A Handy List for Doctors and Patients

Which Conditions Might Cannabis Help Treat?

The medical marijuana initiative passed by California voters in 1996 authorizes physicians to approve the use of cannabis "in the treatment of cancer, anorexia, AIDS, chronic pain, spasticity, glaucoma, arthritis, migraine, or any other illness for which marijuana provides relief." The voters' understanding that cannabis is a remarkably versatile medicine has been confirmed in recent years by researchers who have identified the following conditions as likely targets for cannabis-based medicine.

AIDS Wasting Syndrome

AIDS (Acquired Immune Deficiency Syndrome) wasting syndrome was a very frequent complication of HIV infection prior to the advent of protease-inhibitor drugs (1), and has been associated with major weight loss and cachexia, serving to further debilitate its victims, already weakened by immune system failure and opportunistic infections. Cannabis has been a frequently employed alternative medicine for the condition, particularly in the USA (2), because of its reported benefits on appetite and amelioration of other AIDS symptoms. In the rest of the world, where such medications are seldom affordable, AIDS wasting remains a common problem to the extent that it is known in Africa as 'slim disease' (3).

In a randomized trial (4) in AIDS patients, THC significantly improved appetite and nausea in comparison with placebo. There were also trends towards improved mood and weight gain. Unwanted effects were generally mild or moderate in intensity. The possible benefit of cannabis in AIDS made it one of the lead indications for such treatment in the judgment of the American Institute of Medicine in their study (5).

A safety study was carried out in HIV positive patients to assess whether oral THC or smoked cannabis would produce immunological damage in patients on protease-inhibitor medication (6). No problems were noted with HIV viral loads or CD4 cell counts. The study was subsequently published in expanded form (7), and some weight gain was also observed in THC and cannabis-treated subjects as compared to controls.

It is likely that cannabis-based medicine extracts will have some considerable contribution to offer in future clinical trials in HIV/AIDS.

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Arthritis

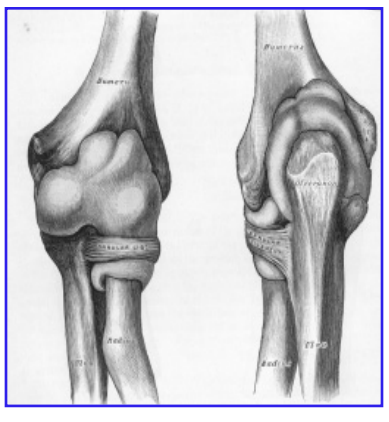
Arthritis refers to a large group of disorders that affect joints and soft tissues to produce chronic pain. The two most common forms are osteoarthritis (OA), a disease of aging and wear and tear) and rheumatoid arthritis (RA), a common autoimmune disorder producing joint pain, swelling and deformity. Cannabis may represent a new treatment option in both categories.

Cannabis has been employed to treat musculoskeletal pain for at least 4000 years, dating to the Ancient Assyrians (1). Marcandier's 1758 work, Traité du Chanvre (2) is of particular interest because European cannabis of that time was fibre hemp that would be devoid of THC, but rich in cannabidiol (CBD).

The role of CBD as an anti-inflammatory and immunomodulatory agent has been of great interest.

Very recently, the role of CBD as an anti-inflammatory and immunomodulatory agent potentially useful in treating autoimmune conditions has been of great interest. Malfait et al. (3) explored its effect in a mouse model of rheumatoid arthritis, and discovered that it arrested progression of the disease and protected joints against severe damage. CBD also blocked the release of tissue necrosis factor-alpha (TNF-a), a key target in modern approaches to RA treatment. These effects alongside anti-inflammatory and analgesic benefits of CBD and THC may represent a novel approach to this difficult clinical problem.

Clinical studies of GW's cannabis based medicine extracts containing THC and CBD are currently in Phase II trials in RA patients.



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Asthma

The use of cannabis in asthma dates to the traditional medicine of India (1), but was also rediscovered in Western medicine in the 19th century (2, 3).

Although it may seem counter-intuitive, cannabis cigarettes such as those marketed by Grimault & Cie to treat asthma were popularly utilized for their bronchodilatory effects. Studies in the 1970s confirmed this benefit of cannabis (4), and in one study (5), inhaled THC produced an increase in FEV1 (forced expiratory volume in 1 second) after one hour that was equal to that of salbutamol. It has now been demonstrated that endocannabinoids regulate broncho-dilation and constriction (reviewed (6)).

Problems remain with the concept, however. Almost no modern authorities feel that asthmatics should smoke cannabis for asthma (7), although it seems that even chronic usage may not lead to emphysematous degeneration (8). Use of THC inhalation in isolation, however, has been proved to induce cough and lung irritation even without concomitant smoke.

