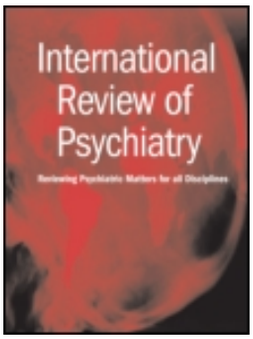

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EDITORIAL

Moving beyond the cannabis controversy into the world of the cannabinoids

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Cannabis remains the most widely used illegal substance in the USA and most other developed countries that regulate its use. Controversy regarding its addictive potential, health consequences, medical use, and legal status has proliferated since the early part of the twentieth century. Pro-cannabis groups have led an ongoing effort to decriminalize and legalize cannabis use, and many respected scientists and medical professionals have argued for legitimizing the medical use of cannabis. Anti-cannabis proponents raise concerns about the psychosocial, health, and psychiatric consequences associated with cannabis misuse and addiction. The fallout from both sides of the controversy has included: lax attitudes towards use of cannabis increasing the probability of use and misuse; failure of the public, scientists, and prevention/treatment specialists to consider cannabis a significant drug of abuse, leading to low rates of treatment seeking and inadequate effort and resources for development of effective treatment services; overly severe penal consequences for possession and use of cannabis; and impediment of science exploring the potential of cannabis and/or its active compounds for treatment of physical and psychiatric disorders. Over the last 15 years, developments in the behavioural, neuro-, and clinical sciences have furthered our knowledge and understanding of the addictive nature of cannabis and the potential therapeutic mechanisms by which cannabinoids may impact physical health and psychiatric disorders. This empirical base has provided the opportunity to conduct studies to resolve the major aspects of this enduring controversy.

Regarding the addictive potential of cannabis, epidemiological, laboratory, and clinical studies have demonstrated the existence, increasing prevalence, and clinical significance of cannabis abuse and dependence disorders. A multitude of experimental and clinical studies have demonstrated that cannabis can produce a clinically important withdrawal syndrome that will likely receive strong consideration as a new entry in the upcoming revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM). Treatment admissions for primary cannabis dependence have increased such that the number of admissions for cannabis rivals that for cocaine or opiates. Together these findings indicate that continued debate over whether or not cannabis is 'addictive' is antiquated. Cannabis misuse and addiction are real and relatively common with significant associated consequences; moreover, these clinical problems reflect a significant public health issue that requires continued attention and resources.

Similarly, the positive results from studies evaluating the therapeutic potential of cannabinoids and manipulation of the endogenous cannabinoid system clearly indicate growing promise of medicinal value. Delta-9 THC, the primary active compound in cannabis, effectively stimulates appetite and food intake and also functions as an anti-nausea and antiemetic agent. In fact, the oral form of THC is approved by the US Food and Drug Administration, and by regulatory bodies in other countries, for AIDS wasting syndrome and cancer patients receiving chemotherapy. Likewise, the synthetic cannabinoid, nabilone, is also approved for use in cancer patients undergoing chemotherapy, and the oromucosal form of a cannabis extract (Sativex®), which contains cannabidiol in addition to THC, is approved to manage the spasticity and neuropathic pain in multiple sclerosis. Indeed, in 1999 the Institute of Medicine and the National Institutes of Health acknowledged the importance of initiating additional scientific study of the risks and benefits of the use of cannabis and cannabinoids for specific medical conditions. Discussion and research addressing other potential therapeutic applications of smoked cannabis, cannabis extracts, oral THC and synthetic cannabinoids for conditions such as pain, neuromuscular disorders, neurodegenerative disorders, anxiety, depression, epilepsy, autoimmune

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diseases, asthma and glaucoma have continued to appear in the literature. However, limited controlled clinical research in these areas thus far has prohibited drawing definitive conclusions about their efficacy and side effect profiles for these indications. Nonetheless, positive suggestive findings indicate that cannabinoids (in some form) or manipulations of the cannabinoid system by other pharmacological agents may be efficacious for a range of different clinical syndromes. However, sometimes advocates, the lay public and legislators mistakenly believe that showing that a drug has therapeutic potential somehow diminishes concerns about its abuse and addictive potential. The error of this view is easily shown when one considers opioids, which have provided both a huge therapeutic advantage and a significant drug problem to humanity.

