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Editorial

Drugs of abuse – its not all bad news

The media and politicians continually tell us that drugs (of abuse) are bad. This sentiment has been immortalized by Mr. Mackey, the fictional high school teacher from the cartoon *South Park*, who was often heard exhorting this view to his pupils. We agree that drug abuse is a terrible condition adversely affecting not only the users, but also those around them. However, to say that 'drugs are bad' is too simplistic. One reason for this is that some drugs of abuse are, or may be, useful therapeutics. The critical parameters are not the drugs themselves, but the dose taken, the route of administration and also the patient's illness. When drugs are taken at inappropriate doses via inappropriate routes by people who don't need to take them then bad things will probably happen.

The august readership of this journal will be aware that some traditional drugs of abuse can be used therapeutically. For example, amphetamine will be known by all to be useful in treating attention deficit hyperactivity disorder (ADHD), many readers will know that amphetamine can be used in narcolepsy and some readers will know that amphetamine has been tested in post-stroke recovery (see Walker-Batson et al., this issue). What about the related psychostimulant methamphetamine? This drug has long been a scourge in the USA, but only now, in part through the television drama *Breaking Bad*, is it becoming better-known elsewhere. Could this devastating drug, known to cause facial lesions, hair and teeth loss, neurotoxicity and cognitive dysfunction (London et al., in press), be useful clinically? Rau and colleagues in this issue, describe its use in traumatic brain injury.

This is currently a good time to consider the potential clinical use of some drugs of abuse. There has been an explosion of research into the physiological role of cannabinoids. After the discovery of tetrahydrocannabinol (THC), two cannabinoid receptors (CB1 and CB2) have been described, their endogenous ligands (AEA and 2-AG) and specific enzymatic machinery for their synthesis and degradation have also been uncovered (Pertwee, 2005). This research has revealed the involvement of associated cannabinoid signaling in numerous important functions in the body. In particular the CB1 receptor is abundantly expressed in the CNS, and is involved in neuroprotection while the CB2 receptor, predominantly expressed in the immune system, has critical roles in inflammation, neurogenesis and immune regulation (Molina-Holgado and Molina-Holgado, 2010). In addition to this explosion in the wealth of knowledge on cannabinoid receptor function there has been another explosion over the last few years; the exponential increase in legal highs. Legal highs, or novel psychoactive substances (NPS) started appearing about 10 years ago. Many of the first NPS were synthetic cannabinoids, with more potent effects at CB1 receptors than THC. Then about 5 years ago there was a huge increase in synthetic cathinones, mephedrone being the prime example (Zawilska, 2014). In 2013 there were an estimated 348 new drugs of abuse (UNODC, 2014) being sold, often legally, over the Internet. There are now likely to be nearer 1000 NPS. These NPS cover many categories including cannabinoids, stimulants, empathogens/entactogens, hallucinogens etc. There has also been another recent development; the gathering pace of clinical trials using drugs of abuse as treatments. There has been a huge amount of recent interest in the use of ketamine in depression (see Rasmussen in the current issue) and in the UK there has been much debate about using psilocybin for treating post traumatic stress disorder (PTSD; Chinthapalli, 2013). Thus the stimuli for this special issue have been these recent phenomena: the fruition of cannabinoid receptor function research, the upsurge in NPS numbers and the recent interest in using ketamine and psilocybin for treating psychiatric disorders.

The first article in the special issue is a general review of the therapeutic potential of cannabis-related drugs. In this review Alexander focuses on the translational aspects of cannabinoid-related drugs, particularly in terms of multiple sclerosis and epilepsy. In the next article Henry and colleagues describe the endocannabinoid system, immune function and psychiatric disorders. Specifically, this review examines the evidence supporting a modulatory effect of endocannabinoids on Toll-like receptors (TLR) mediated immune responses both peripherally and centrally, and the implications for psychiatric disorders such as depression and schizophrenia. Jennings and colleagues discuss the role of the cannabinoid system in stress on inflammatory pain-related behavior. In addition, they analyze the influence of genetic background on this stress-induced hyperalgesia, implicating the endocannabinoid system in the spinal cord and amygdala in these processes. We then have an article by Arevelo-Martin and colleagues focusing on the use of cannabinoids to treat spinal cord injury (SCI). The Authors discuss the current knowledge on the use of cannabinoids on SCI and suggest some future directions that may help to understand the role of the activation of the endocannabinoid system in SCI and how to take advantage of this system to regain function after spinal cord damage. Rounding off this section on the use of cannabinoids in CNS disorders we have an article by Gómez-Gálvez and colleagues focusing on the CB2 receptor as a target for Parkinson's disease. The Authors have provided the first evidence of the up-regulation of CB2 receptors in glial elements in postmortem tissues of Parkinson's patients, which has been confirmed and quantified in an inflammatory model of this disease. More importantly, they have provided evidence on the therapeutic effects of CB2 receptor activation in microglial cells.

