Epilepsy Currents
2019, Vol. 19(6) 382-384

DOI: 10.1177/1535759719874408
journals.sagepub.com/home/epi
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How High Can Patients Get on CBD?

Abuse potential assessment of cannabidiol (CBD) in recreational polydrug users: A randomized, double-blind, controlled trial

Schoedel KA, Szeto I, Setnik B, et al. *Epilepsy Behav*. 2018;88:162-171. doi:10.1016/j.yebeh.2018.07.027. Epub October 2, 2018. PMID: 30286443.

Rationale: Treatment with a highly purified oral solution of cannabidiol (CBD), derived from the plant *Cannabis sativa L.*, demonstrated some evidence of central nervous system–related adverse events in patients enrolled in phase 3 trials for the treatment of childhood-onset epilepsy. Cannabidiol was categorized as a schedule I substance by the US Drug Enforcement Administration; therefore, it was important to test CBD for human abuse potential. Methods: This was a single-dose, randomized, double-blind, double-dummy, placebo- and active-controlled crossover trial. The abuse potential of single oral doses of plant-derived pharmaceutical formulations of highly purified CBD (Epidiolex; 750, 1500, and 4500 mg) was compared with that of single oral doses of alprazolam (2 mg), dronabinol (10 and 30 mg), and placebo in healthy recreational polydrug users. The primary end point to assess abuse potential was the maximum effect (Emax) on Drug Liking visual analog scale (VAS). Other measurements included Emax on Overall Drug Liking VAS, Take Drug Again VAS, positive and negative effects, other subjective effects, and Drug Similarity VAS. Cognitive and psychomotor functions were assessed using the Divided Attention Test, the Hopkins Verbal Learning Test–Revised, and the Digit-Symbol Substitution Task. Pharmacokinetic parameters were determined for CBD and its major metabolites. Standard safety measures and adverse events were assessed. Principal Results: Of 95 eligible patients, 43 qualified for the treatment phase, received at least 1 dose of investigational medicinal product, and were included in safety assessments; 35 patients were included in the pharmacodynamic analysis. Patients receiving alprazolam and dronabinol had significantly higher Drug Liking Emax ($P < .0001$) compared with those receiving placebo, confirming study validity. Compared with placebo, Drug Liking was not significantly different for patients taking 750 mg CBD ($P = .51$). Drug Liking Emax values for 1500 and 4500 mg CBD were significantly different from placebo ($P = .04$ and .002, respectively); however, the mean differences were <10 points on VAS compared with >18-point differences between positive controls and placebo. Alprazolam and dronabinol had significantly higher Drug-Liking, Overall-Liking, and Take Drug Again VAS Emax values compared with all doses of CBD ($P \leq .004$). In contrast to alprazolam, CBD administration had no observable effect on cognitive/psychomotor tests. Pharmacokinetic parameters for CBD in this trial were consistent with previous studies. The majority of adverse events reported during the trial were of mild or moderate severity; no serious adverse events or deaths were reported. Conclusion: Administration of a therapeutic dose of CBD (750 mg) showed significantly low abuse potential in a highly sensitive population of polydrug users. Although high and supratherapeutic doses of CBD (1500 and 4500 mg, respectively) had detectable subjective effects compared with placebo, the effects were significantly lower than those observed with alprazolam and dronabinol.

Commentary

There is interest in identifying drugs that have a potential for abuse before they become widely available so that safeguards can be put into place before distribution. The Food and Drug Administration defines drug abuse "as the intentional, nontherapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect".[1] The determination of abuse potential aims to identify the liklihood that a particular compound will be abused. On a federal level, medications with abuse potential are typically placed into one of 4 schedules (II-V) as schedule I compounds are reserved for those with the potential for abuse and that have no medical benefit.[2] As medications that treat epilepsy act in the central nervous system, they are a natural target for potential drug abuse and may require drug abuse reliability testing.[1] In the past, most antiepileptic drugs (AEDs) have not been scheduled

substances. However, in recent years, several AEDs have been determined to have the potential for abuse.[3-5]

The regulatory environment surrounding cannabidiol (CBD) has been particularly complex and confusing. As CBD is an extract of the *Cannabis* plant, it is a schedule I compound at the federal level and is illegal except for the one approved product (Epidiolex) that has been placed in schedule V. Cannabidiol is a phytocannabinoid, the same drug class as delta9-tetrahydrocannabinol (THC) which is a psychoactive constituent of marijuana. Cannabidiol is not thought to be psychotropic and has a different side effect profile compared to THC. These dissimilarities are thought to be attributed to differences in binding of THC and CBD to cannabinoid receptors.[6]

