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Practical considerations for testing the effects of cannabidiol on human anxiety

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ABSTRACT

Empirical evidence continues to accumulate suggesting cannabidiol (CBD) may have potential as an anxiolytic. Yet, research in the area is insufficient to support strong inferences. Accordingly, there is a need for additional empirical investigation. Research on the effects of CBD and anxiety requires a working knowledge of both. Understanding of contemporary CBD and anxiety research methods is critical to safely and convincingly test predictions regarding potential anxiolytic effects of CBD. The current paper outlines major design, methods, and safety considerations pertinent both to CBD administration and measuring effects on anxiety outcomes in order to facilitate needed research in this domain.

1. Introduction

Cannabis Sativa, a member of the Cannabaceae plant family containing over 100 molecules known as phytocannabinoids, is gaining attention for its potential therapeutic properties. Delta-9-tetrahydrocannabinol (THC) is the most well-studied phytocannabinoid, and has psychoactive effects that include euphoria, anxiety, and increased energy, depending on dose (Hollister & Gillespie, 1973; Lucas, Galettis, & Schneider, 2018). Hemp which, according to the Agriculture Improvement Act (2018), refers to *Cannabis Sativa* plants with less than 0.3 % THC. Another phytocannabinoid that is the subject of increasing empirical inquiry in recent years is cannabidiol (CBD). Psychoactive effects associated with CBD include anxiety and stress reduction (Crippa et al., 2009; Gournay et al., 2021). Notably, CBD does not have *intoxicating* effects, whereas THC can produce problematic and clinically important psychological and behavioral changes, such as impaired judgement (APA, 2013). As such, CBD holds particular therapeutic potential.

There is accumulating evidence that cannabidiol (CBD) can have anxiolytic effects. A relatively large pre-clinical literature and a burgeoning literature with humans is synthesized in multiple review papers (Blessing, Steenkamp, Manzanares, & Marmar, 2015; Schier et al., 2012; Wright, Ciano, & Brands, 2020). While there is promising evidence that continues to emerge in support of the anxiolytic effects of CBD, methodological limitations to existing research render conclusions tentative at this stage (Bahji, Meyyappan, & Hawken, 2020). Accordingly, additional rigorous research testing the effects of CBD on human anxiety is needed.

Conducting research on the effects of CBD is complicated. The legal and regulatory landscape is dynamic and varies across regions. Also, there are several methodological considerations that can substantially influence the effects of CBD. Finally, there is much more to learn about the anxiolytic effects of CBD than has been discovered to date. Anxiety research is similarly complex. Anxiety is often used to describe a variety of affective experiences and clinical diagnoses. Both conceptually and operationally defining anxiety requires careful consideration and awareness of a long tradition of studying anxiety and related states.

As research evolves in this domain, there likely will be researchers relatively familiar with studying either CBD or anxiety, but unfamiliar with studying both. For example, researchers focused on cannabis or its chemical constituents (e.g., phytocannabinoids, terpenes) may have relatively little experience designing a study to evaluate anxiety. The inverse also is true. Anxiety-focused researchers may have little experience studying CBD specifically, and potentially anxiolytic substances more broadly.

The current article aims to advance research efforts in this area by delineating a number of key considerations involved in designing studies to evaluate the anxiolytic effects of CBD among adult human

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participants. Interested readers are referred to other work for detailed reviews of the scientific evidence regarding the effects of CBD on anxiety (Bahji et al., 2020; Blessing et al., 2015; Schier et al., 2012; Wright, Di Ciano, & Brands, 2020) and detailed discussions of medical cannabis dosing for patients (MacCallum & Russo, 2018; Millar et al., 2019).

2. Study design considerations

As is the case with all research studies, those focused on anxiety need to operationally define the dependent variable (known as an endpoint in pharmaceutical trials). Many related but distinguishable terms are used when measuring anxiety and related states. Table 1 provides an overview of several key constructs.

It is critical to carefully consider which of the anxiety-related constructs would be expected to respond to the administration of CBD and how those constructs will be measured. Consider, for example, studies focused on worry versus fear, both of which are distinct from, but related to, anxiety. Worry is conceptualized as a verbal-cognitive response that functions to avoid aversive experiences related to negative emotions (Newman & Llera, 2011), whereas fear is an acute and systemic defensive response to the presence of current threat (Barlow, 2002; LeDoux, 2015). The biological substrates underlying worry likely differ from those of a fear response (Hofmann, Ellard, & Siegle, 2012). For this reason, designing a study to examine the effects of CBD on anxiety needs to take into account how CBD will affect the mechanisms specific to the endpoint being considered, which can vary significantly across different anxiety-related constructs. Precisely defining the endpoint of interest is also critical for selecting the appropriate research paradigm and design that is best suited for detecting effects of CBD on that endpoint. Two well-established paradigms that are useful to consider in this context are experimental psychopathology and clinical study approaches. Although there is substantial variability within both of these paradigms, both are generally well-suited to address different types of research questions related to human anxiety.

