

In a World of Rising Deltas, What is the News with Delta 8-, 9- and 10-THC?

Abstract

Along with the legalization of marijuana throughout the U.S., there has been an increase in use of Delta products as well. These Delta-Tetrahydrocannabinol (THC) are widely available and advertised, however little information about their effects and possible risks are broadcasted to the public.

While marijuana is federally a Schedule 1 substance, the Delta drugs are not regulated. According to the Farm Bill from 2018, hemp derivatives with less than 0.3% THC can legally be bought, sold, and grown in most states within the U.S. For the user this means that there is no assurance of the contents of a purchased product. In addition, there is a risk of Deltas potentially containing harmful by products.

Delta-9-THC is one of the primary psychoactive cannabinoids of marijuana. Delta-9-THC is hemp derived and binds to the same cannabinoid receptors as marijuana. It can induce the same psychoactive effects such as euphoria, feeling "stoned", anxiety or paranoia.

Delta-8-THC is commonly called "marijuana lite" or "diet weed". Marijuana in its natural form contains Delta-8-THC only in a small percentage. The sold Delta-8 product is typically produced by synthetically converting Cannabinol (CBD) to Delta-9-THC into Delta-8-THC. Delta-8-THC binds to the same receptors as Delta-9, but Delta-8-THC is more known to cause visual distortions and difficulties with thinking and speaking. It is also more prone to cause sedation. Little research is available on Delta-8-THC. Concerning are the reports of accidental severe intoxication, resulting in more than 2000 calls to poison control centers between January 2021 and February 2022.

Delta-10-THC, in contrast, is often reported to be more activating and cause more euphoria and energy. Very little research is available regarding its benefits and side effects.

This paper is a systematic review of literature discussing the available data on Delta 8,9,10-THC for psychiatric and medical use. Utilized sources were Pubmed, Ovid, Medline, PsychInfo, EMBASE.

Introduction

The process of legalizing cannabis has been developing over the last two decades and did rather quickly progress in the most recent years, even throughout the Covid-19 pandemic where many other developments came to a hold [1]. At the same time, other cannabinoid products such as the Delta-THCs, also called Deltas, have also gained popularity despite little being known about them.

While cannabis is federally still a Schedule 1 substance and strictly regulated if not legalized per state laws, Deltas are not regulated and are widely, easily accessible. The 2018 Farm Bill federally legalized cannabis and cannabis derivatives with THC concentrations of less than 0.3% [2]. This law created a loophole for the Delta market and other cannabinoid products. There is often times no monitoring of the contents of those products with available sampling showing surprising and worrisome results. To this date, 17 states have banned the sales of Delta-8-THC while 7 others have restrictions in place [3].

The knowledge of Delta products and their toxicity is extremely limited, however an increase in calls to poison control centers related



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to the use of Delta products and case reports about toxicity symptoms in users raise concerns about the threat it poses [4]. Even though several states have moved forward and banned Delta-8 THC, due to online sales this is not a practical barrier to limit the use.

Delta-THCs are especially popular in states where marijuana is not legal or recreationally available, though about 30% of users also report to be using both marijuana, and Delta-THCs [5].

The use of Delta-8-THC is difficult to track as there is no public health surveillance data available. The growth of Delta-THC use can be shown by looking at sales and internet searches on platforms, for example Google. Google searches in the U.S. between 2000 and 2021 have shown an astronomical increase by more than 850%. A higher search rate was seen in states where marijuana was not yet legalized [6].

The sale of Delta products is a growing market. Available data observes that in the last two years, the sales of Delta-THC products in the U.S. exceeded over \$2 billion dollars [7].

In states where cannabis is legalized, about 23% of users are likely to purchase Delta-8-THC as well. A common reason is the more affordable price. According to available surveys about one third of the regular marijuana users also report to be using Delta-8-THC [8].

What are Delta-THC Products?

Delta-THCs differ from the natural form of marijuana in that they are chemically synthesized, most commonly from other cannabinoids (CBD).

Delta-8-THC is a chemical analog from Delta-9-THC and differs in the molecular structure in the location of the double-bond between carbon atoms [5].

While Delta-10-THC is only available in synthetic form, the Delta-8 and 9-THCs are available in the natural form of marijuana but only in such small concentrations that they can't be marketed through natural extraction [9].

There is no standardized approach to produce the Deltas which bears risks. First manufacturers must extract CBD from hemp and

then convert it to psychoactive cannabinoids. For this chemical synthesis process, unsafe household chemicals are frequently used. Those potentially leave residual substances in the Delta-THC, so that the product Delta-THC can contain toxic solvents, for example acetone, heavy metals, or lead. These toxic byproducts can lead to harm in the user and potentially cause lung damage if smoked or vaped [10].

The newbie on the market is Delta-10-THC. This Delta was created by accident by a company in California and is a molecularly close relative to the Delta-9-THC.

