

Michael Cousins Lecture:
Cannabinoid analgesia: Future friend or dead end?

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Extracts of *Cannabis sativa* have been used medicinally, and also misused, in many cultures for millennia. However, our understanding of the scientific basis of cannabinoid pharmacology is altogether more recent: The most significant advance came only 20 years ago when the first cannabinoid receptors were identified. To date, the existence of two G protein coupled cannabinoid receptors has been documented – CB1 (predominantly expressed by central and peripheral nervous system neurones) and CB2 (expressed by immune cells, including glia). Agonists at these receptors (cannabinoids) possess a wide range of pharmacological properties, including effects on immunomodulation, appetite, memory, body temperature regulation and pain. Endogenous ligands (endocannabinoids) at these receptors have been identified and the enzymatic machinery involved in their synthesis and degradation characterised. The presence of receptors and endogenous ligands thus confirms the existence of an endogenous cannabinoid system, the wide-ranging physiological importance of which is now being revealed. It is evident that CB1 is one of the most abundant and widespread CNS receptors. However, in the CNS endocannabinoids do not appear to act as primary neurotransmitters in their own right, but rather modulate activity of primary neurotransmitters at a range of different classes of synapses. We now have a number of synthetic potent selective cannabinoid agonists and antagonists, as well as genetically modified mice, with which we are able to dissect the pharmacology of cannabinoids. One of the therapeutic areas in which attempts are being made to exploit the pharmacological properties of cannabinoids is analgesia. The laboratory evidence base supporting such a strategy is strong: A framework of cannabinoid analgesia has been identified at brain, spinal cord and peripheral levels and both CB1 and CB2 are implicated. This lecture will primarily focus on the spinal cord and periphery, as this is the most plausible strategy for developing therapeutic cannabinoids with an acceptable therapeutic index, but it is emphasised that these sites cannot be seen in isolation – for instance brain stem CB1 receptors are involved in the descending control of spinal nociceptive traffic. Numerous rodent experiments confirm the analgesic effects of natural, endogenous and synthetic cannabinoids in a wide range of inflammatory and neuropathic

pain models. This lecture will focus on the potential of cannabinoids as analgesics in neuropathic pain, where efficacy has been demonstrated in animal models of traumatic and other painful neuropathies including those associated with herpes zoster, diabetes, HIV disease and chemotherapy. A number of high quality randomised controlled trials (RCTs) which assessed the efficacy of cannabinoids in a range of neuropathic pain conditions have now been published. During the lecture a systematic review of these trials will be presented. Five RCTs compared cannabinoids to placebo in patients with multiple sclerosis. In the majority of these the cannabinoid afforded superior pain relief compared to placebo, with two RCTs reporting responder rates (NNT 50% pain relief) of between 3.5 and 3.7, which compares favourably with other treatments for central pain. Similarly in HIV-associated painful peripheral neuropathy two RCTs compared smoked cannabis to smoked placebo and demonstrated clear efficacy of cannabis, with reported responder rates (NNT 30% pain relief) of 3.5 and 3.6. Conversely, four RCTs conducted in subjects with other peripheral neuropathic pain conditions reported no appreciable analgesic efficacy of cannabinoids. However, the therapeutic potential of cannabinoids can only be discussed in the context of the evidence relating to potential adverse effects, especially the risks of mental illness associated with cannabis misuse. Cannabis misuse is associated with the development of acute psychosis and such adverse events have been occasionally reported in clinical trials. Perhaps of greater concern are the strong epidemiological data associating

cannabis misuse and a long term risk of psychosis and schizophrenia. Cannabis misusers, especially adolescents, are two to three times more likely to subsequently develop serious psychotic illness, including schizophrenia, than non users. This risk is dose dependant. Risk factors for cannabis-associated psychosis which have been identified to date include baseline risk factors for psychosis and polymorphisms in the catechol-O-methyltransferase gene. RCTs investigating cannabinoids as analgesics published to date have not been sufficiently powered, nor been of sufficient duration, to ascertain whether this risk is an obstacle to the long-term therapeutic use of cannabinoids in chronic pain. Until such data are available, it would seem appropriate to adopt a precautionary approach, including adequately informed consent, for patients in whom cannabinoid therapy might be considered. It would seem prudent to exclude, both from clinical therapy and RCTs, any patients with

existing risk factors, including genetic, for psychosis or schizophrenia. Furthermore, arrangements for long term follow up of all subjects who have been treated with cannabinoids should be made in order to ascertain whether adverse events are revealed years after the intervention. Finally, the availability of preparations of centrally acting potent CB1 agonists will have misuse potential, which has implications for drug enforcement authorities as well as regulators.

Encouragingly, there are several strategies for the development of cannabinoids with an acceptable therapeutic index, which do not include systemic administration of CNS penetrant CB1 agonists. These avenues essentially seek to circumvent brain CB1, the presumptive site of action of most cannabinoid related adverse effects and misuse potential, whilst retaining analgesia. These include: CB2 agonists, endocannabinoid degrading enzyme inhibitors, non psychoactive cannabinoid like molecules such as palmitoylethanolamide analogues and targeting of CB1 in the peripheral nervous system.

Conflicts of interest: The author has advised several pharmaceutical companies engaged in the development of cannabinoids and other agents for use in neuropathic pain. He is an inventor on a palmitoylethanolamide related patent (WO 2005/079771).

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