2.1. Experimental psychopathology

Experimental psychopathology is a paradigm that involves modeling anxiety in the controlled environment of the laboratory. An independent variable is often experimentally manipulated in order to determine cause-and-effect relations with a laboratory-based provocation procedure (Olatunji, Leen-Feldner, Feldner, & Forsyth, 2007). As examples, worry can be modeled by eliciting worry via guiding thinking exercises (Frala, Mischel, Knapp, Autry, & Leen-Feldner, 2014), anxiety can be modeled by administering unpredictable aversive stimuli (Grillon, Baas, Lissek, Smith, & Milstein, 2004), and fear can be modeled by using safe and controlled administration of carbon dioxide-enriched air (Rapee, Brown, Antony, & Barlow, 1992; Zvolensky & Eifert, 2001). These models allow for testing the effects of CBD on acute worry, anxiety, and fear, respectively. Notably, as a primary aim of experimental psychopathology methods is to inform etiologic models, samples are often non-clinical. This approach controls for confounds introduced by the presence of a positive history of psychopathology (Olatunji et al., 2007). However, it does not allow for inferences regarding the effects of the experimental manipulation on naturalistic anxiety or psychopathology. Clinical studies, discussed next, are particularly useful in this regard. However, experimental psychopathology and clinical studies are not mutually exclusive; laboratory-based experimental inductions of anxiety with clinical samples can be conducted to determine for example, the effects of an intervention.

2.2. Clinical studies

A wide variety of clinical study methods are well-suited for understanding the effects of a manipulation on naturally occurring anxiety and related problems. Qualitative research, surveys, and case studies are

Table 1
Terms Often Used in Relation to Anxiety and Anxiety Research.

	Definition	Widely-Used Measures
Affect	Broad-based construct referring to emotion or mood.	Positive and Negative Affect Scale (Watson, Clark, & Tellegan, 1988); Positive and Negative Affect Scale-Expanded Form (Watson & Clark, 1994)
Anxiety	Future-oriented apprehension about potential threat.	Sate-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983); single-item visual analog scale (e.g., 0 = *not at all anxious* to 100 = *extremely anxious*).
Anxiety disorder	Formal diagnoses (e.g., generalized anxiety disorder, social anxiety disorder) defined in the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychological Association, 2013) requiring the presence of multiple symptoms and distress or impairment.	MINI International Neuropsychiatric Interview (Sheehan et al., 1998); Structured Clinical Interview for DSM-5-Research Version (First, Williams, Karg, & Spitzer, 2015); The Structured Diagnostic Interview for DSM-5 Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders (Tolin et al., 2016).
Anxiety sensitivity	Individual differences in outcome expectancies related to the physical, cognitive, and social symptoms of anxiety (McNally, 1989; McNally, 2002; Reiss & McNally, 1985).	Anxiety Sensitivity Inventory-3 (ASI-3; Taylor et al., 2007).
Anxiety symptoms	Physical (e.g., heart racing, sweating) cognitive (e.g., racing thoughts, excessive worry), and behavioral (e.g., avoidance) characteristics of the anxiety-related disorders (American Psychiatric Association, 2013).	Mood and Anxiety Symptoms Questionnaire (MASQ; Clark & Watson, 1991); Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959); Inventory of Anxiety and Depression Symptoms (Watson et al., 2007).
Fear	Negatively valenced emotion elicited by current environmental threat, resulting in activation of the sympathetic nervous system and escape behavior (LeDoux, 2015).	Fear Questionnaire (Marks & Mathews, 1979); Panic Attack Questionnaire – IV (PAQ-IV; Norton, Zvolensky, Bonn-Miller, Cox, & Norton, 2008); Diagnostic Symptoms Questionnaire (DSQ; Sanderson, Rapee, & Barlow, 1988; Sanderson, Rapee, & Barlow, 1989); single-item visual analog scale (e.g., 0 = *no fear at all* to 100 = *extreme fear*).
Generalized anxiety	A term often used in relation to anxiety, but generally without a precise definition. Typically used to refer to anxiety symptoms generally, as opposed to a specific type of anxiety symptom or an anxiety disorder.	Could be measured with anxiety symptom measures described above.
Nervousness	A term often used in relation to anxiety, but generally without a precise definition. Typically used to refer to a specific anxiety symptom.	Single item on broader anxiety symptom measures, such as the Mood and Anxiety Symptoms Questionnaire (Clark & Watson, 1991) and Beck Anxiety Inventory (Beck, Epstein, Brown, & Steer, 1988).
Panic	A fear response that can be elicited via observable cues (e. g., threat during combat) or unobservable cues (e.g., racing heart; Barlow, 2002).	Panic Attack Questionnaire – IV (PAQ-IV; Norton et al., 2008); Diagnostic Symptoms Questionnaire (DSQ; Sanderson et al., 1988, 1989).
State anxiety	Negatively valenced emotion elicited by future-oriented threat and characterized by avoidance behavior (Barlow, 2002).	State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983); single-item visual analog scale (e.g., 0 = *not at all anxious* to 100 = *extremely anxious*).

