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REVIEW ARTICLE

Pharmacological actions and therapeutic uses of cannabis and cannabinoids

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Summary

This review highlights the pharmacology, pharmacokinetics, pharmacological actions, therapeutic uses and adverse effects of cannabinoids. The effect of cannabinoids on anaesthesia is mentioned briefly. Important advances have taken place in cannabinoid research over the last few years and have led to the discovery of novel ligands. The possible clinical applications of these ligands and the direction of future research are discussed.

Although the term cannabis is used colloquially to describe a single entity, over 60 different compounds have been identified and collectively referred to as cannabinoids [1, 2]. These are largely derived from the female plant of *Cannabis sativa*. The most abundant cannabinoid and the primary psychoactive constituent is δ-9 tetrahydrocannabinol (THC), which was isolated in 1964 [3]. Other natural cannabinoids are δ-8THC, cannabinol and cannabidiol [3]. The THC content is highest in the flowering tops, declining in the leaves, stem and seeds of the plant. Marijuana (THC content = 0.5–5%) is prepared from the dried flowering tops and leaves; hashish (THC content = 2–20%) consists of dried cannabis resin and compressed flowers [4]. Cannabis may be smoked in a joint, which is the size of a cigarette, and tobacco may be added to assist burning. Smokers typically inhale deeply and hold their breath to maximise absorption via the lungs. Although marijuana and hashish may be eaten, they are more usually smoked because titration of blood levels in order to achieve a given psychoactive effect is easier [5].

Pharmacology

Two separate cannabis receptors have been identified (CB_1 and CB_2), which were cloned in 1990 and 1993, respectively [6]. Both receptors are coupled to G proteins and their activation leads to an inhibition of adenyl cyclase, decreased production of cAMP and modulation of the ion channel activity. At the cellular level, cannabinoids act through CB receptors to hyperpolarise neurones by closing voltage-dependent calcium channels and by activating potassium channels [3, 6–8]. CB_1 receptors are distributed widely throughout the central nervous system (CNS) and the peripheral nervous system (PNS). They are present in their greatest concentration around the hippocampus, cortex, olfactory areas, basal ganglia, cerebellum and spinal cord. This pattern accounts for the effects of cannabinoids on memory, emotion, cognition and movement. Increased levels of CB_1 receptors are found in the peri-aqueductal grey matter (PAG) and dorsal horn of the spinal cord, regions involved in the modulation of nociceptive transmission. CB_1 receptors are sparse in the brainstem, which may explain the lack of respiratory depression associated with the administration of these compounds [9, 10]. CB_2 receptors are located peripherally and are closely linked with cells in the immune system, predominantly the spleen and macrophages [6].

Research on endogenous ligands has focused mainly on three ligands:

1 anandamide (from the Sanskrit word *ananda*, meaning bliss);

2 2-arachidonoylglycerol;

3 palmitoylethanolamide.

Anandamide, first described in 1992, produces similar effects to δ-9THC but is a less potent agonist with a shorter half-life [3, 11]. It is a partial agonist for both CB_1 and CB_2 receptors, with less CB_2 than CB_1 efficacy [12]. 2-Arachidonoylglycerol, originally identified in intestinal tissue, is found at 170-fold higher levels than anandamide in the brain [13]. Palmitoylethanolamide may bind to a yet unidentified 'CB_2-like' receptor [12]. With regard to the fate of released endocannabinoids, there is evidence that anandamide and 2-arachidonoylglycerol are removed from the extracellular space by a carrier-mediated, saturable uptake process that is present in neurones and astrocytes (the anandamide transporter) [14]. Once within the cell, anandamide is thought to be hydrolysed to arachidonic acid and ethanolamine by the microsomal enzyme, fatty acid amide hydrolase (FAAH) [14]. Anandamide is a vanilloid receptor (VR_1) agonist. Recent advances include the development of inhibitors of the anandamide transporter and FAAH [12], and the capsaicin analogue Olvanil, which is a potent inhibitor of the anandamide transporter and is also a CB_1 receptor agonist [15]. The endogenous cannabinoid system is involved in analgesia, cognition, memory, locomotor activity, appetite, vomiting and immune control.

