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CANNABIS (B SHERMAN AND R TOMKO, SECTION EDITORS)

The Rise and Risk of Delta-8 THC (Delta-8-Tetrahydrocannabinol)

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Abstract

Purpose of Review The purpose of this review is to differentiate delta-8-tetrahydrocannabinol (delta-8) and delta-9-tetrahydrocannabinol (delta-9) as they relate to human health and disease.

Recent Findings Delta-8 is a novel cannabinoid becoming increasingly used following the passage of the US Agricultural Improvement Act of 2018 and the deregulation of hemp. *Cannabis* spp. naturally produces little delta-8. Retail delta-8 products consist of synthetic delta-8 chemically converted from cannabidiol (CBD). Delta-8 marketing claims a "softer, gentler high" compared to delta-9, but limited data exist to support this claim. A recent screen of delta-8 products found that the majority contained heavy metal contamination and that the reported vs. actual compositions of commercial products did not agree.

Summary The effects of delta-8 on the human body remain largely unexplored, as do the pharmacokinetic differences between delta-8 and delta-9. Because the dietary supplement market is largely unregulated, these products are not tested for contaminants that may also have harmful effects.

Keywords Delta-8-tetrahydrocannabinol · Delta-9-tetrahydrocannabinol · Cannabinoid use disorder · Heavy metals · Adulterants

Introduction

In this review, we wish to explore how the Agriculture Improvement Act of 2018 (a.k.a. The 2018 Farm Bill) single-handedly created an unregulated new pharmaceutical cottage industry and potential health crisis — the explosion in the production, marketing, and sale of over-the-counter delta-8 (delta-8-tetrahydrocannabinol). Specifically, the 2018 Farm Bill provides:

> . . . an amendment to the Controlled Substances Act (21 U.S.C. 802(16)) to exclude hemp from the statutory definition of marijuana as redefined in the 2018 farm bill, provided it contains not more than a 0.3% concentration of *delta-9 tetrahydrocannabinol*—marijuana's primary psychoactive chemical. [*emphasis added*] [1]

The intent was to give US farmers the opportunity to cultivate and market hemp for its commercial value in production of fiber, rope, textiles, food, animal feed, and biofuel. The unintended consequence was to seemingly legalize other psychoactive cannabinoids (delta-8-THC, delta-10-THC, and THC-O-acetate). While the cannabis plant naturally produces very little of these euphorigenic compounds, delta-8 can be readily synthesized in large quantities, in the laboratory, from hemp-derived cannabidiol (CBD). As result, a delta-8 industry has developed exponentially since the Farm Bill was signed into law in December 2018.

The growing popularity of delta-8 is exceeding our understanding of its effects. The first survey of delta-8 users was published in 2021 and revealed alarming but informative trends of user experiences and views of the drug [2••]. This survey study of Facebook and Reddit users ($n = 521$) was weakly representative of gender (57% men) and not representative of race (90% white) and age (mean = 34 years) of the typical cannabis consumer, although this is to be expected with a community-based survey of online applications. 90% of the participants were in states that did not have recreational marijuana (delta-9) available, which supports the hypothesis that consumers may seek delta-8 to replace

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or supplement their supply of delta-9 products. Participants on average reported that delta-8 effects were less intense and shorter than delta-9. Women and older individuals of this survey were more likely to report that delta-8 effects were stronger and lasted longer than delta-9, representing a potential effect of sex and gender that should be explored in further studies. Many participants lauded delta-8 for its manageable high and reduced anxiety compared to delta-9, but also reported inhaled delta-8 being harsher on the lungs than delta-9. Importantly, the FDA Adverse Events Reporting System (FAERS) of delta-8 related products has documented over 200 adverse events associated with this compound as of July 2022, with the large majority of adverse events being respiratory and endocrine issues [3].

We herein compare and contrast delta-8 and the more well-characterized delta-9. The key take-home messages are that (1) while delta-8 may have therapeutic potential and select advantages over its structurally similar delta-9 from marijuana, it has not been extensively studied and is not approved by the FDA (whereas delta-9 has been approved for several medical indications). (2) Delta-8, as currently marketed, is synthetic and not naturally produced. Moreover, in this unregulated environment, the buyer should beware.

Summary of Regulatory and Safety Issues

With the passage of the 2018 US Farm Bill, hemp (cannabis containing less than 0.3% delta-9) was removed from Schedule I drug status. Over recent years, this has led to the boom of the CBD nutritional supplement industry and, more recently, into a growing market for minor cannabinoids such as cannabigerol (CBG), cannabinol (CBN), and delta-8. Interestingly, all tetrahydrocannabinols are still listed as scheduled I substances by the US federal government; however, the specific mention of delta-9 in the Farm Bill has led to the interpretation that delta-8 is no longer federally regulated because it is coming from hemp. Because of the perception that this compound produces a legal, and possibly milder "high," the delta-8 market is rapidly growing. While a few states have taken up regulation to prohibit the sale of delta-8 products, across most of the USA, delta-8 remains readily available in retail and online sales outlets [4•]. Online sales raise another potential legal issue, as this could constitute interstate trafficking of a controlled substance.

