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The Pharmacology Of Cannabis: A Review Of Its Therapeutic Potential

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Abstract :

The legalization of cannabis for medical purposes is an increasingly global trend, supported by a growing body of scientific evidence demonstrating its therapeutic efficacy for a variety of conditions. Concurrently, many prescribers have voiced concerns that this increased utilization may lead to the development of cannabis use disorder in patients. While cannabis use disorder has been extensively studied in recreational users, with findings often extrapolated to medical cannabis patients, research specifically addressing dependence on medical cannabis remains limited, and standardized methodologies for assessing this phenomenon are lacking. This article presents a narrative review of existing research, aiming to determine the relevance and applicability of concerns regarding dependence in recreational cannabis users to patients prescribed medical cannabis. The review focuses on key factors related to medical cannabis and dependence, including the influence of dosage, potency, cannabinoid composition, pharmacokinetics, administration route, frequency of use, and the crucial role of set and setting. Significant differences between medical and recreational cannabis use are highlighted, underscoring the difficulties inherent in extrapolating data from recreational use studies. Given the numerous unanswered questions surrounding the potential for dependence arising from medical cannabis use, it is imperative that these issues be addressed to effectively minimize potential harms. This review culminates in seven recommendations designed to enhance the safety of medical cannabis prescribing practices. It is

anticipated that this review will contribute to a deeper understanding of the complexities surrounding medical cannabis dependence.

Key Words: Medical cannabis, Dependence, Recreational cannabis use, Dosage, Potency, Prescribing practices, Cannabinoid composition, Pharmacokinetics, Administration route, Frequency of use, Cannabis use disorder, Harm reduction, Recommendations, Narrative review.

Introduction :

Medicinal cannabis (or marijuana) has received significant national attention lately. Challenges associated with its use include controversies surrounding legal, ethical, and social aspects; safe administration, packaging, and dispensing; adverse health effects and deaths linked to marijuana intoxication; and therapeutic uses based on limited clinical evidence. The U.S. Drug Enforcement Agency (DEA), under the Controlled Substances Act of 1970, classifies marijuana as a Schedule I controlled substance. This means it's considered to have a high potential for abuse, no currently accepted medical use in the U.S., and a lack of accepted safety data for use under medical supervision.

Cannabis is the most widely cultivated, trafficked, and abused illegal drug globally. The World Health Organization (WHO) estimates that about 147 million people (approximately 2.5% of the world's population) use marijuana annually. In 2014, around 22.2 million Americans aged 12 and older reported current cannabis use, with 8.4% using it in the past month. Public acceptance of cannabis use (both recreational and medicinal) is growing, as seen in legislation, ballot measures, and public opinion polls. A 2016 Gallup poll showed 60% of Americans surveyed favored legalization. A recent Quinnipiac University poll found that 54% of surveyed American voters supported legalizing cannabis without restrictions, and 81% favored legalization for medicinal purposes. Some data suggests healthcare providers might consider this therapy in certain situations. As of January 2017, medicinal cannabis was approved in 28 states, the District of Columbia, Guam, and Puerto Rico.

Fig No .1

The use and acceptance of medicinal cannabis are constantly changing, reflected in the increasing number of states allowing its use for specific medical conditions. The Food and Drug Administration (FDA) is exploring how to support rigorous scientific research on medicinal cannabis claims and continues to review public data on its safety and abuse potential. This article aims to review the historical importance of medicinal cannabis, discuss its pharmacology and pharmacokinetics, examine select evidence on its medicinal uses, and describe the impact of evolving regulations on acute care hospitals.

Historical Aspects :

Cannabis, a plant-derived product, has a long history, with evidence of its use dating back over 5,000 years in present-day Romania.13 However, direct evidence of its medicinal use (specifically, Δ6-tetrahydrocannabinol [Δ6-THC] found in ashes) only goes back to around 400 AD.14 In the U.S., cannabis was commonly used in patent medicines during the 1800s and early 1900s, first appearing in the United States Pharmacopoeia in 1850. Federal restrictions on cannabis use and sales began in 1937 with the Marihuana Tax Act.15,16 Following this act, cannabis was removed from the United States Pharmacopoeia in 1942. Penalties for possession increased in 1951 and 1956 with the Boggs and Narcotic Control Acts, respectively, culminating in federal prohibition under the Controlled Substances Act of 1970.1,17,18 These legislative actions, beyond criminalization, also hindered research by limiting access to cannabis for academic purposes. In 1996, California became the first state to legalize access to and use of botanical cannabis for medical purposes under a doctor's care through the Compassionate Use Act. As mentioned earlier, by January 1, 2017, 28 states, along with Washington, D.C., Guam, and Puerto Rico, had laws regulating the sale and distribution of medicinal cannabis. Twenty-one states and Washington, D.C., had decriminalized marijuana, eliminating prohibition for possessing small amounts. Furthermore, eight states (Alaska, California, Colorado, Maine, Massachusetts, Nevada, Oregon, and Washington) and Washington, D.C., had legalized marijuana for recreational use by adults.10,19.

Fig No 2.

Pharmacology

Pharmacokinetics of Cannabinoids:

The pharmacokinetics of cannabinoids have been extensively reviewed (Agurell et al., 1986; Maykut, 1985). Inhalation of cannabis smoke, such as from a "joint," results in approximately 50% of the tetrahydrocannabinol (THC) being delivered in the mainstream smoke. Nearly all of this inhaled THC is rapidly absorbed through the lungs, entering the bloodstream and reaching the brain within minutes. The effects are perceptible within seconds and become fully apparent within minutes. In contrast, oral ingestion of cannabinoids exhibits significantly lower bioavailability, with blood concentrations reaching only 25-30% of those achieved via smoking the same dose. This reduced bioavailability is primarily attributed to first-pass metabolism in the liver. Furthermore, the onset of effects following oral administration is delayed (0.5-2 hours), while the duration of action is prolonged due to sustained, slow absorption from the gastrointestinal tract.

