Astin et al. ([1]) noted:

"Drawing principally from systematic reviews and meta-analyses, there is considerable evidence of efficacy for several mind-body therapies in the treatment of coronary artery disease (e.g., cardiac rehabilitation), headaches, insomnia, incontinence, chronic low back pain, disease and treatment-related symptoms of cancer, and improving postsurgical outcomes."

Zelter et al. ([2]) looked at a complementary and alternative medicine (CAM) package combining acupuncture and hypnosis for chronic paediatric pain. They reported:

"Both parents and children reported significant improvements in children's pain and interference following treatment."

Nielson and Weir ([3]) looked at multimodal biopsychosocial treatments that include cognitive-behavioural components, studying three systematic reviews of the literature and 21 randomized controlled trials.

They found that these treatments "are effective for chronic low back pain and other musculoskeletal pain for up to 12 months (level 2)," and concluded:

"Future studies of cognitive-behavioral treatments should be condition specific, rather than include patients with different pain conditions. to provide the evidence for this review."

Hypnosis:

In 1995, a panel convened by the United States National Institute of Health (NIH) found that behavioural treatment and relaxation therapies were helpful in chronic pain and insomnia.

The group stated that there was evidence that hypnosis is effective in alleviating chronic pain associated with various cancers. They also found strong evidence that relaxation approaches are effective in treating a variety of chronic pain conditions such as low back pain, arthritis, and headache.

"The role of hypnosis in treating chronic pain patients is uncertain. Some studies have shown that 15 to 20 percent of hypnotizable patients with moderate to severe pain can achieve total relief with hypnosis.

Other studies report that hypnosis reduces anxiety and depression. By lowering the burden of emotional suffering, pain may become more bearable." ([4])

The American Cancer Society, in their Guide to Complementary and Alternative Methods in 2000, noted:

"According to a report from the NIH, there is strong evidence that hypnosis can relieve some pain associated with cancer."

Cognitive techniques: these do not combat the pain directly, but are helpful in providing a range of coping strategies. Implementation of these techniques takes a while to become effective. CBT is used to target the range and level of activity, independence, use of healthcare and possibly (indirectly) pain itself.

Behavioural methods may include goal setting and pacing, use of cues and consequences,

relaxation applied to rest and activity, and reduction of medication.

Cognitive and emotional change may be effected via education, challenging thought patterns and beliefs and working on attention control (the latter not just by distraction, there are other more sophisticated techniques). These address issues such as pain distress, depression, fears about what the pain means, frustration and control.

The 1995 NIH panel found CBT to be: "moderately effective in altering pain intensity."

Common misconceptions about CBT:

Behaviour change is NOT:

- Telling the family to ignore the patient as if social support is disabling
- Assuming secondary gain

Cognitive change is NOT:

- Recommending coping strategies
- Correcting irrational thinking: the patient is neither stupid nor illogical if one looks at the premise from which he/she is working
- Simple distraction
- Dealing with beliefs without mobilising emotions (simply talking dispassionately won't help)
- Not implying that thinking the right thought can close the pain gate!

Relaxation/meditation: these are all helpful adjuncts to drug treatment, but few patients can manage on these pain management techniques solely.

Relaxation techniques involve the practice of two basic components: a repetitive focus on a word, sound, prayer, phrase, or muscular activity, and allowing oneself to neither fight nor focus on intruding thoughts. Done properly, relaxation therapy can lower breathing rate, heart rate, and blood pressure.

The 1995 NIH report found that relaxation is a useful adjunct in patients with chronic pain or insomnia.

Experimental treatments

Memantine hydrochloride, an NMDA antagonist, was launched in Germany by Merz in 1989 for the treatment of dementia, and is now under development for use in treating neuropathic pain.

The manufacturers are in the process of applying for license for this use both in the UK and the US.

Amantadine generally used to treat symptoms of Parkinson's disease, it has also been reported ([5]) to be effective in managing neuropathic pain (in three patients, acute administration resulted in complete resolution of symptoms, which was attributed to termination of the "wind-up" mechanism).

Pud et al([6]) looked at intravenous administration of amantadine for relief of cancer-related neuropathic pain and found that there are indications that suggest it may be of benefit, but they recommend further trials. It is, in fact, also an antiviral agent; it is known to be helpful in relieving muscle stiffness and tremor in neurological conditions such as Parkinson's.

It is also well established to treat fatigue and reduced exercise tolerance in Multiple Sclerosis.

Ngf The completed trial of nerve growth factor (ACTG 291) has been reported in Neurology 2000; 54:1080-1088. NGF did provide significant relief to pain in patients with neuropathy based on Gracely Pain Scale scores. However, during the 18 week trial, quantitative sensory testing did not document return of function in the peripheral nerves.

Intrathecal adenosine: has been found to reduce areas of mechanical hypersensitivity and provides analgesia in patients with neuropathic pain. Experimental studies ([7]) show that the higher doses cause side effects which can be avoided by a lower dose that is just as effective.

Combined morphine and magnesium: Magnesium is a natural NMDA antagonist occurring in the spinal cord.

A recent animal study ([8]) has found that combining morphine (0.1 mg/kg) and magnesium sulfate (125 mg/kg) in rats with mononeuropathy, "exerted a significant anti-allodynic effect".

A clinical study of patients receiving spinal analgesia for labour, the addition of magnesium sulfate to the opioid fentanyl prolonged analgesia with no demonstrated increase of side effects.([9])

Magnesium hydroxide (300-600mg a day) with malic acid (1200-1400mg a day) gave significant pain relief to fibromyalgia patients within 48 hours in clinical trials.

Calcium channel blockers: nifedipine, verapamil etc. have been investigated in animal studies and found to potentiate the effects of opiates. ([10]) in 1995, Romanian article ([11]) discussed the clinical effects of calcium channel blockers in enhancing the analgesic effects of aspirin and paracetamol.

Cannabinoids: As Beaulieu and Rice recently stated ([12]),

"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." ([13])

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. ([14]) 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," ([15]) 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 ([16]) 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 ([17]) 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. ([18])

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 ([19]) of 5 patients 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 ([20]) 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. ([21]) 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 ([22]) 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.

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