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Table 1 (*continued*)

	Definition	Widely-Used Measures
Perceived Stress	The perception that demands in one's environment overload one's ability to cope with those demands (Cohen et al., 1983).	Perceived Stress Scale–10 (PSS-10; Cohen & Williamson, 1988).
Trait anxiety	Persistent, cross-situational state anxiety (Sylvers, Lilienfeld, & LaPrairie, 2011).	Sate-Trait Anxiety Inventory (STAI; Spielberger et al., 1983); Manifest Anxiety Scale (King & Campbell, 1986).
Trait fear	Persistent, cross-situational state fear (Sylvers et al., 2011).	Fear Questionnaire (Marks & Mathews, 1979); Fear Survey Schedule-II (Bernstein & Allen, 1969).
Worry	A verbal-linguistic, future-oriented, and negatively valenced cognitive process (Borkovec, Alcaine, & Behar, 2004; Newman & Llera, 2011; Zebb & Beck, 1998).	Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990).

useful for detecting relations between CBD and naturally occurring and clinically significant anxiety. However, these designs do not readily lend themselves to testing cause-and-effect relations. A gold standard for testing the effects of CBD on anxiety symptoms and related problems is the randomized controlled trial (RCT). There are many different versions of an RCT and the categories of RCTs commonly discussed in the psychological and pharmaceutical literatures do not perfectly align. That said, it is helpful to draw general parallels to facilitate understanding of both literatures. Highly controlled and relatively smaller RCTs are referred to as efficacy studies or phase II studies in the psychological and pharmaceutical literatures, respectively. These types of studies are designed to evaluate whether an intervention can work under highly controlled conditions. Larger-scale studies, typically referred to as effectiveness or phase III trials, are optimal for examining whether an intervention works when administered at a large scale and under conditions that resemble those of actual patient care; typically to a more diverse sample.

Unlike many tests of psychological interventions, CBD administration studies allow for double blind designs. In the case of CBD studies, neither the research staff nor the participant knows if CBD or a placebo is being administered. This is a very powerful tool for methodologically controlling for confounds, such as expectancy effects. Caution is warranted in carefully defining the anxiety-related characteristics of a sample. Structured clinical interviewing is the extensively validated for identifying a sample with clinically significant levels of anxiety-related problems (i.e., diagnoses; Lilienfeld et al., 2015). Alternatively, psychometrically sound measures can be used to identify samples who experience elevated anxiety symptoms, even if in the absence of a diagnosis.

Decisions between experimental psychopathology and clinical trial methods should be driven by which best addresses a research question. Generally, questions focused on the effects of CBD on acute anxiety reactions are best addressed by the laboratory methods used in experimental psychopathology paradigms. Questions focused on the effects of CBD on persistent anxiety symptoms and problems are most effectively addressed using clinical study methods. One key assessment domain in this line of research is functional outcomes (e.g., quality of life, impairment), as such data will meaningfully extend our understanding of the effects of CBD.

2.3. How to administer

How CBD is administered to participants has significant effects on the amount of CBD reaching the bloodstream as well as the timing of the effects of CBD. First, the route of administration needs to be considered. CBD can be administered orally (e.g., oil, soft gel, hard shell capsule, buccal delivery), topically (e.g., transdermal), as a suppository (e.g., rectal, vaginal), via intravenous delivery, or inhalation (e.g., smoked, vaped). Although additional research is needed in order to fully understand the pharmacokinetics and pharmacodynamics of these different routes of administration, there can be substantial and meaningful differences. Oral administration, such as via oils and capsules, tend to have longer delays before reaching peak plasma levels compared to shorter-acting inhaled routes. Research suggests that oral administration may require as long as four hours before peak plasma levels are reached (Millar, Stone, Yates, & O'Sullivan, 2018). This has significant implications for anxiety research as study designs would likely target anxiety induction to correspond with peak plasma levels, thereby suggesting administration of CBD hours before anxiety elicitation.

