Cannabis / Marijuana (Δ ^{9} -Tetrahydrocannabinol, THC)

Marijuana is a green or gray mixture of dried shredded flowers and leaves of the hemp plant *Cannabis sativa*. Hashish consists of resinous secretions of the cannabis plant. Dronabinol (synthetic THC) is a light yellow resinous oil.

Synonyms: Cannabis, marijuana, pot, reefer, buds, grass, weed, dope, ganja, herb, boom, gangster, Mary Jane, sinsemilla, shit, joint, hash, hash oil, blow, blunt, green, kilobricks, Thai sticks; Marinol®

Source: Cannabis contains chemicals called cannabinoids, including cannabinol, cannabidiol, cannabinolidic acids, cannabigerol, cannabichromene, and several isomers of tetrahydrocannabinol (THC). One of these isomers, Δ ^{9}-THC, is believed to be responsible for most of the characteristic psychoactive effects of cannabis. Marijuana refers to the leaves and flowering tops of the cannabis plant; the buds are often preferred because of their higher THC content. Hashish consists of the THC-rich resinous secretions of the plant, which are collected, dried, compressed and smoked. Hashish oil is produced by extracting the cannabinoids from plant material with a solvent. In the U. S., marijuana, hashish and hashish oil are Schedule I controlled substances. Dronabinol (Marinol®) is a Schedule III controlled substance and is available in strengths of 2.5, 5 or 10 mg in round, soft gelatin capsules.

Drug Class: *Cannabis/ Marijuana*: spectrum of behavioral effects is unique, preventing classification of the drug as a stimulant, sedative, tranquilizer, or hallucinogen. *Dronabinol*: appetite stimulant, antiemetic.

Medical and Recreational Uses: *Medicinal*: Indicated for the treatment of anorexia associated with weight loss in patients with AIDS, and to treat mild to moderate nausea and vomiting associated with cancer chemotherapy. *Recreational*: Marijuana is used for its mood altering effects, euphoria, and relaxation. Marijuana is the most commonly used illicit drug throughout the world.

Potency, Purity and Dose: THC is the major psychoactive constituent of cannabis. Potency is dependent on THC concentration and is usually expressed as %THC per dry weight of material. Average THC concentration in marijuana is 1-5%, hashish 5-15%, and hashish oil ³ 20%. The form of marijuana known as *sinsemilla* is derived from the unpollinated female cannabis plant and is preferred for its high THC content (up to 17% THC). Recreational doses are highly variable and users often titer their own dose. A single intake of smoke from a pipe or joint is called a hit (approximately 1/20th of a gram). The lower the potency or THC content the more hits are needed to achieve the desired effects; 1-3 hits of high potency sinsemilla is typically enough to produce the desired effects. In terms of its psychoactive effect, a drop or two of hash oil on a cigarette is equal to a single "joint" of marijuana. Medicinally, the initial starting dose of Marinol® is 2.5 mg, twice daily.

Route of Administration: Marijuana is usually smoked as a cigarette ('joint') or in a pipe or bong. Hollowed out cigars packed with marijuana are also common and are called `. Joints and blunts are often laced with adulterants including PCP or crack cocaine. Joints can also be dipped in liquid PCP or in codeine cough syrup. Marijuana is also orally ingested.

Pharmacodynamics: THC binds to cannabinoid receptors and interferes with important endogenous cannabinoid neurotransmitter systems. Receptor distribution correlates with brain areas involved in physiological, psychomotor and cognitive effects. Correspondingly, THC produces alterations in motor behavior, perception, cognition, memory, learning, endocrine function, food intake, and regulation of body temperature.

Pharmacokinetics: Absorption is slower following the oral route of administration with lower, more delayed peak THC levels. Bioavailability is reduced following oral ingestion due to extensive first pass metabolism. Smoking marijuana results in rapid absorption with peak THC plasma concentrations occurring prior to the end of smoking. Concentrations vary depending on the potency of marijuana and the manner in which the drug is smoked, however, peak plasma concentrations of 100-200 ng/mL are routinely encountered. Plasma THC concentrations generally fall below 5 ng/mL less than 3 hours after smoking. THC is highly lipid soluble, and plasma and urinary elimination half-lives are best estimated at 3-4 days, where the rate-limiting step is the slow redistribution to plasma of THC sequestered in the tissues. Shorter half-lives are generally reported due to limited collection intervals and less sensitive analytical methods. Plasma THC concentrations in occasional users rapidly fall below limits of quantitation within 8 to 12 h. THC is rapidly and extensively metabolized with very little THC being excreted unchanged from the body. THC is primarily metabolized to 11-hydroxy-THC which has equipotent psychoactivity. The 11-hydroxy-THC is then rapidly metabolized to the 11-nor-9-carboxy-THC (THC-COOH) which is not psychoactive. A majority of THC is excreted via the feces (~65%) with approximately 30% of the THC being eliminated in the urine as conjugated glucuronic acids and free THC hydroxylated metabolites.

