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Human Studies of Cannabinoids and Medicinal Cannabis

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Abstract Cannabis has been known as a medicine for several thousand years across many cultures. It reached a position of prominence within Western medicine in the nineteenth century but became mired in disrepute and legal controls early in the twentieth century. Despite unremitting world-wide suppression, recreational cannabis exploded into popular culture in the 1960s and has remained easily obtainable on the black market in most countries ever since. This ready availability has allowed many thousands of patients to rediscover the apparent power of the drug to alleviate symptoms of some of the most cruel and refractory diseases known to

humankind. Pioneering clinical research in the last quarter of the twentieth century has given some support to these anecdotal reports, but the methodological challenges to human research involving a pariah drug are formidable. Studies have tended to be small, imperfectly controlled, and have often incorporated unsatisfactory synthetic cannabinoid analogues or smoked herbal material of uncertain composition and irregular bioavailability. As a result, the scientific evaluation of medicinal cannabis in humans is still in its infancy. New possibilities in human research have been opened up by the discovery of the endocannabinoid system, a rapidly expanding knowledge of cannabinoid pharmacology, and a more sympathetic political environment in several countries. More and more scientists and clinicians are becoming interested in exploring the potential of cannabis-based medicines. Future targets will extend beyond symptom relief into disease modification, and already cannabinoids seem to offer particular promise in the treatment of certain inflammatory and neurodegenerative conditions. This chapter will begin with an outline of the development and current status of legal controls pertaining to cannabis, following which the existing human research will be reviewed. Some key safety issues will then be considered, and the chapter will conclude with some suggestions as to future directions for human research.

Keywords Cannabinoids · Medicinal cannabis · Human research · Therapeutic potential

1 Introduction

The pariah status of cannabis is a relatively modern phenomenon. Cultivation of the plant for hemp extends back to the Stone Age, and medicinal use dates back at least 4,000 years (reviewed by Mechoulam 1986). In China a medical treatise dating from around 2600 B.C.E. recommends its use for relieving the symptoms of malaria, constipation, rheumatic pains and dysmenorrhoea (Grinspoon and Bakalar 1993). There are subsequent records of medicinal use throughout Asia, the Middle East, Southern Africa and South America. Known to European physicians as Indian hemp until christened *Cannabis sativa* by Linnaeus in 1753, it was not until the mid-nineteenth century that it emerged as a mainstream medicine in Britain. The Irish scientist and physician W.B. O'Shaughnessy had observed its use in India as an analgesic, anti-spasmodic, anti-emetic and hypnotic. After testing its safety on dogs, goats and himself he went on to administer cannabis resin in an ethanolic solution to patients with a range of maladies. His report (O'Shaughnessy 1843) of these experiments generated considerable interest, and medicinal use expanded rapidly. By 1854 it had found its way into the U.S. Dispensatory, and "over-the-counter" preparations were soon available in pharmacies throughout England and Scotland. Establishment status was fully achieved through the enthusiastic endorsement of one of Queen Victoria's physicians (Reynolds 1890), but by the end of the century cannabis had passed its zenith as a prescribed medicine and home remedy. Although Sir William Osler was still recommending it for migraine

sufferers in 1913, its popularity was in steep decline for a number of reasons: variable potency of herbal preparations, unreliable sources of supply, poor storage stability, unpredictable response to oral administration, the growing availability of potent synthetic medicines, and commercial pressures. An increasingly influential factor was increasing concern in some countries about recreational use, notably South Africa, Egypt and the U.S.

These concerns were brought to the 1923 meeting of the League of Nations, and thence referred for consideration at the 1925 Geneva Convention on the manufacture, sale and movement of dangerous drugs. Signatory nations agreed to enforce a limitation of the use of cannabis solely for medical or scientific purposes. In 1928 the UK government ratified this convention, but prescription of cannabis remained possible until the Misuse of Drugs Act (1971) brought down the final curtain. This Act provides rules for the manufacture, supply and possession of a long list of controlled drugs. For the purposes of determining penalties for malefactors it places them in three classes according to the "harmfulness attributable to a drug when it is misused". On this basis, cannabis and cannabis resin were assigned to Class B along with amphetamines, barbiturates, codeine and dihydrocodeine. In 2001, the British Home Secretary asked a leading committee of experts [Advisory Council on the Misuse of Drugs (ACMD)] to review the classification of cannabis in the light of current scientific evidence. The ACMD carried out a detailed scrutiny of all the relevant literature and in 2002 concluded that, though certainly not innocuous, cannabis

> ... is less harmful than other substances (amphetamines, barbiturates, codeine-like compounds) within Class B of Schedule 2 to the Misuse of Drugs Act 1971. The continuing juxtaposition of cannabis with these more harmful Class B drugs erroneously (and dangerously) suggests that their harmful effects are equivalent. This may lead to the belief, among cannabis users, that if they have had no harmful effects from cannabis then other Class B substances will be equally safe.

ACMD recommended reclassification of all cannabis preparations to Class C, and in February 2004, despite hostile media comment, the Home Secretary implemented this advice.

An important issue for medicinal cannabis in Britain is its inclusion in schedule 1 of the Misuse of Drugs Regulations (1985). This means that it belongs to a group of controlled drugs [alongside lysergic acid diethylamide (LSD), raw opium and coca leaf] that have no recognised medicinal use, and which are totally prohibited for possession or supply unless authorised by a special licence from the Home Office. However, the Home Secretary is on record as saying in 2001: "Should, as I believe it will, this programme (of trials) be proved to be successful, I will recommend to the Medicines Control Agency that they should go ahead with authorising the medical use" (UK Parliament 2002).

In the U.S., concern about the recreational use of cannabis had reached fever pitch by the 1930s (for a full review, see Mead 2004). This was fuelled by some lurid propaganda largely instigated by the chief of the Federal Bureau of Narcotics, Harry J. Anslinger (Abel 1980). This highly effective campaign, which generated

some baseless myths that survive to the present day, culminated in the Marihuana Tax Act (1937) that effectively ruled out both recreational and medicinal use. In 1941 cannabis was removed from the U.S. Pharmacopoeia. Scientific reports that challenged claims that cannabis use was closely associated with insanity, addiction, violence and crime were ignored by politicians, regulators and the American Medical Association. Cannabis continued to be portrayed as a dangerous, addictive drug that also acted as a "gateway" into opiate or cocaine addiction. In the late 1940s the confused international situation regarding drug control led the United Nations Commission on Narcotic Drugs (CND) to seek an international agreement. In the resulting 1961 Single Convention on Narcotic Drugs, cannabis and cannabis resin were placed in one of the most restricted categories (along with heroin). Signatory nations were obliged to impose complete prohibition and "adequate punishment" for transgressors. The 1971 Convention on Psychotropic Substances and the 1988 Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances were subsequent developments. The 1971 convention placed dronabinol (Marinol), a synthetic formulation of Δ^9-tetrahydrocannabinol (THC) for oral use, in a less restrictive category. Following research funded by the U.S. National Cancer Institute, dronabinol was approved by the U.S. regulatory authority for the treatment of nausea and vomiting associated with cancer chemotherapy.

U.S. Advocacy groups such as the National Organisation for the Reform of Marijuana Laws (NORML) and Alliance for Cannabis Therapeutics (ACT) have vigorously opposed the suppression of medicinal cannabis (Mead 2004). Rescheduling litigation was not, in the end, successful at a national level, but many individual states enacted legislation to make cannabis available to specific patients. Numerous cannabis buyers' clubs sprang up to provide supplies, but these are certainly not immune from prosecution by the federal authorities. California has been a particular focus for activity, and a Center for Medicinal Cannabis Research has been established within the University of California at San Diego.

Nations have some flexibility in implementing the 1961 and 1971 conventions (Mead 2004). For example, if a national court ruled that an individual had a constitutional right to use medicinal cannabis, that nation would be relieved of any obligation to punish such activity. This elasticity has resulted in a marked disparity in approach between countries (for a full review, see Mead 2004).

Unfortunately, the blossoming of recreational cannabis during a period of social turmoil in the 1960s has hardened its image as an agent of alienation and subversion in the eyes of many politicians and regulators. Rigorous prohibition has remained the central policy, despite inescapable evidence that the "War on Drugs" is a futile approach that wastes billions of dollars every year (Robson 1999). The price of black market cannabis continues to fall in real terms, and it remains easily accessible in virtually every country in the world to anyone who wishes to consume it. However, medicinal research involving such a pariah drug presents profound methodological challenges, and this is reflected in the scientific limitations inherent in many of the clinical trials conducted during the last quarter of the twentieth century.

Partly as a result of the discovery of the endocannabinoid system and a growing realisation of its importance in both normal and pathological function, the final years of the twentieth century have seen renewed interest in exploring the poten-

tial of cannabis-based medicines among scientists and politicians in a number of countries. In the UK this has led to pioneering work in developing whole plant medicinal cannabis extracts containing different ratios of active ingredients targeted at different medical conditions (Whittle et al. 2001; Robson and Guy 2004). Whole plant extracts may have advantages over single chemical entities (such as synthetic THC) for several reasons (McPartland and Russo 2001). The non-psychoactive cannabinoid, cannabidiol (CBD), shows therapeutic promise in its own right (Pertwee 2004), and may modulate some of the less desirable actions of THC by both pharmacodynamic and pharmacokinetic mechanisms (Karniol 1973; McPartland and Russo 2001). Other cannabinoids and plant components such as terpenes, flavonoids and phenols may also have medicinal potential (McPartland and Russo 2001). Oromucosal sprays and vapourisers are promising delivery systems which provide greater flexibility for self-titration than the oral route (Whittle et al. 2001).

Conditions have never been more propitious for the rigorous scientific evaluation in humans of many of the hitherto anecdotal accounts summarised below.