Modern research has turned to alternative delivery systems. One, that of cannabis vapourisation, may be applicable (9-11), but to date, potential carcinogens in tobacco smoke have not been totally eliminated. The development of whole cannabis extract inhalers, as currently being researched by GW Pharmaceuticals (12-14) may offer advantages. Certainly, there is rationale behind inclusion of cannabis terpenoids, that have additional anti-inflammatory properties in their own right (15), especially pinene, that also demonstrates a bronchodilatory benefit (16). Further research is clearly required.

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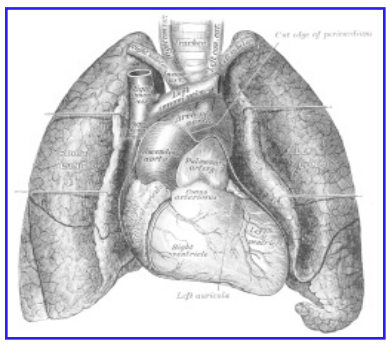

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Crohn's Disease/ InflammatoryBowel Disease

Crohn's disease and ulcerative colitis are chronic, inflammatory conditions of the gastrointestinal tract of autoimmune origin. While ulcerative colitis preferentially affects the colon and lower small intestine, Crohn's disease may affect any portion of the GI tract. Both are associated with tissue ulceration, bleeding, cramping, diarrhoea, weight loss, and the possibility of bowel obstruction with a resulting need for surgery. (1)

A recent epidemiological study (2) has examined the burden of gastrointestinal diseases in UK patients and found that both diseases are becoming more common. Prevalence of ulcerative colitis by age 30 for people born in 1970 is 30/10,000. The prevalence of Crohn's disease by age 30 was 38/10,000. Both Crohn's and ulcerative colitis are associated with considerable psychiatric comorbidity including depression, anxiety, somatisation, and decreased quality of life measures (3).

The long historical usage of cannabis for gastrointestinal complaints has been reviewed (4). Numerous studies in the 1970s indicated that THC slowed intestinal passage of a charcoal meal in rodents. Cannabidiol (CBD) had little effect of its own, but synergized the effects of THC (5). The most topical review of cannabinoid effects on the gastrointestinal tract is that of Pertwee (6). To summarise the major points:

1) The enteric nervous systems of mammals express CB1 and stimulation depresses gastrointestinal motility, especially through inhibition of contractile neurotransmitter release.

2) Observed effects include delayed gastric emptying, some decrease in peptic acid production, and slowed enteric motility, inhibition of stimulated acetylcholine release, peristalsis, and non-adrenergic non-cholinergic (NANC) contractions of smooth muscle, whether circular or longitudinal.

3) These effects are mediated at the brain level as well as in the GI tract

4) These effects are opposed by CB1

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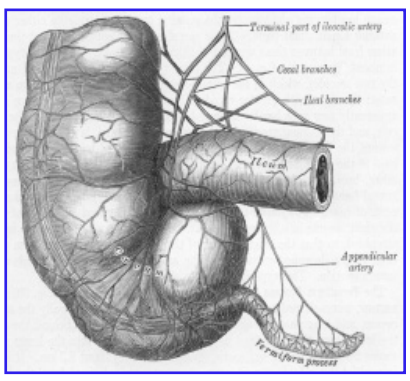
antagonists (e.g., SR141716A).

Holdcroft et al. were able to demonstrate an analgesic (pain reducing) benefit ($p<0.001$) of THC 50 mg per day in 5 split doses in a patient with relapsing familial Mediterranean fever in a double-blind placebo-controlled trial (7). Normally, this form of pain is extremely difficult to control with narcotics or other analgesics. Additionally, anandamide and other cannabinoid agonists inhibit rat serotonin type 3 (5-HT3) receptors (8) that mediate vomiting and pain responses.

The most compelling new data re-



cently has been that of Karen Wright (9). Her group compared immunohistological expression of CB1 and CB2 in normal colonic tissue samples to those from inflammatory bowel disease patients. In normals, CB1 was expressed in the colonic epithelium, smooth muscle and submucosal myenteric plexus. CB2 was expressed on plasma cells and macrophages of the lamina propria. Striking immunofluorescence was demonstrable in the disease state.

