

# Even high doses of oral cannabidiol do not cause THC-like effects in humans

Comment on „*Identification of psychoactive degradants of cannabidiol in simulated gastric and physiological fluid*” by John Merrick and colleagues (Merrick J, et al. Cannabis and Cannabinoid Research 2016;1(1):102-112.)

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## **Summary**

This short study investigated the question, whether the experimental data presented in a study by Merrick and colleagues (2016) are of clinical relevance. These authors found that cannabidiol (CBD), a major cannabinoid of the cannabis plant devoid of psychotropic effects and of great interest for therapeutic use in several medical conditions, may be converted in gastric fluid into the psychoactive cannabinoids delta-8-THC and delta-9-THC to a relevant degree. They concluded that “the acidic environment during normal gastrointestinal transit can expose orally CBD-treated patients to levels of THC and other psychoactive cannabinoids that may exceed the threshold for a positive physiological response.” They issued a warning concerning oral use of CBD and recommend the development of other delivery methods.

However, the available clinical data do not support this conclusion and recommendation, since even high doses of oral CBD do not cause psychological, psychomotor, cognitive or physical effects that are characteristic for THC or cannabis rich in THC. On the contrary, in the past decades and by several groups high doses of oral CBD were consistently shown to cause opposite effects to those of THC in clinical studies. Thus, there is no reason to avoid oral use of CBD, which has been demonstrated to be a safe means of administration of CBD, even at very high doses.

## **1. Introduction**

Cannabidiol (CBD) is a cannabinoid of the cannabis plant devoid of psychotropic effects. It may be of therapeutic value in a large number of diseases, including epilepsy, anxiety disorders, depression, schizophrenic psychosis, inflammatory diseases, dystonia and nausea and vomiting without causing relevant or severe side effects (Grotenhermen et al. 2016).

No biosynthetic enzyme or pathway exists in the human body to convert CBD to THC. However, recently Merrick and colleagues conducted an experimental study, which demonstrated, that CBD rapidly cyclizes to THC in an acidic environment such as in the stomach. They concluded, that patients treated with oral CBD may be exposed to levels of THC, which may cause unwanted psychological effects, and suggest that other delivery methods such as transdermal-based applications, which decrease the potential for formation of psychoactive cannabinoids should be explored.

Two of the six authors were paid consultants of Zynerba Pharmaceuticals and another three of the six authors work for Zynerba Pharmaceuticals, which develops the transdermal CBD preparation CBD Gel – ZYN002. In the acknowledgments authors stated that the study was supported by the company.

## **2. The study**

Merrick et al. (2016) wondered whether some effects of CBD observed in clinical studies (including somnolence) might be due to THC, since when CBD is degraded in an acidic environment, it rapidly cyclizes to delta-9-THC and other psychoactive cannabinoids. This *in vitro* reaction has been known for decades.

To test the hypothesis that CBD might be converted to THC in the acidic environment of the stomach, an *in vitro* study was completed by evaluating the formation of psychoactive cannabinoids as possible degradation products of oral CBD under simulated gastric and physiological conditions.

Due to the limited aqueous solubility of CBD, an approach to improve the solubility was determined. The approach recommended in United States Pharmacopeia (USP) to use a surfactant was implemented and it was found that 1% sodium dodecyl sulfate (SDS) was required.

## **2.1 Method**

A stock solution of 40 mg/mL CBD was prepared in methanol. 1% SDS was added to media to solubilize 1.0 mL of the 40 mg/mL CBD stock solution; the resulting incubation media contained 0.2% methanol. Incubation studies were carried out in two media: one simulated gastric fluid (SGF) and one simulating a physiological buffer.

SGF with 1% SDS was prepared by adding 10 g of SDS to 1 L of SGF prepared from enzyme-free concentrate, equivalent to 0.1 M as hydrochloric acid and 0.2% sodium chloride. Physiological buffer with 1% SDS was prepared similarly by adding SDS to 1 L of HEPES buffer, pH 7.4.

1.0 mL of CBD stock solution in methanol (equivalent to 40 mg CBD) was spiked into separate vessels containing 500 mL of either SGF or HEPES buffer, and the paddles were started. At each time point, 1.0 mL of solution was withdrawn, and the amount of medium withdrawn from the test vessel was replaced with an equal volume of preheated medium. A maximum 3-h assessment time for SGF and 6-h assessment time for HEPES buffer exposure were chosen to nominally represent the maximal time of exposure of the substrate to the environment.