2
Review of Clinical Research

2.1
Symptomatic Relief in Multiple Sclerosis and Spinal Cord Injury

Spasticity is a central feature of multiple sclerosis (MS) and spinal cord injury (SCI). It consists of a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex as one component of the upper motor syndrome (Young 1994). Existing drug therapy is far from satisfactory in terms of efficacy and unwanted effects (Panegyres 1992). Tremor, ataxia and lower urinary tract symptoms are frequently troublesome in MS. Both neuropathic and nociceptive pain (dealt with in Sect. 2.3) are also common in MS and SCI, and dozens of very painful muscle spasms can occur each day. Small wonder that there is also a high incidence of anxiety and depression in these conditions.

THC and other cannabinoids have been shown (Baker et al. 2000) to improve both tremor and spasticity in a well-validated animal model of MS (experimental allergic encephalomyelitis). Antagonism of the CB_1 receptor aggravated these signs, indicating a role for endogenous cannabinoids in the control of tremor and spasticity.

Many patients have reported anecdotally that cannabis can relieve some of the most distressing symptoms of MS and SCI, including spasticity, muscle pain, tremor, spasms on walking, paraesthesiae, leg weakness, trunk numbness, facial pain, impaired balance, nystagmus, anxiety and depression (Grinspoon and Bakalar 1993; Consroe et al. 1997). Hodges (1992) described the severe progression of her MS from its onset in 1983. Prescribed medicine was only moderately effective and produced unpleasant side-effects. Having with reluctance and no small difficulty established an illicit supply of cannabis, she wrote:

> When I smoke it, my body completely relaxes, which relieves the tension and spasms I have. It has had other beneficial effects. I am now more efficient at controlling my bladder, so I don't get the recurrent urinary infections that I was having before. It relieves my nausea and I can now sleep much better, so that I am not tired all the time.

Malec (1982) reported that 21 out of 24 SCI patients with spasticity who had tried cannabis found it had alleviated their symptoms. A recent survey of MS patients in the UK and USA found that between 30% and 97% experienced relief in symptoms with cannabis, depending on the particular symptoms (Consroe et al. 1997). In descending order of improvement, these were: spasticity, chronic pain, acute paroxysmal phenomena, tremor, emotional problems, anorexia/weight loss, fatigue states, double vision, sexual dysfunction, bowel and bladder symptoms, vision dimness, difficulty with walking and balance, and memory loss.

Open or single-blind observations of small numbers of patients on the effects of synthetic THC given orally have provided some support to these reports (Dunn and Davis 1974; Petro 1980; Clifford 1983; Meinck et al. 1989; Brenneissen et al. 1996). Subjective improvements in spasticity are a consistent finding, with some studies also indicating benefits for tremor, bladder control, mobility and mood. Unwanted effects do not seem to have been prominent. Schon et al. (1999) reported amplitude reduction of pendular nystagmus and improved visual acuity in an MS patient following smoked cannabis, but no effect following cannabis capsules or nabilone (a synthetic THC analogue). Of related interest is a report from Russo et al. (2003) describing improved night vision following both THC and cannabis in a single subject.

Brady et al. (2003) carried out an open pilot study in 15 MS patients with refractory lower urinary tract symptoms. They each received whole plant cannabis medicinal extracts (CBME) containing either predominantly THC or an equal proportion of THC and CBD for consecutive 8-week periods. Incontinence episodes, nocturia episodes, incidence of urinary urgency and frequency all decreased significantly, whilst the number of planned or normal voids significantly increased. Most patients experienced mild intoxication during the initial titration phases and two had short-lived hallucinations that disappeared on dose reduction. The authors concluded that CBME may prove to be a safe and effective additional treatment for this harrowing condition. A pilot open label study in 15 patients with overactive bladders as a result of SCI also showed symptomatic improvement following 10 mg THC by either oral or rectal routes (Hagenbach et al. 2001).

The first double-blind placebo-controlled study in MS patients was reported by Petro and Ellenberger (1981). Oral THC in a single dose of 5 or 10 mg was compared with placebo in a crossover design in 9 subjects. Both doses of THC were significantly superior to placebo in relieving spasticity measured by clinical examination or, where feasible, electromyography during quadriceps stretching. One patient receiving THC 10 mg and one receiving placebo reported feeling "high". Ungerleider and colleagues (1987) found in a randomised double-blind crossover study with 5-day treatment periods that THC 7.5 mg produced significantly improved patient ratings of spasticity in comparison with placebo. In

a double-blind, placebo-controlled crossover trial Hanigan et al. (1985) reported that THC 30 mg/day for 20 days significantly improved objective measures of spasticity in 2 out of 5 patients with traumatic paraplegia. Martyn (1995) reported that nabilone 1 mg on alternate days for 1 month was better than placebo in a double-blind crossover study in a single MS patient. Improvement in nocturia, muscle spasm and general well-being were also noted in this patient, with mild sedation the only unwanted effect. On the negative side, a single dose of smoked cannabis (THC content 1.54%) impaired both posture and balance in comparison with placebo in 10 MS patients and 10 normal subjects (Greenberg et al. 1994), a not-unexpected occurrence with any skeletal muscle relaxant.

More recent trials of cannabis-based medicines in MS have given mixed results. Vaney and colleagues (2002) enrolled 57 MS patients in a randomised, crossover comparison of 15 mg THC daily in divided doses for 15 days with placebo. A significant improvement in a subjective rating of spasm frequency was not accompanied by objective improvement as represented by the Ashworth Score (Ashworth 1964). This is a measure of biological impairment, as opposed to disability or handicap, and relies upon an estimation by a clinician. A trend towards improvement in mobility was noted, but no effect on tremor, sleep quality, or lower urinary tract symptoms. Adverse events occurred with similar frequency in the active and control groups, but were more severe in the former. Killestein et al. (2002) reported an unambiguously negative study in 16 MS patients. In a randomised, double-blind crossover design, they compared synthetic THC with a cannabis plant extract containing the same amount of THC and placebo over 4 weeks of treatment. Starting dose was 2.5 mg orally twice daily, with the option to increase this to 5 mg twice daily after 2 weeks if the first dose was well tolerated. There was no improvement in spasticity as represented by the Ashworth Score. Both active medicines were well tolerated, but were inferior to placebo in terms of the patients' subjective global impression of change. An accompanying editorial (Thompson and Baker 2002) pointed out that the study was not powered to detect efficacy, and the writers drew attention to the difficulty in achieving the most appropriate individual dose by the oral route.

The very low water solubility of key cannabis constituents aggravates still further the well-known variability of absorption from the gastro-intestinal tract, resulting in poor predictability of both the timing and intensity of peak effects by the oral route. Titration of dose against symptom relief, as is the norm for most individuals who smoke cannabis medicinally, is very difficult in these circumstances. An additional drawback is the production of larger quantities of the reputedly psychoactive metabolite 11-OH-THC as a result of the hepatic first-pass phenomenon. The use of whole plant cannabis-based medicinal extracts in liquid form delivered by a pump action oromucosal spray (Whittle et al. 2001) represents an attempt to overcome these problems and permit the patient to self-titrate to an optimal individualised daily dose.

This mode of delivery was utilised in a consecutive series of double-blind, randomised, placebo-controlled single patient crossover trials with 2-week treatment periods (Wade et al. 2003). Twenty-four patients received whole plant extracts by oromucosal spray containing primarily THC, primarily CBD, an equal propor-

tion of THC and CBD, or matched placebo at doses determined by titration against symptom relief or unwanted effects within the range 2.5–120 mg/24 h (1–48 sprays). Eligible patients had neurogenic symptoms which had responded poorly to standard treatments, and the majority had MS or SCI. Patients recorded symptom, well-being and intoxication scores on a daily basis using visual analogue scales (VAS), completed standard measures of disability, mood and cognition on regular clinic visits, and recorded adverse events. Average dose following self-titration in the active treatment groups was around 9 sprays/24 h. At the nursing assessments, all three CBMEs significantly improved the subjective measure of spasticity in comparison with placebo, and both THC CBME and THC: CBD CBME improved muscle spasm. Patients' daily diaries showed that THC CBME significantly improved VAS scores of pain, muscle spasm and spasticity, THC: CBD CBME significantly improved spasm and sleep, and CBD CBME significantly improved pain. Four patients withdrew due to unwanted effects, and the percentage of patients with at least one adverse event was considerably higher when THC was not accompanied by an equal proportion of CBD (55% vs 30%). The authors concluded that CBME can improve neurogenic symptoms unresponsive to standard treatments, and that unwanted effects were predictable and generally well tolerated.

An important trial funded by the UK Medical Research Council ("CAMS" study) has explored the effects of synthetic THC (Marinol) and a cannabis extract ("Cannador") given orally on spasticity and other symptoms related to multiple sclerosis (Zajicek et al. 2003). This was a randomised, placebo-controlled trial involving 33 centres and 630 patients, and the primary outcome measure was change in overall spasticity score as represented by the Ashworth scale.

The results of the study were mixed, and a large placebo effect was noted. There was no change in Ashworth score following 15 weeks of treatment with either THC or Cannador, but both active treatments demonstrated significant improvements in subjective measures of spasticity, muscle spasms, pain and sleep, and also in an objective measure of mobility. No effect was apparent on irritability, depression, tiredness, tremor or loss of energy. The authors noted an unexpected reduction in hospital admissions for relapse in the two active treatment groups. The known interaction of cannabinoids with the immune system, and the fact that MS is still regarded as an auto-immune condition led them to comment that this finding was worthy of further investigation. Minor unwanted effects were frequently reported in all three treatment groups, with a higher prevalence for the active treatments. The small number of serious adverse events were evenly spread across the three groups.

