Update Article

https://www.revistardp.org.br doi https://doi.org/10.25118/2763-9037.2026.v16.1611

Management of emergencies related to cannabis, its derivatives, and synthetic cannabinoids: an update

Manejo de emergências relacionadas à cannabis, seus derivados e canabinóides sintéticos: uma atualização

Gestión de emergencias relacionadas con el cannabis, sus derivados y cannabinoides sintéticos: una actualización

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Chief Editor responsible for the article: Rodrigo Nicolato
Authors contributions according to the Taxonomia CRediT: Baldaçara L, Rocha GA, Santos RM, Calfat ELB, Cordeiro Q, Meleiro AMAS, Pereira LA [1-14].
Disclosure of potential conflicts of interest: none
Funding: none
Approval Research Ethics Committee (REC): not applicable
Received on: 2026/05/20
Accepted on: 2026/06/02
Published on: 2026/06/09

How to cite: Baldaçara L, Rocha GA, Santos RM, Calfat ELB, Cordeiro Q, Meleiro AMAS, Pereira LA. Management of emergencies related to cannabis, its derivatives, and synthetic cannabinoids: an update. Debates Psiquiatr. 2026;16:1-32, e1611. https://doi.org/10.25118/2763-9037.2026.v16.1611

ABSTRACT:
Introduction: Cannabis use and the availability of high-potency cannabis-derived products and synthetic cannabinoids have increased worldwide, contributing to a growing burden of emergency presentations involving intoxication, agitation, psychosis, cardiovascular complications, and other acute toxic effects. **Objective:** This review aimed to update the clinical approach to emergencies related to cannabis, cannabis-derived products, and synthetic cannabinoids, while standardizing terminology across these three conceptually distinct categories. **Methods:** A structured literature review was conducted using PubMed, SciELO, EMBASE, and Cochrane databases. Eligible studies included systematic reviews, clinical trials, and observational studies, with no restrictions regarding language or publication date. The search strategy combined controlled vocabulary and free-text terms related to cannabis, cannabinoids, intoxication, poisoning, emergency care, psychiatric complications, and acute management. **Results:** Cannabis and cannabis-derived products are associated with a broad spectrum of acute manifestations, including anxiety, panic attacks, altered consciousness, psychomotor agitation, cannabinoid hyperemesis syndrome, and cannabis-induced psychosis. High-potency preparations, particularly concentrates and edible products, may produce delayed, prolonged, or more severe intoxication. Synthetic cannabinoids present a more unpredictable and potentially severe toxicological profile because many act as full agonists at cannabinoid receptors, increasing the risk of

severe agitation, seizures, psychosis, cardiovascular instability, acute kidney injury, and death. Management is primarily supportive and should follow an A–B–C–D–E emergency framework, with continuous clinical reassessment, cardiovascular and neurological monitoring, correction of metabolic abnormalities, benzodiazepines for agitation, anxiety, and seizures, and antipsychotics when persistent psychotic symptoms are present. **Conclusion**: Emergencies related to cannabis, cannabis-derived products, and synthetic cannabinoids require early recognition, standardized terminology, risk-oriented clinical assessment, and integrated medical, psychiatric, and toxicological management. Specific protocols are essential to improve acute care, reduce complications, and guide prevention strategies.

Keywords: cannabis, cannabis-derived products, synthetic cannabinoids, cannabinoid intoxication, cannabis-induced psychosis.

RESUMO:
Introdução: O consumo de *cannabis* e a disponibilidade de produtos derivados de *cannabis* de alta potência e canabinóides sintéticos aumentaram em todo o mundo, contribuindo para uma carga crescente de apresentações de emergência envolvendo intoxicação, agitação, psicose, complicações cardiovasculares e outros efeitos tóxicos agudos. **Objetivo**: Esta revisão teve como objectivo atualizar a abordagem clínica às emergências relacionadas com a cannabis, produtos derivados da cannabis e canabinóides sintéticos, ao mesmo tempo que uniformiza a terminologia nestas três categorias conceptualmente distintas. **Método**: Foi realizada uma revisão estruturada da literatura nas bases de dados PubMed, SciELO, EMBASE e Cochrane. Os estudos elegíveis incluíram revisões sistemáticas, ensaios clínicos e estudos observacionais, sem restrições de idioma ou data de publicação. A estratégia de busca combinou vocabulário controlado e termos de texto livre relacionados a *cannabis*, canabinóides, intoxicação, envenenamento, atendimento de emergência, complicações psiquiátricas e manejo agudo. **Resultados**: A *cannabis* e os produtos derivados da *cannabis* estão associados a um amplo espectro de manifestações agudas, incluindo ansiedade, ataques de pânico, alteração da consciência, agitação psicomotora, síndrome de hiperêmese canabinóide e psicose induzida por cannabis. Preparações de alta potência, particularmente concentrados e produtos comestíveis, podem causar intoxicações retardadas, prolongadas ou mais graves. Os canabinoides sintéticos têm um perfil toxicológico mais imprevisível e potencialmente grave porque muitos atuam como agonistas completos dos receptores canabinoides, aumentando o risco de agitação

grave, convulsões, psicose, instabilidade cardiovascular, lesão renal aguda e morte. O tratamento é principalmente de suporte e deve seguir um quadro emergencial A–B–C–D–E, com reavaliação clínica contínua, monitoramento cardiovascular e neurológico, correção de alterações metabólicas, benzodiazepínicos para agitação, ansiedade e convulsões, e antipsicóticos quando há sintomas psicóticos persistentes. **Conclusão**: As emergências relacionadas com a *cannabis*, os produtos derivados da *cannabis* e os canabinóides sintéticos requerem reconhecimento precoce, terminologia padronizada, avaliação clínica orientada para o risco e gestão médica, psiquiátrica e toxicológica integrada. Protocolos específicos são essenciais para melhorar o cuidado agudo, reduzir complicações e orientar estratégias de prevenção.

