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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Mark A Ware[1]

[1]Associate professor in Anesthesia and Family Medicine, McGill University, Montreal, Quebec, Canada

E-mail: mark.ware@mcgill.ca

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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

have overlapping expression patterns in neuronal tissues, including the hippocampus and several cortical regions (Dessauer *et al*, 2017). Studies with mice lacking either AC1 ($AC1^{-/-}$), AC8 ($AC8^{-/-}$), or both isoforms (double knockout mice, DKO) revealed that AC1 and AC8 are not required for acute pain responses; however, the behavioral responses to inflammatory stimuli (that is, formalin and CFA) were nearly eliminated or abolished in $AC1^{-/-}$ or DKO mice, respectively (Zhuo, 2012). Unfortunately, the DKO mice showed significant memory deficits, making it imperative to find agents that selectively target AC1. Dr Zhuo and colleagues identified the first selective small molecule inhibitor of AC1, NB001, and demonstrated efficacy in multiple chronic pain models in both mice and rats (Wang *et al*, 2011). NB001 has modest (14-fold) selectivity for AC1 *vs* the closely-related AC8 isoform and had activity consistent with AC1 inhibition in neuronal cells and tissues (Wang *et al*, 2011). We recently screened a small (3040 compounds) natural product-like chemical library and identified an additional small molecule that selectively inhibited AC1, ST034307 (Brust *et al*, 2017). ST034307 is a small chromone derivative with unprecedented selectivity for inhibiting AC1 *vs* the other AC isoforms. The precise site of AC1 engagement is unknown; however, ST034307 appears to have a mechanism of action that is unique from other known AC inhibitors. It was shown to dose-dependently reduce opioid dependence in a cellular model and inhibited allodynia in a phenotypic mouse model of inflammatory pain (Brust *et al*, 2017). These data support the development of additional selective AC1 inhibitors for the treatment of chronic pain conditions as potential alternatives to opioids.

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Val J Watts[1]

[1]Department of Medicinal Chemistry and Molecular Pharmacology, College of Pharmacy, Purdue University, West Lafayette, IN, USA
E-mail: wattsv@purdue.edu

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Novel Synthetic Opioids and Overdose Deaths: Tip of the Iceberg?

The United States is experiencing an unprecedented epidemic of opioid overdose deaths. Illicit heroin is an obvious culprit in the crisis and compelling evidence shows synthetic opioids, especially fentanyl, are having a major impact (Frank and Pollack, 2017). Fentanyl is a prescribed medication that is 50–100 times more potent than morphine. Fentanyl in the recreational (ie, non-medical) drug market is not diverted pharmaceuticals but is illicitly manufactured in Asian laboratories and trafficked via the Internet. Unscrupulous drug dealers are mixing fentanyl with heroin and most users are unaware of their fentanyl exposure.

An alarming new development in the opioid crisis is the increasing availability and misuse of novel synthetic opioids (NSOs) (Prekupec *et al*, 2017). NSOs include analogs of fentanyl and structurally distinct non-fentanyl compounds, which act as μ-opioid receptor agonists. NSOs are used as standalone products, heroin adulterants, or constituents of counterfeit pain pills. The role of NSOs in opioid overdose deaths is difficult to determine, because the substances are not detected by standard toxicology screens, which rely on immunoassays sensitive to heroin, its metabolites, and chemically related compounds. Fentanyl can be detected with a separate immunoassay, but fentanyl analogs may cross-react with the antibody; thus, identifying analogs requires sophisticated analytical methods such as mass spectrometry. In a study examining the presence of fentanyl analogs in opioid overdose deaths, 17% of cases that tested positive by fentanyl immunoassay were found to contain fentanyl analogs (eg, acetylfentanyl) when subjected to confirmatory testing with mass spectrometry (Petersen *et al*, 2016). Medical examiners and forensic toxicologists do not routinely check for the presence of NSOs; thus, the contribution of the substances to overdose deaths could be grossly underestimated.

N-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-2-furamide (furanylfentanyl) and 3,4-dichloro-*N*-[(1R,2R)-2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide (U-47700) are prime examples of NSOs linked to analytically confirmed overdose deaths (Mohr *et al*, 2016) (see Figure 1 for structures). Furanylfentanyl is a fentanyl analog with a furan ring on the carboxamide moiety, whereas U-47700 is a non-fentanyl compound developed in the 1970s as a potential analgesic. Little information is available about the pharmacology and toxicology of furanylfentanyl, U-47700, or other NSOs, most of which were discovered decades ago. There is an immediate need for *in vitro* studies examining the potency and efficacy of NSOs in cells expressing μ-, δ-, and κ-opioid receptors. In addition, *in vivo* studies are warranted to investigate analgesic and reinforcing effects of the drugs in animal models, including opioid receptor knock out mice. The degree