Structurally, delta-8 and delta-9 are very similar, with the only difference being the location of a single double bond (Fig. 1, top structures). Both molecules are agonists at the two major cannabinoid receptors, and capable of inducing euphoria. Despite delta-9 products being readily available in several states either for medicinal or recreational purposes, there still seems to be a market for delta-8 possible due to lower cost or the perceived "softer, gentler" high. However, the safety of current delta-8 products is unclear for three reasons. First, these products are often marketed as natural; however, the *Cannabis* plant produces very little delta-8 (not in amounts to profitably make high concentration delta-8 extracts from plant material). Instead, the delta-8 in these products is being synthetically produced from CBD. Second, these products are not regulated or routinely tested by independent sources and may contain by-products and other undesirable compounds from the synthesis process. Finally, this compound has not been thoroughly investigated for its activity in humans.

The potential safety issue has recently been documented in case reports of toxicity and cannabis-related complications. As one illustrative example, in 2021, a healthy 2-year-old girl ingested nine delta-8 gummies and experienced severe side effects [5•]. Her father had purchased the package earlier and left it unopened on a desk. The patient was flown to the local ER due to sedation and decreased responsiveness. Upon admission to the ER, she displayed a score of 3/15 on the Glasgow Coma Scale, the lowest score possible indicating total loss of consciousness. She required intubation and a dexmedetomidine drip to relieve spasticity. The toxicology team estimated that the total ingested dose of delta-8 was 14.7 mg/kg or 225 mg, which resulted in a serum level over 100 ng/ml and over 700 ng/ml for the active metabolite (11-nor-9-carboxy-delta-8-THC). She was extubated after 12 h and discharged after 48 h in the pediatrics unit. For reference, a dose–response study of pediatric delta-9 oral ingestion reported that ingestion exceeding 5 mg/kg was significantly more likely to require hospital admission and higher ingested quantities of delta-9 led to a higher likelihood of ICU admission [6]. It is important to note that while delta-8 is claimed to be "milder" and less potent than delta-9, the serum concentrations of each to require severe medical intervention are not so different; therefore it is imperative to ask what other delta-9 related complications may arise from increasing delta-8 use.

A complication previously only associated with delta-9, cannabinoid hyperemesis syndrome (CHS) is characterized by cyclical vomiting unresponsive to typical antiemetics, but selectively responsive to warm showers, capsaicin, and haloperidol in the setting of a chronic cannabis user. This syndrome has gained increasing attention due to influx of emergency department (ED) visits from both adult and pediatric patients suffering from intractable vomiting. In 2021, the first report of delta-8 products causing this syndrome was published detailing a 38-year-old woman with intractable vomiting who had been taking nightly delta-8 gummies for 30 days to aid sleep [7•]. After ondansetron provided no relief, a detailed clinical history, and a computed tomography (CT) scan of her abdomen and pelvis revealed no physical etiologies, the physicians suspected CHS. Once her providers administered topical capsaicin cream and IV

