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EDITORIAL

Editorial

Deepak Cyril D'Souza[1] · **Helen Valerie Curran**[2]

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Cannabis: with its growing legalization, commercialization, and medical use, its increasing potency, decreasing risk perception, greater availability, falling price and the availability of an array of cannabis derivatives, there is now increased interest in the pharmacology, clinical utility and toxicity of cannabinoids. This Special Issue on Cannabis and Cannabinoids includes a diverse collection of papers spanning original research and reviews, experimental studies and surveys, studies on phyto and synthetic cannabinoids, studies in humans and animals, and studies on beneficial and harmful effects of cannabinoids.

One concern about the increasing availability of cannabis and cannabis derivatives is addiction. Previous reports have suggested that cannabis may be a 'gateway' drug. Addressing this issue, Braymiller et al., surveyed high school students to find that the use of every cannabis product, particularly the use of cannabis concentrates and poly-cannabis products, was associated with greater odds of subsequent use of other illicit drugs. Using data from the Global Drug Survey Craft et al., report that consistent with their higher potency, synthetic cannabinoids are associated with a longer duration of withdrawal and greater risk of problematic use than natural cannabis. Nieto et al., report that delay discounting rates were significantly greater in alcohol users who were are also using cannabis suggesting an additive effect of cannabis. Miguéns et al., reported that in rats, chronic THC administration delays acquisition of schedule-induced drinking, an animal model of compulsivity. They conclude that chronic THC can disrupt learning, and lead to animals being sensitized when they are re-exposed to the drug after long periods without drug exposure. There are no proven pharmacological treatments for cannabis use disorder. Thus, there is an urgent need for research on understanding the biology of cannabis use disorder and testing treatments. De Wit et al., studied the effects of different doses of THC on a monetary incentive delay (MID) task adapted for electroencephalography (EEG; e-MID) in a within-subjects, double blind design. They report that THC dampens responses to both reward and loss feedback, consistent with the 'amotivational' hypothesis. Understanding the basis of why some individuals become addicted is important given that the increased availability and liberalization of cannabis in some areas has been accompanied by an increase in cannabis use disorder. Kroon et al., studied cognitive control in cannabis users when exposed to cannabis use-tempting situation. This may contribute to the development of cannabis use disorders. Cannabis users might differ from controls in the way they process cannabis-related cues such that cannabis cue exposure may interfere with other cognitive processes under cognitively demanding circumstances. Lorenzetti et al., reviewed the evidence of brain function in cannabis users during a cue-reactivity fMRI task with both cannabis and neutral stimuli. They found greater brain activity in cannabis users while exposed to cannabis vs neutral stimuli in the striatum, prefrontal and parietal cortices. Methodological differences across studies notwithstanding, the evidence suggests that there is greater brain activity during cannabis cue-reactivity in regular cannabis users which may be associated with greater cannabis craving. Woodward et al., investigated the role of endocannabinoids in inhalant misuse. They report that toluene-induced deficits in probabilistic discounting do not seem to involve CB1R activity.

Beyond addiction, other area of interest are the acute and chronic effects of cannabis and cannabinoids on cognitive processes and information processing. Lawn et al., conducted a cross-sectional study of cognitive performance in adolescent cannabis users, adolescent controls, adult cannabis users and adult controls. Consistent with previous research, there was an association between chronic cannabis use and poorer verbal episodic memory but not spatial

✉ Deepak Cyril D'Souza
deepak.dsouza@yale.edu

Helen Valerie Curran
v.curran@ucl.ac.uk

[1] Yale University School of Medicine, New Haven, CT, USA

[2] Clinical Psychopharmacology Unit, Clinical Health Psychology, University College London, Gower Street, London WC1E 6BT, UK