Cannabis extracts may be well suited to treatment of inflammatory diseases due to their multiple mechanisms of action. THC seemingly alleviates pain, spasm and diarrhea, while the CBD component presents the likelihood of immunomodulatory benefits. One recently demonstrated CBD effect is its ability to inhibit TNF-a (tissue necrosis factor-alpha)(10), a proven mechanism of other agents employed to treat inflammatory bowel

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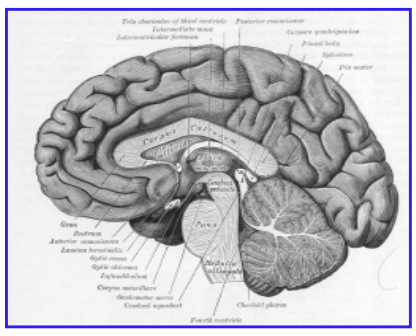
Depression/Mental Illness

The use of cannabis by people with mental illness has historically been associated with claims of both benefits and harms (1, 2). In its recent review, the Institute of Medicine (3) observed (p. 106), 'people with schizophrenia or with a family history of schizophrenia are likely to be at greater risk for adverse psychiatric effects from the use of cannabinoids,' and 'there is little evidence that marijuana alone produces a psychosis that persists after the period of intoxication.'

In modern times, the suggestion



that recreational cannabis use may be a risk factor for schizophrenia was first raised by Andreasson and collegeagues (4). Many of the other studies exploring this apparent association consist of retrospective analyses often relying on unreliable measures such as self-report, and are unable to distinguish association from causation. (5)(6)(7)(8).

A recent retrospective and prospective examination of 232 newly diagnosed schizophrenic patients demonstrated no temporal correlation between substance abuse onset and that of psychosis (6). A recent review (7) concluded that cannabis may precipitate psychosis in vulnerable patients, increase relapse rates or produce dependency in those already affected. Similarly, in Italy (8), data supported a duality of experience such that some schizophrenics employ cannabis as self-treatment while in others it might be one factor predisposing to the disorder.

It is noteworthy that endocan-nabinoid levels are elevated in the brains of schizophrenics (9), although the practical significance of this finding is not yet clear.

The cannabis component cannabidiol may possess anti-psychotic activity

The cannabis component cannabidiol may possess anti-psychotic activity (10), and a single case report was consistent with this (11).

Benefits were noted in depression measures in cancer patients treated with THC (12), and this has been supported by anecdotal reports (13). Both cannabidiol and nabilone (THC analogue) have demonstrated apparent benefit in clinical and experimental anxiety (10, 14, 15, 16).

Anecdotal reports suggest that cannabis may alleviate symptoms of bipolar disease (17).

The recent discovery that endocannabinoids regulate extinction of aversive memories (18) has led some to suggest the use of phytocannabinoids in treatment of post-traumatic stress disorder (PTSD).

Degenerative Diseases

Neuroprotection represents a goal in pharmacotherapy to reduce or eliminate cell death after traumatic or hypoxic insults to the brain such as cerebrovascular accident (CVA) or closed-head injury, or as a result of degenerative diseases, such as Alzheimer's, Huntington's, Parkinson's, amyotrophic lateral sclerosis, multiple sclerosis, severe seizure disorders (epilepsy), or other conditions including glaucoma and diabetes mellitus. The historical record and modern investigations support the prospect of cannabis-based medicines having important applications in such areas.

The first reference describing neuroprotective effects of cannabis may be the Shen Nong Ben Cao Jing, a traditional herbal written down in the 1st or 2nd centuries, but based on the oral traditions from the third millennium BCE (1), in which it was stated of cannabis (p. 148), 'Protracted taking may make one fat, strong, and never senile.'

Queen Victoria's personal physician wrote of his experience with Cannabis indica in dementia

Similar claims were advanced by Sir John Russell Reynolds, Queen Victoria's personal physician, who wrote of his experience with Cannabis indica in dementia in 1890 (2). It not only calmed his patient of his nocturnal agitation, but seemingly arrested progression of the disease for years without increase in dosage.

Modern laboratory experience supports the neuroprotective effects of THC and CBD in preventing cell death due to glutamate excitotoxicity and reactive oxygen species (3).

Initial therapeutic trials of cannabinoids in closed head injury support the clinical benefit of such an approach (see Traumatic Brain Injury/Stroke section). Similar mechanisms are operative to some degree in central nervous system degenerative disorders, presenting the potential for therapeutic intervention (reviewed in (4)).

In Huntington's disease, a striking loss of cannabinoid receptor expression occurring in step with degenerative status has been observed

THC as Marinol(r) has been shown to reduce disturbed behaviour in Alzheimer's disease (5), but a possible impact upon disease progression has not yet been evaluated. In Huntington's disease, a striking loss of cannabinoid receptor expression occurring in step with degenerative status has been observed (6), and may represent a target in therapy. In Parkin-son's disease, the synthetic cannabinoid nabilone reduced dyskinetic movements from L-DOPA therapy (7), and there have been claims of additional therapeutic benefits in prolonged administration of oral herbal cannabis (8). One study has suggested a beneficial effect of CBD in dystonic disorders (9). Similarly, one article has described the palliative use of cannabis in amyotrophic lateral sclerosis (ALS) (10), but the potential neuroprotective effects in this disorder merit further attention, as it is invariably fatal, and existing agents offer little concrete benefit.

