD to help with, in the last 12 months?

(Choose one only)

- o Anxiety (1)
- o Stress (2)
- o Low mood (3)
- o General wellbeing (4)

- o Occasional pain (5)
- o Chronic pain (6)
- o Sleeping problems (7)
- o Fatigue (8)
- o Addiction (9)
- o Psychosis-like symptoms (e.g. hearing voices, unusual experiences) (10)
- o Gastrointestinal problems (e.g. IBS, an upset stomach) (11)
- o Epilepsy (12)
- o Multiple Sclerosis (13)
- o Nausea (14)
- o Trauma (15)
- o Cancer (16)
- o Alzheimer's Disease (17)
- o Huntingdon's Disease (18)
- o Parkinson's (19)
- o Musculoskeletal problems (20)
- o Arthritis (21)
- o Joint problems (22)
- o Inflammation (23)
- o Skin conditions (24)
- o Tourette's syndrome (25)
- o Movement disorders (26)
- o To lessen the effects of medical cannabis (28)
- o To lessen the effects of cannabis or THC used recreationally (29)
- o For relaxation (30)
- o To increase concentration (31)
- o None (0)
- o Other - please state (27)

Skip To: End of Block If Condition: None Is Selected. Skip To: End of Block.

Q53 Have you used any other medications, treatments or remedies for ${Q55/ChoiceGroup/SelectedChoices}, in the last 12 months?

- ▢ Antidepressant medication (1)
- ▢ Anti-anxiety medication (anxiolytics) (2)
- ▢ Prescribed pain relief (3)

- ▢ Shop-bought pain relief (over-the-counter) (4)
- ▢ Nonsteroidal anti-inflammatory drugs (typically over-the-counter) (5)
- ▢ Corticosteroids (6)
- ▢ Anti-epileptic drugs (7)
- ▢ Medications for drowsiness e.g. anti-histamines (8)
- ▢ Sleeping medication (9)
- ▢ Melatonin (10)
- ▢ Alcohol (11)
- ▢ Recreational drugs (12)
- ▢ Herbal remedies (13)
- ▢ Acupuncture (14)
- ▢ Yoga (15)
- ▢ Massage (16)
- ▢ Meditation (17)
- ▢ Mindfulness (18)
- ▢ Healthy eating (19)
- ▢ None (0)
- ▢ Other - please state (20) _____

Q54 What reason(s) influence you taking CBD, rather than other medications, treatments or remedies?

Q55 If you have any other comments on the above questions please state them here (optional)

_____

Start of Block: Section 7A. Beliefs about products - CBD group

Q56 You will now be asked some questions about your thoughts and attitudes about CBD. Please answer the questions based on the main problem or problems you hoped it would help you with.

Strongly disagree (-2) Somewhat disagree (-1) Neutral (0) Somewhat agree (1) Strongly agree (2)

Before I started using CBD, I believed it could help my problem (1)

Since or after using CBD, I believe it has helped my problem (2)

Before using CBD, I was feeling hopeless about previous treatments/medications (3)

Since or after using CBD, I am/was feeling hopeless about future treatments/medications (4)

Q57 If you have any other comments on the above questions, please state them here

_____

Start of Block: Section 8A. Perceived effectiveness and impacts of products - CBD group

Q58 How much do you agree with the following statement:

CBD products have been or were effective in helping me with my main problem

- o Strongly disagree (-2)
- o Disagree a bit (-1)
- o Neutral (0)
- o Agree a bit (1)
- o Strongly agree (2)

Q59 What benefits have you noticed, or did you notice, from using CBD products?