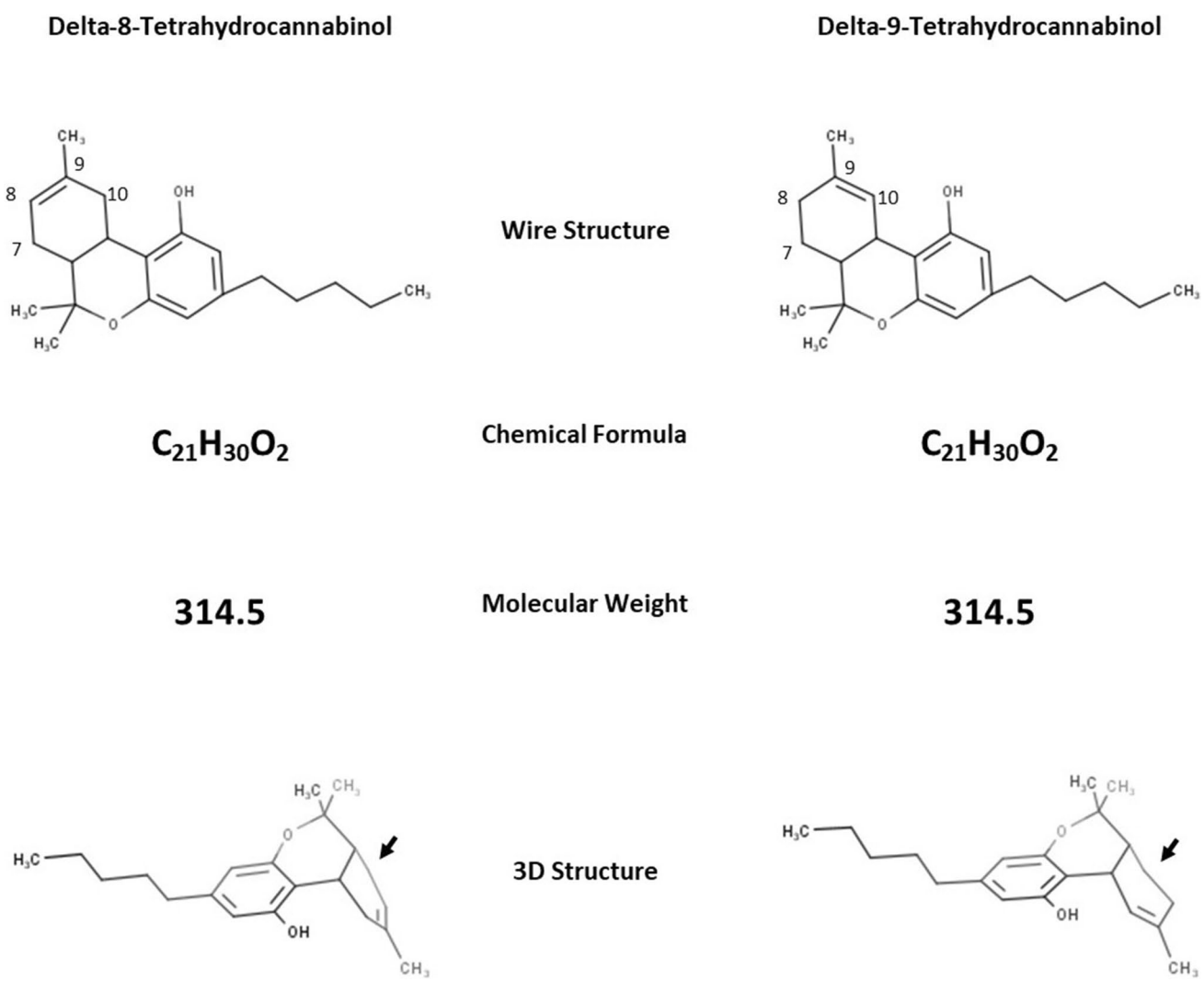

Fig. 1 Here, we denote the similarities and differences of delta-8 and delta-9 THC. The black arrow identifies the "puckers" from different double bond locations. Original artwork using MarvinSketch

haloperidol, she experienced immediate relief and was discharged without follow-up. While these providers did not treat her again, CHS typically induces several emergency department visits and only resolves after complete, sustained cessation of cannabis use [8]. This report confirms public health and ED providers' fears: the increase of chronic delta-8 users (who assume delta-8 to be safer) will increase the number of adverse events associated with cannabis use. There are no evidence-based treatments for acute cannabis toxicity nor CHS, and the science of treating cannabis-related complications is lagging behind the marketing and consumption of cannabis products.

In considering the lack of industry regulation, Meehan-Atrash and Rahman recently published a quality report for 27 delta-8 containing e-cigarette products from 10 commercially available brands [9••]. The authors used mass spectroscopy methods to quantify cannabinoid levels in each product, as well as to identify additional additives, reaction side-products, and heavy metals. Several poor practices in unregulated delta-8 manufacturing and sale are gleaned from this study. First, none of the products contained the reported amount of delta-8, with almost all containing up to 40% less delta-8 than reported. Second, analysis of heavy metals confirmed detectable levels of magnesium, chromium, nickel, copper, zinc, mercury, lead, and silicon which may increase rates of reactive oxygen species production in the respiratory track when the vapor is heated and inhaled. Metal conjugates, like silicon compounds, have been associated with significant lung injury since 2018. E-cigarette and vaping-induced lung injury (EVALI), a US epidemic, had caused more than 2800 hospitalizations until 2020 when the CDC stopped indexing cases [10]. EVALI creates a chemical pneumonitis in airways that results in moderate-to-severe shortness of breath, chest pain, and/or abdominal pain. The

disease is potentially fatal, with almost 50% of cases requiring ventilation and/or intubation [11]. The potential for this disease to interact with pre-existing conditions or COVID infection is great and increases the chance of death from respiratory illness. Third, up to 13% of the mass of each product consisted of unstudied, synthetic cannabinoid products, which can alter the psychoactive and safety profiles of the retail products. Finally, adulterants used in the formulation process were found in all products, suggesting additional risk of respiratory damage from ingestion of strongly acidic compounds such as hydrochloric acid.