Very little is known about this product. The origin of Delta-10-THC goes back to Adelanto, California where the company Fusion Farms purchased outdoor grown biomass/marijuana to produce concentrates. What led to the discovery of Delta-10-THC was that the purchased natural marijuana had been treated with a fire retardant to protect the plant from Californian wildfires. The company started their usual process and discovered Delta-10-THC. This Delta has been gaining increasing interest as it has the “new factor.” It has lower psychotropic potency and is more activating, used to help with focus, creativity and energy with paranoia or other psychotic symptoms occurring less likely [11].

Available routes for use and formulations for Delta-THCs are [12] Edibles: cookies, brownies, gummies.

- ◆ Smoked: buds or flowers.
- ◆ Vape concentrates: hash, wax, dabs, oils.
- ◆ Topical ointments: lotions, oils, patches.
- ◆ Rectal: suppositories.

Mechanism of action Delta-THCs

Delta-THCs are lipophilic and easily and quickly cross the blood-brain-barrier [13]. Like marijuana, the Delta-THCs bind to cannabinoid (CB) receptors, of which are two identified. The CB-1 receptors are expressed centrally in the basal ganglia, the cerebellum, the hippocampus, the association cortices, the spinal cord and in the peripheral nerves. The CB-2 receptors are mainly found in peripheral tissues. In contrast to marijuana, the Delta-THCs are acting predominantly on the CB-2 receptor and have lower affinity to the CB-1 receptors [14].

Delta-THC induces euphoria or a “high” which occurs through the over-activation of the endocannabinoid system, the same system that marijuana in its natural form activates [15].

Delta-THCs also have anti-emetic properties and act on serotonin receptors (5-HT-3) which is the same receptor that conventional antiemetic medications target for example Ondansetron [16].

So far, little has been explored about the possibility of redistribution of Delta-THCs as we know of marijuana. Some lipophilic substances will get distributed and stored in cells of adipose tissue. Hours to days after use, the substance gets slowly redistributed into the blood stream leading to detectable levels of THC in the user’s blood stream long after last use. This is also the cause for the long detection window of THC in urine drug screens and potentially long-lasting effects of the substance [17].

None of the Delta-THCs are approved by the FDA (Food and Drug Administration) for any kind of medical condition. Additionally, there are also no available dosing guidelines [18].

Reported reasons for Delta-THC-use

People report to use Delta-THC for various medical and psychiatric conditions ranging from depression and anxiety, help with concentration, to help with symptoms associated with Multiple Sclerosis, Huntington’s disease, Chron’s disease or Amyotrophic Lateral Sclerosis. Some patients report that the use of Delta-THC has appetite enhancing properties in the setting of cancer treatments or HIV/AIDS. Also, various pain conditions are commonly named by users of Delta-THC, predominantly chronic back or neuropathic pain. In addition, Delta-THC is used as substitute or self-taper from other illicit substances for example opioids. [19]

Differences in effects between the Delta-THCs and marijuana

In comparison to marijuana in its natural form, the Delta-THCs are described as supposedly less potent or intense [20]. The effects of Delta-THC are very compatible with the ones associated with natural marijuana use. However, users report that the Delta-THCs do not cause as severe sedation and cognitive subdueness as marijuana does. There is a strong link between Delta-THC use and the development of anxiety and paranoia, but the cases are less prevalent than they are with marijuana.

For most users, the driving force to use Delta-THCs is that they are cheaper to obtain and, in most states, legal [21].

Toxic effects of Delta-8 THC

Along with the increasing popularity of Delta-THCs, there are also increasing cases of toxicity being reported. During the time between January 2021 and February 2022, the FDA (U.S. Food and Drug Administration) reported over 2,300 calls to national poison control centers [22]. Almost every third person who called poison control required a medical evaluation in a hospital setting, while one person required an inpatient admission [22].

Delta-THCs have psychotropic effects. The Delta-8- and 9-THCs are known to cause sedation, while Delta-10-THC is rather causing energy and increased alertness.

Cognitive distortions are reported with any of the Delta drugs, occurring in the user as altered sense of time, short-term memory deficits or poor concentration [23].

As there is an ongoing debate and research to further investigate the correlation between cannabis and psychosis, there appears to be an increased risk for psychosis with the use of Delta-THCs as well. Delta-THCs also may similarly to cannabis precipitate the first psychotic break or manic episode in users with genetic predisposition. The most common reported psychotic symptom is paranoia (in about 83% of users) [24].

The use of Delta-THCs may also cause autonomic instability as their use may lead to tachycardia or hypertension [25].

The toxic effects of Delta-THCs are particularly dangerous in children. Over 40% of unintentional intoxication with Delta-THCs are reported among children and adolescents. Delta-THCs are

attractive to kids due to their appealing jars or the appearance of regular candy while lacking any kind of child lock or warnings.