The limitations of the Ashworth scale in measuring such a complex phenomenon as spasticity is well known (Hinderer and Gupta 1996) and is acknowledged by the authors. They also noted that the evidence in support of currently available standard drug treatments for spasticity (and many other MS-related symptoms) is weak. Although the study incorporated a titration phase, the fixed twice daily dosing routine was not ideal in seeking to allow patients to optimise the balance between positive and negative effects given the known variations in individual response. An accompanying Lancet editorial (Metz and Page 2003) drew attention to the high variability in degree of spasticity among the trial patients and com-

mented that the primary outcome measure does not correlate with function or other measures of spasticity. It recommended that "future studies should consider the potential confounding effect of including ... patients with severe spinal cord disease and should not rely totally on the Ashworth scale". It was also noted that poor bioavailability of oral cannabinoids may have influenced the outcome.

A significant effect upon a subjective measure of spasticity was the principal finding in another large study of cannabis-based medicine in MS (Wade et al. 2004). The effects of a whole plant extract containing an equal proportion of THC and CBD (Sativex) was compared with placebo in a parallel-group, double-blind, randomised study in 160 MS patients. Eligible patients were experiencing one of the following symptoms which had proved refractory to standard treatment: spasticity, muscle spasms, lower urinary tract symptoms, neuropathic pain or tremor. An oromucosal spray delivered 2.5 mg of each cannabinoid or matched placebo on each activation. After initial standardised dosing in an outpatient clinic, patients gradually titrated the dose upwards at home to a maximum of 48 sprays/24 h, aiming for an optimal balance between symptom relief and unwanted effects. Treatment period was 6 weeks, and the primary outcome measure was a composite derived from the VAS score of each patient's most troublesome symptom. Secondary measures were individual symptom VAS scores, and standardised measures of disability, cognition, mood, sleep and fatigue.

Once again, there was a strikingly large placebo effect. The composite score (max 100) following Sativex fell from a mean (SE) of 74.4 (11.1) to 48.9 (22.0) and from 74.3 (12.5) to 54.8 (26.3) following placebo (ns). Spasticity VAS scores fell by 31.2 following Sativex and by 8.4 following placebo [difference = –22.8; 95% confidence interval (CI): –35.52 to –10.07, $p = 0.001$]. Statistically non-significant improvements were also seen for spasms, bladder control and tremor. A similar pattern of responses was also noted from diary symptom VAS scores recorded by patients on a daily basis. Patients using Sativex assessed the quality of their sleep as significantly improved ($p = 0.047$). No significant adverse effects on cognition or mood were noted. Sativex was generally well tolerated. In particular, intoxication was usually mild, and largely avoidable with careful dose titration.

Clearly, further work is required to clarify the exact role of cannabis-based medicine in the symptomatic treatment of MS and SCI. Perhaps the position at the time of writing is best summarised by the comments of the Chief Executive of the Multiple Sclerosis Trust on the results of the CAMS study. In a press release on 7 November 2003, he stated:

> It is frustrating that the results of the study are somewhat equivocal. We are pleased that the CAMS study confirms the strong anecdotal evidence of the benefit of cannabis for some people with MS. It is particularly encouraging that patients receiving cannabis perceived an improvement in both spasticity and pain, when compared with those on placebo, and that no significant side-effects were reported. However, it is clear that the primary assessment tool used to measure spasticity, the Ashworth Scale, has failed to capture the full impact of this aspect of MS. Spasticity is a complex collection of symptoms encompassing pain and stiffness, some of which can only accurately be as-

sessed using subjective measures. However, overall, we believe that this study, combined with others which demonstrate symptomatic improvement, provides convincing evidence that cannabis may be clinically useful in treating some of the symptoms of MS.

2.2 Symptomatic Relief in Other Neurological Conditions

Stimulated by anecdotal reports that smoked cannabis improved a variety of movement disorders, Consroe and colleagues (1986) gave CBD 100–600 mg daily for 6 weeks to five patients with a variety of dystonic movement disorders. Dose-related improvements in dystonia were noted in all the patients, with maximal improvements ranging from 20% to 50%. Side-effects, described as mild, consisted of hypotension, dry mouth, sedation and light-headedness. However, CBD was "neither symptomatically beneficial nor toxic" in 10 patients with Huntington's disease at a dosage of 10 mg/kg/day for 6-week treatment periods (Consroe et al. 1991).

L-Dopa-induced dyskinesia (LDD) in Parkinson's disease (PD) presents a formidable therapeutic challenge. Overactivity in the lateral globus pallidus has been identified as a possible mechanism (Brotchie 2000) and, noting that this structure is rich in CB_1 receptors, Sieradzan et al. (2001) compared the synthetic THC analogue nabilone (0.03 mg/kg) with placebo in a double-blind, crossover trial in 7 patients. Mean total LDD score was significantly reduced following nabilone in comparison with placebo (17 vs 22, $p < 0.05$). Two patients were withdrawn following nabilone, one complaining of vertigo and the other because of postural hypotension. However, a further placebo-controlled study of 13 patients with primary dystonia (Fox et al. 2001) revealed no beneficial effect of nabilone. A recent survey (Venderova et al. 2003) identified 85 PD patients who had tried illicit cannabis for symptom relief, of whom 39 (45.9%) reported some improvement in rest tremor, bradykinesia, muscle rigidity or LDD. Interestingly, it took an average of 1.7 months for the benefit to appear, and improvement was recorded significantly more frequently by patients using cannabis for 3 months or more, and on a regular basis—at least once daily.

In a study primarily investigating possible appetite-stimulating effects of oral THC (dronabinol) in 12 patients with Alzheimer's disease (Volicer et al. 1997), the prevalence of disturbed behaviour measured by the Cohen-Mansfield Agitation Inventory (CMAI) was also assessed. Patients received THC 2.5 mg twice daily and placebo in a randomised, crossover design with 6-week treatment periods. THC significantly improved CMAI scores in comparison with placebo ($p = 0.05$). Unwanted effects included tiredness, somnolence and euphoria, and one patient experienced an epileptic convulsion (type not specified) soon after receiving the first dose of THC.

A few case studies have suggested that cannabis may produce beneficial effects in Tourette's syndrome (Sandyk et al. 1988; Hemming et al. 1993), although no clear rationale for a mechanism of action has been established. Muller-Vahl et al.

(1999) reported marked amelioration of both vocal and motor tics in an open trial of THC 10 mg in a 25-year-old patient. Improvement began 30 min after dosing, total tic severity was down from 41 at baseline to 7 at 2 h post dose, and benefit lasted for about 7 h. No adverse effects were reported. In a preliminary randomised, double-blind, placebo-controlled study (Muller-Vahl et al. 2003) THC in dosages up to 10 mg/day over a 6-week treatment period were compared with placebo in 24 patients with Tourette's syndrome. Seven patients dropped out, but even so there were some significant benefits for the active treatment using standardised outcome measures (e.g. Tourette Syndrome Symptom List). No serious adverse events were reported. On the basis of these findings the authors hypothesised that central cannabinoid receptors may play a part in the pathology of the syndrome.

2.3 Chronic Pain

Relief of intractable pain is one of the core historical applications of cannabis. There are many modern anecdotes as to its utility in cancer pain, bone and joint pain, migraine, menstrual cramps and labour pain (Grinspoon and Bakalar 1993). Cannabis has been shown to have a dose-dependent antinociceptive effect on experimental pain in healthy subjects (Greenwald and Stitzer 2000).

Unfortunately, scientific evidence for analgesic utility in humans remains scanty. Early studies evaluated oral THC or other synthetic cannabinoids in severe cancer-related, postoperative, or neurogenic pain. Noyes et al. (1975a) compared oral THC in single doses of 5, 10, 15 and 20 mg with placebo in a randomised, crossover design in 10 patients with cancer pain whose regular medication was withheld. A dose-related effect was observed, and the two higher doses gave significantly better pain relief than placebo, but these doses were associated with marked sedation. Other unwanted effects included slurred speech, blurred vision, mental clouding, dizziness and ataxia. Noyes' group went on to compare the efficacy of oral THC 10 and 20 mg with codeine 60 and 120 mg and placebo in a randomised, double-blind trial in 36 patients with cancer pain (Noyes et al. 1975b). A dose-related and equivalent analgesic effect was noted for both drugs, with the higher doses of both significantly superior to placebo. The effect of THC was maximal at 5 h (compared with 3 h for codeine) but 20 mg caused sedation and mental clouding in most patients. THC 10 mg was well tolerated but suitable only for mild pain.

Jain and colleagues (1981) compared intramuscular levonantradol (a synthetic cannabinoid) at several doses with placebo in a randomised, double-blind trial in 56 patients with severe postoperative or trauma pain. There was no apparent dose–effect relationship, but all doses of levonantradol were significantly superior to placebo. Unwanted effects were common but generally mild, with drowsiness occurring in almost half the subjects receiving active drug. Levonantradol subsequently disappeared without trace.

Two detailed single case studies were published in the 1990s. Maurer et al. (1990) compared the effects of oral THC (5 mg), codeine (50 mg) and placebo in a randomised, double-blind crossover study in a patient suffering severe pain

related to muscle spasticity. Analgesic effects of both active drugs were similar and both superior to placebo. It was noted that THC also significantly improved the spasticity. No adverse effects were reported. Holdcroft et al. (1997) compared oral THC (50 mg daily in divided doses) with placebo in a 6-week, double-blind, crossover trial in a patient who required daily morphine to control chronic pain associated with familial Mediterranean fever. The patient was allowed to take morphine tablets as required, and although VAS pain scores remained similar in the THC and placebo conditions, the morphine consumption was significantly reduced ($p < 0.001$) in the THC period.