Synthesis and Structure

One of the conundrums in considering delta-8 versus delta-9 is how they can have differing effects when they have nearly identical structures. They have the same chemical composition ($C_{21}H_{30}O_2$) and identical molecular weights (314.45 g/mole). As shown in Fig. 1, they have structures that vary only in the position of a double bond (starting at carbon number 8 versus starting at carbon 9). Examining a 3-dimensional model (Fig. 1, lower structures) shows a very subtle difference in the "pucker" of the ring containing the "delta" bond. This may account for the perceived differences in the pharmacological and psychological effects described in the next section.

A common fallacy in the hype surrounding delta-8 is that it is a natural and legal form of THC because it is found in hemp. The fact of the matter is that the delta-8 being marketed, sold, and consumed is not isolated from the natural plant; rather, it is synthesized chemically and then added to consumer products. As Pellati et al. have described in great detail, when the cannabis plant condenses geranyl pyrophosphate with olivetolic acid, it does so in such a manner that the double bond (that is destined to become "delta") must be positioned to produce delta-9 [12]. There is a small amount of spontaneous conversion to delta-8, but it is just that … a small amount. It is reported that typical concentrations of delta-8 are generally around 0.1% [4•]. By comparison, commercially available delta-9-dominant cannabis can reach 20 to 30% delta-9 (200 to 300 times the levels of delta-8). Our own recent characterization of six CBG/CBD-dominant strains of hemp produced delta-8 concentrations in extracts from 0.3 to 2.6% (data not shown). The bottom line is simply that there is not enough delta-8 in a plant to isolate in a cost-effective manner.

So, where is all the delta-8 coming from if the plant does not make it in quantity? It is being synthesized in a simple chemical reaction. In a quirk of chemistry, when CBD is heated in the presence of acid, the cyclization that produces THC does so with the double bond in position 8 (delta-8; Fig. 2). The same Farm Bill of 2018 that made hemp legal created a legal source of vast amounts of inexpensive CBD. In addition to being sold as the ubiquitous CBD oil, it did not take long for entrepreneurs to recognize a new and lucrative market. Unfortunately, the unregulated landscape produced an ecosystem in which products not only do not contain the advertised levels of cannabinoids but can have a great many constituents that were not disclosed (e.g., metals, organic solvents) as discussed above. Therefore, these products that are being marketed are not derived from hemp — they have been synthesized in an unregulated laboratory setting.

Pharmacology

Receptor Activity

The activity of different cannabinoids at receptors across the body and brain largely determines their physiological and psychological effects. The euphoric, analgesic, anxiogenic (or anxiolytic depending on the individual and dose), appetitive, and other effects of THC are largely due to activity at the cannabinoid receptor 1 (CB1), the most abundant G-protein coupled receptor in the brain. Immune and indirect effects may result from activity at cannabinoid receptor 2 (CB2). Consuming THC products with high potency, at higher frequencies, is associated with increased risk of psychosis, cannabinoid use disorder, and cannabinoid hyperemesis syndrome (CHS) [13, 14, 15].

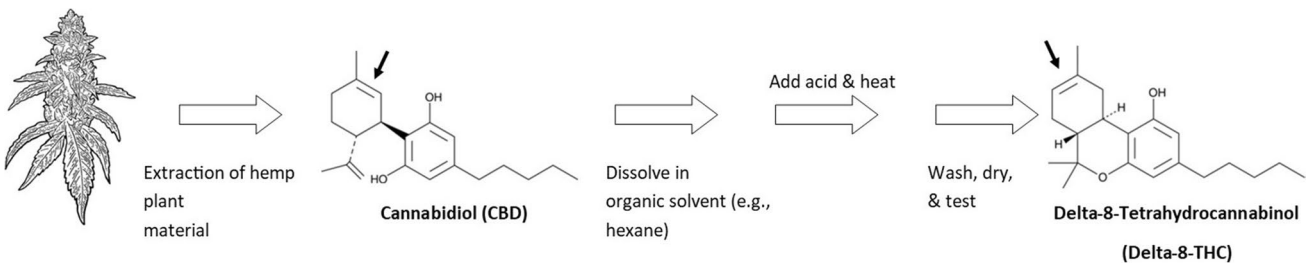

Fig. 2 The conversion process from hemp to delta-8 THC by way of CBD is detailed here. The black arrows denote the different locations of the double bond between CBD and delta-8. Original artwork using MarvinSketch

The only measures of the affinity (Ki) of human CB1 and CB2 for delta-8 are through in vitro models. Two different cell model studies and one structural-activity relationship analysis reported ranges of affinity for delta-8 at CB1 between 44 and 251 nM and CB2 between 12 and 417 nM [16, 17, 19]. These same studies reported delta-9 at CB1 between 18 and 40.7 nM and CB2 between 36 and 309 nM. Taken together, it is likely that delta-8 exhibits less affinity for CB1 than delta-9 THC and about the same affinity for CB2.