## **2.2 Results**

In SGF, CBD degraded about 85% after 60 min and greater than 98% at 120 min (see Figure). The delta-9-THC:delta-8-THC ratio ranged from about 1.25:1 to 1.5:1 over the course of the study period. CBD degradation and THC formation were very rapid, and CBD consumption demonstrated first-order kinetics, with a rate constant of  $-0.031 \text{ min}^{-1}$  ( $R^2=0.9933$ ). Formation of THC isomers followed biphasic kinetics in which THC levels plateaued as CBD was consumed. The THC levels were also impacted by secondary degradation to other related substances. In HEPES buffer, no degradation of CBD to THC or other cannabinoids was observed over the 6-h duration of the study.

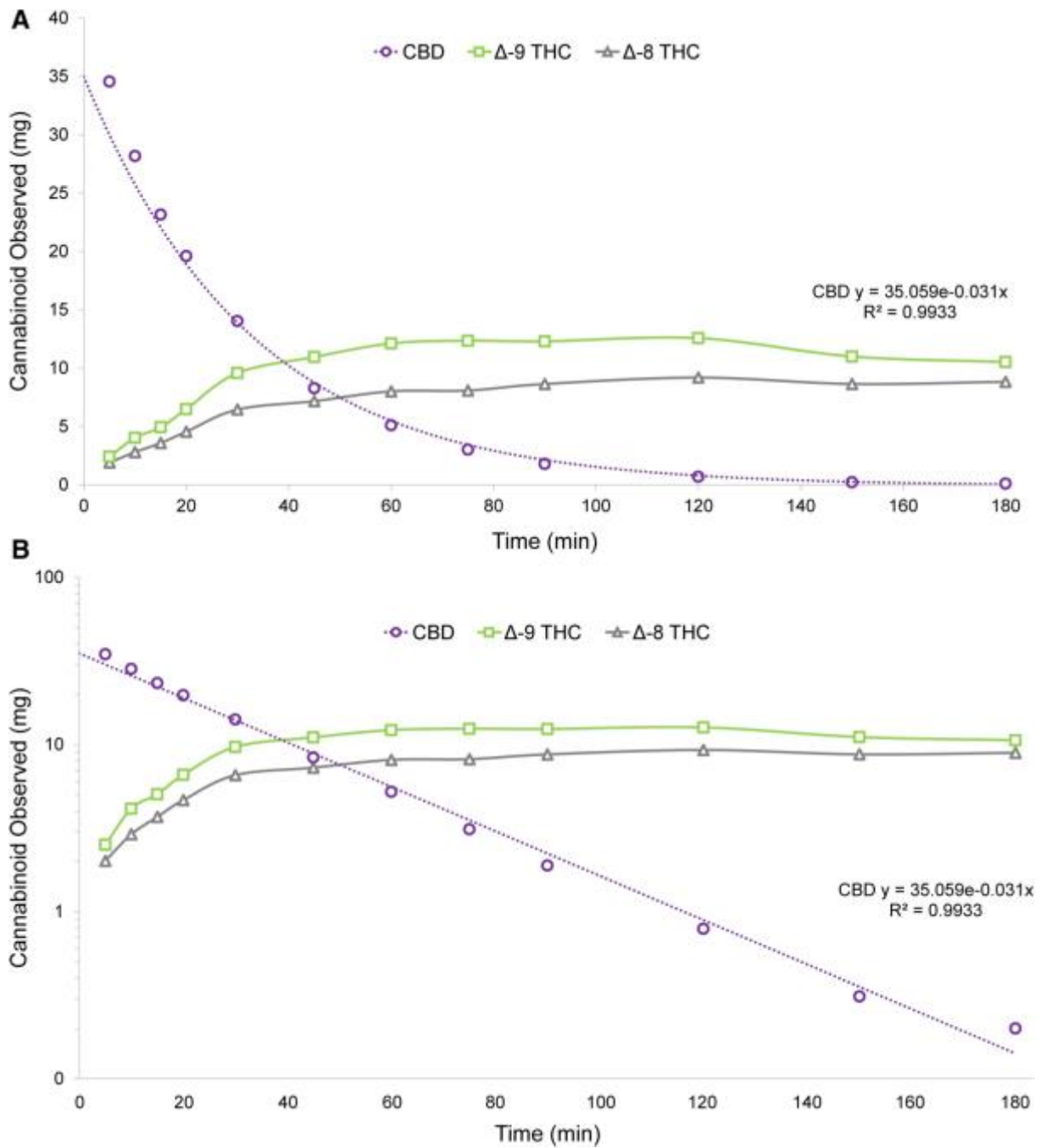


Figure. CBD degradation in simulated gastric fluid (SGF) —kinetics plotted on normal scale (A) and with CBD only on log scale (B). Figure 7 from the study by Merrick et al. (2016).