A series of synthetic compounds has been developed that act on the cannabinergic system, e.g. WIN55212 and CP55940 [6]. Recent developments include the synthesis of new ligands that have CB_1 and CB_2 receptor selectivity [16]. Another significant advance is the development of a cannabinoid receptor agonist (δ8 THC-11-oic acid) that is soluble in water [17]. The removal of the need for a solubilizing agent will facilitate cannabinoid delivery, not only *in vitro* but also clinically, particularly when administration to patients is to be by injection or aerosol. Specific antagonists to both CB_1 and CB_2 receptors have been developed. SR141716A is a selective CB_1 receptor antagonist and SR144528 is a selective CB_2 receptor antagonist [3, 6]. Both these compounds also exhibit the properties of an inverse agonist [18]. Thus, as well as attenuating the effects of CB receptor agonists, it can by itself elicit responses in some CB receptor-containing tissues that are opposite to those elicited by CB receptor agonists. Experiments in animal models have shown that addition of the cannabinoid antagonist SR141716A produces abnormal nociceptive behaviour, indicating that the cannabinergic system is tonically active [3, 19].

Mechanisms of cannabinoid-induced analgesia

There is now unequivocal evidence that cannabinoids are antinociceptive in animal models of pain. Antinociceptive effects have been observed in animal models of acute pain, such as the radiant heat tail-flick test, and in models in which tonic pain is induced by nerve damage or by the injection of an inflammatory agent [17]. In animal models, cannabinoids inhibit behavioural responses to noxious stimuli. These effects of cannabinoids on motor systems have called into question whether the decreased behavioural responses in animal tests were attributable to the antinociceptive actions of these compounds or were the result of motor impairment. Anatomical specificity of cannabinoid-induced nociception at spinal and supra-spinal levels suggests that the analgesic effects of these compounds are distinct from their motor effects [20–22]. For example, direct injections of cannabinoid agonists into specific brain regions, including the PAG and rostral ventromedial medulla, inhibit the tail-flick reflex, whereas injections outside pain modulating areas do not [23]. There is good evidence that cannabinoids can induce antinociception through activation of CB_1 and CB_2 or CB_2-like receptors [17]. Activation of CB_1 receptors leads to a selective inhibition of the processing of nociceptive stimuli, both in the spinal cord and the ventro-postero-lateral (VPL) nucleus of the thalamus. Blocking the CB_1 receptor with its antagonist SR141716A has been shown to prevent the antinociceptive effects of a number of different cannabinoid receptor agonists [19]. CB_1 receptors have also been detected on the central and peripheral terminals of small and large diameter primary afferent sensory neurones. As large diameter primary afferent fibres are far more densely populated with cannabinoid receptors than with μ opioid receptors, it is likely that CB_1 receptor agonists will prove to be more effective than opioids in suppressing pain caused by nerve damage (neuropathic pain), as this kind of pain is thought to be elicited in part by abnormal spontaneous discharge of large diameter myelinated fibres (Aβ and Aδ fibres). Indeed, there is already some evidence from animal experiments that cannabinoid receptor agonists differ from morphine in being no less effective (or even more effective) against neuropathic pain than against acute pain [17, 24, 25].

Lichtman & Martin [20] have shown that the ability of intravenous administration of δ−9THC to increase tail-flick latency can be attenuated by injection of yohimbine into the lumbar region of the spinal cord, suggesting that the antinociception induced by cannabinoid receptor activation depends, at least in part, on the release of norepinephrine from descending neurones acting on final $α_2$ adrenoceptors. This might depend to some extent on the release of opioid peptides onto spinal κ receptors, as

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κ receptor antagonists attenuate the antinociception caused by cannabinoids.

Experiments with mice have shown that cannabinoids can interact synergistically with opioid receptor agonists in the production of nociception. This synergism appears to be receptor-mediated, as both cannabinoid and opioid receptor antagonists can block it [26]. This cannabinoid−opioid synergism has both spinal and supraspinal components.

Not all the effects of cannabinoids are mediated by receptors, and some of these effects may also be of clinical interest. The anti-inflammatory and analgesic property of $1',1'$−dimethyl heptyl δ-8THC-11oic acid depends on its ability to inhibit cyclo-oxygenase-2 (COX-2) rather than on its ability to interact with cannabinoid receptors [27]. It is more potent as an inhibitor of COX-2 than of COX-1, raising the possibility that it may be able to relieve inflammation without producing gastrointestinal or renal toxicity.

Cannabinoids can suppress responses to thermal or mechanical stimuli when these are applied to the hind paws of rats that have been made hyperalgesic by an intradermal injection of capsaicin. In a model of neuropathic pain, WIN55212 reversed mechanical allodynia as well as pinprick, cold and thermal hyperalgesia associated with chronic constriction of the sciatic nerve. The cannabinoid agonist normalises the nociceptive threshold on the injured side without altering thresholds contralateral to the injury. In addition, administration of a CB_1 receptor antagonist exacerbated the hyperalgesia and mechanical allodynia by lowering response thresholds on the injured, but not the contralateral, side [28]. In summary, cannabinoids demonstrate antihyperalgesia and/or antiallodynia in formaline, capsaicin, adjuvant and nerve injury models of persistent pain.