The paper by Schoedel et al presents the results from a study that employs the typical design for a drug liability study.[1] The design was a single-dose, randomized, double-blinded, crossover study consisting of 4 parts including a screening phase, qualification phase, treatment phase, and follow-up period. Interestingly, as most pharmacokinetic and pharmacodynamic studies exclude patients who are drug abusers, this is not the case for a study with a goal of determining the drug abuse potential of a particular compound. In fact, the goal of the qualification phase is to recruit known drug users using certain criteria that verify a minimum threshold of drug use. Inclusion of individuals with experience with particular classes of drugs allows a reliable comparison of the drug being tested to drugs already known to possess particular traits that are considered positive for drug users. For this study, the choices of positive control were based on drug class, with alprazolam being noted to have similarities in pharmacological effects and pharmacokinetic profile to CBD. Due to similarities of THC and CBD and presence of both in plant extracts, a synthetic THC was a logical choice for comparison in order to isolate effects of CBD only. For the qualification phase, enrolled patients were given single doses of positive control drug and placebo. Patients who rated these compounds above placebo in various tests were invited for the treatment phase of the study. Out of 95 patients taking part in the qualification phase, 43 were able to continue to the treatment phase.

The treatment phase should consist of at least 1 dose of a positive control used in the qualification phase with at least 3 doses of the drug being tested.[1] As such, the treatment phase in this study included the same drugs from the qualification phase with 2 different doses of dronabinol (10 and 30 mg) and 3 dose of CBD (750, 1500, and 4500 mg). Cannabidiol tested similar to placebo or lower than positive controls on pharmacodynamics tests. Earlier studies compared THC and CBD products in known marijuana users. Results are consistent in that a combination product (nabiximol: 4, 8, and 16 consecutive sprays or 10.8, 21.6, and 43.2 mg THC with 10, 20, and 40 mg CBD, respectively) performed similarly to positive controls most likely reflecting the THC content in the tested product,[7] and purified CBD products were similar to placebo.[8] A comparison in marijuana users is logical; however, the highest dose of CBD tested was 800 mg and comparisons were not made to other commonly abused classes of drugs. Where the Bababuis study does include potential doses used in the clinic, it did not fulfill the guidance recommendation for the testing of supratherapeutic doses (2-3 times the highest dose considered therapeutic).[1] The design used in the Schoedel 2018 paper includes 3 doses of purified CBD that cover doses considered to be in the therapeutic range (750 mg), a high therapeutic dose (1500 mg), and a supratherapeutic dose (4500 mg). The 4500 mg dose represents a dose that was tolerated as a single dose in a prior study. It is thought that the higher doses represent the likelihood of CBD to be overused or misused by patients or help determine if the drug may become a target for drug diversion in general. The study also included some pharmacokinetic assessments of CBD and THC and their respective metabolites in approximately 39 patients. There is some evidence of potential saturation in absorption in CBD at higher CBD concentrations based on mean Cmax and the area under the plasma concentration time curve (AUC) values; however, the variation in concentrations was relatively high. Several factors such as formulation (liquid vs capsule) and how the drug is administered (with or without food) can contribute to concentration variability.[9] In this study, drug administration was standardized and given under fasting conditions. Although fasting conditions may decrease exposure, the observed saturation at the higher CBD doses suggests that patients achieved maximum exposure of CBD. There was also confirmation of very low concentrations of THC and metabolites ($<$0.6 ng/mL for THC and 11-OH-THC, $<$5 mg/mL for 11-COOH-THC) in the purified CBD product. The safety profile was relatively good overall.

This study presents data to support that CBD has minimal abuse potential as well as a relatively mild side effect profile. Based on current data and testing methodologies, patients are not likely to get high on purified, CBD-only formulations. The incentive for drug diversion also seems to be low. Although there is a federally approved purified CBD formulation, we need to keep in mind that there are many sources of CBD that are available to patients due to various state approvals for CBD, THC, and marijuana for medicinal and recreational purposes. Some of these formulations can be verified as pure CBD, while others may contain other cannabinoids such as THC that may change the abuse potential for that particular product.

By Angela Birnbaum

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