### 2.3 Discussion and conclusion

In their discussion authors wrote: “The quantity of THC formed after oral administration of CBD-containing medications can thus be calculated—provided that the proportion of the CBD dose that would be soluble in the acidic gastric environment and thus “available” for degradation is also known. In a true physiological environment, this proportion depends on multiple factors, including (but not limited to) partitioning out of the lipid dosage form, enzyme activity, emulsification, and fasting state. Determining actual CBD solubility in gastric fluid would require studies in human

subjects. Based on our results, however, it is clear that at least some portion of an orally ingested dose of CBD will be soluble and degrade to THC.”

They made the following estimation: ”In a patient treated with 700 mg oral CBD formulated in a lipid environment (e.g., oil-based solution), even if just 1% of the CBD dose were soluble, total cannabinoid levels, primarily  $\Delta$ 9-THC and  $\Delta$ 8-THC with other degradation products, would be 6.5 mg after 30 min and 13 mg after 60 min. Although the precise activity cannot be definitively determined until *in vivo* data are available, the central finding remains—significant levels of psychoactive  $\Delta$ 9-THC,  $\Delta$ 8-THC, and other related compounds are formed when CBD is taken orally. With higher CBD doses, greater solubility, and/or longer gastric residence time, it is not difficult to envision scenarios in which  $\Delta$ 9-THC levels of 20–30 mg or higher are reached (i.e., 1–1.5 times the maximum recommended daily dose).”

Authors concluded that “the acidic environment during normal gastrointestinal transit can expose orally CBD-treated patients to levels of THC and other psychoactive cannabinoids that may exceed the threshold for a positive physiological response.” They issue a warning concerning oral use of CBD and recommend the development of delivery methods other than oral intake, e. g. transdermal application methods.

### 3. Effects of high doses of CBD in clinical studies

In clinical studies even high doses of oral CBD did not cause THC- or cannabis-like effects (Russo et al. 2006, Devinsky 2016). On the contrary, CBD caused opposite effects to THC (Nicholson et al. 2004, Bhattacharya et al. 2010). THC effects are characterized by typical psychological effects, impairment of psychomotor and cognitive performance and a range of physical effects, including increased heart rate and dry mouth. None of these effects were observed after high doses of oral CBD.

In a study with healthy volunteers, who were given 200 mg oral CBD and alcohol or CBD alone or alcohol alone, CBD alone did not produce any impairments of motor and psychomotor performance (Consroe et al. 1979).

In healthy volunteers oral CBD in a dose of 1 mg/kg body weight reduced the anxiety provoked by THC given simultaneously in a dose of 0.5 mg/kg. This blocking of THC effects “also extended to marijuana-like effects and two other subjective alterations induced by delta-9-THC” (Zuardi et al. 1982).

CBD was evaluated for symptomatic efficacy and safety in 15 neuroleptic-free patients with Huntington's disease (Consroe, et al. 1991). Effects after oral CBD (10 mg/kg body weight per day for 6 weeks) or placebo (sesame oil for 6 weeks) intake were evaluated weekly under a double-blind, randomized crossover design. CBD showed no significant or clinical differences compared to placebo in the *Cannabis* side effect inventory.

Pre-treatment with 600 mg oral CBD significantly reduced anxiety, cognitive impairment and discomfort in patients with generalized social anxiety disorder, who participated in a simulation public speaking test (Bergamaschi et al. 2011).

It is known that THC may induce psychotic states, but CBD has been shown to produce anti-psychotic effects. Much of this work was conducted by the group of Zuardi and colleagues in Brazil. The first case report of a young woman diagnosed with schizophrenia, who experienced severe side effects after treatment with conventional antipsychotics, who was treated with CBD was published in 1995 (Zuardi et al. 1995). She demonstrated significant improvement of symptoms with no

psychoactive and other adverse effects after 4 weeks of treatment with increasing doses of CBD up to 1,500mg/day. CBD monotherapy was administered to three patients with treatment-resistant schizophrenia (initial oral dose of 40 mg, increased to 1,280mg/day) for up to 4 weeks with no side effects reported, even at the highest dose (Zuardi et al. 2006). A similar result was observed in two patients with bipolar affective disorder who received CBD (600-1,200mg/day) for up to 24 days (Zuardi et al. 2010). CBD did not significantly affect cardiac functions or caused psychoactive effects.

The efficacy and safety of CBD on Parkinson's disease patients with psychotic symptoms were studied in a 4-week open trial (Zuardi et al. 2009). A flexible oral dose of CBD, ranging from 150mg/day to 400mg/day in the last week, plus patients' usual treatments showed that psychotic symptoms were significantly reduced; cognitive and motor symptoms were not affected by the cannabinoid and no serious side effects were reported.