To measure intracellular signaling, a similar cell system can be used to measure the amount of G-protein coupled receptor (GPCR) activity after adding a drug of interest. CB1 and CB2 are Gi/o inhibitory GPCRs: when activated they will reduce the activity of adenylyl cyclase. First, a study of GTPγS binding reported delta-8 at CB1 with an EC_{50} of 5820 nM, while delta-9 in the same system was 269 nM [16]. At CB2, the values were similar (524 nM and 327 nM for delta-8 and delta-9, respectively). Another method of measuring activity is using the forskolin assay to stimulate cAMP production. At CB1, the EC50 values for delta-8 and delta-9 were 82 nM and 13 nM, respectively; CB2 was not evaluated in this study [18]. The signaling activity reported in these studies suggests that delta-8 and delta-9 have wide differences in activity after cannabinoid receptor activation, and more studies are needed to measure these differences more thoroughly as well as to characterize delta-8 and delta-9 activity at other common bioactive receptors.

While there have been several studies of delta-8's effects on cannabinoid receptors in rodent and human models, there are no studies, to our knowledge, of this cannabinoid's activity at non-cannabinoid receptors [20••]. Delta-9 and other cannabinoids exhibit activity across a wide range of receptor and channel systems, with high activity at GPR55 and TRP family channels [21]. These systems contribute to the analgesic effects of delta-9, and since there is evidence of differential activity at cannabinoid receptors, it is likely that delta-8 does not affect these channels with the same affinity and activity as delta-9. Finally, unpredictable activity at non-cannabinoid receptors presents the danger of unintended drug interactions in patients with complex pharmacological regimens or those with varying underlying illnesses.

Metabolism

Delta-8 and delta-9 are both metabolized by human liver cytochrome P450 enzyme CYP2C9, which produces a pharmacologically active hydroxyl metabolite of the cannabinoid at the 11 position. For delta-9, this metabolite is more potent at cannabinoid receptors and contributes to the psychoactive effects of ingesting cannabis [22]. Similarly, the 11-OH metabolite of delta-8 appears to be more potent than its parent compound in a small study of intravenous administration [23]. There is additional metabolism by CYP3A4; however, the products of delta-8 metabolism at this enzyme have not been thoroughly studied [24].

Emerging knowledge of cannabinoid pharmacokinetics has revealed the risk of these compounds interfering with medications through drug-drug interactions [25]. Many narrow therapeutic index medications are metabolized by CYP2C9 and CYP3A4 enzymes. Practitioners must therefore be vigilant with asking about all cannabinoid use, including delta-9, CBD, and now delta-8, to prevent drug-drug interactions and adverse events.

Tolerance

A 1977 preclinical study documented that chronic administration of delta-8 in rats producing tolerance to analgesia, heart rate change, and temperature change after 13 days of daily administration [26]. Recently, a preclinical rodent study by Vanegas and colleagues confirmed the results of the previous study in mice [27]. These researchers found that the effects of delta-8 on catalepsy, antinociception, and hypothermia were significantly reduced after 5 days of repeated, subcutaneous injections, and produced cross-tolerance to the CB1R/CB2R agonist WIN 55,212–2 on these metrics. Similar to the rapid tolerance reported with daily delta-9 THC administration, these results suggest that preclinically, there exists a need to ingest increasing amounts of the cannabinoid to maintain analgesic effects.

Reward

Preclinical preference and reward assays are limited in understanding the differences between delta-8 and delta-9. Vanegas and colleagues shed light on the reward qualities of delta-8. These researchers report that repeated administration of delta-8 induces physical dependence, as measured by increased anxiety and withdrawal behaviors after administration of a CB1R/CB2R antagonist rimonabant [27]. Additionally, delta-8 dose-dependently substituted for delta-9 in the drug discrimination paradigm, which measures the ability for the rodents to discern the subjective effects of different drugs. These results were consistent for both male and female mice. This is the most recent and, to our knowledge, only preclinical study on delta-8 reward. A major reason for a dearth of evidence is because reward studies in rodents and primates produce mixed, inconsistent results of the reinforcing properties of delta-9. In humans, however, studies are clearer and there are associations between higher concentrations of THC and altered reward in cannabis users.

Human decision-making studies in the clinical environment shed light onto behavioral patterns of cannabis users and may inform the forthcoming rise in delta-8 use and

complications. Regular and chronic cannabis users tend to change their smoking behavior if they know the reported potency of a product; however, these data are mixed [28]. Some studies report users will use less of a higher potency product, but other studies report that users will continue their typical ingestion patterns with high potency products resulting in more frequent adverse events. Populations of cannabis users who seek the highest potency have the most frequent use, and the highest likelihood for psychological dependence also tend to be the youngest users [29]. The upper limit of THC (regardless of isomer) use is variable for each user, but it seems experienced users will tend to titrate drug to produce desired effects.