Staying with the Parkinson's theme the next article by Mursaleen and Stamford examines not only the utility of drugs of abuse in Parkinson's, but also deleterious effects of drugs of abuse in this condition. They highlight the uniqueness of Parkinson's patients in that the disease (and treatments) directly affect the brain reward system.

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Encouraging results with addictive drugs can be found for nicotine, caffeine, cannabinoids and MDMA, with many of the positive effects on reducing L-DOPA induced dyskinesia. This paper also includes some interesting survey data of Parkinson's patients and their mostly positive views on the use of drugs of abuse as treatments. We then come to an article by Rasmussen where the use of ketamine in depression and anxiety is reviewed. The author first focuses on major depressive disorder and bipolar disorder, but then goes on to discuss the use of ketamine in other conditions such as eating disorders, obsessive compulsive disorder and PTSD. Safety issues with ketamine are then described before the author concludes with the various mechanism of action of ketamine and some future directions. These future studies include improved clinical study designs to ensure 'blinded' patients and the parametric analysis needed (e.g. dose, infusion rate, frequency of treatment) to enhance ketamine-evoked response rates in mood disorders.

Moving back to neurological problems the next article by Walker-Batson and colleagues examines the use of amphetamine in stroke patients and focuses on post-stroke aphasia. They first briefly review the pre-clinical literature supporting the use of amphetamine in stroke then describe the current pharmacotherapies for aphasia. We are then presented with some pilot data on the use of amphetamine and donepezil, paired with behavioral treatment, in aphasia after stroke. Finally we look to the future use of amphetamine in post-stroke deficits and find that time is important; a time of 30-60 min between amphetamine dose and behavioral treatment appears optimal and this intervention should be within the first 90 days of a stroke. In addition, the number of treatment hours (intensity of language therapy) is critical. Carrying on the theme of using psychostimulants, Rau and colleagues review the literature on using low dose methamphetamine in models of stroke and traumatic brain injury. While highlighting that repetitive high doses of methamphetamine are neurotoxic, we are also told that low doses can reduce apoptosis, increase neurogenesis and improve neuro-motor and cognitive impairment after acute brain injury. The final stimulant-like drug reviewed is MDMA and Danforth and colleagues review its use on social anxiety. We are told that 1133 subjects have taken MDMA for research purposes with no serious adverse events (SAEs). The behavioural effects of MDMA in animals and its effects in humans are reviewed. Finally we are presented with a suggested protocol for phase 1 and 2 clinical studies using MDMA with psychotherapy for social anxiety disorder, especially in autistic patients. Moving to the use of hallucinogens in clinical conditions, Bogenschutz and Johnson review the literature on the use of hallucinogens in the treatment of addictions. They focus on the use of LSD in alcoholism where meta-analysis has shown beneficial effects of LSD. More recent trials with psilocybin-assisted treatment in nicotine and alcohol dependence are also examined. Finally mechanisms of action beyond the 5-HT_{2A} receptor are discussed and these include neurotrophic and psychological factors and the relative safety of hallucinogens is discussed.

Switching briefly from CNS disorders, Velasco and colleagues review the use of cannabinoids as anticancer treatments, not just from the point of view of pain relief but as a genuine anticancer drug. This review summarizes the observations that have already helped to set the basis for the developments of the first clinical studies to investigate the potential clinical benefit of using cannabinoids in anticancer therapies. Moreover they discuss the possible future avenues of research in this area. Finally Davidson and Schifano review the large number of legal highs (novel psychoactive substances; NPS) that have recently come to light. Many are very similar to current drugs of abuse and some clinically used drugs. Although these NPS have never been tested in clinical conditions one would assume that at least some of the approximately 1000 NPS may be clinically useful. The major categories of NPS include synthetic cannabinoids, synthetic cathinones, new MDMA-like drugs, novel stimulants, synthetic opioids, novel tryptamine derivatives, GABAergic drugs and dissociatives.

Taken together we hope that the reader will gain a new appreciation of drugs of abuse and consider them, along with their more well-respected relatives in the current pharmacopoeia, for both pre-clinical or clinical testing in suitable conditions.

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