Following absorption, THC and other cannabinoids undergo rapid distribution to all tissues, with the rate of distribution dependent on blood flow . Due to their extreme lipophilicity, cannabinoids accumulate in adipose tissue, reaching peak concentrations within 4-5 days. Subsequently, they are slowly released back into other body compartments, including the brain. This sequestration in fat results in a tissue elimination half-life of approximately 7 days for THC, and complete elimination of a single dose may require up to 30 days (Maykut, 1985). Consequently, repeated dosing can lead to substantial accumulation of cannabinoids within the body, with continued delivery to the brain. Within the brain itself, THC and other cannabinoids exhibit differential distribution, with high concentrations observed in neocortical, limbic, sensory, and motor areas.

The distribution of THC after a single administration in plasma and body tissues. Note the ‘biphasic’ disappearance in plasma. The rapid phase (in minutes) indicates a rapid uptake of the drug by fat-containing tissues. The slow phase (in days) shows the release of THC by these tissues (Nahas & Richter, 1975). THC, tetrahydrocannabinol.)

Hepatic metabolism is the primary route of cannabinoid metabolism. A major metabolite, 11-hydroxy-THC, is potentially more potent than THC itself and may contribute to the overall pharmacological effects of cannabis. Over 20 other metabolites have been identified, some of which are psychoactive, and all of which exhibit long half-lives of several days. Excretion of metabolites occurs partially in the urine (25%), but primarily via the biliary system into the gut (65%), where they can undergo enterohepatic recirculation, further prolonging their actions. Due to these complex pharmacokinetic characteristics of cannabinoids – including sequestration in fat and the presence of active metabolites – there is a weak correlation between plasma or urine concentrations and the degree of cannabinoid-induced intoxication.

Pharmacodynamics of cannabinoids:

Cannabinoids elicit their effects through interactions with specific endogenous cannabinoid receptors, a discovery pioneered by Devane et al. (1988). The neuronal cannabinoid receptors, designated CB1 receptors, have been identified in the brains and peripheral nerves of various species, including rats, guinea pigs, dogs, monkeys, pigs, and humans. A second cannabinoid receptor, CB2, was subsequently identified by Munro et al. (1993) in macrophages within the spleen and is also present in other immune cells. The distribution of CB1 receptors closely mirrors that of systemically administered THC, encompassing regions such as the cerebral cortex, limbic areas (including the hippocampus and amygdala), bas al ganglia, cerebellum, thalamus, and brainstem (Herkenham, 1995).

The identification of cannabinoid receptors naturally prompted a search for their endogenous ligand. This endogenous substance was isolated from the porcine brain by Devane et al. (1992) and found to be chemically distinct from plant-derived cannabinoids. Characterized as a derivative of the fatty acid arachidonic acid (arachidonyl ethanolamide), it is structurally related to prostaglandins . This endogenous compound was named Anandamide, derived from the Sanskrit word for bliss, ananda. Anandamide exhibits a high affinity for CB1 receptors and shares a similar pharmacological profile with THC. Thus, analogous to the discovery of opium, opioid receptors, and endogenous opioids, the investigation of cannabis has revealed a parallel system involving cannabinoid receptors and anandamide.

Clinical Implications and Limitations of Cannabis Use

Clinical Implications:

* Cannabis use is associated with an increased risk of accidents involving road, rail, and air transportation.

* Chronic cannabis use can result in the development of tolerance, dependence, withdrawal symptoms, and potentially long-term cognitive impairment.

* Long-term cannabis use is associated with respiratory, cardiovascular, and other adverse health outcomes.

Limitations:

* The lack of a clear correlation between cannabinoid concentrations in biological fluids and the degree of psychomotor impairment complicates the development of effective traffic safety policies.

* Longitudinal, prospective, controlled studies are necessary to quantify the health risks associated with chronic cannabis use.

* Further research is required to elucidate the specific effects of individual cannabinoids and their interactions with tetrahydrocannabinol (THC).

Actions of cannabis in human :

Cannabis exerts a multifaceted influence on the human body, impacting nearly every system. Its pharmacological profile is complex, exhibiting characteristics reminiscent of alcohol, tranquilizers, opiates, and hallucinogens. It can act as an anxiolytic, sedative, analgesic, and psychedelic, while also stimulating appetite and inducing a range of systemic effects. Notably, its acute toxicity is remarkably low, with no documented fatalities directly attributable to acute cannabis use. This review focuses on a selection of cannabis's effects; for a more comprehensive overview, readers are directed to the works of Paton & Pertwee (1973), Pertwee (1995), Adams & Martin (1996), and numerous other researchers.

Psychological Effects:

Cannabis use is associated with a variety of psychological effects, primarily impacting mood, perception, and cognitive and psychomotor functions. These effects are described in more detail below.

* Effect on Mood: Cannabis can induce a range of mood alterations, varying from euphoria and relaxation to anxiety and dysphoria. The specific mood effect is influenced by factors such as the individual's mindset, the social context of use, the strain and dose of cannabis, and prior experience with the drug.

* Effect on Perception: Cannabis can alter sensory perception, leading to heightened awareness of stimuli, distortions in time and space perception, and in some cases, visual or auditory hallucinations. These perceptual changes contribute to the drug's psychoactive properties.

* Effects on Cognition and Psychomotor Performance: Cannabis use can impair cognitive functions, including attention, memory, and decision-making. It can also negatively impact psychomotor performance, affecting coordination, reaction time, and balance. These effects can have implications for activities such as driving and operating machinery.

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