The ongoing controversy surrounding the putative superior efficacy of smoked forms of cannabis is likely to continue, not only because this route can produce high levels of THC, but also because this route of administration is the most common method used by recreational cannabis users and those who develop problems with cannabis addiction. However, smoking cannabis results in intoxication, which can be considered an adverse side effect to those using cannabis for a therapeutic indication. In addition, cannabis smoke includes many carcinogens and other compounds, and poses adverse consequences on the respiratory system and introduces carcinogens to the body. The practical problem of delivering accurate doses of THC posed by the manufacturing (growing and storing) of cannabis and a smoking delivery system also must be measured. These problems make it difficult to consider smoked cannabis as a truly medical intervention. Availability of other forms of THC delivery, such as oromucosal sprays, or inhaled THC from vaporizers and metered-dose dispensers could address the concerns of using smoked cannabis as well as the limitations of oral dosing, such as delayed onset and variable absorption, and yet provide accurate, uncontaminated doses of THC.

Another strategy to capture the therapeutic potentials attributed to cannabis has been to generate synthetic compounds that target specific elements of the endogenous cannabinoid system. Since the late 1980s, rapid scientific advancements have described the different components of the endogenous cannabinoid system. In addition, they have delineated its ubiquitous impact on multiple central and peripheral functions, including its dysregulation in certain medical conditions. Given the central role of endogenous cannabinoid ligands as retrograde messengers to modulate the activity of both inhibitory and excitatory neurotransmitter systems, perhaps it is not surprising that cannabinoids are capable of influencing so many different biological processes and have the potential as medications for such an array of medical problems. The characterization of the endogenous cannabinoid system has provided valuable targets that can be manipulated for therapeutic gain. As described in more detail in the accompanying reviews, two G-protein coupled receptors and arachidonic acid-based endogenous ligands for those receptors, as well as the enzymes to control synthesis and degradation of the more well known ligands, have been identified as its principal components. These components have been located in key areas that correspond well to the known effects of cannabis, and to the hypothesized role of this system in various medical conditions. Medicinal chemists have created a host of compounds that function as selective agonists, antagonists and allosteric modulators at the CB_1 and CB_2 receptor subtypes, as well as indirect agonists that are inhibitors of degradation and transport of the endogenous ligands.

The majority of these potential medications remain in the early stages of development; further animal testing and future clinical studies are needed to demonstrate their therapeutic efficacy. Verification of the participation of the other putative cannabinoid receptors, as well as the identification of additional control enzymes for the endogenous ligands, will also present valuable future targets for medications development. With these advances, there is much optimism that subsequent research on the endocannabinoid system and newly discovered cannabinoids will result in the development of effective alternative medications that could reproduce the desired effects of cannabis, without the potentially problematic effects of smoked cannabis such as abuse potential, sedation, disruption in psychomotor performance, problems with memory and other cognitive processes, carcinogenicity, and respiratory system complications. Importantly, these discoveries will also inform the underlying neurobiological processes of cannabis and other drug use disorders and provide guidance for development of additional pharmacotherapies for the management of cannabis and other substance addictions.

This special issue of the *International Review of Psychiatry* offers the reader a series of articles that provide snapshots of the current knowledge and recent advancements relevant to the understanding and treatment of cannabis addiction, the neuroanatomy and functioning of the endogenous cannabinoid system, the involvement of exogenous and endogenous cannabinoids in certain CNS and psychiatric disorders, and the potential for administering cannabinoids and selectively targeting endogenous cannabinoid systems as a pathway for intervening on multiple clinical disorders. Below we

provide an annotated overview of the contributions of accomplished scientists who were invited to share their knowledge of cannabis and the cannabinoids in their respective areas of expertise.

In the initial articles, the prevalence, treatment and neurobiology of cannabis-use disorders are considered. First, Copeland and Swift present an overview of the clinical epidemiology of cannabis use and cannabis use disorders, and review the growing treatment literature illustrating the public health significance of cannabis misuse and addiction. They highlight the many negative associations with initiation of cannabis use at an early age, i.e. increased risk for cannabis and other substance addiction, impaired mental health, delinquency, lower educational achievement, and risky sexual behaviour. They inform us that the relative risk of developing abuse or dependence after sampling cannabis is lower than for other illicit substances (perhaps indicating a relatively lower addictive potential). However, because the absolute number of those who try cannabis is so much larger than the number that try other illicit substances, many more people develop a problem with cannabis than with other less sampled drugs such as cocaine or opiates. Increased treatment-seeking for cannabis use problems has led to the development and evaluation of multiple behavioural therapies. The authors inform us that such interventions are efficacious, but have response rates (and relapse rates) similar to those observed for treatments of other substances indicating the resistant and persistent nature of cannabis addiction. The need for continued clinical research to enhance prevention efforts and treatment effectiveness is made clear. Efforts to develop pharmacotherapies and other behavioural interventions such as contingency management are offered as promising alternatives.