Taken together, less potent, but still euphoric, cannabinoids like delta-8 might encourage increased ingestion with the intention to mimic the high potency THC that a chronic user is familiar with. This presents a major issue for younger users, who will likely have greater access to the unregulated retailers of delta-8. Conversely, adults who desire non-euphoric effects of THC might seek delta-8 from perceived opportunity to titrate effects at a lower range of CB1 activity to minimize psychoactive effects, but maximize other desired effects such as appetite stimulation or analgesia. There are no studies suggesting that this optimization is possible at CB1, and differential receptor availability, density, and distribution across subpopulations of users make this difficult to confirm or refute.

Human Effects

There are less than ten published studies of delta-8 consumption by humans in a clinical environment. The major advantages of clinical studies over survey studies include known concentrations of administered cannabinoids, understanding potential pharmacokinetic interference, and metrics of psychological and physiological arousal. These studies examined the effects of delta-8 through intravenous (IV), oral, and smoked routes of administration. Each of the studies have significant design and control limitations; moreover, no new data were published between 1995 and 2022. This lack of research has left researchers and practitioners unarmed in the face of the deluge of delta-8 interest, consumption, and potential misinformation.

The first known and largest sample ($n=77$ males) of delta-8 ingestion was reported as a lecture by Roger Adams in 1942, but the lecture notes have little quantitative data [30]. Later studies use small sample sizes ($n=1$ to $n=8$) with almost all subjects being healthy, adult, cannabis-naïve males. Three studies used a placebo group but none of these studies used similar outcome measurements (heart rate, subjective effects) [31, 32, 33]. One study reported "over 480" pediatric cancer patients treated with edible delta-8 as an anti-emetic, but only describe eight of those patients along with their side effects [34]. Finally, Wurz and colleagues described a case series of three male chronic cannabis users who smoked delta-8 THC while researchers observed impairment and breath/blood pharmacology [35]. The results indicated similar self-reported impairment, objective impairment as measured by horizontal gaze nystagmus (HGN), and half-lives (in blood and breath) of delta-8 and delta-9. This important case series serves to emphasize the need for development of guidelines for impairment of novel psychoactive cannabinoids.

Future Imperatives — Clinical Trials

Comprehensive clinical studies, albeit challenging, would account for the following factors:

- A large population of healthy men and women, age-matched and cannabis-experience matched.
- Several doses administered, by the same route of administration.
- Documentation of dietary supplements, medications, and foods that may affect pharmacometabolic enzymes.
- A detailed and validated psychoactive effect matrix to report outcomes.

Despite the difference in potency at the human cannabinoid receptors, many external factors may affect the subjective differences and consumption behaviors of delta-8 and delta-9 users. First, when users purchase delta-8 products, they are subject to the effects of marketing and suggestion of the retail websites, conversations with sellers, and anecdotes from other users. Second, the lack of regulation and stringency of quality control on delta-8 products will contribute to the amorphous effects reported by consumers, as illustrated by the Rochester study [9••]. This highlights the importance of safe supply of cannabinoid products. Consumers of delta-8 products are likely not ingesting the reported amount of delta-8 and other cannabinoids reported by sellers. Third, in cases where users are consuming the easily available delta-8 to replace restricted-use delta-9, they may intentionally or unintentionally ingest more amounts of delta-8 to reach the same potency of delta-9 subjective effects. While this serves as a monetary boon to delta-8 sellers, there may be unforeseen effects of increased concentration of delta-8 at other receptors as well as an accumulated toxicity of adulterants, unintended by-products, and heavy metals [9••].

Conclusion

In conclusion, the data are still unclear of the effects of delta-8 on the human body. The pharmacological studies that have been performed suggest this cannabinoid may be

a less potent agonist of CB1 receptors compared to delta-9, with similar effects at CB2 receptors. Delta-9 is known to also be an agonist at GPR55 and several TRP channels, while it is an antagonist at TRPM8; unfortunately, there are no data regarding the activity of delta-8 at these receptors. While the two compounds are metabolized in a similar manner, the half-life of delta-8 in humans has not been examined. There are also safety issues to consider with the current market of delta-8 products. As dietary supplements, these products are largely unregulated (even in states that otherwise regulate THC-dominant cannabis products). A recent report has shown that the quality of delta-8 products does not reflect the package labeling with regard to cannabinoid content. Additionally, heavy metals have been detected in these products, likely a result of growing conditions and the process by which delta-8 is produced from CBD. Smoking or vaping impure products with heavy metal contamination has been linked to respiratory illnesses, like EVALI. It is therefore important that if consumers are going to use these products, they source from reputable companies that provide a detailed, independent analysis of each lot or batch of the product.