This limited body of work was subjected to meta-analysis (Campbell et al. 2001), and the authors reached the following conclusion:

> Cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the central nervous system that limit their use. Their widespread introduction into clinical practice for pain management is therefore undesirable. In acute postoperative pain they should not be used. Before cannabinoids can be considered for treating spasticity and neuropathic pain, further valid randomised controlled studies are needed.

The validity of this conclusion was challenged by several correspondents to the editor of the journal. For example, Iversen (2001), noting that "a wealth of animal data support a role for cannabinoids in pain modulation" in contrast to the paucity of controlled human studies available for review, criticised the authors for "coming to a series of emphatic but ill-founded conclusions".

A further study of oral THC in postoperative pain has also given negative results (Buggy et al. 2003). THC 5 mg was compared with placebo in a randomised, double-blind, single-dose study in 40 women who had undergone abdominal hysterectomy. Measurement of summed pain-intensity difference at 6 h post dose revealed no difference between THC and placebo. However, there was also no difference between the groups in the incidence of adverse events, so the negative findings may be the result of a sub-therapeutic dose of THC.

Emerging evidence from basic science (e.g. Bridges et al. 2001; Fox et al. 2001; and Walker and Hohmann, this volume) implies that cannabis may benefit neuropathic pain. The 1997 National Institute of Health workshop on medical cannabis concluded: "Neuropathic pain represents a treatment problem for which currently available analgesics are, at best, marginally effective. Since Δ^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." The UK House of Lords Science and Technology Committee (1998) came to a similar conclusion: "... pain which originates from damaged nerves might respond to cannabinoids.... An example of such pain is phantom limb pain following amputation.... [There is] anecdotal evidence that cannabis can relieve this pain [and] ... trials of cannabis should be undertaken in such patients."

Notcutt and colleagues (1997) reported their qualitative experience of the use of nabilone (synthetic THC analogue) in the treatment of 43 patients with severe pain resulting from MS, SCI and other sources of peripheral or central nerve damage,

or malignancy. Of 43 patients, 25 were deemed to have benefited, and the main unwanted effects of nabilone were drowsiness and dysphoria.

More recent human studies focusing primarily on neuropathic pain have generally provided positive results. Wade et al. (2003) investigated the effects of three whole plant cannabis extracts (CBME) in a series of 24 single-case, double-blind, placebo-controlled crossover studies (see MS section above, Sect. 2.1, for details of the design) in patients with intractable neurogenic symptoms including pain. Significant analgesic effects in comparison to placebo were seen with both THC CBME and CBD CBME. The latter finding was considered particularly notable since CBD is a non-psychoactive cannabinoid. Using a similar design and the same extracts, Notcutt et al. (2002) reported the results of a series of trials involving 29 patients who were experiencing refractory pain as a result of MS or nerve damage following surgery or trauma. Significant improvements were seen in pain, sleep, depression, activity and general health. Three patients experienced postural hypotension during the initial self-titration, and some degree of intoxication was reported by several patients. One of these extracts (Sativex), containing equal proportions of THC and CBD, was compared with placebo in a double-blind, randomised trial over 3 weeks of treatment in 70 patients with chronic refractory neuropathic pain due to MS or other defects of neurological function (Sharief et al. 2004). Treatment difference in pain scores (BS-11) was 0.39 boxes in favour of Sativex ($p = 0.332$; 95% CI: –1.18, 0.4). Median percentage of days on which escape medication was used was 5% for Sativex and 45% for placebo ($p = 0.006$; 95% CI: –47.62, 0.00). Treatment was generally well tolerated, withdrawals were similar in both groups. Sleep disturbance was improved following Sativex ($p = 0.052$). The authors concluded that, on the basis of a reduced need for rescue medication, Sativex was efficacious in the treatment of chronic neuropathic pain.

Sativex has been the focus of two further controlled trials. Young and Rog (2003) compared it to placebo in a randomised, double-blind, parallel-group trial over 4 weeks of treatment in 64 patients with intractable central neuropathic pain due to MS. Patients were allowed to self-titrate their dose over a period of 1 week to a maximum of 48 sprays daily. At the end of the 4-week treatment period, pain relief following Sativex was significantly superior to placebo on both a BS-11 scale ($p = 0.005$) and the Neuropathic Pain Scale ($p = 0.039$). A subjective measure of sleep disturbance was also improved by Sativex ($p = 0.003$), and patients reported a greater overall impression of benefit following the CBME ($p = 0.005$). Most patients (88%) experienced at least one adverse effect on CBME (placebo = 69%) and one patient in the Sativex group withdrew from the study. Cognitive function was tested using the Brief Repeatable Battery of Neurological Tests. CBME showed a small but statistically significant difference ($p = 0.009$) in favour of placebo in one of the five components of the battery (the long-term storage component of the Selective Reminding Test). The authors concluded that Sativex was effective in reducing pain and sleep disturbance in MS-related central neuropathic pain, and is mostly well tolerated.

The effect of Sativex and THC CBME in treating refractory pain due to traction injuries of the brachial plexus has been studied in a randomised, placebo-controlled, crossover trial in 45 patients (McKerral et al. 2003). This injury produces

a highly characteristic pain syndrome that is particularly difficult to treat. The authors note that opioids, anticonvulsants and tricyclic antidepressants are routinely used in the treatment of this pain, but are partially effective at best. Eligible patients continued on previously stabilised medicines, and received each test medicine for 2 weeks. During the first week of each treatment period, they were instructed cautiously to self-titrate to an optimal individualised dose within a daily maximum of 48 sprays. Both CBMEs produced moderate but highly statistically significant improvements (Sativex: $p < 0.002$; THC CBME: $p < 0.005$) in BS-11 pain scores in comparison with placebo. Sleep quality was also significantly improved by both CBMEs. Average number of sprays/24 h was 9.2 (placebo), 7.3 (THC CBME) and 6.9 (Sativex). The authors speculated that these relatively low doses might have been a result of the relatively short treatment periods limiting scope for self-titration, the fact that patients remained on their pre-existing analgesics, and patients' need to avoid dosing if they intended to drive. Taking into account the low doses achieved and the refractory nature of this type of neuropathic pain, the authors concluded that CBME "may represent a significant advance in treatment."

A small controlled study (Svendsen et al. 2003) suggests that dronabinol (synthetic THC) may also be useful in MS-related pain. THC (maximum dose of 10 mg/day) was compared with placebo in a randomised, double-blind, crossover trial with 3-week treatment periods in 24 patients with central neuropathic pain. Spontaneous pain intensity and pain relief were both significantly improved by THC. There was no comment on unwanted effects in this conference abstract.

Abrams et al. (2003) reported the effects of smoked cannabis in painful peripheral neuropathy secondary to human immunodeficiency virus (HIV) and/or antiretroviral treatment. In a preliminary uncontrolled pilot study (in preparation for a planned placebo-controlled trial) "excellent" correlation was reported between cannabis dosing and pain improvement, with 10 of 16 participants experiencing a greater than 30% reduction in pain. These results provide the ethical justification to proceed with the controlled trial.

Finally, the synthetic cannabinoid CT-3 was compared (Karst et al. 2003) with placebo in a randomised, double-blind, crossover trial in 21 patients with chronic neuropathic pain (cause unspecified). In 1-week treatment periods, patients received 4 capsules (10 mg CT-3 or placebo) daily in divided doses for the first 4 days and 8 daily for the following 3 days. Pain VAS scores were significantly improved by CT-3 in comparison with placebo ($p = 0.02$), although there was no dose–response relationship. Unwanted effects (most commonly dry mouth and tiredness) occurred more frequently following CT-3. The authors concluded that this preliminary evaluation suggested that CT-3 was effective in reducing chronic neuropathic pain.

2.4 Effects on Nausea and Vomiting

Many cytotoxic drugs used in the treatment of malignant disease are powerful emetics, and the distress caused by drug-induced nausea and vomiting is the

major limiting factor in determining patients' acceptance of cancer chemotherapy (Carmichael 1992). Premedication with anti-emetics is routine, but severe vomiting induced by such drugs as cisplatin, dacarbazine or cyclophosphamide can be very difficult to control.

The anti-emetic properties of cannabis were rediscovered in the 1960s, when recreational users receiving cancer chemotherapy told their doctors it relieved their nausea. Anecdotal reports (e.g. Grinspoon and Bakalar 1993) preceded a range of controlled clinical trials in the 1970s and 1980s. These established that natural and synthetic forms of THC were invariably superior to placebo (Chang et al. 1979; Orr and Mckernan 1981; Jones et al. 1982). Controlled comparisons of THC with the anti-emetics available at the time suggested that it is either equivalent (Ungerleider et al. 1982) or superior (Formukong et al. 1989; Plasse et al. 1991; Orr and Mckernan 1981; Einhorn et al. 1981; Niiranen and Mattson 1985; Dalzell et al. 1986; Niederle et al. 1986; Pomery et al. 1986; Chan et al. 1987; Penta et al. 1981; Levitt 1986) to such drugs as prochlorperazine, domperidone, alizapride, dexamethasone and metoclopramide. Commonest unwanted effects included somnolence, dry mouth, ataxia, dizziness, dysphoria, and postural hypotension. Oral THC and nabilone often produced more unwanted effects than comparison drugs, yet THC was usually preferred by patients (Ungerleider et al. 1982; Einhorn et al. 1981; Niiranen and Mattson 1985; Dalzell et al. 1986).

