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,

in herbal and extracted forms, with a range of delivery system options, are needed. Access to a range of cannabis strains is needed: due to the complex pharmacology of cannabis and the varying levels of its constituents (including cannabinoids, terpenes, and flavonoids) across different strains, generalization of the effects of one strain to another may be complicated as effects seen with one trial may be unique to the specific chemical properties of that strain. While this may appear to be of most relevance to therapeutic applications, the increasing use of a variety of cannabis products for non-medical use demands that we learn more about these products and their properties to inform consumers and policy makers alike.

Research on cannabis also demands important methodological innovations. Cannabis is a complex botanical substance and defies reduction to single agent pharmacology. Considerations of credible placebos and candidates for active control groups are needed for clinical trials. Studies that estimate and control for the effects of expectations are needed (cannabis perceptions range from risk of severe harm to anticipation of cure) (Chabrol *et al*, 2006; Stark-Adamec *et al*, 1981). Cannabis-specific screening tools, and outcome measures to measure and standardize cannabis use and associated behaviors, are needed to enable comparisons between studies and over time. In the short term, emphasis on the randomized controlled trial as the 'gold standard' may need to be revisited with consideration given to pragmatic observational and 'real world' study designs (Frieden, 2017). In a world of self-report and experience, the importance of case reports, narrative and qualitative research and registries becomes poignant (Bottorff *et al*, 2013; Wade, 2015).

No discussion of research challenges is complete without consideration of funding, but this is also complex. Drug, device, and product development is typically the purview of industry (pharmaceutical as well as commercial), but here barriers pertaining to intellectual property and health claims (as well as access issues mentioned above) lead to limitations in investment in the standard drug development pathway and commercialization. Research on new cannabinoid drugs, devices, and technologies (eg DNA sequencing, extraction, isolation) and data capture (eg registries, 'big data') need to be supported along with investments in laboratory testing methods, standards, and capacity.

A changing global cannabis policy environment is therefore a unique opportunity to address research challenges with novel and robust approaches to deliver meaningful and relevant data.

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Selective Adenylyl Cyclase Type 1 Inhibitors as Potential Opioid Alternatives For Chronic Pain

Chronic pain is a major health concern that costs the US more than $635 billion per year (Gaskin and Richard, 2012). The drugs used for the management of chronic pain include opioid analgesics, neuronal stabilizers such as anticonvulsants, and antidepressants. Opioids are the most widely used analgesics; however, there are significant problems associated with long-term opioid therapy for chronic pain, including diversion and addiction (Volkow and McLellan, 2016). Moreover, the pharmaceutical industry has retreated from studying novel pain therapeutics due to the enormous risk and low probability of success that reflect in part, a lack of predictive animal models and biomarkers (Skolnick and Volkow, 2016). These observations indicate an essential need for academic investigators to identify new agents acting on unique targets in the war on chronic pain. Neurobiological, genetic, and preclinical studies have implicated neuronal adenylyl cyclase type 1 (AC1) as a potential new target (Zhuo, 2012). Adenylyl cyclases (AC) are members of an enzyme family that serve as effectors for numerous G-protein-coupled receptors (for example, opioid receptors) and produce the second messenger cAMP from ATP. The nine membrane-bound isoforms of AC share a similar structure and each is uniquely regulated by G protein subunits, Ca^{2+}, protein kinases, and subcellular localization (Dessauer *et al*, 2017). Membrane-bound ACs are highly expressed in the central nervous system and generally have overlapping expression patterns. Animals lacking one or multiple AC isoforms have been essential tools to inform on the physiological roles of AC signaling in the central nervous system.

AC1 and AC8 are robustly activated by Ca^{2+}/calmodulin (Ca^{2+}/CaM) and