- ▢ I feel more calm and/or relaxed (1)
- ▢ Less pain (2)
- ▢ Less depressed / down (3)
- ▢ Better focus / concentration (4)
- ▢ More relaxed muscles / less tension (5)
- ▢ Better self-esteem (6)
- ▢ I take less of my other medications (7)
- ▢ More energy (8)
- ▢ Better memory (9)
- ▢ Sexual enhancement (10)
- ▢ Reduced symptoms of trauma or PTSD (post-traumatic stress disorder) (11)
- ▢ Less nausea / sickness (12)
- ▢ Euphoria / high (13)
- ▢ Less tired (14)
- ▢ Improved gastrointestinal symptoms (15)
- ▢ Less dizzy (16)
- ▢ Better sleep (17)
- ▢ Less seizures (18)
- ▢ Improved heart rate or palpitations (19)
- ▢ Less worrying (20)
- ▢ Problems with bowels / incontinence improve (21)
- ▢ None (0)
- ▢ Other (please specify) (22) _____

Q60 What side effects have you noticed, or did you notice, from using CBD products?

- ▢ Dry mouth (1)

- ▢ Fatigue (2)
- ▢ Dizziness (3)
- ▢ Nausea (4)
- ▢ Gastrointestinal problems e.g. an upset stomach (5)
- ▢ Rapid heartbeat (6)
- ▢ Diarrhoea or incontinence (7)
- ▢ Headache (8)
- ▢ Anxiety (9)
- ▢ Psychotic symptoms (e.g. hearing, seeing, smelling or feeling unusual experiences) (10)
- ▢ Sexual problems (11)
- ▢ Vomiting (12)
- ▢ Fainting (13)
- ▢ Liver problems (14)
- ▢ Seizures (15)
- ▢ Problems sleeping (16)
- ▢ Movement or mobility problems (17)
- ▢ Weight gain (18)
- ▢ Weight loss (19)
- ▢ None (0)
- ▢ Other (please specify) (20) _____

_____

Start of Block: Section 9A. Covid-19 - CBD group

Q61 Please answer the following questions, thinking about whether your attitudes to medications or remedies have changed during the Covid-19 pandemic, i.e. since March 2020.

	Strongly disagree (-2)	Disagree a little (-1)	My attitudes haven't changed (0)	Agree a little (1)	Strongly agree (2)
I am more likely to use herbal or 'natural' remedies or alternative therapies (1)					
I am more likely to take prescribed medications (2)					
I am more sceptical of the pharmaceutical industry (3)					

Q62 If you have any other comments on the above questions please state them here

_____

Appendix 9: Qualitative comments from the survey

Survey section	Theme	Example comments CBD user-group
CBD acceptability		
	More research and regulations are required	‘M*y understanding is that there is not enough research to be sure what they help with/what levels are effective. I wouldn't be opposed to taking them if I thought the research supported this*’
		‘I believe that GMP certified products should be available on the NHS. Observational trials should be recognised by MHRA and HMG and HMG should put in place the training and funding infrastructure to enable consultants and GPs to prescribe with confidence’
	Distrust and frustration regarding lack of regulations	*‘I use prescription CBD oil/flowers but need better quality/strength & not corrupt people to get it from*’.
	Improvements on quality of life	‘*I have used the oil and ointment on a bad knee for a few weeks. Prior to using it I would play 9 holes and be in pain. I now can play 18 without any pain’.*
What reason(s) influence you taking CBD, rather than other medications, treatments or remedies?	More natural	*‘It works better and does not have nasty side effects’*
		‘Natural qualities’
	Wanting to try something different	*‘Lower risk of intrusive side effects, more 'natural', public advocation, desperation’*
		Something different that might work

Survey section	Theme	Example comments	
		CBD-user group	**Non-user group**
Attitude change since Covid-19	Scepticism of the pharmaceutical industry increased	*'More awareness of the pharmaceutical industries profiting from the use of prescription medicine/drugs to treat symptoms of disease rather than promote cures/treatments or to promote healthy lifestyle changes and the use of traditional/herbal remedies or medicines'*	
	Scepticism of the pharmaceutical industry decreased	*'I have always been sceptical of the pharmaceutical industry, but since the success of covid vaccinations I think has reduces the scepticism slightly, even though that's one small part of the entire industry, so it feels like I've been biased by the vaccinations recently'*	*'I never get the flu jab but was keen to get the covid jab... it felt more important for some reason'*
			'My opinion of the Pharmaceutical industry has improved as a result of their response to Covid'