In a related vein, research utilizing oral administration of CBD needs to take into consideration whether participants are fed or if they should fast during the protocol. This has major implications for both internal and external validity. When orally ingested, there are a number of factors that influence the degree to which CBD can pass from the digestive system to the blood. Research suggests eating high fat foods around the time of dosing increases the bioavailability of CBD (Stott, White, Wright, Wilbraham, & Guy, 2013). Standardizing the amount of food and fat content can be an important method for controlling the bioavailability of CBD. Researchers also need to consider the population for whom results may be generalized. If researchers are interested in understanding the benefits of CBD for a population having difficulty eating, developing or integrating technology that can improve bioavailability during fasted conditions may be necessary when utilizing oral formulations.

2.4. What to administer

There are a number of terms used in cannabis-related work that need to be understood when deciding on what to administer in a study of CBD. Table 2 defines some of the more common and important terms. Regional regulations need to be consulted at this stage of study design. These regulations vary widely across countries. In the United States for example, the Agriculture Improvement Act (2018) made hemp federally legal. However, regulations regarding the study of CBD continue to take shape as regulatory bodies, such as the Food and Drug Administration (FDA), develop policy. A critical issue at the center of ongoing discussions is whether CBD can be studied without an Investigational New Drug application (IND). Chemicals that alter biological systems in order to ameliorate a disease are typically classified as drugs and require completion of an IND, which can be a lengthy process (https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application). However, chemicals that are used to normalize biological structures or functions without an intent to treat clinical problems may not require an IND as these chemicals are often not considered drugs. This regulatory landscape continues to shift as it catches up to increasing legal and societal acceptance of CBD. It is therefore an integral part of the study design process to understand the requirements and prohibitions regarding administering CBD within a researcher's region. Working with legal and regulatory consultants to understand regional laws and regulations is helpful.

Researchers will likely have several options for deciding what to administer within a given local legal and regulatory framework. A critical decision at this stage is to determine if the research question is best addressed by administering a standardized amount of CBD to all participants or to allow the amount to vary. The standardized administration approach offers experimental control and therefore is beneficial for internal validity of a study (e.g., Masataka, 2019). However, there are multiple reasons why a researcher may want to administer different amounts of CBD across participants. A researcher may want to allow participants to self-titrate to a point where they are noticing optimal gains while experiencing minimal aversive side effects (e.g., Rosenberg, Louik, Conway, Devinsky, & Friedman, 2017). This type of design is informative for selecting doses to be subsequently studied. A

Table 2
Key Terms Used in Cannabidiol Research.

Bioavailability	The percentage of a drug and rate at which that drug reaches system circulation.
Cannabis indica	A term that historically referred to a species of the cannabis genus within the cannabaceae family plant that was commonly thought to contain lower THC concentrations than sativa varieties. Due to genetic variation over time, this term no longer captures meaningful genetic or phytocannabinoid variability in the cannabis plant.
Cannabis ruderalis	A term that historically referred to a species of the cannabis genus within the cannabaceae family that grew wild in northern climates and had low levels of delta-9-THC. Due to genetic variation over time, this term no longer captures meaningful genetic or phytocannabinoid variability in the cannabis plant.
Cannabis sativa	A term that historically referred to a species of the cannabis genus within the cannabaceae family that was commonly thought to contain relatively higher THC concentrations than indica varieties. Due to genetic variation over time, this term no longer captures meaningful genetic or phytocannabinoid variability in the cannabis plant.
Certificate of analysis	A document detailing whether a product or ingredients meet predetermined specifications for quality (e.g., cannabinoids terpenes, bacteria, pesticide, heavy metals). Typically, results outside acceptable guidelines or regulations are flagged.
CBD distillate (sometimes referred to as broad-spectrum)	A refined product made from the cannabis plant (that may express high levels of CBD) that is processed such that the distillate contains very high levels of CBD (e.g., 80 %) along with other chemicals from the cannabis plant (phytocannabinoids, terpenes), but only traces of delta-9-THC remain.
CBD isolate	A highly purified CBD product (e.g., 98−99 % CBD) that may include minimal trace amounts of other phytocannabinoids, terpenes or other chemicals.
Full-spectrum extract	A refined product made from the cannabis plant that includes all of the phytocannabinoids and terpenes found in the cannabis plant, including CBD and delta-9-THC.
Hemp	A term used in the Agriculture Improvement Act (2018) to refer to cannabis plants with less than 0.3% delta-9-THC.
Pharmacodynamics	The branch of pharmacology that is concerned with the effects of drugs on the body.
Pharmacokinetics	The branch of pharmacology that is concerned with the route that drugs take as they move through the body.
Phytocannabinoids	Cannabinoids contained in the cannabis plant. The two major phytocannabinoids that have been studied are THC and CBD.
Terpene	Organic aromatic hydrocarbon compounds found in many plants, including cannabis, that impact aroma and flavor and can have direct or synergistic effects on outcomes of interest.