Children are especially vulnerable to the toxic effects due to their smaller body size. Especially if kids happen to consume the Delta-THC in high quantities, it can lead to life-threatening conditions that may require intubation and intensive care treatment [26].

Furthermore, there are cases reported of Cannabis Hyperemesis Syndrome in the context of Delta-THC use. This condition occurs during intoxication and causes nausea and vomiting in the user. A thorough history and timeline of events is necessary to make the diagnosis. One indication for the presence of the syndrome can be a history of symptom improvement while taking hot showers [27].

Diagnosis and Treatment

It is clinically very difficult to differentiate which Delta-THC was used prior to presentation as well as to differentiate Delta-THC from regular marijuana use. A thorough history is most important for the diagnosis including the timeline of use and onset of psychiatric or medical symptoms. Also, collateral information from relatives and friends is also helpful.

Toxicology screening assays for Delta-8-THC are not readily available in most medical facilities. The most commonly used urine drug screen technique, ELISA, patient samples will be positive for THC with any of the Delta drugs. A more specific urine test is necessary to detect the specific Delta-THC used, for example the GC-MS (gas chromatography-mass spectrometry) test, which is significantly more expensive and takes more time to receive a result, especially if the sample needs to be sent to an outside laboratory. For emergency presentations this form of diagnostic might not be feasible, however for outpatient follow-up it can help with clinical guidance [28].

The severity of intoxication from Delta-THCs is dose dependent. Clinically, in patients presenting with euphoria, visual hallucinations, paranoia, difficulties thinking, reading, speaking or in a dream like state, the intoxication with Delta-THCs should be considered [29].

There is no antidote available for Delta-THC intoxication. The treatment consists of symptomatic treatment. Antipsychotic medications might be necessary to manage symptoms and agitation. In the case of the Cannabis Hyperemesis syndrome, antiemetic medications usually do not provide relief [30].

Other Risks associated with Delta- THC-use

Another risk regarding the use of Delta-THCs use are concerns regarding the purity and labeling of Delta-THC-products. Several studies have focused on 8-THC products and their contents.

Scientists from the University of Rochester analyzed 17 Delta-8-THC products and compared them with their label. There were significant discrepancies detected, and products contained harmful byproducts of heavy metals such as lead and mercury, as well as levels of Delta-9-THC [31].

Other research groups confirmed concerns regarding the accuracy of the label of Delta-8-THC products as well, pointing out that products contain more of the compounds than what the label

claimed. The purity of cannabidiol (CBD) products appears to be a frequent problem. Leafreport.com, a peer reviewed watchdog webpage tested 38 CBD products or their contents and found in more than half of them illegal levels of Delta-9 THC. Out of these samples, only 32% had the advertised amount of Delta-8-THC. The remainder contained higher levels, ranging from 10.7% to 102.7% more than advertised [32].

After increasing calls to Michigan poison control centers, the Michigan Department of Health and Human Services got notified about the potential risk and danger associated with Delta-8-THC use. Consecutively law enforcement seized Delta-8-THC products that turned out to be falsely labeled CBD products. The Michigan poison control center sent out warning letters to the public about the adverse health effects from their use [33].

Further research conducted by J. Meehan-Atrash and I. Rahman tested 27 Novel Delta-9-THC Vaporizers. None of the tested products contained the amount of Delta-8 they claimed. All tested products once again revealed harmful levels of toxic byproducts lead and mercury [34].

These concerns extend to Delta-THC products falsely labeled as "Pure Delta-8" or "100% natural" as the drug is derived and requires compounds for synthesis.

A laboratory analysis of Delta-8-THC products in Maryland revealed that only 60 % of the tested products contained any kind of warning statements. Only 44% included expiration dates, while only 44% included a certificate of analysis [35].

Furthermore, easy access to Delta-THC products, even in states where for example Delta-8-THC is banned, creates unease. Delta-THC products are conveniently available from online sources. C Nali et al inspected the characteristics and compliance of online Delta-8-THC sellers. The group looked at 110 unique hyperlinks associated with 7085 tweets that included marketing and selling activity for Delta-8 THC. In over half of the vendors, there was no age verification required. 60 of the vendors did not report a physical address. Tracking back the internet protocol addresses revealed that 64.18% were located in the United States while all others were international. Of these online vendors, 45% sold Delta-8 products direct-to-consumer and 90.54% of detected vendors shipped Delta-8 products to addresses in states that prohibit sales [36].

The use of Delta-8-THC bears a significant risk for adolescents. The packaging of these products is not "child resistant", commonly depicting cartoon-like images that are appealing to children. Also, Delta-THC vape products come in a range of sweet and fruity flavors which can be tempting. Frequently, the exposure is accidental if for example the Delta-THC product was confused with candy or a food product. The toxic effects of Delta-THC products are easily more severe in children and adolescents [37].

