

(www.drugtestinganalysis.com) DOI 10.1002/dta.1440

Cannabinoids Part I – Legal policies and physiological effects

Cannabis spp. has been used for a variety of purposes for thousands of years, and has been the subject of chemical investigations since the 1800s; however, it wasn't until 1964 that the correct structure for THC was characterized.^[1] THC is the major psychoactive component of ca. 85 cannabinoids estimated to be synthesized by *Cannabis sativa*.^[2–4] Receptors for cannabinoids were difficult to identify because of their highly lipophilic nature. During the 1980s, Pfizer embarked on a major effort to synthesize analogues based on the THC structure, one of which, CP55,940, a high affinity CB1 ligand, led to identification of two receptors for THC in the early 1990s. CB1 is primarily localized in the central nervous system,^[5,6] and CB2 in cells associated with the immune system.^[7]

Finding a balance between therapeutic, spiritual, and recreational uses, and the resulting legal policies, is difficult and contentious.^[8] Marijuana is classified by the Drug Enforcement Agency (DEA) as a Schedule I drug, which by definition has no accepted medical use; however, numerous studies demonstrate that marijuana can mitigate chronic pain, alleviate nausea and vomiting associated with chemotherapy, treat wasting syndrome associated with AIDS, and has also demonstrated efficacy for treatment of numerous other maladies. Many studies state that the palliative benefits of marijuana outweigh the adverse effects of the drug, and recommend that marijuana be administered to patients who have failed to respond to other therapies. Despite well-documented supporting evidence, the DEA refuses to reclassify marijuana as a Schedule II drug, which would allow physicians to prescribe marijuana to suffering patients.

Dealing with dopamine-related effects of cannabinoids, Joseph Cheer *et al.* at University of Maryland School of Medicine present a comprehensive case for the use of 'mesolimbic measurements' to 'provide a robust indicator of cannabinoid abuse liability'.^[9] Pioneered by Dr John W. Huffman, the eponymous JWH series of cannabinoid derivatives heralded the onset of synthetic THC analogues which inevitably found their way into use/abuse by the general population, resulting in a rapid rise in hospital/poison-control centre visits by recreational users. The authors point out that this has justifiably resulted in state and federal control, unfortunately with unintended results. Citing Huffman (and this reviewer had a recent communication with JWH that confirms this remains his opinion), many federal and state governments have relegated cannabinoids and their analogues to Schedule I status, which impedes research on their therapeutic utility and elucidation of their physiological roles. Differentiation between direct agonists (including THC), which directly bind to and stimulate cannabinoid receptors, and indirect agonists, which indirectly stimulate these receptors by increasing levels of endogenous CB transmitters, is central to their argument. A comprehensive review of the literature

reveals that behavioural animal models yield inconsistent and often contradictory results; however, all drugs of abuse increase dopamine levels in the nucleus accumbens; a convincing argument is made that the degree of abuse potential of a very diverse group of compounds acting on completely different targets via independent mechanisms can reliably be predicted by monitoring dopamine release. Their conclusion is based on a comprehensive literature review, resulting in a convincing argument for a more reasoned approach to the regulation of cannabinoids.

Marijuana is the most widely used illicit drug by pregnant women in the world. *In utero* exposure to 79-tetrahydrocannabinol (79-THC), a major psychoactive component of marijuana, is associated with an increased risk for anencephaly and neurobehavioural deficiencies in the offspring, including ADHD (attention deficit hyperactivity disorder), learning disabilities and memory impairment. Delphine Psychoyos discusses recent studies that demonstrate that the developing central nervous system (CNS) is susceptible to the effects of 79-THC and other cannabimimetics, including the psychoactive ingredients of 'Spice'. These exocannabinoids interfere with the function of an endocannabinoid (eCB) system, present in the developing CNS from E12.5 (week 5 of gestation in human), and required for proliferation, migration, and differentiation of neurons.^[10] Until recently, it was not known whether the eCB system is also present in the developing CNS during the initial stages of its ontogeny, i.e. from E7.0 onwards (week 2 of gestation in human), and if so, whether this system is also susceptible to the action of exocannabinoids. Here, psychoyos review current data, in which the presence of an eCB system during the initial stage of development of the CNS is demonstrated. Furthermore, psychoyos focus on recent advances on the effect of cannabimimetics on early gestation. The relevance of these findings and potential adverse developmental consequences of *in utero* exposure to marijuana and/or other cannabimimetics during this period is discussed. Finally, she addresses the implication of these findings in terms of the potential dangers of synthetic cannabinoid use during pregnancy, and the ongoing debate over legalization of marijuana.