Prospective clinical trials of cannabis based medicines raise formidable methodological challenges, but the pre-clinical data provide compelling evidence in support of this direction.

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Eating Disorders

The appetite stimulating power of cannabis and THC are among its most well known effects. This phenomenon was first documented in Western literature by the physician and explorer, Garcia da Orta, in India in the 16th century (1), as he observed (p. 56), "Those of my servants who took it, unknown to me, said that it made them so as not to feel work, to be very happy, and to have a craving for food."

Similar benefits of Indian hemp were noted by O'Shaughnessy in India, as extracts of Indian hemp successfully treated the spasms and cachexia of tetanus (lockjaw) and allowed survival from that disease for the first time (2). Later in the Victorian era, the famed pharmacologist Dixon, described it as a useful 'food accessory' (3).

Various experiments in the 1970s-1980s supported the benefits of cannabis and THC in cancer chemotherapy and subsequently, in AIDS (see corresponding sections), leading to the approval in 1986 of Marinol(r) (synthetic THC) for the former indication.

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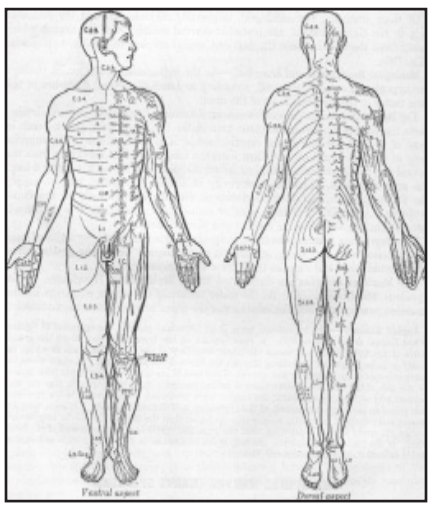
Cannabis also increased food intake in normal subjects.

Cannabis also increased food intake in normal subjects (4).

Subsequent work with Marinol has supported its benefit in boosting appetite in Alzheimer disease (5), and that of cannabis in one case of amyotrophic lateral sclerosis (6). Similar gains seem worthy of exploration in other wasting conditions, especially since adjunctive use of cannabis may offer additional advantages in the form of broader symptom relief. The recent demonstration that anandamide and endocannabinoids have a basic regulatory function on appetite (7) highlights the importance of this potential therapy.

In the opposite direction, the cannabinoid antagonist, SR141716A (Rimonabant(r)) has demonstrated anti-obesity effects in mice (8), and is currently in human clinical trials. Preliminary results (9) demonstrate reduction of hunger and food intake in obese male subjects in the short term, and weight reduction in the long term. The recent discovery of an endocannabinoid antagonist, virod-hamine (10), ensures that many interesting discoveries are forthcoming with respect to therapeutic modifications of appetite. It is possible that further research into other phytochemical components of cannabis will also contribute other useful agents for appetite modulation.



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Epilepsy/Seizure Disorders

Epilepsy affects 1% of the UK population and 200,000 patients take anticonvulsant medication (1). Historically, cannabis has been used as a treatment for seizures (2, 3, 4).

CBD seems consistently anti-convulsant, whilst the picture with THC is less clear-cut.

Experiments in the 1970s explored the anticonvulsant potencies of various cannabinoids in test animals (5). CBD seems consistently anti-convulsant, whilst the picture with THC is less clear-cut. A case report describes an adult who improved his seizure control by smoking cannabis alongside standard medicines (6). A small double blind study in refractory patients compared cannabidiol (CBD) with placebo (7). Three of eight treated patients had complete seizure control, one was improving but moved away, and one other was markedly improved. No major adverse effects were noted. Another double-blind placebo-controlled study of CBD in South Africa with similar dosages in 12 subjects (8), failed to demonstrate benefit. Similarly, an unpublished series of studies (9) revealed no effect of CBD on seizure frequency in 10 subjects over six months.

There have been reports of seizure exacerbation in humans by THC but no clear correlation to dosage or timing of administration. There are anecdotal reports of successful treatment of seizure disorders in humans with cannabis (10, 11).

A BMA report concluded (1)(p. 52), "With such scanty human data, the role of cannabinoids as possible therapeutic agents in epilepsy remains speculative. It is unlikely that psychoactive cannabinoids such as THC, which have dual convulsant-anticonvulsant effects, will be therapeutically useful." Similarly, the American Institute of Medicine stated (12), "Given the present state of knowledge, clinical studies of cannabinods in epilepsy are not indicated."

