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Toward a Translationally Relevant Preclinical Model of Cannabis Use

As the political and public landscape surrounding cannabis continues to shift, there is an urgent need to better understand how cannabis use impacts the brain and behavior. Preclinical studies are advantageous in this respect; however, there are drawbacks with current approaches that limit their translational value. Perhaps due to DEA-imposed restrictions, synthetic CB1R agonists have become the drug of choice in rodent models of cannabis exposure. However, the pharmacological properties of these compounds differ tremendously from that of cannabis, with synthetic CB1R agonists and THC recruiting different intracellular signaling pathways (Laprairie *et al*, 2014). Thus, the cellular effects of synthetic CB1R agonists often used in preclinical studies may not be indicative of the effects of THC, let alone cannabis. When THC is used, dosing is often excessively high and exposure regimens are not representative of human use patterns since a bolus THC injection differs dramatically from that of titrated cannabis inhalation. Moreover, cannabis is comprised of more than THC. There are over 120 phytocannabinoids in the cannabis plant, each with its own unique pharmacodynamic profile and the interaction between these phytocannabinoids may influence its effects. For instance, cannabidiol can inhibit THC-dependent intracellular signaling (Laprairie *et al*, 2016) and attenuate THC-induced paranoia and memory deficits in humans (Englund *et al*, 2013). Therefore, THC alone may produce effects that are not indicative of human cannabis consumption. This is supported by human studies indicating that intravenous THC delivery produces a myriad of adverse events that are most often associated with higher doses and faster infusion rates (Carbuto *et al*, 2012). In this regard, it is not surprising that intravenous THC self-administration has been notoriously difficult to demonstrate in rodents. Finally, inhalation is the most common route of cannabis administration and the pharmacokinetics vary markedly depending on whether the drug is injected, inhaled, or injested. Additionally, whereas intraperitoneal THC elicits conditioned avoidance, intrapulmonary THC actually produces a place preference in rats (Manwell *et al*, 2014). Thus, in order to effectively model cannabis use and understand its effects on the brain and behavior, there must be a fundamental shift in the experimental approach. To this end, we are currently developing a novel vapor inhalation model that uses 'e-cigarette' technology to deliver discrete 'puffs' of vaporized cannabis extracts in a response-contingent manner. This approach mimics the most common route of administration in humans while bypassing the aversive nature of forced drug exposure and avoiding the invasiveness of intravenous catheterization. Passive delivery of vaporized cannabis extracts has recently been validated (Nguyen *et al*, 2016), and our preliminary data indicate that cannabis vapor self-administration supports stable, physiologically relevant rates of drug delivery and produces robust conditioned drug-seeking behavior. Establishing this more translationally relevant model will afford empirical evaluation of mainstream beliefs regarding the effects of cannabis (eg, more deleterious effects following early-onset cannabis use or the use of high THC preparations), permit finer interrogation of the effects of cannabis on the brain, and help to identify genetic or environmental factors that may increase vulnerability for developing cannabis-related problems.

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Setting the Legal Age for Access to Cannabis in Canada: Bridging Neuroscience, Policy, and Prevention

The United States and Canada are both engaged in cannabis policy reforms with a number of US states legalizing

or decriminalizing use, possession, cultivation, and sale, and the Federal Government of Canada poised to legalize cannabis in 2018. Perhaps the most contentious debate in Canada has been about setting the legal minimum age for access to the substance, following the recommendation from Canada's Federal Task Force on Cannabis Legalization and Regulation of age 18 (Government of Canada, 2016), their rationale being that setting the age of access lower will divert youth access from illicit, unregulated markets to a safer and tightly regulated supply, while reducing the numbers of youth charged for possession and entering the criminal justice system. This is particularly important as Canadians aged 18–24 are the demographic with the highest prevalence of cannabis use (Spithoff *et al*, 2014). The recommendation for age 18 was also intended to harmonize the age for legal access to cannabis with alcohol and tobacco, which is 18 or 19 years across Canada's provinces and territories.

This policy issue intersects with the interests of *Neuropsychopharmacology* readership because of the ways in which neuroscience expertise is frequently cited by those who favor a higher age of access. For example, policy-makers often make generalizations such as 'evidence from brain scientists shows cannabis is harmful to developing brains'. Not only does this overstate scientific consensus about how cannabis use during adolescence affects brain structure and functioning, it also neglects key confounders in adolescents' substance use, including the effects of alcohol and polysubstance use (Weiss *et al*, 2017). To the contrary, the updated *Lower Risk Cannabis Use Guidelines* recently published in Canada avoid specifying an age, but instead prioritize addressing how early onset and greater frequency of use during adolescence are likely to be associated with harms and future problematic use (Fischer *et al*, 2017). Without casting cannabis as benign or 'safe', as adolescent substance-use researchers we are concerned about the overriding emphasis on 'protecting young brains' being mobilized in the policy discourse, primarily by associations representing the health professions, stakeholders who hold sway and authority with the public but who are not themselves experts in cannabinoid science.

Another important consideration we have identified through our youth-engaged research is that telling youth that something is harmful to the brain requires a nuanced approach to make it an actionable prevention strategy, with concrete steps that can be taken to make the use smarter and safer, and to minimize potential harms (Moffat *et al*, 2013; Jenkins *et al*, 2017). As the move towards decriminalization and legalization policies gains momentum both within and beyond Canada, we call for greater involvement of our neuroscience colleagues in media forums, in policy conversations, and in collaborative prevention research with members of the health and social science research community—to dispel misinformation and to support the development of evidence-based cannabis prevention for adolescents in the context of drug policy reform.

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Medical Cannabis Research: Issues and Priorities

For 25 years, cannabis policy discussion has evolved regarding medical cannabis use. Recent consideration of regulating non-medical cannabis use has begun to move from a prohibitionist model to a more controlled system of access. What does this mean for research?

There exists now, on an international scale, a variety of medical and non-medical cannabis policy options, and this gives rise to what is essentially a global social experiment. Given this unique landscape, it is pertinent to consider what the research community can do to maximize the likelihood that lessons learned can feed back into policy development to ensure that decisions are made based on best available evidence. However, appeals for more research without addressing some fundamental barriers to research are meaningless. Transition to a public health model of cannabis regulation allows for correction of these institutional factors.

One major (and often politically charged) hurdle is access to cannabis materials (Frood, 2009). Restrictions on drug scheduling and supply lead to a paucity of standardized cannabis products, with sufficient quality for regulatory approval for research, and in formulations that are of relevance to lived experience. A variety of cannabinoid levels, as well as other ingredients,