As Beaulieu and Rice recently stated ([i]),

"The cannabinoid system is a major target in the treatment of pain".

In 1997, reviewing a series of trials in 1997, the U.S. Society for Neuroscience concluded that "substances similar to or derived from marijuana ... could benefit the more than 97 million Americans who experience some form of pain each year." ([ii])

In the same year, National Institutes of Health in the USA published a

"Workshop on the Medical Utility of Marijuana: Report to the Director,"

in Washington, D.C. ([iii]) in which it was noted,

"Neuropathic pain represents a treatment problem for which currently available analgesics are, at best, marginally effective. Since delta-9-THC is not acting by the same mechanism as either opioids or NSAIDS [nonsteroidal anti-inflammatory drugs], it may be useful in this inadequately treated type of pain."

Authors of the 1999 Institute of Medicine (IOM) report,

"Marijuana as Medicine: Assessing the Science Base," ([iv])

described 3 types of pain that may be ameliorated by cannabinoids: somatic pain, visceral pain, and neuropathic pain.

The researchers concluded that cannabinoids reduce painful stimuli to an extent comparable to opiates in potency and efficacy.

"In conclusion, the available evidence from animal and human studies indicate that cannabinoids can have a substantial analgesic effect."

A 1998 University of California rat study ([v]) explained that THC, one of the active constituents of cannabis, affects circuitry at the base of the brain, modulating pain signals in a similar way to opiates.

The authors concluded,

"These results show that analgesia produced by cannabinoids and opioids involves similar brain stem circuitry and that cannabinoids are indeed centrally acting analgesics with a new mechanism of action."

Another component, anandamide, had also been found to produce effects in the pain-processing areas of the brain and spinal cord that appear to ease the sensation of pain.

Rats in an Italian study ([vi]) treated with a synthetic agent that blocked the action of anandamide demonstrated a longer and greater reaction to pain. Also, anandamide in conjunction with the endogenous compound PEA (Palmitylethanolamide) has been observed to reduced pain 100-fold. ([vii])

Cannabis has been found to be effective not only in pain associated with various conditions, including multiple sclerosis and spinal cord injury, but also other symptoms associated with these conditions, such as muscle spasms and spasticity.

A 1986 study([viii]) of 5patients with traumatic paraplegia found the administration of delta-9-tetrahydrocannabinol (THC) "clinically beneficial" in two patients, controlling their previously intractable spasticity.

In 1990, Swiss neurologists reported([ix]) on the treatment of a paraplegic patient suffering from spasticity and painful spasms in his leg following spinal cord injury.

A double-blind study was performed comparing 5 mg of THC, 50 mg of codeine, and a placebo. Delta-9-THC and codeine both had an analgesic effect in comparison with placebo, but only delta-9-THC showed a significant beneficial effect on spasticity.

The IOM report (see above) noted:

"There are numerous anecdotal reports that marijuana can relieve the spasticity associated with ... spinal cord injury, and animal studies have shown that cannabinoids affect motor areas in the brain - areas that might influence spasticity."

In 1998, a review article by Growing et al. ([x]) noted that the distribution of cannabinoid receptors in the brain suggests that they may play a role in movement control.

The authors hypothesized that cannabinoids might modify the autoimmune cause of Multiple Sclerosis, and thus may both relieve symptoms of MS and retard its progression.

A survey in 1997 ([xi]) in the UK and US found that 30-97% of people with MS who smoked cannabis experienced relief in symptoms such as spasticity, chronic pain of extremities, acute paroxysmal phenomenon, tremor, emotional dysfunction, anorexia/weight loss, fatigue states, double vision, sexual dysfunction, bowel and bladder dysfunctions, vision dimness, dysfunctions of walking and balance, and memory loss (in descending order).

Various studies are currently underway in the UK, mostly involving patients with MS, although a

few chronic pain patients are now being included.

GW Pharmaceuticals plc is developing non-smoked cannabis -based preparations and have been conducting clinical trials at Phase III level. In their November 5th. 2002 Press Release, the company stated that each of 4 randomised, double-blind, placebo-controlled trials using whole plant medicinal cannabis extract in patients with Multiple Sclerosis and neuropathic pain has reported positive data. There had been significant reductions in neuropathic pain, spasticity and sleep disturbance.

The GW product, Sativex?, is a whole plant medicinal cannabis extract containing Tetranabinex™ extract (tetrahydrocannabinol, THC) and Nabidiolex™ extract (cannabidiol, CBD) as its principal components.

At the end of March 2003, GW submitted its regulatory dossier for Sativex to the UK regulatory authority, the recently renamed Medicines and Healthcare Products Regulatory Agency (MHRA), for an authorisation to market the product in two therapeutic indications:

- relief of symptoms in patients with Multiple Sclerosis

- relief of Neuropathic Pain (nerve-damage pain).

Subject to UK regulatory approval, GW aims to make Sativex available on prescription in the UK by the end of 2003.

GW is using three drug delivery technologies in the development of its products, specifically:

- Sub-lingual (under the tongue) spray - This technology is being utilised for the Group's lead product which is now in Phase III trials. The spray pump is already approved by the Medicines Control Agency (MCA) in the UK and similar agencies elsewhere for use with specific medicines.

- Sub-lingual tablet - These tablets, which are intended to dissolve under the tongue rather than be swallowed by patients, have been developed in-house by GW and have been used in one of the Group's Phase II trials.

- Inhaler - GW is developing an innovative inhalation device for the delivery of its medicines, aiming to enable patients to benefit from the rapid relief associated with inhaled delivery but without exposure to the carcinogens produced when cannabis is smoked.

Watch out for an update on this article in the next few months

---

[i] Beaulieu P, Rice AS. *Ann Fr Anesth Reanim* 2002 Jun; 21(6): 493-508[The pharmacology of cannabinoid derivatives: are there applications to treatment of pain?]

[ii] Society for Neuroscience Press Conference, October 26, 1997. http://www.calyx.com/%7Eolsen/MEDICAL/POT/analgesia.html

[iii] http://www.medmjscience.org/Pages/reports/nihpt3.html

[iv] http://www.druglibrary.org/schaffer/Library/studies/iom/IOMReport.htm

[v] Meng I et al. *Nature* 1998;395: 381-383 An analgesic circuit activated by cannabinoids.

[vi] Calignano A et al., *Nature* 1998;394 : 277-281. Control of pain by endogenous cannabinoids

[vii] ACM Bulletin, July 26, 1998. Science: Cannabinoid/anandamide-receptor systems involved in peripheral control of pain

[viii] Hanigan W et al., *American Society for Clinical Pharmacology and Therapeutics* 1986: 198 The Effect of Delta-9-THC on Human Spasticity

[ix] Maurer M *European Archives of Psychiatry and Clinical Neuroscience* 1990; 240: 1-4 Delta-9-Tetrahydrocannabinol Shows Antispastic and Analgesic Effects in a Single Case Double blind Trial

[x] Growing L et al., Drug and Alcohol Review 1998; 17: 445-452. Therapeutic use of cannabis: clarifying the debate
[xi] Consroe P et al. European Neurology 1997; 38: 44-48. The Perceived Effects of Smoked Cannabis on Patients with Multiple Sclerosis