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Edible Cannabis Products: It Is Time for FDA Oversight

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The legalization of cannabis (marijuana) for medical and recreational purposes in states throughout the United States has greatly increased its availability and use by adults and teens. Much of the earlier research on cannabis focused on its administration by smoking. Very little recent research has been conducted on the administration of cannabis by the oral route, the presumption apparently being that the 2 routes of administration are equivalent in terms of both their psychoactive effects and their toxicity. As the use of cannabis-laced "edibles" continues to increase, it is becoming clear that this presumption may not be correct.

Several reports of severe cannabis-induced toxicity have appeared in both the lay press[1] and in the medical literature.[2] One man, a 19-year-old college student, ate a cannabis-laced cookie (approximately 6.5 "servings," although the product was not tested for potency or content uniformity) and shortly thereafter began rambling incoherently and subsequently jumped to his death from the balcony of a Denver, Colorado, hotel. The Denver coroner listed cannabis intoxication as a significant factor in his death.[2] A second man developed hallucinations and rambling speech after eating cannabis-containing candy and concomitant ingestion of an unidentified prescription medication, and in the midst of an apparent psychotic break, fatally shot his wife while she was calling 911 for help.[1] In early September 2014, five high school students in the San Francisco, California, area, aged 14–16, became ill after eating brownies that had been laced with cannabis.[3] Three of the students developed nausea and vomiting, and 2 became unconscious and were hospitalized. The brownies were sold to the students by a classmate. There are no toxicology results indicating if the brownies contained other drugs or if they contained only cannabis. What was the common denominator in these cases? In every instance, those affected consumed the cannabis orally, rather than by smoking.

Although nausea, vomiting, lightheadedness, and occasional adverse psychiatric or paranoid reactions have been associated with smoking cannabis since the 1960s, reports of severe alterations in consciousness requiring hospitalization have been quite rare. If the brownies contained only cannabis (tetrahydrocannbinol, THC), aside from overdosage, what caused such severe reactions (psychosis, unconsciousness)? The answer may reside in the differences in metabolism between orally ingested and smoked cannabis.

Smoked cannabis is absorbed into the pulmonary circulation and returned to the heart through the pulmonary vein. From the heart, it is distributed systemically, without passing through the liver. However, orally ingested THC is subject to both transmural absorption and metabolism in the gastrointestinal tract and "first-pass" hepatic metabolism as it passes through the liver. As a result, THC is metabolized more extensively by the oral route, leading to the synthesis of a much larger amount of 11-OH-THC than is generally formed following smoking. The 11-OH-THC metabolite is psychopharmacologically active and can combine its psychotropic effects with those of THC to produce a more robust psychotropic effect in the CNS.[4,5] The magnitude of the effect of the combined 11-OH-THC and THC most likely was the cause of the psychotic reactions and loss of consciousness described in the cases reported above.

As far back as 1973, Lemberger et al[6] demonstrated the psychotropic effects of the 11-OH-THC metabolite when he administered tritiated intravenous doses of THC, 11-OH-THC (formulated in ethanol) or ethanol alone under blinded conditions, to 9 casual cannabis users. Following the administration of 1 mg of 11-OH-THC, a marked tachycardia and euphoric "high" occurred in 3–5 minutes, and the psychologic

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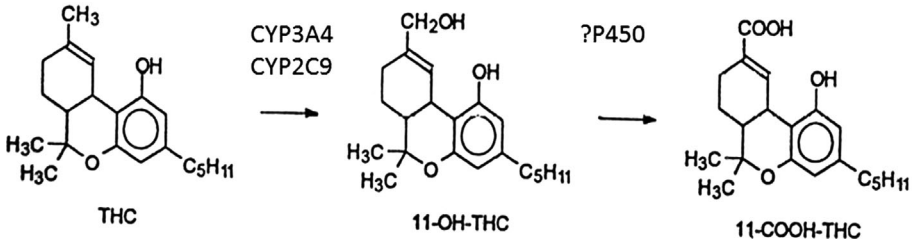

Figure 1. Metabolic fate of THC in humans.

effects correlated well with 11-OH-THC plasma levels. However, intravenous administration of 1 mg of THC required a latency period of 10–20 minutes after intravenous administration before the peak subjective "high" was reported by the subjects. The authors concluded that the psychologic effects of THC were at least partially mediated through the 11-OH-THC metabolite and that the latency period was indicative of the time required to convert the THC to the active 11-OH-THC metabolite.[6]

THC (Figure 1) normally undergoes oxidation to the 11-OH-THC metabolite by the polymorphic CYP2C9 enzyme, as well as by CYP3A4, which is then finally oxidized to the inactive, 11-nor – 9-carboxy-THC (THC-COOH) acid that appears in blood and urine.[7] The enzyme involved with the oxidation of 11-OH-THC is poorly defined in the literature. When THC is smoked, far less 11-OH-THC is formed, and the magnitude of the effect is less than with 11-OH-THC and THC together.[8] The polymorphism of CYP2C9 in the population makes the magnitude of this effect hard to predict in the individual user.