Penta and colleagues (1981) reviewed 12 studies that examined the anti-emetic effects of THC (9) or nabilone (3) involving 600 patients. They reported that THC was "effective" in 8/9 and nabilone in 3/3. Levitt (1986) reviewed 55 studies, of which 32 were of randomised, double-blind design. Low-dose preventative treatment gave better results than targeting established vomiting. Levonantradol produced a higher frequency of dysphoric effects than nabilone or THC. A review by Formukong et al. (1989) suggested that the emesis produced by certain drugs (e.g. methotrexate, doxorubicin, cyclophosphamide, fluorouracil) responded better to THC than others (e.g. nitrosoureas, mustine, cisplatin). Younger patients responded better than older. Plasse and colleagues (1991) reviewed clinical experience with dronabinol (capsules of THC in sesame oil), which was first marketed in the U.S. in 1987. Meta-analysis suggested that an optimal balance of efficacy and unwanted effects is achieved with relatively modest doses of THC (i.e. 7 mg/m^2 or less). Sedation and psychotropic effects were commonly reported but were usually only of mild to moderate intensity and resolved rapidly on discontinuation.

Children seemed to respond well to nabilone (Dalzell et al. 1986; Chan et al. 1987) and to be tolerant of adverse effects, but confirmation is required. A small pilot study (Abrahamov et al. 1995) indicated a positive response to Δ^8-THC in 8 children receiving highly emetic antineoplastic therapy for various blood cancers. Vomiting was reported in 60% children receiving metoclopramide, but when Δ^8-THC was given orally 2 h before chemotherapy and repeated every 6 h for 24 h, no vomiting occurred on any of the 480 occasions this strategy was applied. Two children reported unwanted effects: both were "slightly irritable" and one (age 4) showed "slight euphoria". Surprisingly, this very promising result has not been followed up with a more definitive study.

The introduction of the highly effective (though expensive) 5-HT_3 antagonists including granisetron, ondansetron and tropisetron seems to have undermined interest in cannabis-based medicines for this indication. There have been no recent trials, so no information is available as to how they may compare with these newer and highly effective treatments. However, the combination of an anti-emetic effect alongside other attributes (e.g. analgesia, muscle relaxation, sedation) still provides a compelling case for exploration of a potential role for cannabinoids in conditions such as acquired immunodeficiency syndrome (AIDS), cancer, or perioperative pain. Of additional interest is the emerging evidence that non-psychoactive cannabinoids such as CBD may have anti-emetic properties (Parker et al. 2002; Javid et al. 2002).

2.5 Appetite Stimulation

Recreational users are familiar with the appetite-stimulating effect of cannabis ("the munchies"), and controlled studies in healthy subjects have confirmed this (Hollister 1971; Foltin et al. 1986). Kirkham and Williams (2001) have provided a comprehensive review of the effects of exogenous and endogenous cannabinoids on appetite and weight in animals and humans. There appears to be a link to the reward mechanisms that mediate the incentive value of food.

Open studies in cancer patients (Plasse et al. 1991; Nelson et al. 1994) suggested that THC has a positive effect on appetite and weight. In a double-blind study in 54 patients with various cancers, Regelson et al. (1976) found that oral THC (0.1–0.4 mg/kg four times daily) produced a significant ($p < 0.05$) gain or preservation of weight in comparison with placebo. THC also improved depression and "tranquillity" scores, but somnolence, dizziness and disassociation were troublesome in a quarter of the patients and led to 9 dropouts. A more recent study (Jatoi et al. 2002) compared dronabinol alone (2.5 mg BD) or in combination with megestrol acetate (MA: 800 mg/day) with MA alone in 469 patients with advanced cancer who were troubled with recent poor appetite or weight loss of at least 2.268 kg (5 lb). MA alone was significantly superior to dronabinol alone ($p = 0.0001$ for appetite; $p = 0.02$ for weight gain), and the addition of dronabinol to MA resulted in no significant improvements in appetite or weight over those that occurred with MA alone. Impotence was a significant problem for MA-treated men. The relative absence of typical THC-related unwanted effects suggests a sub-optimal dose.

Progressive weight loss is a major problem in AIDS. Beal and colleagues (1995) carried out a randomised, controlled trial of dronabinol in 139 late-stage AIDS patients (of whom 88 were "evaluable") who had experienced at least 2.5 kg reduction from their normal weight. Oral THC 5 mg daily significantly improved appetite in comparison with placebo ($p < 0.015$) and also reduced nausea ($p = 0.05$). There was a trend towards mood improvement in the dronabinol group ($p = 0.06$) and there was a tendency toward weight gain. THC produced significantly more adverse effects than placebo ($p < 0.001$), the most frequent being euphoria, dizziness, "thinking abnormalities", and sedation, but three quarters of these fell into the

mild or moderate categories. Drop out rates between active and placebo groups were similar. Beal et al. (1997) followed up 94 patients from this study for a further 12 months. These subjects continued to receive dronabinol 2.5 mg once or twice daily, and consistent improvement in appetite was noted, typically at least twice baseline levels. Unwanted effects were as expected from a THC-containing medicine but were generally well tolerated.

Apart from appetite improvement, AIDS patients have reported a number of other benefits from cannabis including reduction in nausea, reduced anxiety, relief of aches and pains, improved sleep, and inhibition of oral candidiasis (Grinspoon and Bakalar 1993; Plasse et al. 1991). Commonest reasons for smoking cannabis given in a recently published survey (Sidney 2001) of HIV-positive subjects were to feel better mentally or reduce stress (79%), improve appetite or gain weight (67%) and decrease nausea (66%).

The study team who conducted the U.S. Institute of Medicine Review (1999) concluded (page 177), "For patients such as those with AIDS or who are undergoing chemotherapy, and who suffer simultaneously from severe pain, nausea, and appetite loss, cannabinoid drugs might offer broad-spectrum relief not found in any other single medication."

Concern has been expressed that HIV-infected individuals may be more vulnerable to the immunosuppressive effects of cannabis or THC. Kaslow and colleagues (1989) monitored the progress of nearly 5,000 HIV-positive men for 18 months and found no evidence that use of psychoactive substances (including cannabis) had any discernable effect upon T helper lymphocyte counts or progression to AIDS. A randomised controlled trial (Bredt et al. 2002) compared the effects of marijuana cigarettes (0.9 g, 3.95% THC, up to 3 daily), dronabinol (2.5 mg up to 3 times daily) and placebo over a 3-week treatment period in 62 HIV-positive subjects being treated with protease inhibitor anti-retroviral drugs. Neither active treatment produced any significant effects on the percentage of $CD4^+$ and $CD8^+$ T cells, T cell activation, changes in cytokine flow cytometry, natural killer cell number and function, or in a lymphoproliferation assay. Within the limitations of a short-term study, the authors concluded that there were no detrimental effects of cannabinoids on any of the immune parameters measured. A separate analysis of the same patient group (Abrams et al. 2003) revealed no significant effects on viral load as represented by HIV RNA levels.

Another condition frequently associated with decreased appetite and malnutrition is senile dementia of Alzheimer type. Eleven patients with Alzheimer's disease were treated for 12 weeks on an alternating schedule of dronabinol (THC: 2.5 mg twice daily) and placebo (6 weeks of each treatment). The dronabinol treatment resulted in substantial weight gains and a decline in disturbed behaviour (Volicer et al. 1997). No serious side-effects were observed. One patient had a seizure and was removed from the study, but the investigators were unsure whether this was attributable to dronabinol. Patel and colleagues (2003) recently reported an open study in this population. Forty-eight patients with Alzheimer's disease with uncontrolled agitation and anorexia were given dronabinol 5–10 mg daily for a month. The authors reported weight gain in all patients.

2.6 Appetite Suppression in Obesity

A growing understanding of the role of central cannabinoid systems in the regulation of appetite (Williams and Kirkham 1999) has raised the possibility that blocking CB_1 receptors might inhibit appetite (Kirkham 2003). Testing this hypothesis has become a possibility with the development of the selective CB_1 receptor antagonist SR141716A (rimonabant). Studies in various animal models have demonstrated that this produces marked reduction of food intake, body weight and adiposity (e.g. Ravinet et al. 2002).

At the time of writing, seven phase III clinical trials are in progress focusing on rimonabant's effect on weight loss and smoking cessation. None of these has yet been published in peer-reviewed journals, but two have been completed and the results presented at a U.S. cardiology conference in 2004. According to information supplied by the manufacturer, overweight patients treated with rimonabant 20 mg daily for 1 year lost significantly more weight than placebo patients ($p < 0.001$). Improvement in some associated cardiovascular risk factors (e.g. waist circumference, HDL cholesterol and triglyceride plasma levels, C-reactive protein levels) were also reported. Unwanted effects were described as consisting mainly of mild and transient nausea and dizziness, though twice as many patients dropped out on rimonabant 20 mg than placebo. A second study suggested that smokers seeking abstinence were twice as likely to be successful when treated with rimonabant 20 mg for 10 weeks in comparison with placebo ($p = 0.002$). Rimonabant also appeared to protect against the weight gain commonly seen following smoking cessation. Once again, however, there were twice as many dropouts on active treatment. It must be noted that these results await peer review.

2.7 Glaucoma

Glaucoma is the commonest cause of blindness in the Western World. Raised intraocular pressure (IOP) is usually due to an obstruction to the outflow of aqueous humour at the front of the eye, and by far the commonest deficit is primary open-angle (chronic simple) glaucoma. A range of topical and systemic drugs are used to treat this, but efficacy is variable and there are many possible unwanted effects.

The discovery that cannabis lowers IOP was first reported by Hepler and Frank (1971), and the mechanism by which this is achieved still remains to be clarified. Controlled studies in healthy subjects (Hepler et al. 1976; Perez-Reyes et al. 1976; Jones et al. 1981) have shown that oral, injected or smoked THC produces dose-related reductions of IOP as much as 30% below baseline, though tolerance may occur on chronic dosing.

In the 1970s, anecdotal reports of symptom relief by smoked marijuana appeared and a small number of glaucoma patients successfully argued in the U.S. for legal access to the drug (Grinspoon and Bakalar 1993). Hepler and colleagues (1976)

carried out a pilot study of smoked marijuana and oral THC (15 mg) in 11 patients. IOP reductions averaging 30% were seen in 7, whilst 4 had no response.

