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Cannabinoids: Friend or Foe?

B Le Foll¹ and RF Tyndale²

¹Translational Addiction Research Laboratory, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health and Departments of Psychiatry, Pharmacology, Family and Community Medicine and Institute of Medical Sciences, University of Toronto, Toronto, Ontario, Canada

²Pharmacogenetics Laboratory, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, and Departments of Pharmacology & Toxicology, and Psychiatry and University of Toronto, Toronto, Ontario, Canada

This issue of *Clinical Pharmacology & Therapeutics* focuses on cannabinoids. Our understanding of these interesting endogenous and synthetic compounds, and their role in the cannabinoid system, has evolved dramatically, in part due to the acquisition of new research tools. Cannabis has been used for centuries by humans for recreational and medicinal purposes, however, there is substantial evidence that cannabis use can expose people to varying complications (e.g. risk of addiction, cognitive impairment...), thus it is important to determine the benefit/risk of cannabis with precision and to implement policy measures based on evidence to maximize the benefits and minimize the harm. Novel cannabinoid drugs are emerging for medicinal use (e.g. dronabinol, nabiximols...) and as illicit drugs (e.g. Spice, K2...) perpetuating the perception that cannabinoid drugs can be a friend or foe. This special issue will cover these various aspects of cannabinoid pharmacology and therapeutics ranging from basic chemistry, pharmacokinetics, pharmacodynamics, and clinical trial results, to policy and education efforts in this area.

The endogenous cannabinoid system consists principally of endocannabinoids (primarily anandamide and 2-arachidonoylglycerol), two cannabinoid receptors (CB1 in the brain and CB2 mostly in the periphery), enzymatic degradation systems (through the fatty acid amide hydrolase enzyme for anandamide and the monoacylglycerol lipase enzyme for 2-arachidonoylglycerol) and cannabinoid transport reuptake system. Cannabinoid receptors are the most extensively expressed of the G-protein coupled receptors in the brain, suggesting wide-spread central effects, as well as their effects in the periphery.

Many drugs interact with the cannabinoid system by intent, or as a side effect. In this issue, Vemuri and Makriyannis provide an overview of the different drugs that are available to modulate this system and Su et al examine the metabolism of these drugs including both classic cannabinoids and the new synthetic cannabinoids such as K2 and spice. Cannabis, defined here as the plant product marijuana, has been used for centuries by humans for recreational and medicinal purposes. It is difficult to precisely estimate its use in the

Conflicts of Interest

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population, as people may not accurately report their use of illicit substances. Despite those reporting limitations, it is clear that cannabis is the most widely used illicit drug with very high prevalence of use. The National Epidemiological Survey of Alcohol and Related Conditions study (n = 43,093) (1) estimated that around 21% of the American population reported lifetime cannabis use relative to 84% for lifetime alcohol use and 6% for lifetime cocaine use. Likewise the National Comorbidity Survey Replication study provided high estimates of prevalence; around 43% lifetime use of cannabis compared to 92% for alcohol and 16% for cocaine (2). Cannabis possesses addictive properties that are thought to be induced by D9-Tetrahydrocannabinol (THC) acting on the CB₁ receptors located in the brain regions responsible for reward in the brain; Panlilio et al. discuss the preclinical and clinical findings in cannabinoid abuse and addiction. Around 8–9% of users will develop cannabis dependence at some point in their life (3), but more will develop abuse at some point of their life (4). Allsop *et al.* discuss the potential of Sativex to alleviate cannabis withdrawal syndrome in their practice article. Cannabis exposure can also alter the brain, impacting cognitive abilities, driving abilities and exposing subjects to risk for mental health problems (e.g. psychosis or mood/anxiety). The extent of the impact of some of these effects is still debated, but two aspects have relatively wide spread agreement, that exposure at a young age is detrimental and that heavy use is associated with increased risk for mental health problems. Due to its importance, and the current lack of clarity, the relationship between cannabis use and mental health problems is still the subject of active investigation, as discussed in the context of youth by Crocker and Tibbo and Porath-Waller et al. At the same time, upcoming large scale initiatives such as the Brain initiative and the ABCD longitudinal cohort from NIH will likely provide greater clarity about the causality of these relationships.

Cannabis possesses some beneficial medicinal properties as discussed by Abrams and Guzman. However, as cannabis cannot be patented, these medical effects have largely not been studied using rigorous clinical trials compared to the trials for pharmaceutical drugs. Cannabis research has also been difficult to perform due, in part, to its status as an illicit and scheduled substance. This is unfortunate as it has left many questions unanswered for political or financial reasons. However, the policy landscape is now changing as multiple states in the USA allow medical use of cannabis and some states are even allowing its recreational use. The impact of those legislation changes in the US are discussed Hall and Weier The long term impact of those policy changes on cannabis use is somewhat unknown, but there is information from experience accumulated over time in different countries. In this issue, in a point/counterpoint debate, Kalant discusses some of the risks associated with a premature change in cannabis policy while Rehm and Fischer propose a legalization approach with strict regulation, following the recent policy document provided by the Centre for Addiction and Mental Health (5).

There are also cannabinoid drugs available for human use and Bolognini and Ross discuss the use of synthetic cannabinoids vs cannabis in their discovery article. The drugs currently on the market are agonists for the cannabinoid system. Nabilone is a synthetic THC analog used for AIDS related anorexia. Nabiximols (THC-cannabidiol mixture) are used for spasticity and pain associated with multiple sclerosis and for analgesia in cancer. This field

is also expanding as other components of cannabis are being explored for their therapeutic potential (i.e. cannabidiol, cannabidivarin, cannabinol...). This issue covers the use of cannabinoid drugs in various medical conditions such as epilepsy (xxx et al.), cancer (Abrams and Guzman, Fowler), Alzheimer's disease (Ahmed et al.) nausea (xx et al and Parker et al), pain and cannabis withdrawal (Allsop et al). There are also compounds targeting other aspects of the endocannabinoid system including the fatty acid amide hydrolase, the monoacylglycerol lipase and CB2 receptors that are being tested for various indications (See Vemuri and Makryiannis article). A CB1 antagonist (Rimonabant) was developed for obesity/metabolic syndrome treatment, however it was removed from the market because of psychiatric side effects (6). As a result, many pharmaceutical companies stopped developing cannabinoid drugs. However, some peripheral CB1 blockers or neutral CB1 ligands may retain therapeutic efficacy without presenting the psychiatric side effects profile and are being actively studied. The use of brain imaging of the cannabinoid system may also enhance our understanding of this system, as outlined by Hiroven, and its potential as a drug target. In any case, it is clear that health care providers are not sufficiently educated in this area and there are tremendous educational challenges and opportunities as presented by Ware and Ziemianski.

Conclusion

These are interesting time for cannabinoid research and clinical application; much more needs to be done to translate the potential of cannabinoid drugs to medicinal use and to identify the conditions that could benefit from this class of drugs. There is as yet untapped potential in the areas of pain and addiction, obesity, metabolic syndrome and epilepsy. The social status of cannabinoid drugs is highly debated and we believe that those discussions should be done without a priori prejudices using an evidence base. As always in medicine a guiding principle should be to maximize the benefits and reduce the overall harm to society. We hope that the contributions within this Clinical Pharmacology and Therapeutics issue on cannabinoids will help readers to make informed decisions about this highly controversial and rapidly changing medical and societal landscape.

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