Palavras-chave: *cannabis*, produtos derivados da *cannabis*, canabinóides sintéticos, intoxicação por canibinoides, psicose induzida por *cannabis*.

RESUMEN:
Introducción: El consumo de cannabis y la disponibilidad de productos derivados del cannabis de alta potencia y cannabinoides sintéticos han aumentado en todo el mundo, contribuyendo a una carga cada vez mayor de presentaciones de emergencia que involucran intoxicación, agitación, psicosis, complicaciones cardiovasculares y otros efectos tóxicos agudos. **Objetivo**: Esta revisión tuvo como objetivo actualizar el enfoque clínico de las emergencias relacionadas con el cannabis, los productos derivados del cannabis y los cannabinoides sintéticos, al tiempo que estandariza la terminología en estas tres categorías conceptualmente distintas. **Métodos**: Se realizó una revisión estructurada de la literatura utilizando las bases de datos PubMed, SciELO, EMBASE y Cochrane. Los estudios elegibles incluyeron revisiones sistemáticas, ensayos clínicos y estudios observacionales, sin restricciones en cuanto a idioma o fecha de publicación. La estrategia de búsqueda combinó vocabulario controlado y términos de texto libre relacionados con el cannabis, los cannabinoides, la intoxicación, el envenenamiento, la atención de emergencia, las complicaciones psiquiátricas y el manejo agudo. **Resultados**: El cannabis y los productos derivados del cannabis se asocian con un amplio espectro de manifestaciones agudas, que incluyen ansiedad, ataques de pánico, alteración de la conciencia, agitación psicomotora, síndrome de hiperemesis cannabinoide y psicosis inducida por el cannabis. Las preparaciones de alta potencia, en particular los concentrados y los productos comestibles, pueden producir una intoxicación retardada, prolongada o más grave. Los cannabinoides sintéticos presentan un perfil

toxicológico más impredecible y potencialmente grave porque muchos actúan como agonistas completos de los receptores de cannabinoides, lo que aumenta el riesgo de agitación grave, convulsiones, psicosis, inestabilidad cardiovascular, lesión renal aguda y muerte. El tratamiento es principalmente de apoyo y debe seguir un marco de emergencia A–B–C–D–E, con reevaluación clínica continua, monitorización cardiovascular y neurológica, corrección de anomalías metabólicas, benzodiazepinas para la agitación, ansiedad y convulsiones, y antipsicóticos cuando hay síntomas psicóticos persistentes. **Conclusión**: Las emergencias relacionadas con el cannabis, los productos derivados del cannabis y los cannabinoides sintéticos requieren un reconocimiento temprano, una terminología estandarizada, una evaluación clínica orientada al riesgo y un manejo médico, psiquiátrico y toxicológico integrado. Los protocolos específicos son esenciales para mejorar la atención aguda, reducir las complicaciones y guiar las estrategias de prevención.

Palavras clave: cannabis, cannabinoides sintéticos, productos derivados del cannabis, intoxicación por cannabinoids, psicosis inducida por cannabis.

Introduction

Psychiatric emergencies encompass behavioral alterations that pose real and immediate risk, requiring prompt therapeutic intervention to prevent serious outcomes for the patient or others. Conditions such as psychomotor agitation, acute psychotic episodes, suicidal ideation, and intoxications due to psychoactive substances are among the most frequent reasons for emergency psychiatric care [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. In this context, cannabis use and its derivatives stand out as major precipitants of acute mental health crises [11, 12, 13, 14, 15].

Cannabis is currently the most widely used illicit substance worldwide, and its consumption has increased particularly among young people, driven by legalization processes and the misconception that it is a low-risk drug. This perception contrasts with the growing body of literature demonstrating consistent associations between cannabis use and various adverse psychiatric outcomes, including anxiety, depression, cognitive deficits, and especially psychotic and agitation episodes that often require emergency intervention [11, 12, 13, 14, 15, 16, 17].

From an epidemiological perspective, approximately 10% of users develop dependence, and up to 30% present some type of cannabis-related disorder [18 - 19]. Moreover, up to 50% of patients presenting to

emergency departments with cannabis-induced psychotic symptoms will eventually develop schizophrenia, underscoring the clinical and prognostic relevance of these events [16, 20]. In pediatric populations, there has been a notable rise in accidental intoxications, especially through edible cannabis products. Presentations range from lethargy and ataxia to profound decreased consciousness, respiratory depression, and need for hospitalization [11, 15].

The use of synthetic cannabinoids has increased and leading to important challenges in the management of their complications in emergency psychiatric care. Seeking emergency medical treatment following synthetic cannabinoids use was a main finding of the Global Drug Survey, which has been a leading information source on the topic since it was first conducted in 2015. The Survey found that synthetic cannabinoids use involves a significant risk of dependence and withdrawal, presumably higher than natural cannabis products. Brazil has actively participated in the Global Drug Survey since 2015, joining over 50 other nations in the survey that year. Although the survey's data are not representative, 1.8% of the Brazilian respondents reported using SC in 2015 [21, 22, 23, 24, 25].

Given this scenario, the development of specific protocols for managing emergencies related to cannabis, its derivatives and synthetic canabinoides is essential. Understanding underlying mechanisms, risk factors, and clinical manifestations is crucial for guiding effective and safe interventions and informing preventive strategies and public health education.