Seizure threshold appears to be mediated by cannabinoid mechanisms

Some subsequent laboratory work has changed the landscape. Seizure threshold appears to be mediated by cannabinoid mechanisms (13). In rats (14), THC produced a 100% reduction in seizures, whereas phenobarbital and diphenylhydantoin did not. The animals demonstrated both acute increases in endocannabinoid production and a long-term up-regulation of CB1 production as apparent compensatory effects counteracting glutamate excitotoxicity. The anticonvulsant effect was present at sub-sedating levels.

While available clinical evidence provides no compelling support for THC having proconvulsant properties in humans, clinical researchers must remain cautious, as animal data do raise that possibility. Further testing with CBD-rich extracts seem warranted.

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Glaucoma

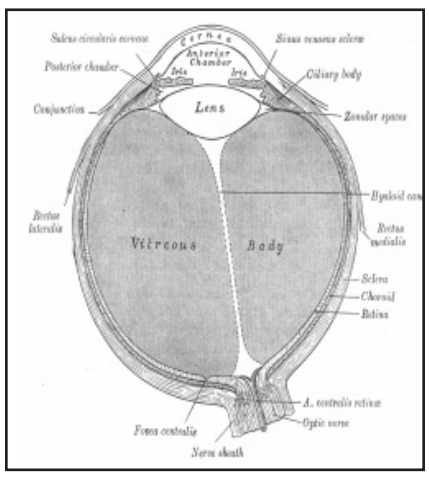
Glaucoma is a common condition in which there is a build-up of intraocular pressure (IOP) in the eye. This may cause eye and head pain, haloes in the vision, constriction of the visual field, or merely a progressive loss of vision without other symptoms. It is the major cause of irreversible blindness in Western societies. A variety of oral medicines or eye drops are customarily employed, but are not uniformly effective (1).

The ability of cannabis and THC to lower intra-ocular pressure in glaucoma was serendipitously discovered in the late 1970's by a variety of patients and researchers (2, 3). Several patients in the U.S. Compassionate Use Investigational New Drug Program maintained their vision while employing large amounts of daily cannabis in situations where standard drug therapy failed (4).

The 1999 US Institute of Medicine report noted the ability of cannabis to lower IOP, but did not endorse its usage due to its relatively short effects and concerns about the need to smoke the drug on a chronic basis (5).

Glaucoma may represent a progressive vascular retinopathy that requires a neuroprotectant to preserve vision

A very interesting development was the discovery that the endocannabinoid anandamide acts as a regulator of intraocular pressure (6). However, it is



apparent that there is more to glaucoma treatment than merely controlling IOP, as even effective management may fail to avert visual loss over time. An emerging concept is that glaucoma represents a progressive vascular retinopathy that requires a neuroprotectant to preserve vision (1). Some of the resulting optic nerve damage accrues due to NMDA hyperexcitability, an effect that THC and CBD may counter as neuroprotective antioxidants (7). Thus, glaucoma is an area where cannabis and cannabinoids may offer particular advantages over available single ingredient ocular antihypertensive agents. Delivery methods remain an exacting challenge.

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Intractable Breathlessness

There are a number of lung diseases that are capable of producing short-

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ness of breath that is often extremely distressing to the patient. Many of these conditions are irreversible, so it becomes necessary to target the symptom itself.

The sensation of breathlessness is a complicated phenomenon that seems to depend upon central processing through respiratory and non-respiratory mechanisms. Ideally, a treatment would relieve the unpleasant sensation without further compromising respiratory function. Opioids and benzodiazepines produce some relief but may have the dangerous side effect of depressing respiration.

Patients have reported anecdotally that cannabis can relieve breathlessness by relieving anxiety and promoting relaxation. CB1 receptors are virtually absent from the part of the brain-stem which drives respiration (1), so it is to be hoped that symptom relief may be achieved without negative effects upon breathing. THC has been shown to have anxiety-reducing and sedating effects (2, 3), as has CBD (4). Additionally, CBD is thought to have useful modulating effects on some of the undesirable effects of THC (5).

Exploratory research of THC/CBD combinations in refractory breathlessness is indicated, incorporating careful monitoring of respiratory function.

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Migraine

Migraine is a severe headache disorder producing pain, hypersensitivity to light and noise (photophobia and phonophobia), and occasional visual loss or distortion. While it most commonly occurs in discrete attacks, frequently perimenstrual in young women, it does affect both sexes at any age, and may develop into chronic or daily forms (1). Some 8-14% of teens and young adults may be affected (2) and the economic losses attributable to migraine in the USA in 1992 were as much as $17 billion (3).