researcher may also systematically vary doses as a function of participant weight or body mass index (e.g., Thiele et al., 2018). This can allow for better experimental control over plasma levels of CBD and therefore improve internal validity even relative to administering a standardized dose across participants. Researchers need to be cautious about dosing based on percent CBD in plant material (such as percent CBD in cannabis flower). As discussed above, the amount of CBD that makes it into the bloodstream and the time to peak plasma concentrations can vary significantly depending on route of administration (Millar et al., 2018). For example, vaping 10 % CBD flower may deliver a different amount of CBD into the bloodstream than smoking 10 % CBD flower, both of which are likely to result in very different levels of CBD when a comparable amount of CBD is administered orally. Route of administration is ideally held constant within a study testing the effects of CBD on anxiety in order to enhance internal validity.

Another timing-related dosing consideration involves choosing between a single dose to examine its acute effects, or repeated dosing to examine its effects across longer periods of time. Human researchers have adopted both of these approaches. Single administration studies have, for example, documented that such dosing reduces acute reactions to laboratory-based social anxiety inductions (e.g., Linares et al., 2019). Research also has shown that repeated daily administration reduces severity of social anxiety disorder (Masataka, 2019). Thus, each dosing schedule has unique merits and constraints; researchers should therefore carefully consider the hypotheses being tested when deciding upon a dosing schedule.

Another complicating factor when considering dose is the observation of what has been labeled an "inverted U" when describing the effects of CBD an anxious responding (Linares et al., 2019). At particularly low and high doses, CBD appears to have relatively little effect on anxiety. For example, in a single-administration study focused on social anxiety, compared to placebo, 100 mg and 900 mg of CBD did not reduce anxiety elicited by a public speaking task, but 300 mg did yield an anxiolytic effect (Zuardi et al., 2017). Similar patterns have been observed in studies using pre-clinical models of anxiety (Campos & Guimarães, 2009). Given limited understanding and replication of the inverted U observation, future studies may benefit from administering multiple different doses in order to determine what the optimal dose of CBD is for obtaining maximal anxiety reduction; higher doses do not necessarily correspond to greater benefit. Currently, careful consideration of empirical precedent is the best tool available for guiding dosing decisions (for further discussion, see MacCallum and Russo (2018) and Millar and colleagues (2019)).

There are multiple pathways by which a researcher may obtain CBD for a study. Products with varying amounts of CBD can be obtained through contracts with manufacturers, the National Institute of Drug Abuse, or via over-the-counter products. Researchers need to be careful when considering the CBD being used by, or administered to, participants. Currently, it is recognized that products labeled as containing CBD can vary widely in CBD content (Bonn-Miller et al., 2017; Vandrey et al., 2015). Not only does CBD content vary across products by design, it also varies in ways that do not necessarily align with the product labeling. Moreover, THC content can vary in products marketed as CBD. As a result, studying uncontrolled use of CBD or administering CBD products purchased from the retail market can (1) result in unclear levels of CBD administration, (2) obfuscate conclusions regarding effects of CBD on anxiety (because the presence of other substances, such as THC and terpenes, may impact the effects of CBD; Russo, 2011), and (3) potentially increase risk to participants. Researchers should acquire a certificate of analysis for the CBD product being studied, either by analyzing a product independently or obtaining such a certificate from the supplier. These certificates describe the specific content of a variety of materials that are present in a tested product. In this context, they typically include amounts of phytocannabinoids, terpenes, solvents, and potentially dangerous materials such as heavy metals (e.g., lead), bacteria, and pesticides. Certificates of analysis also are helpful for educating institutional review boards about what exactly is and is not being administered to participants.

3. Safe and responsible conduct of research with human subjects

In addition to the design features that need to be carefully considered in order to conduct a state-of-the-art study of the anxiolytic effects of CBD, there are specific considerations pertinent to the safe and responsible conduct of research with human subjects that warrant discussion.