working memory or response inhibition. Interestingly, they found no evidence for heightened adolescent vulnerability to cannabis-related cognitive impairment. Hatami et al., report that relative drug-naïve controls, cannabis users have lower brain activation in brain regions relevant to Episodic Future Thinking (EFT) a cognitive function that allows individuals to imagine novel experiences that may happen in the future. Ruey-Ming et al., studied the role of CB1 receptors in timing-related impulsive action by amphetamine in rats and found that activation and blockade of CB1Rs differentially modulate the effects of amphetamine on an operant behavioral test of timing and behavioral inhibition. The findings may have relevance to understanding and developing treatments for maladaptive impulsivity. Verdejo-Garcia et al., studied the relationship between plasma endocannabinoids and brain connectivity in homeostatic and reward circuits across hunger and satiety states. They found that peripheral anandamide levels are sensitive to homeostatic changes and linked to neural communication in reward and salience networks. Mismatch negativity (MMN) is an event related potential that indexes pre-attentive information processing. Greenwood et al., studied the individual and interactive effects of delta-9-tretrahydrocannabinol (THC) and cannabidiol (CBD) on mismatch negativity in infrequent and frequent users of cannabis. There appear to be complex individual and interactive effects of THC and CBD on MMN that vary as a function of prior cannabis exposure. Fisher et al., report that cannabis users show sensory gating deficits. Further, the acute administration of nicotine does not appear to impact sensory gating function in cannabis users. The interactive effects of cannabis and alcohol on automobile driving is another public health concern. Brands et al., studied the interactions of smoked cannabis (12.5% THC) and alcohol (target BrAC 0.08%) on simulated driving performance, subjective drug effects, cardiovascular measures and self-reported perception of driving ability. Combinations of alcohol and cannabis increased weaving and reaction time and tended to produce greater subjective effects compared to placebo and the single drug conditions suggesting a potential additive effect. The fact that participants were unaware of this increased effect has important implications for driving safety. Al'Absi studied the interactive effects of chronic cannabis and nicotine use on adrenocortical, cardiovascular, and psychological response to stress. They found that nicotine but not cannabis use, was associated with blunted cortisol and cardiovascular responses to stress. Furthermore, men exhibited larger cortisol responses to stress than women. While commonly used by pregnant women, the consequences of prenatal combined nicotine and cannabis use are not well understood. Thomas et al., report that combined prenatal exposure to nicotine and THC delayed sensorimotor development, even though neither drug produced impairments on their own. In contrast, prenatal exposure to either nicotine or THC impaired motor coordination, whereas combined exposure exacerbated these effects, particularly among females. Kuc et al., report the results of an online survey about the interactions between psychedelics and cannabis. They report a possible interaction between the cannabis and psychedelics on acute subjective experiences. Lastly, co-exposure of cannabinoids with amphetamines is also of interest. Fischer et al., review the animal and human studies on cannabis/cannabinoid couse or exposure on amphetamine-related outcomes. While human studies suggest cannabis use as an adverse risk factor among non-medical amphetamine users, animal studies suggest otherwise.

Beyond addiction, there is increasing interest in the relationship between cannabis, cannabinoids and psychosis. Cannabis and its principal psychoactive constituent THC have been linked to a number of psychosis outcomes. A smaller but robust literature also suggests that synthetic cannabinoids (SCs) which are full and more potent agonists of CB1 receptors are also linked to psychosis. In a well-controlled experimental study, Theunissen et al., show that a moderate dose of JWH-018 induces pronounced psychotomimetic symptoms in healthy participants with no history of mental illness, which confirms that SCs pose a serious risk for public health, and provides yet another piece of evidence linking exocannabinoids to psychosis. Gunasekera et al., review the existing literature and conclude that THC and CBD modulate reward processing and its neural substrates but whether such effects underlie the psychotomimetic/antipsychotic effects of these cannabinoids remains unclear. Beyond psychosis, there is emerging evidence suggesting that cannabis is associated with mood disorders. Kuhns et al., reviewed the literature to conclude that the existing evidence while limited and mixed, suggests a bidirectional relationship between cannabis use, CUD and the onset of depression. The evidence more consistently points to cannabis use preceding onset of bipolar disorder.