Methods

Eligibility criteria

Inclusion criteria were systematic and non-systematic reviews, trials, observational studies. There were no language or date restrictions. Exclusion criteria were case or series case report, qualitative studies.

Information sources: Pubmed, Scielo, EMBASE, Cochrane.

Terms

This study standardized the terminology by distinguishing three categories: cannabis as the plant material itself; cannabis-derived products, including extracts, oils, resins, and other preparations obtained from the plant; and synthetic cannabinoids, defined as laboratory-produced compounds designed to interact with the endocannabinoid system and mimic or modulate cannabinoid receptor activity.

Search strategy: the search strategy combined controlled vocabulary (MeSH/DeCS) and free-text terms related to cannabis, its derivatives, and synthetic cannabinoids ("Cannabis", "Marijuana", "Cannabinoids", "Cannabidiol", "cannabis derivatives", "Delta-9-Tetrahydrocannabinol", "Synthetic Cannabinoids", "K2", "Spice"), emergency conditions ("Emergency Service, Hospital", "Emergency Medical Services", "Intoxication", "Poisoning", "Overdose", "Adverse Events", "Cannabinoid Hyperemesis Syndrome", "Substance-Induced Psychosis", "Agitation"), and management or treatment approaches ("Management", "Treatment", "Therapeutics", "Supportive Care", "Clinical Protocols"). Boolean operators AND and OR were used to combine terms, and no language or date restrictions were applied. The complete search strategy was adapted for each database according to its specific syntax.

Selection process
All records identified through database searching were imported into a reference management software, and duplicates were removed. Two independent reviewers screened titles and abstracts to determine potential eligibility, with disagreements resolved by consensus or by a third reviewer. Full-text articles of all potentially relevant studies were then assessed for eligibility according to predefined inclusion and exclusion criteria. Studies that did not meet the criteria, lacked adequate methodological quality, or did not address the management of emergencies related to cannabis derivatives were excluded, with reasons documented. The final selection included only studies providing clinical data, protocols, case series, or observational evidence on emergency care related to cannabis or its derivatives.

Data collection process
The data collection process was performed independently by two reviewers using a standardized extraction form developed a priori. For each included study, reviewers extracted information on study design, setting, population characteristics, type of cannabis derivative involved, nature of the emergency presentation, diagnostic approaches, interventions or management strategies, and clinical outcomes. Additional variables such as adverse events, follow-up duration, and methodological quality indicators were also recorded when available. Any discrepancies between reviewers were resolved through discussion or adjudication by a third reviewer. When necessary, authors of primary studies were contacted to

obtain missing or unclear data. All extracted information was cross-checked for accuracy and consistency before synthesis.

Synthesis methods
The synthesis methods followed a structured and transparent approach. Studies were grouped according to type of cannabis derivative involved (natural, synthetic, or mixed), clinical presentation, and interventions used in acute management. Any discrepancies in interpretation were resolved through consensus among reviewers.

RESULTS AND DISCUSSION

Cannabis sativa and derivatives
Cannabis plant derivatives
Marijuana: There is obtained from the dried flowers of the female Cannabis plant that contain THC [18]. There are several types, and the concentrations of THC and CBD vary depending on the intended use [18, 26]. A marijuana is the most common natural derivative of Cannabis sativa and indica. Its THC concentration may range from 5 to 30%, and CBD from 1 to 20%, depending on the strain and purpose. It can be used recreationally or medically through inhalation, oral ingestion, or topical application [18, 26].

Hashish: The concentrated derivative of the resin from the female Cannabis sativa or indica plant, obtained from the resin glands (trichomes). It contains 20 to 80% of THC and a small amount of CBD. It is usually smoked, vaporized, or ingested, and its effects are stronger and longer lasting than those of marijuana. It consists of agglutinated resin rich in THC and CBD in smaller proportion, as well as other phytocannabinoids. It appears as a solid or pasty mass, brown to golden in color, with a strong aroma and variable texture [18, 26].

Cannabis Oil: The most widely used medicinal derivative of marijuana. It is a concentrated oily extract obtained from Cannabis sativa or Cannabis indica. It contains the main phytocannabinoids THC, CBD [18, 26], and others (CBN, CBG, CBC) dissolved in a lipid vehicle, generally coconut (MCT) oil or olive oil. It may be THC [1,4]-rich, CBD [3,4]-rich, or balanced, depending on the intended recreational, therapeutic, or pharmaceutical use. It can have high potency (up to 70% THC or be non-psychoactive (CBD-rich). Used sublingually, orally, or topically, it has medical applications in pain management, epilepsy, anxiety, and inflammatory conditions [18, 26 - 27].

Hemp: the non-psychoactive variety of Cannabis sativa, with THC < 0.3% and CBD between 2 and 20 %. It is used in the textile, food, cosmetic, and pharmaceutical industries and is the main source of CBD for therapeutic formulations. Cultivated specifically for industrial or mild medicinal use, its low THC content prevents psychoactive effects. It is employed for a wide range of purposes, from textile fibers to building materials, as well as in oils and cosmetics [18, 26].