3.1. Research team

A carefully-constructed research team is important to ensure both scientific rigor and participant safety particularly for scientists who are just beginning to conduct research on CBD and anxiety. Such a team may include the following collaborators, consultants, and staff. First, collaboration with a medical expert (e.g., medical doctor, nurse practitioner, physician's assistant) in the development of a safety plan is important so that there is a clear approach for responding to any unexpected medical occurrences. This is often a requirement for Institutional Review Board approval for studies in which CBD is being administered. Second, consultation with an expert in the safety and effects of CBD is useful in, for example, identifying safe and potentially effective dosing strategies. Relatedly, working closely with industry partners or regulatory bodies is important to ensure that the product being administered is safe and aligns with federal regulations (e.g., with regard to the presence of THC). Fourth, engaging subject area experts (e.g., an expert in panic disorder or fear for studies related to these constructs) in the study design phase is critical for maximizing study safety and validity. Finally, well-trained diagnostic interviewers will ensure that the screening phase of the study includes an accurate assessment of the inclusion and exclusion criteria.

3.2. Clinical versus nonclinical samples

Depending upon the specific research question, researchers may elect to matriculate participants with or without mental disorders. For example, if a question pertains to the *development* of a problem, nonclinical samples where that problem is not yet present are often optimal (O'Connell, Boat, & Warner, 2009). Here, widely-used structured clinical interviews (e.g., Mini-International Neuropsychiatric Interview; Sheehan, Lecrubier, & Sheehan, 1998) can be utilized to comprehensively address participant exclusion criteria related to mental health history. In this context, it is important to consider substance use disorders. Although CBD is not associated with increased risk of tolerance or dependence (Schoedel et al., 2018) and in fact holds promise for the treatment of substance use problems (Chye, Christensen, Solowij, & Yücel, 2019), participants' drug use history and potential susceptibility to substance use problems should be carefully considered in the context of any drug administration study.

Questions related to the maintenance or treatment of a problem are often best addressed with a clinical sample where the problem is already present (Weisz, Sandler, Durlak, & Anton, 2005). Studying the impact of CBD on anxiety is no different. For example, if a question pertains to the impact of CBD use on anxiety symptoms, the sample likely will include people who endorse the presence of anxiety symptoms; researchers may elect to enroll CBD naïve participants to best isolate the effects of CBD on anxiety symptoms.

3.3. Existing medication and mental health treatment regimens

Related to the decision to enroll a clinical versus non-clinical sample, careful consideration needs to be given to how existing medication and mental health treatment regimens should be handled. Although an exhaustive or prescriptive discussion of this issue is not possible given the scope of the current article and the rapidly-changing literature base, several considerations are included here. First, a researcher may choose to allow participants to maintain a stable medication regimen throughout the study. This has the ethical benefit of avoiding removal of effective treatments, while allowing a researcher to see any potential benefits of adding CBD to existing treatments. However, some researchers may decide to exclude for existing medication use. A study of acute anxiety reactions could be problematically confounded if participants use a benzodiazepine, for example, prior to participating in an anxiety induction. In this case, a researcher may decide to exclude for the presence of any anxiolytic medication use in order to isolate the effects of CBD. These decisions should not be taken lightly, as they can impact both study validity and the labelling of a medication that is developed for FDA approval.

Second, researchers should make decisions about ongoing psychological treatment. Researchers seeking to evaluate the effects of CBD among clinically-anxious samples have to wrangle with the potentially confounding effects of participants receiving mental health treatment. One option is to exclude participants who are enrolled in therapy to isolate the effects of CBD on anxiety symptoms. This limits the generalizability of findings to non-treatment-seeking individuals. Given the pragmatic and ethical challenges of asking participants to discontinue mental health treatment, an alternative would be to carefully measure and monitor participants' therapeutic activities during the study so that potential effects can be described. This approach could have the benefit of testing additive or interactive effects of CBD and other types of mental health treatment.