Two small placebo-controlled studies of smoked and topical THC confirmed a significant IOP reduction in glaucoma patients. Merrit and colleagues (1980) compared smoked THC (2%) with placebo in a double-blind parallel-group study in 18 patients. IOP was significantly reduced in comparison with placebo between 1.5 and 2.5 h after dosing. Unfortunately, these effects were accompanied by reductions in blood pressure, increases in heart rate, and "alterations in mental status" which were not propitious for clinical utility. Merritt (1981) went on to investigate THC eye-drops in a double-blind, placebo-controlled study in 8 patients. Dose-related reductions in IOP were recorded using 0.05% and 1% drops with minimal unwanted effects. Parallel reductions were noted in the untreated eye, suggesting a systemic rather than a local mode of action.

It is now apparent that raised IOP is not the only pathological mechanism in glaucoma. Impaired auto-regulation in arteries supplying the optic nerve head may interfere with perfusion and cause neural damage (Prunte et al. 1998). The discovery that CB_1 receptors are present in micro-vasculature (Sugiura et al. 1998) and the ability of endogenous cannabinoids to produce vasodilation (Sugiura et al. 1998) suggests the possibility that exogenous cannabinoids may alleviate this deficit. Antioxidant and *N*-methyl-D-aspartate (NMDA) receptor neuroprotective properties of cannabinoids (Hampson et al. 1998) raise the hope that they might improve survival of ischaemic retinal ganglion cells. Future prospects have been reviewed by Jarvinen et al. (2002). Non-irritant local delivery using cyclodextrins and non-psychoactive cannabinoids offers considerable promise.

2.8 Epilepsy

Epilepsy afflicts around 1% of the world's population, and historically was an important target for medicinal cannabis (O'Shaugnessy 1843; Reynolds 1890). Modern anti-epileptic drugs fail to provide satisfactory control in up to 30% of patients, and all can produce disabling or even life-threatening unwanted effects.

A confusing picture emerges when cannabinoids are evaluated in animal models of epilepsy (Karler and Turkanis 1981; Consroe and Snider 1986). CBD has anticonvulsant properties with a spectrum distinct from standard anticonvulsants, apparently not hampered by the development of tolerance but with a varying profile according to the species tested. THC can produce seizures in some circumstances but is anticonvulsant in others. In a recent study, THC (10 mg/kg) completely abolished spontaneous seizures in the rat pilocarpine model of epilepsy (Wallace et al. 2003). The results also indicated that endogenous cannabinoid tone may modulate seizure termination and duration via the CB_1 receptor.

Human research data are almost non-existent. There are anecdotal reports of beneficial effects of cannabis in human epileptics (Grinspoon and Bakalar 1993) and a couple of published single case reports. A man with grand mal epilepsy stopped taking his anticonvulsants and suffered no fits for 6 months. He then

smoked cannabis on seven occasions over a 3-week period and suffered three fits during this time, though these were unrelated to periods of intoxication (Keeler and Reifler 1967). In contrast, a young man whose seizure control was poor began smoking 2–5 cannabis cigarettes nightly in addition to his conventional medication and found this terminated his seizures (Consroe et al. 1975).

One solitary controlled trial is on record, comparing CBD (200–300 mg daily for up to 4.5 months added to standard therapy) with placebo in a double-blind, parallel-group design in 15 poorly controlled patients with "secondary generalised epilepsy" (Cunha et al. 1980). Half the CBD patients remained "almost free" of fits throughout the experiment and all but one of the others showed "partial improvement". With a single exception, the placebo patients remained unchanged. Drowsiness in a quarter of the patients was the only unwanted effect associated with CBD.

In view of the continuing uncertainty as to whether cannabis and its constituents pose a risk to individuals with past or present epilepsy or on the contrary offer a novel mode of treatment, a properly powered controlled trial is urgently required.

2.9 Psychiatric Disorders

There is some evidence that nabilone may have an anxiolytic effect. Fabre and McLendon (1981) compared nabilone 3 mg daily with placebo in a randomised, double-blind, parallel-group study in 20 anxious patients. "Dramatic improvements" in anxiety scores were reported for nabilone relative to placebo ($p < 0.001$). Commonest unwanted effects were dry mouth, dry eyes and drowsiness. Ilaria et al. (1981) compared nabilone 2–5 mg daily with placebo in a double-blind crossover study over a 2-week period in 11 anxious patients. Significant improvements in outcome scores were accompanied by postural hypotension in most patients, though this tended to tolerate out over time.

Cannabis and THC are known in certain circumstances to induce anxiety or panic, and Zuardi and colleagues (1982) reported that CBD antagonises anxiogenic effects of THC along with some other marijuana-like effects in healthy volunteers. At a dose of 300 mg orally it reduced anxiety in comparison with placebo in a simulated public speaking task (Zuardi et al. 1993). CBD was also found to behave like an atypical antipsychotic in the apomorphine-induced stereotypy model in rodents (Zuardi et al. 1991). In a report of a single case, CBD (in doses up to 1500 mg/day) was found to improve psychotic symptoms without toxic effects in a psychotic patient who had experienced intolerable unwanted effects with haloperidol (Zuardi et al. 1995).

A controlled trial in 15 insomniac volunteers suggested that CBD (160 mg) may be an effective hypnotic (Carlini and Cunha 1981), but in a more recent sleep laboratory study in healthy subjects (Nicholson et al. 2004) much smaller doses of CBD (5 and 15 mg) appeared to have alerting properties. When CBD (15 mg) was given in combination with THC (15 mg) at 10 pm, it counteracted the morning-after sedative effects seen when THC was given alone and increased wakeful activity

during sleep. Effects on sleep architecture were modest, but some effects of both cannabinoids on slow wave sleep were reported. Overall, these results suggest that the improvement in sleep quality frequently reported in clinical trials is mainly due to nocturnal symptom relief rather than a primary hypnotic effect.

THC (0.1 mg/kg) was reported to have anti-depressant properties in cancer patients (Regelson et al. 1976). There are anecdotal reports that cannabis may act as a mood stabiliser in bipolar affective disorder (Grinspoon and Bakalar 1998).

The discovery that the endogenous cannabinoid system has a central function in extinction of aversive memories (Marsicano et al. 2002) raises the fascinating possibility that CB_1 agonists may prove therapeutic in phobias or post-traumatic stress disorder.

2.10 Asthma

Although cannabis was used as a bronchodilator in the nineteenth century, modern human research seems to have been limited to a brief period in the 1970s. Small controlled studies in asthmatic volunteers (Tashkin et al. 1974; Williams et al. 1976; Tashkin et al. 1977) showed that oral, smoked and aerosolised THC had significant bronchodilator activity comparable to that of salbutamol, though slower in onset. Dose-related tachycardia and intoxication occurred at higher doses. An inhaled aerosol avoided systemic absorption of THC but induced cough and chest discomfort, which limited its usefulness.

3 Safety Issues with Cannabis-Based Medicines

Cannabis is known to demonstrate very low acute toxicity. To the best of this author's knowledge, it remains the case that no human death has been reliably ascribed to cannabis toxicity alone. It has been estimated, based on extrapolation from mouse to man, that the lethal dose to effective dose ratio is around 40,000:1 (Grinspoon and Bakalar 1993, p 138). Minor adverse events (AEs) including intoxication, dizziness and dry mouth occur frequently with THC-containing medicines, but are generally mild or moderate in intensity and well tolerated by patients. In a recent large study (Zajicek et al. 2003), out of 417 patients allocated to THC or cannabis extract, only 9 patients discontinued treatment because of intolerable AEs, and serious or life-threatening AEs were no more frequent following active treatments than placebo.

Cannabis and THC are known to increase heart rate, cardiac output and supine blood pressure, and can cause orthostatic hypotension (Jones 2002). Because of the resulting increase in cardiac work, cannabis and THC are probably best avoided by patients with clinically significant cardiovascular disorders. Cardiovascular effects tend to tolerate out over chronic dosing (Benowitz and Jones 1981). A survey of myocardial infarction survivors set out to investigate whether smoking marijuana

might have been a trigger for this event (Mittleman et al. 2001). Unfortunately, only 124 of the 3,882 patients surveyed admitted to smoking marijuana. The risk of infarction appeared to be elevated 4.8 times over baseline during the 60 min following marijuana use but decreased rapidly thereafter. However, this conclusion has been much criticised, not least because the sample of subjects upon which it is based (those who had smoked cannabis within 1 h of infarction) amounted to only 9 individuals, of whom 3 admitted at least one other "triggering activity" (e.g. cocaine use or sexual intercourse). Epidemiological data on 65,000 patients in the San Francisco Bay Area do not support an increased risk of cardiac events in cannabis smokers (Sidney et al. 1997).

Animal and human data regarding effects of recreational cannabis on fertility, pregnancy and birth outcomes, teratogenicity, and possible neurodevelopment effects on the infant are conflicting and no clear conclusions are possible. In these circumstances, it would be prudent for couples seeking to conceive and pregnant women to avoid cannabis-based medicines. THC is transferred into breast milk and may reach concentrations eight times higher than those in maternal plasma (Astley and Little 1990).