Synthetic cannabinoids

Dronabinol: Dronabinol is the synthetic form of THC, designed to mimic the natural phytocannabinoid and produced in laboratories. It was developed in the United States during the 1980s and approved by the FDA in 1985. Each capsule or oral solution contains pure dronabinol (synthetic THC) dissolved in sesame oil or ethanol/glycerol. Capsules may contain 2.5 mg, 5 mg, or 10 mg of dronabinol, or 5 mg/ml in liquid form. It does not contain CBD or other phytocannabinoids and is psychoactive. It can be administered sublingually or orally, with an onset of action 30–90 minutes after ingestion and a duration of 4–6 hours. It acts as a partial agonist of CB1 and CB2 receptors in the endocannabinoid system. It has been approved internationally (by agencies such as the FDA and EMA) for the control of nausea and vomiting caused by chemotherapy and for severe weight loss related to medical conditions such as AIDS or cancer [18, 26, 28].

Nabilone: Nabilone is another synthetic cannabinoid, meaning it is produced in laboratories and not extracted from the plant. It is chemically similar to natural THC and mimics its effects on the endocannabinoid system [18, 19, 24, 29, 30]. Approved by agencies such as the FDA and Health Canada, nabilone does not contain natural THC or CBD [18, 19, 24, 26, 29, 30], but acts as a THC analog, binding directly to CB1 and CB2 receptors of the endocannabinoid system. Each capsule contains 1 mg or 2 mg of pure nabilone for oral use [18, 19, 24, 29, 30]. It acts as a partial agonist of CB1 receptors (in the brain) and CB2 receptors (in the immune system). It produces effects like THC but in a more stable and controlled manner. It is used as an antiemetic, analgesic, mild anxiolytic, and sedative [18, 19, 24, 29, 30].

Other synthetic cannabinoids: A variety of lab-synthesized compounds have been created to mimic the action of THC or CBD [18, 19, 24, 29, 30]. Therapeutic cannabinoids (e.g., nabilone) are safe and regulated; experimental cannabinoids (e.g., HU-210, CP-55,940) are used exclusively in research; and recreational synthetic cannabinoids (e.g., JWH-018, AB-

FUBINACA) are highly dangerous, with severe toxic potential, and are not legalized; K2, and K9: K2 (also known as Spice, Black Mamba, Scooby Snax, etc.) and K9 are herbal mixtures sprayed with synthetic cannabinoids designed to imitate THC's effects, but they do not originate from the Cannabis sativa plant [18, 19, 24, 29, 30]. The active compounds are artificial molecules (created in laboratories) that act on CB1 and CB2 receptors, but in a much more intense and unpredictable way. K2 and K9 are not cannabis, but chemical substances sprayed onto inert herbs to appear "natural." They contain compounds such as JWH-018, JWH-073, AB-FUBINACA, AM-2201, XLR-11, among others. These are full agonists of CB1 and CB2 receptors, whereas natural THC is only a partial agonist. This means they overactivate these receptors, leading to severe toxic effects [18, 19, 24, 29, 30]. Adverse effects: anxiety, panic, extreme agitation, mental confusion, delusions, hallucinations, tachycardia, hypertension, nausea, vomiting, convulsions, acute kidney injury, arrhythmias, and psychotic episodes often accompanied by violent behavior. There have been documented cases of hospitalization and death due to K2/K9 intoxication.

Other forms and products

Kief: Kief is the collection of trichomes that detach from marijuana flowers when they are handled, sifted, or ground. It is rich in cannabinoids (THC, CBD, CBG) and terpenes, since trichomes are the plant's structures responsible for storing these substances. It appears as a fine, yellowish-green powder with a sandy texture and undergoes no chemical processing. Kief can be considered a concentrated natural form of cannabis resin. The THC content can be quite high, up to 60%. It is typically smoked, vaporized, or pressed into hashish [19, 26, 30].

Bubble hash (or ice hash): a cannabinoid concentrate obtained from the trichomes of Cannabis sativa or indica plants. It is considered a natural derivative because no chemical solvents are used in the extraction process. Its name derives from the small bubbles that are formed when heated, indicating high purity and cannabinoid content. It has a THC concentration greater than 50% and low CBD. It can be consumed by vaporization, smoking, or in edibles [19, 26, 30].

Shatter, BHO, Budder, Crumble: These are concentrated cannabis derivatives produced by extracting the resin rich in cannabinoids (mainly THC and CBD) from the plant's flowers. They can have THC levels above 70–90% and are much more potent than marijuana (10–25%). Known as

"concentrates," some, such as shatter, BHO, budder, and crumble, are made using solvent-based extraction (usually butane) [18, 19, 26, 30].

Rosin: a natural and concentrated cannabis extract obtained by pressure and heat, without solvents. It contains 50 to 80% of THC or CBD, depending on the plant used) and is consumed mainly by vaporization. It is valued for its purity, safety, and high therapeutic value, being considered one of the cleanest modern cannabis derivatives [18, 19, 26, 30].

Edibles: Or fit for eating, the most popular form of marijuana ingestion. They are foods or beverages that contain active cannabinoids, mainly THC and/or CBD. They are produced from cannabis extracts (oil, butter, resin, or distillate) and ingested orally. After ingestion, cannabinoids are absorbed by the gastrointestinal tract, producing effects that are slower but longer lasting than smoking or vaporization. They are obtained from ground dried flowers, cannabis oils rich in THC or CBD, cannabutter, and concentrated extracts. Because THC and CBD are lipophilic, they need to be dissolved in fat or oil to become bioavailable. Common forms range from candies to beverages or capsules. They have a slow onset of action, with effects beginning between 30 and 90 minutes and lasting 6 to 10 hours [18, 19, 26, 30].