Pharmacokinetics

Absorption
Tetrahydrocannabinol and other cannabinoids are rapidly absorbed after inhalation, and the effects become fully apparent in a matter of minutes. The amount absorbed varies between 20 and 45% of the THC content. It is therefore possible to titrate the levels of THC in the systemic circulation against the desired effect. When taken orally, THC seems to undergo variable absorption from the gastrointestinal tract and has a rather narrow therapeutic window. Blood concentrations reached are 25−30% of those obtained by smoking the same dose. This is due to the fact that some of the THC is degraded by metabolism in the liver before reaching the circulation (first-pass metabolism), although the metabolite 11-hydroxy δ-9THC is also psychoactive. The onset of effect is delayed (0.5−2 h) and the duration may be prolonged by continued slow absorption from the gut [29].

Distribution
After smoking or intravenous administration, maximum brain concentration is reached within 15 min, coinciding with the onset of maximum psychological and physiological effects. The psychological effects then reach a plateau that can last 2−4 h before slowly declining. After oral administration, maximal effects occur after 1 h or more and may last 5−6 h because of continued absorption from the gut, but some psychomotor and cognitive effects persist for much longer [30, 31]. Cannabinoids also cross the placenta, enter the foetal circulation and penetrate into breast milk. Cannabinoids are highly lipid soluble and accumulate in fatty tissues from where they are released slowly back into the bloodstream. Because of this sequestration, elimination from the body is extremely slow and can take many days. With repeated dosage, cannabinoids accumulate and continue to reach the brain over a longer period.

Cannabinoids are metabolised in the liver, and a major metabolite is 11-hydroxy-δ9THC, which is more potent than δ-9THC and may be responsible for some of the psychological and physiological effects of cannabis. There are large interindividual differences in rates of metabolism, and metabolism is likely to be slowed in the elderly and in the presence of liver disease. The effects of cannabinoids are summarised in Table 1.

Acute effects
Cannabis produces euphoria and relaxation, perceptual alteration, time distortion and the intensification of normal sensory experiences such as eating. Short-term memory and attention, motor skills, reaction time and skilled activities are impaired while a person is intoxicated. In occasional users, the feeling of euphoria is replaced by anxiety and panic reactions and this is a common reason for discontinuation of use [2, 32]. Effects on the cardiovascular system include tachycardia, with heart rate increasing by 20−50% within few minutes; this effect lasts for up to 3 h. Blood pressure decreases when standing but not in the sitting position [33].

Psychomotor effects
Cannabis produces a dose-related impairment in cognitive and behavioural functions that may impair driving or the operating of machinery. These effects are potentiated with concomitant alcohol intake [34].

Effects of chronic cannabis use

Cellular effects and immune systems
Cannabinoids impair cell-mediated and humoral immunity in rodents. They decrease resistance to infection and

Table 1 Summary of the effects of cannabinoids.

Central nervous system	
Psychological effects	Euphoria, dysphoria, anxiety, depersonalisation, aggravation of psychotic states
Effects on perception	Heightened sensory perception, distortion of space and time sense, misperceptions, hallucinations
Sedative effects	Generalised CNS depression, drowsiness, sleep, additive effect with other CNS depressants
Effects on cognition and psychomotor performance	Fragmentation of thoughts, mental clouding, memory impairment, global impairment of performance
Effects on motor function	Increased motor activity followed by inertia and incoordination, ataxia, dysarthria, tremulousness, weakness, muscle twitching
Analgesic effects	Similar in efficacy to codeine
Anti-emetic effects	In acute doses; effect reversed with larger doses or chronic use
	Increased appetite
Tolerance	To most behavioural and somatic effects including the 'high' with chronic use
Dependence, abstinence syndrome	Rarely observed but has been produced experimentally following prolonged intoxication
Cardiorespiratory system	
Heart rate	Tachycardia with acute dosage; bradycardia with chronic use
Peripheral circulation	Vasodilatation, conjunctival redness, postural hypotension
Cardiac output	Increased output and myocardial oxygen demand
Cerebral blood flow	Increased acutely, decreased with chronic use
Ventilation	Small doses stimulate, larger doses depress
Bronchodilation	Coughing, but tolerance develops
Airways obstruction	Due to chronic smoking
Eye	Decreased intraocular pressure
Immune system	Impaired bactericidal activity of macrophages in lung and spleen
Reproductive system	Decreased sperm count and sperm motility in males
	Suppression of ovulation, complex effects on prolactin secretion, increased obstetric risks

non-cannabinoids in cannabis smoke impair alveolar macrophages. The relevance of these findings to human health is uncertain because of the very high dose of the THC used in the animal studies [35].