Cannabis was a mainstream medication for migraine between 1842 and 1942 in Europe and America

Drug therapy consists of treatment for individual attacks, and a preventive approach for frequent or daily afflictions. Treatment failure rates with the many available agents still approach 30%, and there are no specific cures, although various 19th century authorities claimed success with Indian hemp (cannabis) preparations (4, 5). Cannabis was a mainstream medication for migraine between 1842 and 1942 in Europe and America (4, 5). Its use for this purpose was endorsed even in 1971 by the neuroscientist, Solomon Snyder (6).

Cannabis and its components interact in a potentially beneficial way with a number of systems of relevance to this disease: effects on serotonergic, dopaminergic, opioid, substance P, calcitonin gene-related peptide and NMDA receptors by cannabis components have been extensively supported (5). Although no clinical trials of cannabis treatment in migraine have been performed, it has recently been suggested that migraine may represent a clinical endocan-nabinoid deficiency (CECD) disorder (7), and that the ability of cannabidiol (CBD) to regulate anandamide levels (8) may contribute a key to its long-term control. It is hoped that clinical trials may be undertaken in the future.

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Multiple Sclerosis

Multiple sclerosis (MS) is a disease affecting the Central Nervous System (CNS). MS exacerbations appear to be caused by abnormal immune activity that causes inflammation and the destruction of myelin (the protective covering of nerve fibres) in the brain or spinal cord.

MS usually commences in early adult life, most frequently presenting at onset as a relapsing and remitting disorder, where symptoms come and go, and is more common in females. Current treatment of MS is primarily symptomatic, focussing on such problems as spasticity, pain, fatigue, bladder problems and depression.

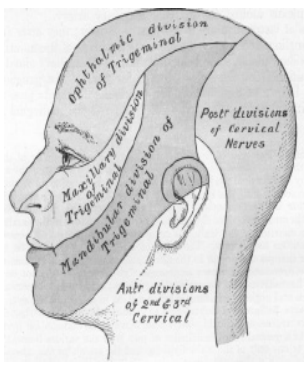
In the last 15 years, immunotherapy approaches have become available, but their efficacy in producing long-term benefits has been questioned (1). MS is one of the most frequent reasons that patients employ cannabis. Excellent reviews of THC, cannabis and MS are available (2, 3).

Interim results of a small study (11 patients) of cannabis based medicine extracts (CBMEs) in bladder dysfunction were presented at a meeting of the International Association for Cannabis as Medicine (IACM)(4). Improvements were shown, compared to placebo, in nocturia, daytime frequency and incontinence episodes.

Data supporting the benefit of cannabinoid treatment of spasticity in MS is now as strong as for any available pharmaceutical agent

A recent study in the UK of more than 600 MS patients has demonstrated improvement with twice-daily oral THC and a THC/CBD cannabis extract on walking times, and subjective measures of pain and spasticity, although an objective measure of spasticity (Ashworth score) did not show a significant effect (5). The authors concluded that their findings provide evidence that cannabinoids could be clinically useful in the treatment of symptoms related to MS. Although, the effects were modest, an accompanying editorial pointed out that current data supporting the benefit of cannabinoid treatment of spasticity in MS is now as strong as for any available pharmaceutical agent (6).

The results of a Phase II study of CBME have also been published (7), performed in 24 subjects (18 with treatment-resistant MS) and employing



a consecutive series of double-blind, randomised, placebo-controlled single patient cross-over trials. Twenty of the subjects completed the trial. Pain relief was significantly superior to placebo and there were subjective improvements in spasm frequency, bladder control, spasticity and sleep. Of particular note was the finding that non-psychoactive cannabidiol (CBD) appears to have significant analgesic and anti-spasticity effects. Adverse effects in the trial were predictable and well tolerated.

Subsequent Phase III GW Pharmaceuticals trials have shown positive results including statistically significant reductions in neuropathic pain, spasticity and sleep disturbance. These results, summarized in a Nov. 22 GW press release, are currently awaiting publication.

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Nausea

The anti-emetic properties of cannabis have been studied in humans more widely than any other indication. Nausea and vomiting following chemotherapy was felt to be one of the best supported therapeutic uses of cannabis and cannabinoids by the British Medical Association in their review of 23 studies (1), and was also supported by the American Institute of Medicine (2).

This indication for cannabis has become common knowledge among patients, was the subject of a popular book (3), and has received endorsement from some American oncologists in a survey study (4). It was also the original indication for Marinol(r) (synthetic THC) when it was released in the USA in 1986.

A pilot study in Israel also showed efficacy of delta-8 in allaying nausea and vomiting in cancer chemotherapy in children (5), where it was 100% effective in allaying vomiting in 480 dose applications without significant adverse effects.

A large body of knowledge has now been amassed in this context as a result of state-sponsored studies in the USA in cancer chemotherapy (6). Pooling available data in some 768 patients, oral THC provided 76-88% relief of nausea and vomiting, while smoked cannabis figures supported 70-100% relief in the various surveys. However, there are no comparative trials with newer agents, such as the selective 5HT3 antagonists (e.g. ondansetron, granisetron).