Vapor/vape products: Cannabis sativa vapes are among the most modern and discreet forms of consumption, but they also require greater caution. Vapes are electronic devices that heat cannabis oil, resin, or extract to release its active compounds (THC, CBD, terpenes) in the form of vapor, without combustion. Cartridges or liquids used in cannabis vapes generally contain THC extract, CBD, or both; terpenes that provide aroma and flavor; and oily carriers. The onset of effect is almost immediate (1–5 minutes), with an average duration of 2–3 hours. The levels typically range from 60 to 90% of THC or CBD [18, 19, 26, 30].

Topical products: cannabis topical products do not produce psychoactive effects and have growing medical, cosmetic, and therapeutic use. They are preparations applied directly to the skin, containing active cannabinoids (mainly CBD and, in some cases, small amounts of THC diluted in creams, ointments, oils, or gels. They act locally by interacting with endocannabinoid receptors in the skin (CB1, CB2, and TRPV1) without crossing the blood–brain barrier. They usually contain isolated CBD or full-spectrum extract; small amounts of, (≤ 0.3%) when derived from full-spectrum extracts; plant oils (coconut, hemp seed, olive); cosmetic or pharmaceutical bases (beeswax, shea butter, glycerin); and adjuncts such

as arnica, menthol, aloe vera, etc. They act on CB1 and CB2 receptors in the skin by reducing local inflammation and pain, and through TRPV1 receptors, they decrease the sensation of heat, promoting healing and sebaceous balance [18, 19, 26, 30].

Mechanism of action and pharmacokinetics by route of use (inhalation vs ingestion)

Cannabis and its derivatives, whether natural phytocannabinoids (e.g., THC, CBD), synthetic cannabinoids (e.g., K2, Spice), or concentrated extracts (e.g., hash oil), exert their effects primarily through interaction with the endocannabinoid system. This system comprises CB1 and CB2 receptors, endogenous ligands such as anandamide and 2-AG, and the enzymatic machinery responsible for their synthesis and degradation. CB1 receptors are widely distributed throughout the central nervous system, particularly in the prefrontal cortex, hippocampus, basal ganglia, cerebellum, and limbic structures, correlating with the cognitive, perceptual, emotional, and motor effects of cannabinoids. CB2 receptors, in contrast, are more prevalent in peripheral immune tissues but have also been identified in microglial populations within the CNS [15, 31, 32].

Mechanism of action

Delta-9-tetrahydrocannabinol (THC), its main psychoactive component, acts as a partial agonist at CB1 and CB2 receptors, modulating neurotransmitters such as dopamine and glutamate. This mechanism accounts for its euphoric, anxiogenic, pro-psychotic, and cognition-impairing effects [33 - 34]. In contrast, cannabidiol (CBD), a non-psychoactive constituent, exhibits anxiolytic properties and potential antipsychotic effects, although its therapeutic efficacy remains uncertain [35]. The increasing prevalence of cannabis preparations with high THC and low CBD concentrations has heightened the risk of negative psychiatric outcomes [17].

The literature further highlights persistent neurocognitive impairments associated with chronic cannabis use, including deficits in memory, attention, processing speed, and executive functions, particularly when use begins during adolescence. Structural and functional alterations in brain regions such as the hippocampus, prefrontal cortex, and cerebellum have been consistently documented [18, 19, 36].

Δ9-Tetrahydrocannabinol (THC)

THC is the primary psychoactive component of *Cannabis sativa*. As a partial agonist at CB1 and CB2 receptors, it modulates the release of

neurotransmitters including dopamine, GABA, and glutamate [34]. Activation of CB1 receptors in dopaminergic pathways contributes to the reinforcing and euphoric properties of cannabis, while effects in the prefrontal cortex and hippocampus are implicated in altered cognition, memory impairment, perceptual distortions, and the development of acute psychosis [19]. THC also exhibits dose-dependent anxiogenic and pro-psychotic properties, with increasing potency of modern cannabis products amplifying these risks [17].

Cannabidiol (CBD)

CBD, in contrast, is non-psychoactive and displays complex pharmacodynamics. Evidence suggests that CBD may act as a negative allosteric modulator of CB1 receptors and interact with serotonergic (5-HT1A), vanilloid (TRPV1), and adenosine pathways, contributing to anxiolytic, anti-inflammatory, and potential antipsychotic effects [35]. CBD may attenuate some of the cognitive and psychotomimetic effects of THC, though its clinical efficacy remains under investigation.

Synthetic cannabinoids

Synthetic cannabinoids (e.g., JWH compounds, AM series, "K2", "Spice") show much higher affinity and efficacy at CB1 receptors compared to THC, often functioning as full agonists (rather than partial agonists). As a result, they are associated with severe toxicity, including intense agitation, seizures, psychosis, hyperemesis, cardiotoxicity, and a significantly higher risk of fatal outcomes [16, 37]. Their potency and unpredictable pharmacological profiles markedly increase their danger in emergency settings.

Other derivatives

Highly concentrated preparations such as hashish, hash oil, and butane hash oil (BHO) deliver substantially higher doses of THC, producing more rapid onset, greater intoxication, and elevated risk of acute psychiatric manifestations. Edible extracts may contain inconsistent THC concentrations, contributing to overdose and delayed toxicity, particularly in children [11, 15].

Pharmacokinetics by route of use

Inhalation (smoking or vaporization)

Inhaled cannabinoids reach the bloodstream rapidly through pulmonary alveoli, producing effects within seconds to minutes. Peak plasma THC concentrations occur within 10 minutes of smoking [34]. This route

provides high bioavailability (10–35%), though influenced by puff volume, depth of inhalation, and combustion efficiency.

Due to high lipophilicity, THC quickly distributes to the brain, adipose tissue, liver, and spleen. Psychoactive effects appear swiftly and decline over 2–3 hours, though measurable levels may persist longer due to redistribution into fatty tissues [15].