3.4. Inclusion and exclusion criteria

Participant safety is a major consideration when deciding on a sampling strategy. Carefully selected criteria for inclusion and exclusion can help to minimize participant risk and ensure study rigor. Research designs are differentially amenable to the screening procedures necessary for the implementation of such criteria. For example, a naturalistic observational study of changes in anxiety symptoms among people using CBD likely would not include robust inclusion and exclusion criteria because the procedures necessary to do so may be prohibitive in such designs (e.g., laboratory blood tests). In contrast, a more intensive design that involves detailed screening procedures can embed more inclusion and exclusion criteria, along with the requisite laboratory tests, structured clinical interviews, medical chart reviews, and other tests to increase precautions in place to protect human subjects. Understanding both benefits and risks of CBD is rapidly advancing with ongoing research programs in the area. Therefore, it would not be prudent to suggest specific inclusion and exclusion criteria in this discussion because they may change by the time an interested researcher reads this article. For instance, recent studies in the area typically excluded people with liver problems from participation in studies involving CBD administration because of evidence that CBD can result in liver-related abnormalities (Huestis et al., 2019). However, a recent study of more than 800 adults using oral CBD for at least 60 days found no evidence of liver disease (Validcare, 2021). Liver toxicity observed in the study appeared to be attributable to concomitant medication use, which would help explain perhaps why it was observed in previous studies. Although this is a preliminary report to the FDA (making changes to liver-related exclusion criteria would be premature), these findings speak to the ever-changing landscape in this burgeoning area and point to the importance of researchers carefully monitoring the emerging evidence as they make decisions about study design or ensure ongoing study protocols continue to meet safety criteria. The examples provided here regarding inclusion and exclusion criteria are therefore not an exhaustive list but rather a broad set of considerations that researchers can address in the context of the specific research question being asked in a given study.

At a broad level, researchers may wish to place parameters on body mass index (e.g., enrolling participants between 18 and 35 kg/m^2) as body mass can affect plasma drug concentrations (Luscombe, 1977). Allergies to CBD specifically or to the delivery vehicle more generally also should be considered. For example, CBD softgels may contain medium chain triglyceride oil or flavorings such as peppermint, about which prospective participants should be queried for allergies. There is also the question of prior experience using CBD. Participants with a positive use history may have expectancies about CBD's effects; in the absence of placebo controls, it would be difficult to draw strong conclusions about the effects of CBD administration on anxiety in such a sample. Enrolling CBD-naïve participants, by contrast, carries somewhat

more risk, given participants may be unaware of allergic or other adverse reactions. This approach is may be defensible, however, as a growing body of research on the effects of CBD in human samples, as well as commercial use of CBD products, suggests few adverse effects following CBD use.

Despite CBD's good risk-benefit ratio, there are risks involved with taking CBD that necessitate caution (Bergamaschi, Queiroz, Zuardi, & Crippa, 2011; Brown & Winterstein, 2019). CBD also can interact with other drugs (Brown & Winterstein, 2019). Based on the currently available evidence, medication that is moderately to strongly metabolized by cytochrome p450 enzymes CYP3A4, CYP1A2, CYP2C9, and CYP2C19 should be considered for exclusion (Qian, Gurley, & Markowitz, 2019; Stout & Cimino, 2014; Ujváry & Hanuš, 2016). Researchers need to review the current literature during the study design stage and then monitor emerging evidence during a study in order to prevent problems and quickly adjust to the emergence of evidence suggesting any additional contraindicated medications. Based upon current evidence, researchers should consider excluding participants taking any of the following medications from CBD administration studies: Warfarin, Clobazam, Valproic Acid, Phenobarbital, Mechanistic Target of Rapamycin [mTOR] inhibitors, Oral Tacrolimus. Further, to limit confounding effects, past 30-day exposure to THC, barbiturates, amphetamines, benzodiazepines, and/or opiates may be useful exclusion criteria. In this vein, although clinical trials for the FDA-approved CBD drug Epidiolex did not include adults over the age of 55 years, there is theoretical reason to suggest older adults may be more susceptible to adverse side effects observed in clinical trials (e.g., somnolence, diarrhea, orthostatic hypotension; Calderon & Sayre, 2020). Older adults are predisposed to experience adverse side effects as they are more likely to have polypharmacy, cognitive impairment, and other mental and physical co-morbidities (Lucas et al., 2018). Research suggests that older adults can benefit from cannabinoids like CBD; however, more research is needed to understand the risks and benefits for older adults and use should be carefully monitored.

Little is currently known about the effects of a pregnant woman taking CBD on the developing fetus. Care needs to be taken to ensure that a woman is not and does not become pregnant while participating in a CBD administration study. In fact, it is good practice to exclude both men and women who are engaging in unprotected sex and to request that eligible participants continue to use contraception for at least 30 days following study completion.

With regard to mental health issues, researchers may wish to exclude participants with elevated suicidal risk behavior and certain current mental health problems (e.g., presence of psychotic symptoms, given links between THC and psychosis). Allowing for a positive history of other conditions, such as current or lifetime mood and anxiety disorders would depend on the research question being addressed and the population to which findings are generalized. Cognitive impairment or neurological symptoms are also concerns insofar as they limit participants' ability to provide informed consent and comply with protocol requirements.