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Declarations

Conflict of Interest The authors declare no competing interests.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Conaway KM. HR 2–115th Congress (2017–2018): Agriculture Improvement Act of 2018. /bill/115th-congress/house-bill/22018.
2.•• Kruger DJ, Kruger JS. Consumer experiences with delta-8-THC: medical use, pharmaceutical substitution, and comparisons with delta-9-THC. Cannabis Cannabinoid Res. 2021. https://doi.org/10.1089/can.2021.0124. (**Survey of delta-8 users noting intended and perceived use of the cannabinoid compared to delta-9.**)
3. Kumar A. The newly available FAERS public dashboard: implications for health care professionals. Hosp Pharm. 2019;54(2):75–7. https://doi.org/10.1177/0018578718795271.
4.• Babalonis S, Raup-Konsavage WM, Akpunonu PD, Balla A, Vrana KE. Delta(8)-THC: legal status, widespread availability, and safety concerns. Cannabis Cannabinoid Res. 2021;6(5):362–5. https://doi.org/10.1089/can.2021.0097. (**Review of delta-8 legality and safety status.**)
5.• Akpunonu P, Baum RA, Reckers A, Davidson B, Ellison R, Riley M, et al. Sedation and acute encephalopathy in a pediatric patient following ingestion of delta-8-tetrahydrocannabinol gummies. Am J Case Rep. 2021;22:e933488. https://doi.org/10.12659/ajcr.933488. (**Case report of altered mental status and coma in a 2-year-old girl who ingested her father's delta-8 gummies.**)
6. Heizer JW, Borgelt LM, Bashqoy F, Wang GS, Reiter PD. Marijuana misadventures in children: exploration of a dose-response relationship and summary of clinical effects and outcomes. Pediatr Emerg Care. 2018;34(7):457–62. https://doi.org/10.1097/PEC.0000000000000770.
7.• Rosenthal J, Howell M, Earl V, Malik M. Cannabinoid hyperemesis syndrome secondary to delta-8 THC use. Am J Med. 2021;134(12):e582–3. https://doi.org/10.1016/j.amjmed.2021.06.048. (**Case report of a 38-year-old woman ingesting delta-8 gummies for 1 month and developing cannabinoid hyperemesis syndrome, the first published report of this complication coming from delta-8 products.**)
8. Nachnani R, Hushagen K, Swaffield T, Jhaveri P, Vrana KE, Alexander C. Cannabinoid hyperemesis syndrome and hypophosphatemia in adolescents. JPGN Reports. Forthcoming. 2022.
9.•• Meehan-Atrash J, Rahman I. Novel Δ8-tetrahydrocannabinol vaporizers contain unlabeled adulterants, unintended byproducts of chemical synthesis, and heavy metals. Chem Res Toxicol. 2022;35(1):73–6. https://doi.org/10.1021/acs.chemrestox.1c00388. (**Thorough chemical characterization of numerous delta-8 companies and products detailing lack of safety regulations and third party testing.**)
10. (CDC) CfDCaP: Outbreak of lung injury associated with the use of e-cigarette, or vaping, products. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html (2020). Accessed.
11. Layden JE, Ghinai I, Pray I, Kimball A, Layer M, Tenforde MW, et al. Pulmonary illness related to E-cigarette use in Illinois and Wisconsin — final report. N Engl J Med. 2020;382(10):903–16. https://doi.org/10.1056/nejmoa1911614.
12. Pellati F, Borgonetti V, Brighenti V, Biagi M, Benvenuti S, Corsi L. Cannabis sativa L. and nonpsychoactive cannabinoids: their chemistry and role against oxidative stress, inflammation, and cancer. BioMed Res Int. 2018;2018:1–15. https://doi.org/10.1155/2018/1691428.
13. Di Forti M, Quattrone D, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. Lancet Psychiatry. 2019;6(5):427–36. https://doi.org/10.1016/s2215-0366(19)30048-3.
14. DeVuono MV, Parker LA. Cannabinoid hyperemesis syndrome: a review of potential mechanisms. Cannabis Cannabinoid Res. 2020;5(2):132–44. https://doi.org/10.1089/can.2019.0059.
15. Petrilli K, Ofori S, Hines L, Taylor G, Adams S, Freeman TP. Association of cannabis potency with mental ill health and addiction: a systematic review. Lancet Psychiatry. https://doi.org/10.1016/S2215-0366(22)00161-4.
16. Husni AS, McCurdy CR, Radwan MM, Ahmed SA, Slade D, Ross SA, et al. Evaluation of phytocannabinoids from high-potency Cannabis sativa using in vitro bioassays to determine structure–activity relationships for cannabinoid receptor 1 and cannabinoid receptor 2. Med Chem Res. 2014;23(9):4295–300. https://doi.org/10.1007/s00044-014-0972-6.
17. Govaerts SJ, Hermans E, Lambert DM. Comparison of cannabinoid ligands affinities and efficacies in murine tissues and