THC undergoes hepatic metabolism via CYP2C9, CYP2C19, and CYP3A4, forming active metabolites such as 11-OH-THC, which also crosses the blood–brain barrier. Terminal elimination half-life ranges from 25 to 36 hours for acute users but can extend significantly in chronic users due to depot release [18 - 19].

Ingestion (edibles, capsules, oils)
Oral ingestion leads to slow and erratic absorption, with onset of action delayed by 30–90 minutes and peak effects occurring after 2–4 hours [11]. Bioavailability is lower (4–12%) due to extensive first-pass hepatic metabolism.

Ingestion produces a higher proportion of active metabolite 11-OH-THC, which is more potent and crosses the blood–brain barrier more efficiently than THC itself. This contributes to stronger and longer-lasting psychoactive effects [15].

Effects may persist for 6–12 hours, with prolonged psychomotor impairment, making overdose more common among inexperienced users who re-dose during the latency period.

Clinical manifestations of toxicity
The general effects of marijuana include euphoria, altered time perception, increased appetite, relaxation, xerostomia, tachycardia, short-term memory impairment, and, at higher doses, anxiety.

Cannabis sativa intoxication results predominantly from the pharmacological action of Δ9-tetrahydrocannabinol (THC), the plant's principal psychoactive constituent. Following inhalation, THC is rapidly absorbed into the systemic circulation and reaches the central nervous system within minutes; by contrast, oral administration is associated with slower and more variable absorption, leading to more sustained concentrations of the active metabolite 11-hydroxy-THC, which is even more potent. THC acts as a partial agonist at CB1 and CB2 cannabinoid receptors, which are widely distributed throughout the prefrontal cortex,

hippocampus, basal ganglia, cerebellum, and limbic system, thereby accounting for the broad range of neuropsychiatric manifestations observed during intoxication.

Activation of these receptors modulates neurotransmitters such as GABA, glutamate, and dopamine, culminating in cognitive, perceptual, and autonomic alterations, including tachycardia, anxiety, impaired working memory, and distortion of temporal perception. Although intoxication is often self-limited, it may progress to more severe clinical presentations, such as cannabis-induced psychosis, severe panic attacks, and, less commonly, acute cardiovascular events.

The emergence of highly concentrated products, such as "dabs," "wax," "shatter," and vaporized oils, has produced a distinct toxicological profile due to extremely high THC levels, which may exceed 60% to 90% concentration. Exposure to these preparations results in abrupt and intense CB1 receptor activation, producing more pronounced psychoactive effects and a greater risk of autonomic dysregulation. Clinical studies and case reports have described a higher incidence of psychomotor agitation, episodes of acute psychosis, intractable vomiting, and the precipitation or exacerbation of cannabinoid hyperemesis syndrome (CHS). This phenomenon is thought to result from prolonged stimulation of cannabinoid receptors in the gastrointestinal tract and central emetic pathways, leading to recurrent cycles of nausea and vomiting that, in severe cases, require hospitalization.

Synthetic cannabinoids, marketed under names such as K2 and Spice, pose a substantially greater risk of severe intoxication than natural cannabis derivatives. Unlike THC, which acts as a partial agonist, these compounds function as full agonists at CB1 and CB2 receptors, often with affinities 10- to 100-fold greater. This heightened potency, combined with chemical variability across batches and the presence of toxic solvents and impurities, gives rise to highly unpredictable clinical effects. Toxicological manifestations include severe psychomotor agitation, delusions, hallucinations, seizures, marked hypertension, tachyarrhythmias, acute myocardial infarction, acute kidney injury, and, in extreme cases, death. In addition, the pharmacokinetics of these compounds are unstable, with substantial variability in bioavailability and duration of action, which further complicates clinical management and increases the risk of severe adverse events.

Whereas natural cannabis intoxication tends to be self-limited and rarely results in fatal complications, synthetic cannabinoids are associated with a more aggressive toxicological profile, characterized by a higher incidence of acute psychosis, seizures, and critical cardiovascular events. This distinction reflects not only the greater receptor affinity of synthetic compounds, but also their capacity to produce full agonism, resulting in uncontrolled activation of the endocannabinoid system. Moreover, the absence of naturally occurring regulatory mechanisms present in the plant—such as non-psychoactive cannabinoids, terpenes, and endogenous modulators—likely contributes to the intensity and unpredictability of their effects. Accordingly, synthetic cannabinoid intoxication represents an emerging challenge for emergency services, requiring prompt recognition and a multimodal therapeutic approach.

Although generally regarded as safe, CBD oil may lead to intoxication when used at high doses, in formulations of uncertain provenance, or in vulnerable individuals. Intoxication generally results from overdose, adulterated products, concomitant use with other central nervous system depressants, or drug-drug interactions, particularly with medications metabolized by the CYP2C19 and CYP3A4 enzymes.

Management of intoxication
General measures in the management of acute intoxication should be conducted in a systematic, hierarchical, and risk-oriented manner, with primary emphasis on the preservation of vital functions and structured around the **A–B–C–D–E** approach, which provides a pragmatic, physiology-based framework for clinical decision-making [38].

A (airway) requires immediate assessment and protection of the airway through appropriate positioning, suctioning, and, when indicated, the use of supraglottic devices or endotracheal intubation in patients with depressed consciousness or loss of protective reflexes.

B (breathing) involves careful evaluation of ventilation and oxygenation, with supplemental oxygen, assisted ventilation, and investigation of hypoxemia or hypercapnia, recognizing respiratory depression as a leading cause of mortality in acute intoxication.