A double-blind study with 42 patients diagnosed with schizophrenia or schizophreniform disorder conducted at the University of Cologne showed that oral CBD (800mg daily) significantly reduced psychotic symptoms after 2 to 4 weeks of treatment and induced fewer side effects, such as extrapyramidal symptoms, increased prolactin levels, and weight gain, compared to amisulpride (Leweke et al. 2012). No relevant cardiovascular or THC characteristic psychological effects were noted.

A 19-year old female with a history of cannabis addiction received CBD 300mg on day 1, 600mg/day divided into two doses days 2 through 10, and CBD 300mg on day 11 (Crippa et al. 2010). During treatment with CBD, the patient did not report any marijuana withdrawal symptoms, and she did not experience anxiety or dissociative symptoms, as assessed by standardized rating scales.

In a double-blind, cross-over, placebo-controlled study with 16 healthy male volunteers, which compared the effects of 10 mg oral THC and 600 mg oral CBD there were no differences between CBD and placebo on any investigated variable (Martin-Santos et al. 2012). The intake of THC on the other hand was associated with anxiety, dysphoria, positive psychotic symptoms, physical and mental sedation, subjective intoxication and an increase in heart rate.

In a study entitled "Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology" with 15 healthy men with minimal early exposure to cannabis THC and CBD had opposite effects on regional brain function (Bhattacharya et al. 2010). Oral THC (10mg) and oral CBD (600mg) had opposite effects on activation in the striatum during verbal recall, in the hippocampus during the response inhibition task, in the amygdala when subjects viewed fearful faces, in the superior temporal cortex, when subjects listen to speech, and in the occipital cortex during visual processing. In a second experiment pre-treatment with intravenous CBD (5mg) prevented that acute induction of psychotic symptoms by THC (1.25mg).

In an open-label multicenter trial, 214 patients (aged 1-30 years) with severe, intractable, childhood-onset, treatment-resistant epilepsy were given oral CBD at 2-5 mg/kg per day, up-titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day (depending on study site) (Devinsky et al. 2016). 162 (76%) patients who had at least 12 weeks of follow-up after the first dose of cannabidiol were included in the safety and tolerability analysis. Adverse events reported in more than 10% of patients were somnolence in 25%, decreased appetite in 19%, diarrhoea in 19%, fatigue in 13%, and convulsion in 11%. Five (3%) patients discontinued treatment because of an adverse event. No THC specific side effects were noted.

#### **4. Discussion**

In their study Merrick et al. (2016) noted that oral CBD showed a relatively high incidence of somnolence and fatigue in children with epilepsy. They wondered whether these effects were due to the isomerization of CBD to THC after oral intake in gastric fluid.

However, these side effects observed in paediatric subjects, who participated in clinical studies, are not characteristic for THC. On the contrary, high oral CBD doses caused opposite effects to THC or marijuana/cannabis, e.g. reduced appetite, improved cognition and anti-psychotic effects, in clinical trials.

Given the data observed in the study by Merrick et al. (2016) and the observations in clinical studies presented here there may be mainly two explanations for these divergent results.

1. In real-life CBD may not be degraded to such a degree to psychoactive cannabinoids as under experimental conditions used in the study by Merrick and colleagues.
2. It is known that CBD antagonizes psychological and cardiovascular THC effects, so that small amounts of THC may not influence the overall effects of CBD.

There may also be a combination of both. Whatsoever the reason for this discrepancy is, the observations in clinical studies finally count as most relevant. Thus, there is no reason to believe that the possible degradation of CBD to psychoactive cannabinoids in simulated (!) gastric fluid “may affect clinical response and lead to adverse events” (Merrick et al. 2016, P. 111). Thus, there is no need “to eliminate the potential for psychotropic effects by developing different delivery methods, such as transdermal-based systems.

#### **5. Conclusion**

Even if the experimental approach taken by Merrick and colleagues is of interest, whether this result is of clinical relevance can only be demonstrated in the clinic. We have enough data to be reassured, that the acidic gastric environment during normal gastrointestinal transit DOES NOT “expose patients treated with oral CBD to levels of THC and other psychoactive cannabinoids that exceed the threshold for a physiological response” (Merrick et al. 2016, P. 111).

The conclusion by Merrick et al. (2016) may be more based on the commercial interest of Zynerva Pharmaceuticals than on a thorough analysis of the overall available scientific data, which suggests the opposite conclusion, that is to say, that oral administration of CBD is a safe and easy way to use CBD, even at high doses, in a therapeutic context.

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