3.5. *Specific informed consent considerations*

CBD administration studies require at least two specific additions to the informed consent process. First, although the World Health Organization (2017) concluded that CBD is well tolerated and has a good safety profile, side effects such as diarrhea, nausea, and headache have been observed in studies using substantially larger doses than is typical in human anxiety research (e.g., 6000 mg; Taylor, Gidal, Blakey, Tayo, & Morrison, 2018). Fully informed consent may require disclosure of these observed effects. Relatedly, as this literature grows, it will be critical to continue documenting adverse effects (AEs) or serious adverse effects (SAEs) linked to CBD administration. Investigators will need to establish systems for AE/SAEs during the study itself, as well as procedures for reporting such events to local oversight bodies (e.g., Institutional Review Board) and sponsor partners, particularly if sponsors maintain a pharmacovigilance program, which is a coordinated effort to create a repository of AEs and SAEs. Monitoring for any unexpected physical, psychological, or behavioral can be done in a number of ways, including asking participants to let the researcher know if they experience any unexpected effects during or after the study, behavioral monitoring during the study, and direct queries during and after the study.

Second, participants need to be aware of the potential for a false positive drug test. Although the legal limit for THC in hemp is 0.3 %, the presence of any THC could trigger a positive drug test result. Nearly all CBD products, even those that are highly purified, are likely to have at least trace amounts of THC. Moreover, THC is lipophilic and therefore can accumulate in fatty tissue. As a result, when CBD products with even very small amounts of THC are repeatedly taken, THC can accumulate in the body over time. This can lead to positive THC tests. Also, drug tests can yield false positive results. In fact, one recent study documented that even without detectable levels of THC in participants' systems, there can be positive tests for THC (although rarely; Spindle et al., 2020). Fully informed consent is critical here.

4. Conclusion

At this point in the development of the knowledge base, it is difficult to speak to the clinical implications of using CBD to manage and/or treat anxiety-related problems. There is evidence that CBD can reduce cue-driven anxious responding (Crippa et al., 2011), and one small double-blind study suggesting effects on social anxiety symptoms following four weeks of daily dosing (Masataka, 2019). There is also some work suggesting CBD may facilitate certain aspects of extinction learning (Das et al., 2013). These data point to the potential for CBD to facilitate short-term anxiety reduction as well as possible longer-term effects on anxiety symptoms. However, there are no direct data suggesting treating anxiety disorders with CBD would result in benefits that persist after discontinuing use of CBD. Future work in this area could usefully focus on a number of relevant questions including, for example, whether CBD can facilitate treatment gains following cognitive-behavioral therapy for anxiety in light of evidence suggesting CBD reduces activity in key neurobiological structures linked to anxious arousal (Crippa, Zuardi, & Garrido, 2004; Fusar-Poli, Crippa, & Bhattacharyya, 2009) and some evidence that CBD may reduce ambient subjective stress (Gournay et al., 2021). The objective of the current paper is to encourage both the foundational basic and translational research as well as clinical trials that would empirically address possible opportunities and limitations of using CBD to manage and/or treat anxiety.

There is substantial potential in continued investigation of the anxiolytic effects of CBD. A variety of challenges related to study design, methods, and safety can be overcome via careful and sophisticated study planning. Furthermore, appropriate presentation and interpretation of study findings is crucial to moving this field of research forward. Researchers should follow good research practices (e.g., study preregistration, thorough method description to permit replication, making data publicly available; Aguinis, Banks, Rogelberg, & Cascio, 2020; Asendorpf et al., 2013) and situate the interpretation of study findings within the constraints on generalizability, including with regard to the study sample, dosing schedule, and anxiety-related measurement. The majority of the considerations discussed herein can generalize to research with other phytocannabinoids and terpenes. For instance, there is pre-clinical evidence suggesting linalool, a terpene found in the cannabis plant (and in some other plants), has anxiolytic effects (de Sousa, Hocayen, Andrade, & Andreatini, 2015). Considering the design, anxiety model, and product selection, acquisition, and validation, for example, apply to additional research examining linalool's anxiolytic effects among humans. Pursuing additional research with CBD, other phytocannabinoids, and terpenes has significant potential for improving

our understanding of ongoing and widespread global use of CBD and cannabis as well as potential applications to help millions of people manage anxiety. We hope this brief primer informs and inspires continued work elucidating how and why CBD impacts anxiety reactions and symptoms.

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