C (circulation) encompasses continuous hemodynamic monitoring, early establishment of venous access, prompt correction of hypotension or hypertension, management of life-threatening arrhythmias, and targeted

metabolic assessment, including blood glucose and hydroelectrolytic and acid–base disturbances.

D (disability) refers to a structured neurological assessment, with immediate identification and treatment of seizures, hypoglycemia, and severe toxic syndromes, as well as an active and broad differential diagnosis of clinical and neurological conditions that may mimic intoxication; at this stage, decisions regarding decontamination procedures and the use of specific antidotes should be made judiciously, guided by toxicological profile, time since exposure, and a careful risk–benefit analysis, avoiding routine interventions without clear clinical indication. Finally.

E (enhanced elimination) includes strategies such as activated charcoal, urinary alkalinization, or extracorporeal methods, reserved for well-defined situations. This dynamic process requires continuous reassessment, vigilant monitoring for cardiovascular, respiratory, and neurological complications, coordination with poison control centers, and planning for continuity of care, including psychiatric and psychosocial evaluation after clinical stabilization, recognizing acute intoxication as a sentinel event of heightened clinical and behavioral vulnerability [38].

Management of clinical complications

The medical problems most frequently reported following cannabis and derivatives use include central nervous system depression, sympathomimetic cardiovascular toxicity, and psychiatric disturbances [13, 14, 39, 40]. Acute clinical complications commonly include tachycardia, hypertension, chest pain, hyperthermia, acute kidney injury, seizures, and severe autonomic instability. Combined use of alcohol or other psychoactive substances may intensify these effects, increasing the likelihood of severe presentations [5, 8, 10, 13, 14, 38, 39, 40]

As no antidote exists, management is supportive and follows standard emergency medicine principles. Initial evaluation requires rapid assessment of airway, breathing, and circulation, along with point-of-care glucose and electrolyte testing. Cardiovascular monitoring is essential due to the risk of arrhythmias, myocardial ischemia, and QT prolongation [41]. Intravenous fluids should be initiated promptly in cases of rhabdomyolysis, dehydration, or hyperthermia, and creatine kinase levels must be monitored closely [42 - 43]. In the presence of hyperthermia, aggressive external cooling is indicated. Acute kidney injury, often precipitated by rhabdomyolysis or nephrotoxicity, requires hydration and strict fluid

balance control. Differential diagnoses such as stimulant intoxication, serotonin syndrome, and metabolic derangements should always be considered because of symptomatic overlap [43] [Table 1]

Management of psychiatric complications

Cannabis and derivatives may be associated with acute and severe neuropsychiatric presentations that exceed those typically observed with Δ9-THC exposure. Acute cannabis effects have long been linked to ED admissions, particularly for anxiety-related symptoms such as panic attacks [13, 14, 39]. Psychiatric manifestations include agitation, persecutory delusions, hallucinations, disorganized behavior, dissociation, suicidal ideation, and frank psychosis. Management agitation may use previous guidelines [1, 44, 45, 46, 47, 48]. Benzodiazepines constitute the first-line treatment for agitation, sympathomimetic symptoms, and convulsive activity [43]. For suicide behavior use specific guidelines too [2, 8, 44, 49, 50, 51, 52] . Suicidal ideation can occur during intoxication, particularly in individuals with underlying mood disorders or intense dysphoria resulting from autonomic hyperactivation. A structured suicide risk assessment should be conducted once the patient is clinically stable. Persistent suicidal ideation after intoxication resolution warrants psychiatric hospitalization [2, 8, 44, 49, 50, 51, 52]. Table 2.

Patients may also present with overwhelming anxiety, derealization, or a sense of impending doom. Benzodiazepines remain first-line agents due to their rapid anxiolytic effect. Reassurance in a low-stimulus environment is beneficial. Antipsychotics should be avoided in isolated panic reactions unless psychotic symptoms coexist [12, 53, 54, 55]

Some patients develop acute delirium characterized by fluctuating consciousness, disorientation, and perceptual disturbances. Management includes identifying reversible causes such as electrolyte imbalance, hypoxia, or infection, while minimizing environmental overstimulation. Pharmacologic treatment mirrors agitation protocols, with benzodiazepines preferred; antipsychotics may be used cautiously.

Following stabilization, patients should receive a brief intervention on substance use, psychoeducation about risks, and referral to addiction services. Individuals with repeated intoxication episodes or persistent psychiatric symptoms benefit from long-term psychiatric follow-up due to the elevated risk of recurrence and potential emergence of primary psychotic disorders [34, 38, 56, 57, 58]

Management of induced psychosis

Cannabis-induced psychosis (CIP) is a cluster of psychotic symptoms that emerge in the context of substance use and frequently resolve with cessation of consumption [59]. However, the distinction between an induced psychotic episode and the onset of a primary psychotic disorder, such as schizophrenia or bipolar disorder, can be complex in the acute phase [20, 59, 60, 61].

Although CIP should, by definition, resolve with cessation of use, symptoms persisting for more than a few days or weeks after cannabis discontinuation should raise suspicion of a primary psychotic disorder [59, 61]. Ricci et al. (2024) highlight that SIP is generally considered a more transient condition, with symptoms that typically resolve with sustained abstinence from the substance [62]. Brief psychotic symptoms or functional impairments (e.g., social isolation, decline in academic performance) prior to the acute episode may indicate an underlying vulnerability [59]. Repetitive psychotic episodes, especially in the absence of continuous cannabis use, increase the likelihood of a primary disorder [20, 59].