The biochemical basis of this anti-emetic effect is still being explored, but it is known that cannabinoids experimentally inhibit the activity of 5-HT3 receptors (7), the primary mode of action for the standard drugs ondansetron and granistetron.

Recent data also supports the anti-emetic properties of cannabidiol in experimental animals (8-10). The combination of CBD and THC in cannabis extracts may well have additive or synergistic effects that deserve investigation in clinical trials.

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Obstetric Probems

Cannabis has been employed quite frequently throughout history for obstetric and gynaecological indications, dating from the Ancient Assyrians (1). The topic has been extensively reviewed recently (2), and has included use as an aid to childbirth from Ancient Egypt (3) to 19th century England (4) and 20th century America (5). Additionally, cannabis has been utilised for uterine bleeding (6), dysmenorrhoea (7, 8), hyperemesis gravidarum (morning sickness) (9, 10), and even as a protective agent against miscarriage from Ancient Persia to modern folk use in Jamaica (11, 12).

Modern pharmacological studies have demonstrated the basis for these claims (2, 13, 14). Drugs are rightly eschewed when possible in pregnancy, but cases arise frequently wherein such treatment is necessary, even to save the life of mother and child. Close scrutiny of the literature supports the relative safety of cannabis in such applications, though the ethical and methodological challenges to conducting modern clinic trials seem formidable indeed.

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Pain

The analgesic or pain reducing properties of cannabis have been known for at least 4000 years, from the time of the Ancient Assyrians (1). The modern era of scientific study of cannabinoids and pain began in 1974 with the studies of Noyes et al. (2-4), in which it was noted that numerous types of pain were treatable with cannabis or THC, and that the latter produced analgesia equivalent to codeine in one small clinical trial.

The historical and scientific aspects of cannabis and cannabinoids in pain management have been thoroughly reviewed (5, 6). Key areas of cannabis therapeutics revolve around its roles in neuropathic pain (7, 8), as an anti-inflammatory agent, and usage in musculoskeletal pain.

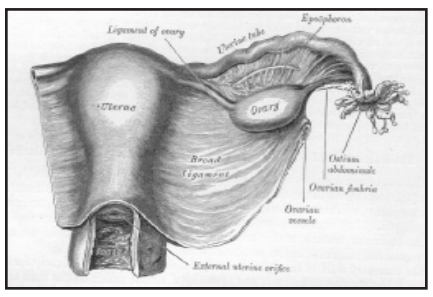
THC is the main contributor of cannabis to control of pain, via its actions on the central nervous system cannabinoid receptors

One of the primary functions of the endogenous cannabinoid system is modulation of pain control, in parallel with the endogenous opioid and vanilloid systems. THC is the main contributor of cannabis to control of pain, via its actions on CB1, the central nervous system cannabinoid receptors that occur in key pain-modulating areas of the spinal cord, and brainstem.

Although a review of the analgesic effects of cannabinoids concluded that they have little demonstrated benefit to date (9), the controlled clinical studies available for analysis were few and most had design flaws. This review was itself the subject of a critical response (10, 11).

The potential of various cannabis extracts in both nociceptive and neuropathic pain are currently being explored in several centres. Initial results are encouraging, including reduction of pain in MS patients in two studies (12, 13; see MS section of this article) and intractable pain unresponsive to standard treatment in 34 patients (14).

Interim results have been presented at the The Pain Society Annual Scientific Meeting 2003 on THC and THC:CBD in brachial plexus avulsion, a condition that often follows traction injuries and that frequently produces a highly characteristic pain syndrome (15). Both CBME extracts decreased pain and improved sleep.



Interim data was also presented at the 19th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (16). Significant mean reductions favouring CBME were found in both the primary outcome of pain and sleep disturbance, and patients treated with CBME were more likely to feel "much" or "very much improved" than those receiving placebo.

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16. 19th Congress of the European Committee for Treatment and Research in Multiple Sclerosis Sept.17-20, 2003, Milan

Phantom Limb Pain

Phantom limb pain often follows amputations, and consists of unusual and painful sensations that appear to originate in the absent limb. It is often refractory to standard analgesics, including drugs for neuropathic pain. However, anecdotal reports supporting the efficacy of cannabis have been documented (1).

Mechanisms by which cannabis may be of value include effects locally (2) and at spinal (3, 4) and central levels (reviewed (5, 6)).