Molecular Interactions / Receptor Chemistry: THC is metabolized via cytochrome P450 2C9, 2C11, and 3A isoenzymes. Potential inhibitors of these isoenzymes could decrease the rate of THC elimination if administered concurrently, while potential inducers could increase the rate of elimination.

Blood to Plasma Concentration Ratio: 0.55

Interpretation of Blood Concentrations: It is difficult to establish a relationship between a person's THC blood or plasma concentration and performance impairing effects. Concentrations of parent drug and metabolite are very dependent on pattern of use as well as dose. THC concentrations typically peak during the act of smoking, while peak 11-OH THC concentrations occur approximately 9-23 minutes after the start of smoking. Concentrations of both analytes decline rapidly and are often < 5 ng/mL at 3 hours. Significant THC concentrations (7 to 18 ng/mL) are noted following even a single puff or hit of a marijuana cigarette. Peak plasma THC concentrations ranged from 46-188 ng/mL in 6 subjects after they smoked 8.8 mg THC over 10 minutes. Chronic users can have mean plasma levels of THC-COOH of 45 ng/mL, 12 hours after use; corresponding THC levels are, however, less than 1 ng/mL. Following oral administration, THC concentrations peak at 1-3 hours and are lower than after smoking. Dronabinol and THC-COOH are present in equal concentrations in plasma and concentrations peak at approximately 2-4 hours after dosing.

It is inadvisable to try and predict effects based on blood THC concentrations alone, and currently impossible to predict specific effects based on THC-COOH concentrations. It is possible for a person to be affected by marijuana use with concentrations of THC in their blood below the limit of detection of the method. Mathematical models have been developed to estimate the time of marijuana exposure within a 95% confidence interval. Knowing the elapsed time from marijuana exposure can then be used to predict impairment in concurrent cognitive and psychomotor effects based on data in the published literature.

Interpretation of Urine Test Results: Detection of total THC metabolites in urine, primarily THC-COOH-glucuronide, only indicates prior THC exposure. Detection time is well past the window of intoxication and impairment. Published excretion data from controlled clinical studies may provide a reference for evaluating urine cannabinoid concentrations; however, these data are generally reflective of occasional marijuana use rather than heavy, chronic marijuana exposure. It can take as long as 4 hours for THC-COOH to appear in the urine at concentrations sufficient to trigger an immunoassay (at 50ng/mL) following smoking. Positive test results generally indicate use within 1-3 days; however, the detection window could be significantly longer following heavy, chronic, use. Following single doses of Marinol®, low levels of dronabinol metabolites have been detected for more than 5 weeks in urine. Low concentrations of THC have also been measured in over-the-counter hemp oil products – consumption of these products may produce positive urine cannabinoid test results.

Effects: Pharmacological effects of marijuana vary with dose, route of administration, experience of user, vulnerability to psychoactive effects, and setting of use.

Psychological: At recreational doses, effects include relaxation, euphoria, relaxed inhibitions, sense of well-being, disorientation, altered time and space perception, lack of concentration, impaired learning and memory, alterations in thought formation and expression, drowsiness, sedation, mood changes such as panic reactions and paranoia, and a more vivid sense of taste, sight, smell, and hearing. Stronger doses intensify reactions and may cause fluctuating emotions, flights of fragmentary thoughts with disturbed associations, a dulling of attention despite an illusion of heightened insight, image distortion, and psychosis.

Physiological: The most frequent effects include increased heart rate, reddening of the eyes, dry mouth and throat, increased appetite, and vasodilatation.

Side Effect Profile: Fatigue, paranoia, possible psychosis, memory problems, depersonalization, mood alterations, urinary retention, constipation, decreased motor coordination, lethargy, slurred speech, and dizziness. Impaired health including lung damage, behavioral changes, and reproductive, cardiovascular and immunological effects have been associated with regular marijuana use. Regular and chronic marijuana smokers may have many of the same respiratory problems that tobacco smokers have (daily cough and phlegm, symptoms of chronic bronchitis), as the amount of tar inhaled and the level of carbon monoxide absorbed by marijuana smokers is 3 to 5 times greater than among tobacco smokers. Smoking marijuana while shooting up cocaine has the potential to cause severe increases in heart rate and blood pressure.