3.1 Cognitive/Motor Effects

Any medicine containing THC may produce similar acute cognitive effects to recreational cannabis if taken in sufficient dosage. These effects include: euphoria, sensory enhancement, increased social conviviality, and a sense of relaxation and contentment; perceptual effects including distorted time and space estimation and alteration in sensory modalities; impairment in both sustained and divided attention; impairment in reaction time, motor control and dexterity; impairment in various aspects of memory and higher cognitive function including associative and abstractive processes, planning and organisational strategies (reviewed by Solowij 1998: pp 29–40). The possible implications for those receiving cannabis-based medicines who wish to continue driving have been reviewed by Hadorn (2004). Interestingly, analysis of responsibility for traffic collisions has repeatedly indicated that drivers with only cannabis in their systems (and especially no alcohol) were, if anything, less culpable than drug-free drivers. In prospective studies using driving simulators or road tests, cannabis does impair subjects' ability to maintain road position and constant following distances. However, cannabis users generally seem aware of being impaired and compensate by driving more cautiously. Alcohol consistently produced greater impairment than cannabis in comparable social doses, tended to induce more aggressive driving and, in contrast to cannabis smokers, alcohol subjects lacked insight into their impairment and thus made no attempt to compensate. These studies suggest that, as should be the case with many other prescribed drugs, patients receiving cannabis-based medicines should simply be warned to avoid driving and other potentially hazardous tasks at any time they feel impaired.

Do any of these acute deficits persist after cannabis has been discontinued and fully metabolised? A large and expanding scientific literature has still not fully resolved this question. Recognising the methodological shortcomings that have dogged much of this research, Gonzalez et al. (2002) proposed seven "minimal criteria" which should be applied to any study purporting to explore non-acute cognitive effects of cannabis: only 13 out of 40 eligible studies met these basic criteria. The authors point out that negative results have been disseminated in the media without any acknowledgement of these serious shortcomings.

A major problem lies in distinguishing long-lasting but reversible residual effects (due to slow metabolism of cannabis components or withdrawal phenomena) from irreversible effects. Pope et al. (2002) tested 77 current heavy users and 87 controls. The former showed significant memory deficits at 0, 1 and 7 days of abstinence, but by day 28 were virtually indistinguishable from control subjects. There was no association between duration of cannabis use and cognitive performance after 28 days of abstinence. This conflicts with the finding of Solowij et al. (2002) that deficits on several neuropsychological measures were correlated with lifetime duration of cannabis exposure. In seeking to explain this, Pope et al. (2002) point out that even well-controlled studies depend on the assumption that, after adjustment for more obvious confounding factors, cannabis users and non-users are comparable on all factors other than exposure to cannabis. Additionally, heavy use of an illegal drug may produce non-pharmacological deficits such as family alienation or school drop-out that impact outcome measures. Grant et al. (2003) carried out a meta-analysis of studies examining non-acute cognitive effects, and found no substantial, systematic or detrimental effect of recreational cannabis on neuropsychological performance. They concluded:

> The small magnitude of effect sizes from observations of chronic users of cannabis suggests that cannabis compounds, if found to have therapeutic value, should have a good margin of safety from a neurocognitive standpoint under the more limited conditions of exposure that would likely obtain in a medical setting.

3.2 Dependency/Abuse

Properties of THC that may have a bearing on its dependency and abuse potential have been investigated in numerous animal models, but how reliable these may be in predicting human behaviour is open to question. Despite the cripplingly expensive War on Drugs, recreational cannabis is still easily available, cheaper in real terms and used extensively throughout the world, so it seems sensible to examine what actually happens outside the laboratory.

The evidence for cannabis dependence in humans has been reviewed by Johns (2001). Characteristic components of a dependence syndrome are the need over time to take more of the drug to maintain the desired effect (tolerance), a predictable group of symptoms and signs over a consistent time course when the drug

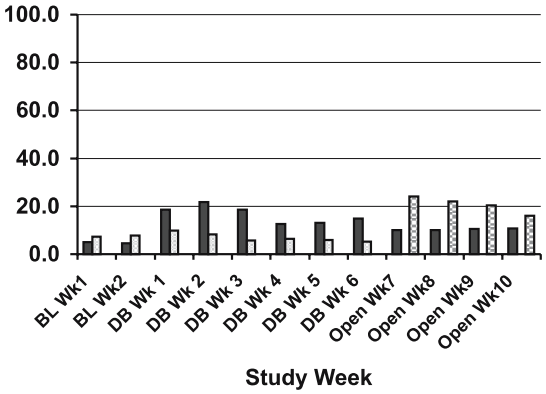
is withdrawn, difficulty in keeping consumption under control, and a preoccupation with the drug that interferes with the normal activities of living.

Tolerance to the subjective effects of marijuana has been reported (Georgotas and Zeidenberg 1979), and a minority (16%) of regular smokers experienced at least one of the following symptoms following abrupt withdrawal of cannabis: irritability, insomnia, tremor, sweating, gastro-intestinal disturbance or appetite change (Wisbeck et al. 1996). These effects peak between 2 and 6 days after abrupt withdrawal (Budney et al. 2003). It has been reported that a third of regular users experienced some difficulty in controlling their use of the drug (Thomas 1996). All research in this area is dogged by serious methodological problems, including highly selected samples, non-validated measures, poor response rates in community surveys, and the existence of many confounding variables. However, it seems reasonable to accept that psychological dependence will occur in a small minority of cannabis smokers. The existence of a clear-cut physical dependence syndrome is much less convincing on the basis of the published literature. If it exists at all, it is probably mild and transient, and is likely to consist of a few days of sleep disturbance and somatic symptoms of anxiety in heavy daily users who abstain abruptly.

In an interview study (Robson and Bruce 1997), the dependence potential of various street drugs was assessed in 201 problem and 380 "social" users of heroin, cocaine or amphetamine using the well-validated Severity of Dependence Scale (SDS). Scores (maximum = 15) in the problem group were 12.9 for heroin, 9.6 for other opioids, 6.1 for amphetamine and 5.5 for crack cocaine. All of these scores were consistent with findings in other studies. Cannabis SDS score was 2.6 and comparable with those of LSD (3.1) and ecstasy (1.3), two drugs that are generally not associated with physical or psychological dependence. In the parallel sample of social users, the cannabis SDS was similar at 3.4.

Attempting to define and investigate cannabis dependence in patients is still more challenging, especially if the individual is experiencing a beneficial therapeutic effect. Developing an emotional attachment or preoccupation with a drug that has helped with previously intractable, life-impairing symptoms is a very different matter from becoming over-preoccupied with a recreational drug. It would hardly be surprising for a patient abruptly denied such a medicine to yearn for it and become preoccupied with re-establishing a supply. Is the diabetic addicted to insulin? Experience in the therapeutic setting with much more powerfully addictive drugs than cannabis is encouraging. For example, the abuse of opiates is extremely unusual among patients treated appropriately for pain and other symptoms (Porter and Jick 1980; Portenoy 1990), and this is very likely to be the case with cannabis-based medicines. Support for this is provided by the intoxication data from a recent study (Wade et al. 2004) comparing a THC-containing cannabis extract (Sativex) with placebo for a 6-week treatment period in patients with MS. At the end of the trial, all patients re-titrated on to the active medicine for a further 4 weeks. Intoxication scores were recorded in a daily diary on a 100 mm VAS scale shown in Fig. 1. Average peak scores reached only around 20/100, and levels appeared to diminish over time. There was no evidence that Sativex was abused by any of these patients.

Figure One - Diary Card Intoxication Scores



presence or direction of causality. Five prospective studies have been subjected to critical review (Arsenault et al. 2004). The authors' conclusion was that cannabis smoking by young adolescents confers an overall twofold increase in the risk of developing schizophrenia. However, they state that "cannabis use appears to be neither a sufficient nor a necessary cause for psychosis. It is a component cause, part of a complex constellation of factors leading to psychosis". They further conclude:

> Although the majority of young people are able to use cannabis in adolescence without harm, a vulnerable minority experiences harmful outcomes. The epidemiological evidence suggests that cannabis use among psychologically vulnerable adolescents should be strongly discouraged by parents, teachers and health practitioners alike.

However, the five studies reviewed in this paper have been criticised elsewhere for methodological shortcomings including: presence of clinical or sub-clinical psychiatric illness prior to cannabis consumption; lack of a clear temporal link between cannabis use and subsequent psychiatric illness; poor reliability of the diagnosis of schizophrenia; confusion between acute toxic states and functional mental illness; confusion of association with causation; confounding effects of other recreational drugs and environmental risk factors for mental illness; unreliability of self-report of an illegal activity; and a lack of a correlation in epidemiological studies between prevalence of cannabis consumption and schizophrenia. The UK Advisory Council on the Misuse of Drugs (ACMD) reviewed the evidence in depth and concluded (2002, p. 8) "... no clear causal link has been demonstrated." Degenhardt and Hall reached a similar conclusion (2002): "Time trends in schizophrenia and cannabis use are not consistent with the hypothesis that cannabis use causes schizophrenia de novo."

In conclusion, the link between functional mental illness and recreational cannabis use in previously healthy subjects with no psychiatric history remains controversial, and a causative link has not yet been established. However, it would seem advisable for individuals with existing psychiatric illness or a strong family history to avoid THC-containing medicines.

4 Future Directions

Notwithstanding all the hard work summarised above, the scientific evaluation of medicinal cannabis in humans is in its infancy. The role of cannabis-based medicines in all the clinical indications so far discussed requires clarification through further well-controlled, adequately powered randomised trials. The rapidly expanding knowledge of the structure and function of the endocannabinoid system raises the hope of exciting new pharmacological entities. To give a few examples: It may be possible to enhance the activity of endocannabinoids by inhibiting degradation mechanisms such as fatty acid amide hydrolase, and since there appears to be local up-regulation of endocannabinoids in certain pathological conditions, this gives the added possibility of site selectivity (Baker et al. 2001); the discovery

that the CB_2-selective cannabinoid agonist AM1241 suppresses capsaicin-evoked thermal and mechanical hyperalgesia and allodynia (Hohmann et al. 2004) along with associated pain behaviour in rats raises the possibility of novel treatments for pain, free from unwanted psychoactive effects; it may be possible to develop CB_1 agonists that do not cross the blood–brain barrier (Chaperon and Thiebot 1999). Other possibilities are discussed elsewhere in this book, but these developments are all for the future. Of more immediate concern is the question as to which new directions are worthy of clinical pursuit with the synthetic and plant-derived materials available right now?