in transfected cells expressing human recombinant cannabinoid receptors. Eur J Pharm Sci. 2004;23(3):233–43. https://doi.org/10.1016/j.ejps.2004.07.013.
18. Gerard CM, Mollereau C, Vassart G, Parmentier M. Molecular cloning of a human cannabinoid receptor which is also expressed in testis. Biochem J. 1991;279(1):129–34. https://doi.org/10.1042/bj2790129.
19. Bow EW, Rimoldi JM. The structure–function relationships of classical cannabinoids: CB1/CB2 Modulation. Perspect Med Chem. 2016;8:PMC.S32171. https://doi.org/10.4137/pmc.s32171.
20.●● Tagen M, Klumpers LE. Review of delta-8-tetrahydrocannabinol (Δ 8 -THC): comparative pharmacology with Δ 9-THC. Br J Pharmacol. 2022;179(15):3915–33. https://doi.org/10.1111/bph.15865. (**Thorough review of pharmacology of delta-8 vs. delta-9 THC in different models, species, and metrics.**)
21. Muller C, Morales P, Reggio PH. Cannabinoid ligands targeting TRP channels. Front Mol Neurosci. 2018;11:487. https://doi.org/10.3389/fnmol.2018.00487.
22. Lemberger L, Martz R, Rodda B. Comparative pharmacology of Δ9 tetrahydrocannabinol and its metabolite, 11 OH Δ9 tetrahydrocannabinol. J Clin Investig. 1973;52(10):2411–7. https://doi.org/10.1172/JCI107431.
23. Hollister LE. Structure activity relationships in man of cannabis constituents, and homologs and metabolites of Δ9 tetrahydrocannabinol. Pharmacology. 1974;11(1):3–11. https://doi.org/10.1159/000136462.
24. Watanabe K, Yamaori S, Funahashi T, Kimura T, Yamamoto I. Cytochrome P450 enzymes involved in the metabolism of tetrahydrocannabinols and cannabinol by human hepatic microsomes. Life Sci. 2007;80(15):1415–9. https://doi.org/10.1016/j.lfs.2006.12.032.
25. Kocis PT, Vrana KE. Delta-9-tetrahydrocannabinol and cannabidiol drug-drug interactions. Med Cannabis Cannabinoids. 2020;3(1):61–73. https://doi.org/10.1159/000507998.
26. Hine B, Toreelio M, Gershon S. Analgesic, heart rate, and temperature effects of delta8-THC during acute and chronic administration to conscious rats. Pharmacology. 1977;15(1):63.
27. Vanegas SO, Reck AM, Rodriguez CE, Marusich JA, Yassin O, Sotzing G, et al. Assessment of dependence potential and abuse liability of Δ(8)-tetrahydrocannabinol in mice. Drug Alcohol Depend. 2022;240:109640. https://doi.org/10.1016/j.drugalcdep.2022.109640.
28. van der Pol P, Liebregts N, Brunt T, van Amsterdam J, de Graaf R, Korf DJ, et al. Cross-sectional and prospective relation of cannabis potency, dosing and smoking behaviour with cannabis dependence: an ecological study. Addiction. 2014;109(7):1101–9. https://doi.org/10.1111/add.12508.
29. Korf DJ, Benschop A, Wouters M. Differential responses to cannabis potency: a typology of users based on self-reported consumption behaviour. Int J Drug Policy. 2007;18(3):168–76. https://doi.org/10.1016/j.drugpo.2006.08.002.
30. Adams R, Pease DC, Cain CK, Baker BR, Clark JH, Wolff H, et al. Conversion of cannabidiol to a product with marihuana activity. A type reaction for synthesis of analogous substances. Conversion of Cannabidiol to Cannabinol. J Am Chem Soc. 1940;62(8):2245.
31. Gong H Jr, Tashkin DP, Simmons MS, Calvarese B, Shapiro BJ. Acute and subacute bronchial effects of oral cannabinoids. Clin Pharmacol Ther. 1984;35(1):26–32. https://doi.org/10.1038/clpt.1984.4.
32. Karniol IG, Carlini EA. Comparative studies in man and in laboratory animals on 8 - and 9 -trans-tetrahydrocannabinol. Pharmacology. 1973;9(2):115–26. https://doi.org/10.1159/000136375.
33. Levander S, Binder M, Agurell S. Pharmacokinetics in relation to physiological and psychological effects of delta 8 THC. Acta Pharm Suec. 1974;11(6):662–3.
34. Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. Life Sci. 1995;56(23–24):2097–102. https://doi.org/10.1016/0024-3205(95)00194-b.
35. Wurz GT, Montoya E, Degregorio MW. Examining impairment and kinetic patterns associated with recent use of hemp-derived Δ8-tetrahydrocannabinol: case studies. J Cannabis Res. 2022;4(1). https://doi.org/10.1186/s42238-022-00146-9.