Duration of Effects: Effects from smoking cannabis products are felt within minutes and reach their peak in 10-30 minutes. Typical marijuana smokers experience a high that lasts approximately 2 hours. Most behavioral and

physiological effects return to baseline levels within 3-5 hours after drug use, although some investigators have demonstrated residual effects in specific behaviors up to 24 hours, such as complex divided attention tasks. Psychomotor impairment can persist after the perceived high has dissipated. In long term users, even after periods of abstinence, selective attention (ability to filter out irrelevant information) has been shown to be adversely affected with increasing duration of use, and speed of information processing has been shown to be impaired with increasing frequency of use. Dronabinol has an onset of 30-60 minutes, peak effects occur at 2-4 hours, and it can stimulate the appetite for up to 24 hours.

Tolerance, Dependence and Withdrawal Effect: Tolerance may develop to some pharmacological effects of dronabinol. Tolerance to many of the effects of marijuana may develop rapidly after only a few doses, but also disappears rapidly. Marijuana is addicting as it causes compulsive drug craving, seeking, and use, even in the face of negative health and social consequences. Additionally, animal studies suggests marijuana causes physical dependence. A withdrawal syndrome is commonly seen in chronic marijuana users following abrupt discontinuation. Symptoms include restlessness, irritability, mild agitation, hyperactivity, insomnia, nausea, cramping, decreased appetite, sweating, and increased dreaming.

Drug Interactions: Cocaine and amphetamines may lead to increased hypertension, tachycardia and possible cardiotoxicity. Benzodiazepines, barbiturates, ethanol, opioids, antihistamines, muscle relaxants and other CNS depressants increase drowsiness and CNS depression. When taken concurrently with alcohol, marijuana is more likely to be a traffic safety risk factor than when consumed alone.

Performance Effects: The short term effects of marijuana use include problems with memory and learning, distorted perception, difficulty in thinking and problem-solving, and loss of coordination. Heavy users may have increased difficulty sustaining attention, shifting attention to meet the demands of changes in the environment, and in registering, processing and using information. In general, laboratory performance studies indicate that sensory functions are not highly impaired, but perceptual functions are significantly affected. The ability to concentrate and maintain attention are decreased during marijuana use, and impairment of hand-eye coordination is dose-related over a wide range of dosages.Impairment in retention time and tracking, subjective sleepiness, distortion of time and distance, vigilance, and loss of coordination in divided attention tasks have been reported. Note however, that subjects can often "pull themselves together" to concentrate on simple tasks for brief periods of time. Significant performance impairments are usually observed for at least 1-2 hours following marijuana use, and residual effects have been reported up to 24 hours.

Effects on Driving: The drug manufacturer suggests that patients receiving treatment with Marinol® should be specifically warned not to drive until it is established that they are able to tolerate the drug and perform such tasks safely. Epidemiology data from road traffic arrests and fatalities indicate that after alcohol, marijuana is the most frequently detected psychoactive substance among driving populations. Marijuana has been shown to impair performance on driving simulator tasks and on open and closed driving courses for up to approximately 3 hours. Decreased car handling performance, increased reaction times, impaired time and distance estimation, inability to maintain headway, lateral travel, subjective sleepiness, motor incoordination, and impaired sustained vigilance have all been reported. Some drivers may actually be able to improve performance for brief periods by overcompensating for self-perceived impairment. The greater the demands placed on the driver, however, the more critical the likely impairment. Marijuana may particularly impair monotonous and prolonged driving. Decision times to evaluate situations and determine appropriate responses increase. Mixing alcohol and

marijuana may dramatically produce effects greater than either drug on its own.

DEC Category: Cannabis

DEC Profile: Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence present; pupil size normal to dilated; reaction to light normal to slow; pulse rate elevated; blood pressure elevated; body temperature normal to elevated. Other characteristic indicators may include odor of marijuana in car or on subject's breath, marijuana debris in mouth, green coating of tongue, bloodshot eyes, body and eyelid tremors, relaxed inhibitions, incomplete thought process, and poor performance on field sobriety tests.

Panel's Assessment of Driving Risks: Low doses of THC moderately impair cognitive and psychomotor tasks associated with driving, while severe driving impairment is observed with high doses, chronic use and in combination with low doses of alcohol The more difficult and unpredictable the task, the more likely marijuana will impair performance.

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