

Expert Committee on Drug Dependence

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Expert Peer Review for Cannabidiol (CBD)

1. Comments based on the review report

a. Evidence on dependence and abuse potential

Dependence potential: Animal studies assessing the dependence potential of cannabidiol (CBD) are sparse. One animal study was identified. Male mice received once daily i.p. injections of escalating doses of CBD (0.1, 1 or 3 mg/kg) of CBD or Δ^9 THC (1, 3 or 10mg/kg) for 14 days. Although tolerance to the effects of THC was observed, no tolerance was observed at any of the doses of CBD administered.

Human studies: No studies assessing the dependence potential (withdrawal and tolerance) of CBD in humans could be identified.

Abuse potential: In animal studies, available literature is not supportive of an abuse potential for CBD:

- In the intracranial self-stimulation (ICSS) paradigm in rats, CBD did not exhibit reinforcing properties and decreased the reward-facilitating effects of morphine. This suggests that CBD is unlikely to have abuse potential *per se* but rather interferes with the brain reward mechanisms responsible for the acute reinforcing properties of opioids (Katsidoni et al 2013). In another study in rats (French et al, 1997), Δ^9 THC but not CBD was shown to increase dopamine release in the cells of the ventral tegmental area of the brain (VTA). Drugs of abuse activate the brain reward pathway which involves several parts of the brain including the VTA, the nucleus accumbens, and the prefrontal cortex. This pathway plays a key role in mediating the reinforcing properties of most drugs of abuse.
- CBD administered alone appears to have little effect on conditioned place preference in rats (Vann et al 2008). CBD also does not seem to induce THC-like discriminative stimulus effects in rats (Vann et al 2008) or pigeons (Jarbe et al, 1977).

- In another study using a rat experimental model, CBD (5-20mg/kg) specifically inhibited reinstatement of cue-induced heroin seeking behavior (Ren et al 2009). This is in contrast to evidence from other studies showing that THC enhances heroin self-administration in rats (Solinas et al, 2004; Ellgren et al, 2007).

Human studies, evidence from available clinical studies is not supportive of an abuse potential for CBD

- In one well-controlled within-subject designed study, 16 healthy male volunteers were randomized to receive a single oral dose of THC (10mg), CBD (600mg) or placebo. CBD did not differ from placebo on the Addiction Research Inventory (ARCI) scales, a 16 item Visual Analogue Mood scale, subjective levels of intoxication and psychotic symptoms. In contrast, THC was associated with changes in the ARCI scales (reflecting sedation and hallucinations), subjective intoxication and euphoria, increased psychotic symptoms and anxiety. THC increased heart rate but no changes in physiological measures were noted in the CBD or placebo group (Martin-Santos et al, 2012).
- In another randomized, double-blind, within-subject designed study, non-treatment seeking healthy cannabis users were recruited to test the influence of pretreatment of a range of doses of CBD (0, 200, 400, 800mg, po) on the effects of smoked cannabis (inactive: 0.01 THC or active:5.30-5.80% THC). CBD alone produced no significant psychoactive, cardiovascular or other effects. Cannabis-self-administration, subjective effects and cannabis ratings did not vary as a function of CBD dose relative to placebo. The authors concluded that oral CBD, does not reduce the reinforcing, physiological or positive subjective effects of smoked cannabis (Haney et al 2016).
- A secondary analysis of the data (*vide supra*) with the aim of examining the abuse liability profile of oral cannabidiol (CBD), smoked THC and placebo showed that CBD was placebo-like on all measures collected (VAS, psychomotor performance, heart rate, blood pressure) compared to the active cannabis. They concluded that CBD did not produce any signs of abuse liability (Babalonis et al 2017).

b. Risks to individual and society because of misuse

No case reports of abuse or dependence relating to the use of pure CBD have been identified. No public health concerns (such as driving under the influence, comorbidities) have been identified.

c. Magnitude of the problem in countries (misuse, illicit production, smuggling etc)

Information to address this question could not be found.

d. Need of the substance for medical (including veterinary) practice

CBD is being investigated for a variety of indications such as epilepsy and it is in this area that most advances have been made. A list of other indications for which the efficacy of CBD is being assessed are listed in the pre- review.

e. Need of the substance for other purposes (e.g. industrial)

None identified.

f. Measures taken by countries to curb misuse

No reports of misuse of CBD could be found.

g. Impact if this substance is scheduled

Based on available evidence CBD lacks psychoactivity, reinforcing properties and abuse liability. On the other hand, emerging findings suggest promising therapeutic usefulness. Scheduling this substance could impact accessibility for scientific and medical research.

2. Are there absent data that would be determinative for scheduling?

None.

3. Other comments or opinions

None.

4. Expert reviewer's view on scheduling with rationale

Cannabidiol is a cannabinoid found in the Cannabis sativa plant. Unlike Δ^9 THC it has low affinity for the CB1 receptor, is devoid of psychoactive properties such as the ability to produce euphoria. Existing evidence (both clinical and pre-clinical) does not support potential for abuse, including the lack of reinforcing properties. CBD is showing promise in the treatment of epilepsy and possibly substance use disorders among other indications. Currently CBD is not listed in the schedules of the 1961, 1971 or 1988 United Nations International Drug Control Conventions. The information provided in the Pre-Review report does not warrant scheduling of this substance.