Cooper and Haney's article describes the actions of exogenous cannabinoids at the receptor level as a means of explaining the mechanism for the rewarding effects of smoked cannabis that promotes addiction. Data across a range of species demonstrate that cannabis abuse and dependence is mediated by delta-9-THC binding to the cannabinoid CB1 receptor. The article also reviews research demonstrating the role of the receptor in the expression of cannabis withdrawal syndrome. Here, the reader will find a concise review of the human and non-human literature establishing the validity of cannabis withdrawal syndrome. The authors also touch on the interaction of the cannabinoid and opioid systems and the possible opioidergic moderation of the cannabinoid's reinforcing effects. Thorough working knowledge of these neurobiological mechanisms that mediate cannabis addiction is vital for better understanding the addictive process and for development of potential pharmacotherapies.

Next, Breivogel and Sim-Selley provide an overview of the neuropharmacology and neuroanatomy of the cannabinoid system. The article describes the central effects of cannabis and cannabinoids, particularly as they relate to psychiatric issues, such as drug abuse and dependence, anxiety, depression and psychotic disorders, and how these effects correlate well with the location of the components of the endocannabinoid system in the brain. In addition to presenting the role of the known G-protein-coupled cannabinoid CB_1 receptor (GPCR) subtype, they also introduce the possibility of novel central sites of action, including cannabinoid-specific ion channels, nuclear receptors and at least one additional GPCR, as well as receptors found on glial cells. Another exciting advancement in this area noted by the authors that could have a significant impact on the field is the recent discovery of the coupling of CB_1 with dopamine D_2 and μ-opioid receptors to form heterodimers, which alters their ligand-binding and signalling characteristics providing another mechanism for functional interactions between these neurotransmitter systems.

Janero, Vadivel and Makriyannis present an overview of the components of the endocannabinoid system that have been targeted for drug development for CNS and psychiatric disorders, the rationale and expected therapeutic benefit of drugs selective for those sites of action, and the structural characteristics of those compounds that impart selectivity at the targets. This article provides the reader with an idea of the pharmacological tools that are available or under development for future study and management of the CNS and psychiatric disorders reviewed in this issue. Of particular note are neutral CB_1 antagonists that do not inhibit agonist-independent constitutive activity of CB_1 receptors and are therefore hypothesized to have a more acceptable side-effect profile compared to CB_1 inverse agonists such as rimonabant, but with similar therapeutic indications, such as obesity/metabolic syndrome. Indirect agonists that elevate levels of endogenous cannabinoid ligands in a site- and activity-dependent manner by preventing their metabolism, such as fatty acid amide hydrolase and monoacylglycerol lipase inhibitors, or preventing their reuptake by blocking the putative endocannabinoid transporters, also appear to have significant promise as therapeutics.

The remaining articles published in this issue focus on principal CNS and psychiatric conditions for which a significant role for the endogenous cannabinoid system is hypothesized, or for which cannabinoid-based medications may be particularly useful. In the first of these, Beardsley, Thomas and McMahon review the preclinical and clinical data

supporting the use of an inverse CB_1 agonist (rimonabant) to manage nicotine, opioid, stimulant and alcohol dependence. The reinforcing effects of abused drugs have been attributed, at least in part, to mesocorticolimbic dopamine elevations, and CB_1 receptors are found within these neuronal pathways, suggesting that rimonabant or similar drugs could attenuate their reinforcing effects, which might be particularly useful given that individuals are sometimes dependent on multiple drugs. Importantly, the authors begin by cautioning readers about the non-specific effects of rimonabant that can complicate interpretations about their ability to modify drug-seeking and drug-taking behaviour. CB_1 receptor inverse agonist/antagonists can alter locomotor behaviour and disrupt lever-pressing behaviour, which could impact responding maintained by drugs independent of changes in reinforcement. Nonetheless, the results of the studies reviewed in that article indicate that rimonabant and similar drugs can attenuate the abuse-related effects of drugs, although neutral antagonists might represent a more promising pharmacological strategy for future research.