Serena Deiana describes the documented and potential roles of THC and related cannabinoids in either exacerbating or ameliorating schizophrenia.^[11] The inclusion of relevant quotations from the scientific literature interspersed throughout adds perspective. Beginning with a short history of cannabis use extending over several millennia, the discussion shifts primarily to cannabidiol (CBD), an abundant cannabinoid with no psychotropic activity, but with effects on a range of pharmacological pathways that include cannabinoid and serotonin receptors. CBD has been and continues to be used to treat medical conditions such as Alzheimer's, Parkinson's, multiple sclerosis, and more recently schizophrenia. The genetic and biochemical bases

of schizophrenic pathophysiology are controversial, and alternative views are comprehensively presented. Long-term epidemiological studies and ongoing clinical trials demonstrate the complexity of cannabinoid effects and justify the lack of consensus among professionals on the therapeutic use of these compounds. The disparate results of clinical and preclinical trials are presented in detail and a coherent summary based on presented data, ending with a somewhat controversial – but readily defensible – policy suggestion.

Paul Armentano^[12] emphasizes the vagaries of enforcement policies involving the impact of THC and analogues on psychomotor performance, focused on on-road traffic accidents. Implementation of enforcement is difficult because of the absence of reliable tests that can be immediately administered with any degree of certainty, the long-term persistence in blood of cannabinoids far beyond the time that they have any significant performance-impairing effects, and the highly variable effects of these compounds on individuals. A well-documented, rational case is presented that while cannabinoid intoxication can have some effects (decreased performance in critical tracking and divided attention tasks, reduced speed, and decreased reaction time), these are minimal compared to alcohol and benzodiazepines, especially among chronic, heavy users of THC and analogues. The conclusion that these issues will have to be addressed before there is any possibility of legalizing and regulating cannabinoids in a manner similar to alcohol is well supported using a variety of legal and scientific sources.

The problem of drug addiction as a widely recognized chronic relapsing illness that affects both women and men is addressed by Liana Fattore.^[13] While significant progress has been made in the addiction field in recent decades, relatively little is known about the origins of, treatments for, and prevention of substance abuse disorders among women. Yet, gender is a major factor in the modulation of the pharmacological effects of drugs of abuse, including cannabis, and sex differences have been reported in various phases of the addiction cycle in both humans and other animals. A craving for and the propensity to reinstate marijuana use after abstinence may also develop differently between men and women, requiring distinct treatment approaches. On the basis that the male and female brain responds differently to marijuana exposure, this paper discusses the importance of considering gender differences in detoxification treatments of marijuana smokers to provide a next step on the path to truly personalized healthcare.

Eric Seigny examines the bases for the widely accepted assumption that average marijuana potency has progressively and substantially increased over the last four decades in the United States.^[14] A number of reasons for this trend are presented, including a shift from foreign to domestic cultivation; advances in cultivation techniques; and cultivars with enhanced tetrahydrocannabinol (THC) levels, especially the switch to higher quality sinsemilla products. Broken down by decade, the 1970s were characterized by poor quality, and low potency kilobrick marijuana; the 1980s and 1990s by a mid-quality mix of kilobrick products; and the

2000s with a dramatic increase in market share by high quality, high potency sinsemilla products. This has led to the widespread belief that potency has increased by a factor of 10 during the last four decades; however, when adjusted for artefacts introduced by substantially reduced seizure-to-analysis times and modified analytical techniques with increased sensitivity, the actual increase is a factor of 6–7. While still significant, the documented differences can have a significant effect on enforcement policies proposed and implemented by governmental agencies. This is an impartial and well-documented statistical study that presents, for the first time, trends in potency adjusted for sampling, storage protocols, and analytical techniques.

It is the purpose of the paper in this, part 1 of a series of special issues on cannabinoids, to provide unique perspectives on specific areas of focused cannabinoid research and related legal and other policy issues. It is only through spirited and informed debate that appropriate policy and enforcement decisions can be formulated.

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