The answer to that question will reflect to some extent the personal interests of the respondent, but it seems logical that target conditions should satisfy at least one of the following two requirements: historical or anecdotal evidence which suggests that cannabis may be helpful, and currently available treatment is unsatisfactory either because of limited efficacy or unacceptable toxicity; the activity profile of cannabis or its components in some relevant in vitro or in vivo models indicates a potentially beneficial effect on symptoms/signs or disease progression. Given the rapid expansion in basic research involving both exogenous and endogenous cannabinoids over recent years, there are many conditions that satisfy both requirements. The following is by no means an exhaustive list.

4.1 Inflammatory Conditions

These disorders certainly satisfy both the above categories. Musculoskeletal pain features prominently in historical accounts. In a recent survey (Ware et al. 2003) of 2,969 people who agreed to fill in a questionnaire about medicinal cannabis, nearly a quarter gave symptom relief for arthritis as the reason for smoking cannabis. This was the fourth-commonest indication after chronic pain, MS and depression. Elucidation of the anti-inflammatory and immunomodulatory effects of several cannabis constituents (see chapters by Cabral and Staab, this volume, and Pertwee, also in this volume) has provided a strong scientific rationale for clinical evaluation. Of particular relevance was the discovery (Malfait et al. 2000) that CBD given either intraperitoneally or orally inhibited disease progression in a murine model of rheumatoid arthritis (RA). Clinical improvement and joint protection were related to a combination of lymphocyte and granulocyte suppression and inhibition of the inflammatory cytokine tumour necrosis factor (TNF). RA is the commonest form of inflammatory arthritis and afflicts up to 3% of the population of Western countries. Non-steroidal anti-inflammatory drugs and corticosteroids form the backbone of treatment, but are often seriously toxic. TNF antagonism looks a promising approach (Taylor 2001) but available agents (e.g. etanercept, infliximab) are expensive and have to be given by injection.

The combination of analgesic and anti-inflammatory effects is also highly relevant for inflammatory bowel conditions such as Crohn's disease. Dysregulation of immune mechanisms are strongly implicated in the disease process with excess production of inflammatory cytokines, particularly TNF, by lymphocytes and

macrophages in the gut wall. Disruption of mucosal function leads to chronic diarrhoea and weight loss. In these circumstances certain cannabinoids may produce beneficial symptomatic effects by depressing gastrointestinal motility, delaying gastric emptying, and inhibiting peristalsis by both central and peripheral mechanisms (Pertwee 2001). Examination of human biopsy specimens has demonstrated the presence of CB_1 receptors in the epithelium and smooth muscle of both normal and diseased colon, implying a role for the endocannabinoid system in gastrointestinal physiology (Wright et al. 2003).

4.2 Chronic Nociceptive Pain

Existing (albeit flawed) research reviewed above suggests that cannabis and THC offer few advantages over standard treatments for nociceptive pain, but recent research has indicated that a combination of THC with opioids may provide benefits greater than the sum of the two parts. This synergy was certainly recognised by nineteenth century physicians.

The combination of analgesic agents with different modes of action is a well-accepted principle (Dahl and Raeder 2000), and the anti-emetic activity of THC is important since nausea and vomiting are the most troublesome and dose-limiting unwanted effects of opioids. However, the important work of Welch, Cichewicz and colleagues shows that the advantages go well beyond this. Small doses of THC not only enhance the analgesic effects of opioids (Cichewicz and McCarthy 2003) but also prevent the development of tolerance and physical dependence (Cichewicz and Welch 2003) and extend the duration of action of both morphine and codeine (Cichewicz et al. 2003). Clinical research to explore the exciting potential of this combination in humans is urgently required, and at the time of writing a large multi-centre study of THC in combination with patient-controlled morphine analgesia in postoperative patients is getting underway in the UK.

4.3 Neuroprotection

Brain trauma or ischaemia and a range of neurodegenerative disorders including MS, Parkinson's disease, Huntington's disease, Alzheimer's disease and motor neuron disease share common mechanisms of neuron damage. These include excitotoxic effects resulting from excessive release of glutamate, which massively increases intracellular calcium concentration through overstimulation of NMDA, *S*-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors, and damage from reactive oxygen species. Following the demonstration by Hampson and colleagues (1998) that both THC and CBD could protect against these effects in vitro, there is now a considerable literature in this area (see chapters by Pertwee and Guzmán, this volume). Encouraging results have been found in animal models of cerebral ischaemia, closed head injury, Hunting-

ton's disease, Parkinson's disease, amyotrophic lateral sclerosis (SOD_1 model), and soman-induced seizures. Vulnerability to excitotoxicity is probably a major factor in the progression of MS, so the discovery that CB_1 agonists limit neurodegeneration in an animal model of MS (Pryce et al. 2003) is of considerable interest. This gives potential significance to the observation by Zajicek et al. (2003) that MS patients receiving THC or a cannabis extract experienced fewer hospital admissions for relapse than placebo patients.

The investigation of neuroprotective activity in humans poses daunting ethical, financial and methodological challenges. Timely enrollment of stroke and trauma patients is difficult, and the inherent variability in progression of neurodegenerative conditions means large numbers of subjects are needed. Outcome measures are often unreliable or expensive. Brain imaging techniques are likely to be central. These include structural and function magnetic resonance imaging, magnetic resonance spectroscopy, positron emission tomography, and single-photon emission computerised tomography. Unfortunately, in many conditions lesions revealed by these techniques show little relation to clinical disease progression, and still more focused measures may be required such as imaging the MRS neuronal marker *N*-acetylaspartate in MS (Mathews et al. 1998).

Dexanabinol (HU-211), a non-psychoactive synthetic cannabinoid, has been the subject of the only controlled study yet to be reported in humans (Knoller et al. 2002). In a randomised, double-blind comparison with placebo, single doses of either 48 or 150 mg dexanabinol were given intravenously to neurosurgical inpatients within 6 h of severe closed head injury. Since outcome measures did not indicate a dose-related response, comparisons were made between combined active dose groups and placebo. Significant beneficial effects on intracranial pressure and cerebral perfusion pressure independent of systemic blood pressure were seen in the active treatment groups. Neurological outcome as assessed by the Glasgow scale was better ($p = 0.04$) in the combined active groups at 3 months, but this was no longer significant ($p = 0.14$) at 6 months. Dexanabinol appeared well tolerated and there was no significant difference between placebo and active groups in the incidence of unwanted effects.

4.4 Anti-cancer Effects

The symptomatic benefits of cannabis and its derivatives in patients with cancer has been discussed above, but considerable evidence has accumulated from in vitro and in vivo animal studies that cannabinoids may inhibit the growth of various types of tumour cell (For a review see Guzmán's contribution in this volume and Guzmán 2003). Possible mechanisms include the selective promotion of cancer cell apoptosis and inhibition of tumour vascularisation. Preliminary clinical studies have been initiated but no results reported at the time of writing. An issue to be determined is whether effects will be apparent at the tissue levels achievable in humans by systemic dosing—in some circumstances it may be preferable to seek ways to deliver the cannabinoid direct to the target site (Guzmán 2003).

4.5 Drug Withdrawal Treatments

In contrast to contemporary concerns about the addictive potential of cannabis, the drug was used in the nineteenth century in the treatment of dependencies on various other substances including alcohol, cocaine, chloral hydrate and morphine. Anyone who discusses the problems of opiate withdrawal with a modern heroin addict is likely to be told of the beneficial effects of marijuana in allaying withdrawal symptoms, and this anecdotal evidence is given some scientific credibility by a number of studies in animals (Hine et al. 1975; Bhargava 1976; Chesher and Jackson 1985). In animal pain models THC inhibits the development of opioid tolerance and physical dependence (Chichewicz and Welch 2003). At the time of writing, the efficacy of a combination of THC and CBD (Sativex) in alleviating the opioid withdrawal syndrome is being explored in a double-blind, placebo-controlled study.

There are anecdotal reports that cannabis is useful in countering both the withdrawal symptoms (Labigalini et al. 1999) and paranoia and weight loss (Dreher 2002) associated with smoking crack cocaine.

See above (Sect. 2.6) for the promising preliminary outcome of a trial evaluating the CB_1 receptor antagonist rimonabant as an aid to abstaining from tobacco smoking.

4.6 Migraine

This is a common disorder in which attacks, sometimes preceded by an aura, consist of intense headache along with nausea and sensitivity to light and sound lasting anywhere from a few hours to several days. In historical times, cannabis was widely used in the treatment of headache, and there are numerous modern anecdotes (Grinspoon and Bakalar 1993). The pathology underlying the disorder remains controversial, but serotonergic, dopaminergic, inflammatory and brain stem mechanisms have been implicated.

In a detailed review, Russo (2001) considers how cannabinoids may impact on these systems and makes a compelling case for initiating controlled clinical trials.

4.7 Intractable Breathlessness

A number of lung diseases (e.g. chronic bronchitis and emphysema) are capable of producing shortness 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 (Guz 1996). Ideally, a treatment would relieve the unpleasant sensa-

tion 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. CB_1 receptors are virtually absent from the part of the brain-stem which drives respiration (Herkenham et al. 1990), so it seems possible that symptom relief may be achieved without negative effects upon breathing. THC has been shown to have anxiety-reducing and sedating effects (Fabre and McLendon 1981; Nicholson et al. 2004), as has CBD in larger doses (Zuardi et al. 1997). CBD is also thought to have useful modulating effects on some of the undesirable effects of THC (McPartland and Russo 2001).

At the time of writing, exploratory research of THC/CBD combinations in refractory breathlessness is getting underway, incorporating careful monitoring of respiratory function.

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