The other side of the coin is that some other cannabinoids like CBD may have antipsychotic effects. Chesney et al., review the therapeutic potential of CBD in early psychosis and discuss how future clinical trials with CBD in early psychosis can address the issues raised by previous studies. Hong et al., studied the therapeutic potential of CBD for methamphetamine-related disorders in an in vitro model. They found that CBD significantly inhibits methamphetamine-induced DA release through modulation of the DRD1-MeCP2-BDNF-TrkB signaling pathway. Cornish et al., studied whether CBD or cannabidiolic acid (CBDA) attenuate methamphetamine-induced sensitization of locomotor hyperactivity in rats, a putative model of psychosis and drug dependence. CBD but not CBDA reduced methamphetamine-induced sensitization providing some preclinical support for the antipsychotic potential of CBD. There is also interest in the therapeutic potential of CBD for

other disorders. Bolsoni et al., studied whether CBD reduces the distress from recalling traumatic events in individuals diagnosed with posttraumatic stress disorder (PTSD) and if its potential effects interfere with the reconsolidation of aversive memories. CBD did not have any effects on anxiety, alertness, and discomfort induced by the recall of the traumatic event. Likewise, Bloomfield et al., conducted a RCT with CBD and found that it did not produce effects on brain responses to emotional faces, cognitive measures of emotional processing, or modulate experimentally-induced anxiety, relative to placebo. These studies add to the mixed results on the therapeutic potential of CBD.

In addition to CBD, there is considerable interest in the therapeutic potential of cannabis, THC and terpenes. This is an important area of research given that the use of cannabis and cannabis derivates for neuropsychiatric indications has far outpaced the evidence to support their therapeutic use. Leung et al., report the results of a survey of cannabis use for medicinal purposes in North America estimating its prevalence and investigating the reasons for use. They found that a substantial proportion of the population reported ever using cannabis for a variety of medicinal reasons. The most common reasons for use included pain, anxiety, sleep, depression, PTSD, headaches, appetite, and nausea/vomiting. Sakal et al., review Project Twenty21 (T21), the UK's first medical cannabis registry, launched in August 2020 which may provide real world data to assess the effectiveness and efficacy of cannabis based medical products. Moore et al., report that oral THC produced long lasting antinociception, hypothermia, hyper- and hypolocomotion, and catalepsy in animals while CBD increased mechanical pain sensitivity and produced sex-dependent effects on body temperature and locomotor activity. Wilkerson et al., studied the effects of terpenes on a mouse model of neuropathic pain. They report that α-terpineol, β-caryophyllene, and γ-terpinene produced dose-related reversal of mechanical allodynia and thermal hyperalgesia. Cannabis and opioids are often used separately and together to manage pain, therefore understanding their interactions is clinically important. Taffe et al. studied whether heroin and THC interact in an additive or independent manner to alter nociception, body temperature and spontaneous locomotor activity when inhaled or injected in rats. The co-administration of heroin and THC by either inhalation or injection produced additive effects on thermal nociception but not on other measures suggesting that the additive effects of THC with an opioid may not generalize to other all their potential behavioral or physiological effects. Cannabis and THC have been of interest in the treatment of Tourette's disorder.

Lastly, there is growing recognition of sex- and gender-based differences in the response to cannabis and cannabinoids, cannabis patterns of use, health consequences and underlying biological mechanisms. Bassir-Nia et al., investigated the sex/gender differences in the acute subjective, psychotomimetic, cognitive and physiological effects of intravenous THC. They report that there are significant sex/gender differences in the acute subjective effects of THC in healthy individuals, with women reporting greater effects at lower dose of THC. Wardle studied the effects of THC on a task assessing motivation in healthy young women and found that cannabis acutely reduces motivation to earn non-drug rewards. Henderson-Redmond studied sex-specific mechanisms of cannabinoid tolerance to inform their therapeutic potential and dependence liability. They report that disruption of the GRK/βarrestin2 pathway of desensitization alters tolerance to THC but not CP55,940 in male but not female mice suggesting gender differences in the development of cannabinoid tolerance.

We hope this editorial has given a flavor of the many papers on Cannabis and Cannabinoids that this Special Issue contain.