Figure 2. Typical cannabis "edible" product.

A review of the package insert for the Food and Drug Administration (FDA)-approved synthetic Δ^9- tetrahydrocannabinol, dronabinol indicated that during clinical trials, adverse psychotropic effects similar to those reported above occurred in 3% to 10% of patients and that the dronabinol was the most probable cause of the dizziness, euphoria, paranoid reaction, somnolence, and abnormal thinking reported in the manufacturer's labeling.[9] The FDA-approved dose of dronabinol is 2.5–5 mg 2–3 times per day for appetite stimulation or relief of chemotherapy-induced nausea. After marketing, severe overdosage of dronabinol was reported to cause panic reactions in apprehensive patients and other significant central nervous syst em symptoms that were not specifically defined.[9]

Currently, manufacturers of cannabis edibles are not regulated at all by the Food and Drug Administration. Critically, there are no safe levels of THC established for these products, nor has there been a maximum dose established, with the exception of the doses of purified synthetic Δ^9- tetrahydrocannabinol used for appetite stimulation or relief of chemotherapy-induced nausea described above. One manufacturer of an edible form of THC distributes chocolate truffles with a THC content of 150 mg per piece (Figure 2). This product and others like it, which contain a psychoactive substance currently classified by the Drug Enforcement Administration as Schedule I, carry only the labeling as shown in Table 1.

In February, 2016, Colorado Regulators enacted new rules for edible cannabis products, including new restrictions on the content of THC in these items, limiting each "unit" of edible to no more than 10 mg THC, with no more than 100 mg THC permitted per package of edible products.[10] It is not clear on what

Table 1. Product Information From a Typical Cannabis Edible Product

- ONLY AVAILABLE AT MEDICAL CENTERS
- When you consume an Edible, the THC is processed in your liver—transforming from a Δ-9 to a more potent 11-hydroxy
- Edibles can take longer to take effect than other methods of THC uptake, but the effects often last much longer, too
- Edibles are triple laboratory tested for consistency and quality

basis this limit was chosen, nor is it clear that other states where cannabis has been legalized will follow Colorado's lead.

The American College of Clinical Pharmacology (ACCP) believes that it is time for sensible regulation and labeling of edible cannabis products by the Food and Drug administration. Manufacturers of edible cannabis products should have to conform to specific guidelines regarding maximum THC levels per unit of edible product (eg, cookie, brownie, etc.). Furthermore, specific warnings about the danger of enhanced 11-OH-THC exposure with these products need to be displayed prominently on the packaging. Other products available over the counter (eg, pain relievers, cough and cold preparations), which are unscheduled substances, are required to carry specific labeling for dosing and adverse events. It seems odd, to say the least, that edible cannabis, which contains a known psychoactive substance, is not held to the same standard as a bottle of acetaminophen tablets. Finally, there is a desperate need for more clinical pharmacology research in the area of orally administered THC. The rapid legalization of cannabis in state after state has created a regulatory vacuum that, as the case reports demonstrate, could result in serious harm to consumers consuming edible cannabis products. The ACCP believes that states legalizing cannabis need to invest part of the financial gains made through taxation of these products into studies investigating the safety and dose-response characteristics of edible THC products.

The assumption made by many users of edible cannabis products—that it is a "natural" product and is therefore safe—is ill-conceived, at best. Opium and cocaine are also natural products and can certainly be lethal if misused and overdosed. In point of fact, the available evidence indicates that significant harm may be caused by the use of these over-the-counter THC products in the absence of sensible regulations regarding dosing and administration. Since at the current time cannabis seems to be here to stay, both in the medical and recreational settings, ACCP believes it is overdue to strongly reject the false presumption that cannabis is innocuous and devoid of toxic effects, and fund the clinical pharmacology research needed to elucidate its dose-response characteristics and establish its toxicity profile in order to make the use of these products safer for those who may benefit from medical cannabis, and those who use it for recreational purposes. Dose-response characteristics and toxic effects must be determined and communicated to the end user, just like every other drug. There is no such thing as a drug without side effects, and cannabis is no different.

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