Welch's review encompasses the preclinical and clinical data on the involvement of cannabinoid and opioid systems and their interactions in nociception. The results from those studies provide compelling evidence that a combined opioid and cannabinoid CB_1 agonist therapy might allow for the use of low doses that produce minimal side effects and would not result in the tolerance typically observed following chronic administration of opioids alone. Another promising future direction for this area will be the clinical evaluation of selective CB_2 agonists, which are effective in animal models of acute and chronic pain and should lack the central side effects of CB_1 agonists. CB_2 agonists should also be particularly effective in inflammatory pain because of the actions of those compounds on the CB_2 receptors present in the immune system in addition to the centrally mediated analgesia.

Sewell and colleagues' article on the cannabinoids and psychotic disorders addresses a rapidly advancing field of increasing scientific and public interest. Review of case-, quasi-experimental, and longitudinal studies informs the reader of a longstanding suggestive relationship between cannabis use and risk of psychotic symptoms including development of schizophrenia. This research group's human pharmacological studies show that cannabinoids can induce a full range of transient positive, negative, and cognitive symptoms in healthy individuals that are somewhat similar to those seen in schizophrenia. The article discusses how cannabinoids interact with various neurotransmitter systems and how these pathways may impact psychosis and the associated cognitive dysfunction. The authors offer a discussion of the various factors that inform a working model specifying cannabis exposure as a 'component' cause that interacts with other factors to cause psychosis or psychotic-like disorder. It becomes clear that recent advances in knowledge about cannabinoid receptor function have kindled research designed to identify the factors that underlie individual vulnerability to cannabinoid-related psychosis and to elucidate the biological mechanisms underlying this risk.

Kirkham presents his and others' research on the centrally mediated, CB_1 selective influence of the endogenous cannabinoid system in the control of eating behaviour, particularly as it pertains to the psychological aspects of appetite. As noted above, the principal therapeutic indication for cannabinoids such as THC and nabilone has been as appetite stimulants, and recent laboratory studies, reviewed in his article, have begun to uncover the biological basis for this effect. Kirkham proposes that endogenous cannabinoids impact different aspects of eating behaviour including the initiation of eating, the amount of food consumed and the palatability of food, and that CB_1 antagonists can attenuate these effects. These hyperphagic effects have been localized to certain hypothalamic nuclei, as might be predicted given their known role in regulating food intake, and interestingly, the shell of the nucleus accumbens and elevations in synaptic dopamine in this region also appear to be involved, in agreement with their hypothesized role in the reinforcing effects of stimuli. He also describes how the hyperphagic effects of cannabinoids also seem to involve endogenous opioids, a system closely linked to the cannabinoid system, as reviewed in other articles in this issue. This article concludes with a review of the available clinical data suggesting a dysregulated cannabinoid system in eating disorders, and the possibility of modulating cannabinoid function to correct these conditions.

Orgado, Fernández-Ruiz and Romero focus on the changes in the endocannabinoid system that can be observed in Alzheimer's disease, Parkinson's disease and ischemia. They discuss the therapeutic value of various cannabinoid ligands to treat these neurodegenerative diseases, and changes in the expression of components of the endocannabinoid system in particular brain structures or cell types that could be used as biological markers to predict the likelihood of developing Alzheimer's and Parkinson's. Another particularly interesting aspect of this area is the multiple mechanisms of action through which cannabinoid drugs could be effective at managing these neurodegenerative diseases. For example, direct actions at both CB_1 and CB_2 receptors and activity at non-cannabinoid proteins such as NMDA

receptors or acetylcholinesterases, as well as the antioxidant properties of certain cannabinoids, contribute to their predicted therapeutic efficacy. Additional insights on such biochemical mechanisms of neuroprotection will likely allow cannabinoid compounds to emerge as valuable therapeutic tools in neurodegenerative diseases.

These past 15 years have been exciting scientific times for those interested in the cannabinoids. Advances in our understanding of the neurobiological underpinnings of cannabis reinforcement and the behavioural pharmacology of cannabis use together with the growing clinical data on the validity, prevalence, and consequences of cannabis dependence has provided the empirical base for what would seem incontrovertible evidence for deeming cannabis a substance with significant addictive potential and important public health implications. As important, the rapidly increasing knowledge of the multiple influences of the endogenous cannabinoid system and actions of the exogenous cannabinoids has reaffirmed that the active compounds in cannabis have therapeutic potential for affecting multiple disease states. The research presented in this special issue illustrates the ubiquitous nature of cannabinoids, their complex interactions with other neurobiological systems and how they may be used to treat clinical disorders in the future. Hopefully, the reader will come away with an informed and thoughtful appreciation of cannabis and the cannabinoids and their potential for both abuse and medicine.

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