The exposure and intoxication with Delta-8-THC products caused 2363 reports to national poison control centers between January 1, 2021, and February 28, 2022, with 40% involving accidental exposure to Delta-THC. Of those 40% where 82% among youth, 70% required evaluation at a health care facility, 8% were admitted to a critical care unit, and one pediatric death was reported [22].

The FDA (Food and Drug administration) issued a warning letter in May of 2022 in response to 104 reported cases with adverse events between December 2020 and February 2022. Of these cases, 77% involved adults, 8% involved pediatric patients less than 18 years of age, and 15% did not report age. More than half of these cases required an evaluation at a medical facility or an inpatient admission. 66% described adverse events after ingestion of Delta-8 THC-containing food products (e.g., brownies, gummies) [38].

The warning letter addressed five companies selling products for unapproved treatment of medical conditions as well as taking part in illegal marketing and drug misbranding.

The FDA pointed out that Delta-8-THC is not approved by the FDA for treatment of any form of medical condition. The FDA warned about misbranded drugs, adulterated foods, and inadequate directions for safe use [39].

Discussion

Next to marijuana, the Delta-THCs are gaining increasing popularity in the U.S. and it is important for physicians to learn and know about Deltas in order to be able to educate their patients about their effects and risks.

Even though pharmacologically, the Delta-THCs supposedly are less psycho-active due to lower affinity to the CB-1 receptor, their effects are not so insignificant after all.

As seen from calls to national poison control centers, use is associated with risks of not only sedation, psychosis, and impaired cognition but also hemodynamic instabilities involving decreased blood pressure and respiration [19].

The use of Delta-THCs by children and adolescents bears even more severe dangers as the effects of Delta-THC are even stronger and more impairing due to their smaller size [37]. Unfortunately, there was even a fatality involving a child reported to the poison control center between January 1, 2021, and February 28, 2022, who ingested Delta-THCs. The colorful wrapping of these Delta-THCs and their fruity and sweet flavors, like candy or other daily foods, are tempting for children and make the products difficult to identify as a drug [26].

We learnt from recent years though that the effects of the Delta-THCs can be unpredictable and leading to medical or psychiatric emergency situations in adults as well which are very similar to clinical presentation caused by cannabis intoxication [25,26].

Per legal regulations, Delta-THCs are limited to a content of less than 0.3% THC. However, due to the lack of regulation of these products and no laboratory testing being done, the content is frequently above this legal limit, shown by reports stemming from analyzed samples. Also, the risk of contamination with byproducts puts the user at risk to unknowingly ingest heavy metals or other toxic solvents. As per current regulation, the user cannot know with certainty the content of the Delta-THC product that they are using [4,16, 22].

Some states are trying to fix the federal loophole by creating state laws banning the sales and use of Delta-8 THC, but those restrictions are only limiting the sales in stores but not online sales. As displayed by studies, online merchants are nonetheless selling into restricted states [3, 8].

The online market also makes Delta-THCs available to minors as there is frequently no age verification requirement. For the online customer, there is no guarantee of origin of these products either as merchants sell to the U.S. from foreign territories.

There are no barriers to potentially regulate Delta-THC products due to the rising market and potential revenues creating a push from the economy against them. In addition, regular users of Delta-THC will be opposed to new regulations in order to continue to have easy, uncomplicated access without added expenses as there are already in some states with medical cannabis programs.

Conclusion

Delta-THCs are gaining popularity although they are not well-researched. More clinical studies are needed to understand the effects, doses, and toxicity of these substances. As per knowledge, Delta-THC products cannot be recommended for any medical or psychiatric condition. The FDA also has clearly stated that there is no FDA-approved clinical indication for the use of Delta-THCs and warns about their unpredictable effects and toxicity.

The lack of regulation of Delta-THCs and clinical testing demands improvement in order to provide some oversight of the contents of these products and protect the user.

There should be a set and enforced age requirement to prevent online sales to minors. Even one pediatric fatality is too many. Delta-THC products need to be clearly marked as such to avoid accidental exposure from confusing them with similar looking food items. Also, these products need to be kept out of reach from children.

The public needs to be educated and warned about the dangers associated with the use of these commonly available Delta-THC products. Laboratory testing should be legally required for these products. Since Delta-THC products are available in local convenience stores or gas stations, this creates a false perception that these products are harmless and that their use is without any dangers.

Public education needs to be implemented regarding the risks of Delta-THC use. The Delta-THCs should have proper labeling including warnings clearly stating the presences of psychotropic compounds.

Due to the growing popularity of Delta-THC, it is important that medical providers are getting familiar with these new emerging substances as they are most likely going to see patients presenting with intoxication questions or patients seeking advice for their use.

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