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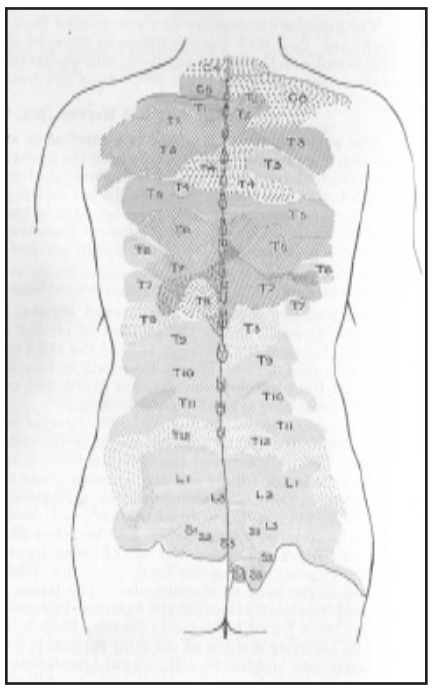
Tumors



Legitimate concerns surround the use of smoked cannabis, and its contribution to pulmonary irritation, bronchitis symptoms, and possible neoplastic sequelae (1, 2). However, a recent study indicates that THC and even cannabis smoke block the activity of a key enzyme in pulmonary carcinogenesis (3).

THC also has been demonstrated to promote apoptosis (programmed cell death) in malignant conditions including: leukemia (4) via CB2 stimulation, gliomas (5), and melanoma (6), in which tumour angiogenesis is also inhibited. Additionally, two types of breast tumor cell lines were inhibited by THC (7), apparently via prolactin receptor effects.

Pheochromocytoma, a tumour recalcitrant to most therapeutic approaches, also has been demonstrated to be positively affected by cannabinoid treatment (8).

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Recently, it has also been observed that cannabidiol inhibits glioma cell growth independent of cannabinoid and vanilloid receptor effects through promotion of apoptosis (9).

Finally, limonene, a cannabis terpenoid, has also proven to promote apoptosis of breast cancer cells in large doses in Phase II clinical trials (10, 11).

In lay terms, cancer occurs because cells become immortalized; they fail to heed normal signals to turn off growth. A normal function of remodelling in the body requires that cells die on cue. This is called apoptosis, or programmed cell death. That process fails to work in tumors. It is hoped that THC may promote its reappearance so that tumour cells will heed the signals, stop dividing, and die. Another method by which tumours grow is by ensuring that they are nourished: they send out signals to promote angiogenesis, the growth of new blood vessels. It is also hoped that cannabinoids may turn off these signals as well.

Two excellent reviews on this topic have recently been published (12, 13). The potential ability of THC and CBD to combat tumours directly , and simultaneously provide anti-emetic and analgesic support (see other sections on this website) portend an exciting area for further research of cannabis based medicine extracts.

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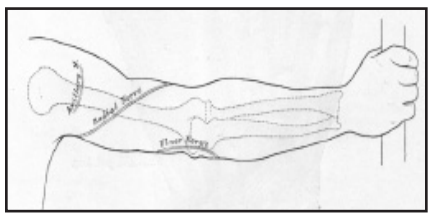

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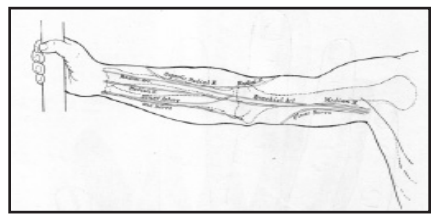
Withdrawal

In contrast to contemporary concerns that cannabis itself may have addictive potential, Indian hemp was used in the 19th century to treat dependencies on other substances. O'Shaughnessy observed benefit of cannabis extracts for delirium tremens in alcoholics (1), Clendinning shortly thereafter in



morphine withdrawal (2), and Mattison in cocaine and chloral hydrate addiction (3). In fact, in an early 20th century text on addiction, the only mentions of cannabis were in relation to its therapeutic benefits (4).

The LaGuardia Commission Report (5) contained an account of a group of 56 morphine and heroin addicts. Those who were cannabis-treated had less severe withdrawal symptoms and left the hospital earlier and in better shape than those receiving standard therapy.

Modern anecdotal support for utilization of cannabis for addiction withdrawal continues to accrue (6-8). A formal study in Brazil (9) demonstrated that 17/25 subjects (68%) were successful in abrogating 'crack' cocaine habits over the course of nine months through the use of cannabis, and claimed it able to allay cravings and induce other subjective benefits.

Dreher in Jamaica has documented cannabis as the most effective treatment in stopping crack cocaine use in 33 women (10).

Cannabinoid interactions with the dopamine system have been offered as a possible mechanism for some of the beneficial effects of cannabis in opiate withdrawal (11). A recent study provides objective evidence of the ability of THC to mitigate opiate-withdrawal symptoms, and block the formation of physical dependency (12). Clinical trials of cannabis based medicine extracts in the treatment of opiate addiction seem amply justified.

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