The early onset of cannabis use, particularly before the age of 18, is a significant risk factor for the development of psychosis and for a worse prognosis [60, 63, 64] Furthermore, the frequency of use and substance potency (especially high Δ9-tetrahydrocannabinol – THC – content) are consistently associated with a higher risk of psychosis development and a worse prognosis [60, 64, 65]

Positive psychotic symptoms, like those observed in schizophrenia, are also described in CIP. Delusions are frequently persecutory in nature; however, delusions of reference and influence are also common [60]. Hallucinations can occur in any sensory modality, with auditory hallucinations being the most frequent, although visual hallucinations are also reported [60, 66]. Other described positive symptoms include thought disorganization (illogical speech, derailment) and behavioral disorganization (bizarre and contextually inappropriate acts) [59 - 60]. Regarding other dimensions of psychotic psychopathology, patients with CIP frequently exhibit intense anxiety and fear, especially in the context of persecutory delusions [20, 59], also cite irritability, mood symptoms, and sleep problems.

The therapeutic management of cannabis-induced psychosis (CIP) in the emergency department setting requires a multifaceted approach. The main objectives are ensuring patient and environmental safety, controlling

agitation, and alleviating psychotic symptoms. Although the distinction between CIP and a first episode of primary psychosis is crucial for long-term planning, in the emergency setting, the focus is on symptomatic treatment [59].

The creation of a calm and safe environment, with verbal de-escalation techniques, is fundamental for reducing agitation and paranoia. Immediate cessation of cannabis use is a critical component of acute management. Psychoeducation regarding the relationship between substance use and psychotic symptoms should be initiated as soon as the patient is receptive [2, 8, 44, 49, 50, 51, 52, 59]. Benzodiazepines can be employed for rapid control of agitation and severe anxiety, generally in combination with antipsychotics, to stabilize the patient in the initial phase [59].

Regarding pharmacotherapy, antipsychotics are the first-line treatment for acute psychotic symptoms. Second-generation antipsychotics (SGAs), such as Risperidone, Olanzapine, and Aripiprazole, are frequently preferred due to their more favorable side effect profile compared to first-generation antipsychotics (FGAs) [60, 66]. Chuenchom et al. (2024) observed that almost all patients (98.7%) received antipsychotics in the acute phase, with risperidone being the most frequently prescribed (83.6%), followed by Haloperidol (19.9%). Furthermore, the combination of intramuscular Haloperidol and intravenous Diazepam was commonly used to control acute psychotic symptoms [66].

Cannabidiol (CBD) has been investigated for its potential antipsychotic effects and its ability to modulate the psychotomimetic effects of THC [60, 67]. While promising, CBD is not yet an approved treatment for cannabis-induced psychosis and requires further research, including randomized clinical trials, to establish its efficacy and safety [60]

Despite the prevalence of comorbidity between psychosis and cannabis use disorder, there is a notable scarcity of systematic research on specific treatments. An author point to a striking paucity of information on the outcomes, treatments, and best practices for substance-induced psychotic episodes [61]. Robust randomized clinical trials (RCTs) are lacking, and there are no specifically approved treatments for cannabis use disorder in patients with psychosis [67]. Clozapine shows promise, but more RCTs are needed [20].

CONCLUSION

Cannabis is one of the most widely used psychoactive substances worldwide. With the global trend toward decriminalization and legalization, it is opportune to assess the psychiatric effects of cannabis components. The potential for increased cannabis consumption is likely to lead to increased emergency room visits related to cannabis use. This highlights the need for a better understanding of its risks, including the acute induction of psychotic symptoms and other psychiatric symptoms.

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Table 1. Major clinical complications associated with cannabis, its derivatives, and synthetic cannabinoids

Clinical Category	**Key Findings**	**Notes / Frequency**
Cardiovascular	Tachycardia, hypertension, chest pain, arrhythmias, myocardial ischemia	Tachycardia frequently reported; severe cases documented
Neurological	Generalized seizures, status epilepticus, altered consciousness	Seizures in 3–15% of cases
Renal	Acute kidney injury, nephrotoxicity, rhabdomyolysis	Multiple AKI cases with creatinine >3 mg/dL
Gastrointestinal	Nausea, vomiting, abdominal pain	Vomiting noted in 13–94% of presentations.
Metabolic	Hypokalemia, hyperglycemia, acidosis	Hypokalemia in up to 28% of patients.
Thermoregulatory	Hyperthermia	Often secondary to agitation or seizures.
Respiratory	Respiratory depression, hypoxia	Observed in severe intoxications requiring airway support.

Source: The authors

Table 2. Major psychiatric manifestations associated with cannabis, its derivatives, and synthetic cannabinoids

Psychiatric Category	Description	Clinical Notes
Agitation	Severe psychomotor agitation, aggression, disorganized behavior	Most common psychiatric reason for ED presentation
Acute Psychosis	Persecutory delusions, hallucinations, disorganized thinking	Often more severe and prolonged than THC-related psychosis
Anxiety / Panic	Panic attacks, derealization, overwhelming fear	Frequently reported even in low doses.
Mood Disturbances	Dysphoria, irritability, affective lability	Common in moderate to severe intoxication.
Suicidality	Suicidal ideation, impulsive self-harm	Higher risk in vulnerable patients during intoxication.
Delirium	Fluctuating consciousness, confusion, disorientation	Requires assessment for medical contributors.
Persistent Symptoms	Prolonged psychosis, recurrent episodes	Symptoms may persist for days to weeks.

Source: The authors

https://doi.org/10.25118/2763-9037.2026.v16.1611