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Editorials

Cannabinoids for pain and nausea

Some evidence but is there any need?

Papers pp 13, 16

This is an exciting time for cannabinoid research. The discovery of cannabinoid CB_1 receptors (expressed by central and peripheral neurones)[1] and CB_2 receptors (expressed mainly by immune cells)[2] and endogenous agonists[3] for these receptors has renewed the scientific community's interest. Independently of these developments society at large has continued an aggressive debate about the therapeutic use of cannabinoids, including demands for their more liberal availability. [4] [5] Cannabinoids have been suggested to have therapeutic value as analgesics and in various conditions, including migraine headaches, nausea and vomiting, wasting syndrome and appetite stimulation in HIV-infected patients, muscle spasticity due to multiple sclerosis or spinal cord injury, movement disorders such as Parkinson's disease, epilepsy, and glaucoma.[6] When new therapeutic indications are suggested, two major factors should be taken into account: what are the adverse effects of the treatment and how does its effectiveness compare with that of existing alternatives?

In this week's issue two high quality systematic reviews shed light on the therapeutic potential of cannabinoids in the management of pain (p 13)[7] and the nausea and vomiting induced by chemotherapy (p 16).[8] Campbell et al sought and examined all randomised controlled trials that compared the efficacy and safety of cannabinoids with those of conventional anaglesics.[7] The nine trials included 222 patients, of whom 128 had cancer (five studies), two chronic non-malignant pain (two studies, one patient per trial), and the rest postoperative pain. Cannabinoids were no more effective than codeine in controlling acute and chronic pain and they had undesirable effects in depressing the central nervous system. These studies are mostly from the 1970s. Since then we have learnt to use non-steroidal anti-inflammatory analgesics alone and in combination with opioids in both cancer related and postoperative pain. There is thus no need for cannabinoids for these indications.

In chronic non-cancer pain, however, we do need more effective analgesics than those currently available. Cannabinoids have anti-inflammatory effects, but it is difficult to believe that they would beat the anti-inflammatory drugs available today. Neuropathic pains, particularly those with spastic components, are one area where cannabinoids may have potential.

In the second systematic review Tramèr et al analysed the effectiveness of cannabinoids in chemotherapy induced nausea and vomiting among 1366 patients in 30 randomised controlled trials.[8] Across all trials cannabinoids showed some antiemetic efficacy compared with active comparators (prochlorperazine, metoclopramide, chlorpromazine,

tiethylperazine, haloperidol, domperidone, and alizapride) and placebo. Cannabinoids were antiemetic when the control patients suggested a medium emetogenic setting. In highly emetogenic settings, however, they did not show any efficacy. Most of these studies were performed in the 1980s. The serotonin receptor antagonists were introduced in the 1990s and they have changed the practice of antiemesis in chemotherapy induced nausea and vomiting. The American Society of Clinical Oncology guidelines recommend no routine antiemetic before chemotherapy with low emetic risk, a corticosteroid for patients being treated with agents of intermediate emetic risk, and the combination of a serotonin receptor antagonist and a corticosteroid before chemotherapy with high emetic risk.[9] Serotonin receptor antagonists and corticosteroids have shown the highest therapeutic index whereas cannabinoids share a lower

therapeutic index with dopamine antagonists, butyrophenones, and phenothiazines that is, those agents against which they were compared in the systematic review.

As the currently available cannabinoids clearly loose the battle in both efficacy and safety with the competitors of today one can still ask whether a lower price would be a reason for their use. Yet if a healthcare system can afford high technology surgery and expensive chemotherapy it certainly can afford safe and effective pain relief and antiemetic therapy.

Future research may provide us with better cannabinoid compounds with potential new therapeutic applications.[10] However, the current information is that the adverse effects of cannabinoids outweigh their effectiveness. [11] [12] About a year ago in the *BMJ* Strang et al asked for a more informed debate about the therapuetic use of cannabinoids,[13] and this week's two systematic reviews contribute to this debate. On current evidence cannabinoids can be recommended only for use in controlled clinical trials in carefully selected conditions for which there is no effective treatment. The launch of the first large multicentre trial on cannabis in the control of pain and tremors in multiple sclerosis[14] is the first step on this way.

Eija Kalso, *associate professor*.

Pain Clinic, Department of Anaesthesia and Intensive Care Medicine, Helsinki University Hospital, PO Box 340, FIN-00029, Finland (eija.kalso@hus.fi)

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