Respiratory system
Chronic cannabis smoking is associated with increased symptoms of chronic bronchitis, such as coughing, production of sputum and wheezing. Long-term cannabis smoking may also increase the risk of respiratory cancer [36, 37]. There have been reports of cancer in the aerodigestive tract in young adults with a history of heavy cannabis use [38, 39].

Reproductive effects
High doses of THC in animals result in lower testosterone secretions, impaired sperm production, motility and viability, and disruption of the ovulatory cycle [40]. Several studies have shown that cannabis smoking in pregnancy can decrease birth weight. There is suggestive evidence that infants exposed to cannabis *in utero* suffer behavioural and developmental effects during the first few months of life [41].

Behavioural effects in adolescence
Once recruited to cannabis use, social interactions with drug-using peers and greater access to illicit drug markets, adolescents are more likely to use other illicit drugs [42].

Dependence syndrome
Animals develop tolerance to the effects of repeated doses of THC and studies suggest that heavy smokers of cannabis also develop tolerance to its subjective and cardiovascular effects. Some report withdrawal symptoms on the abrupt cessation of cannabis use [43, 44].

Cognitive effects
Cannabis produces subtle impairment of memory, attention and the organisation and integration of complex information. The longer cannabis has been used, the more pronounced the cognitive impairment [45].

Psychosis
Large doses of THC produce confusion, amnesia, delusions, hallucinations, anxiety and agitation [46]. Cannabis use can exacerbate schizophrenia.

Therapeutic uses of cannabinoids

Spastic disorders
Muscle spasticity, with recurrent painful muscle cramps and various combinations of weakness, tremor and dystonia, occurs in a number of chronic and debilitating neurological conditions including multiple sclerosis, cerebral palsy and spinal cord injuries. It is somewhat paradoxical that cannabinoids are reported to be of therapeutic value in neurological disorders associated with spasticity, ataxia and muscle weakness, because very

similar symptoms can be caused by cannabis itself. Several anecdotal reports suggest that cannabis can alleviate symptoms in patients with multiple sclerosis after other drugs have failed or have produced unacceptable side-effects. Petro [47] studied nine patients with multiple sclerosis and found that oral THC 5–10 mg significantly decreased objectively rated spasticity compared with placebo. Ungerleider *et al.* [48] observed 12 patients and noted significant subjective improvement after oral THC 7.5 mg compared with placebo, but no change in objective measurements of weakness, spasticity, coordination, gait or reflexes. Adverse effects were common and most of these patients did not request further treatment with THC. Clifford [49] conducted an open trial in eight patients with severe multiple sclerosis who received placebo or THC 5–15 mg every 6 h for up to 18 h. Five patients showed mild subjective, but not objective, improvement in tremor and well-being with THC. Martyn *et al.* [50] reported the effects of Nabilone in a double-blind, placebo-controlled crossover study of one patient with multiple sclerosis. The patient took Nabilone 1 mg every second day for two periods of 4 weeks, alternating with 4-week periods of placebo. There was a clear improvement in general well-being, muscle spasms and frequency of nocturia during the two periods on Nabilone. A questionnaire study by Consroe *et al.* [51] supported the impression given by anecdotal reports that considerable numbers of patients with multiple sclerosis take cannabis covertly for symptom relief. Of the 112 subjects in this survey, the mean percentage reported improvement after taking cannabis was 96.5% for spasticity, 91.5% for pain in muscles, 90.7% for tremor of the arms or head and 90.6% for depression. Dunn & Davis [52] surveyed the perceived effects of cannabis in 10 patients with a range of problems arising from spinal cord injury. Five of eight with spasticity and five of nine with headache noted improvement; four of nine with phantom limb pain noted improvement, but two of 10 reported worsening of urinary symptoms. Malec *et al.* [53] conducted a questionnaire survey that indicated that 21 of 24 patients with spinal cord injuries who had used cannabis found that it decreased spasticity. The only double-blind controlled trial [54] concerned a single patient in whom oral THC 5 mg was compared with oral codeine 50 mg and placebo, each administered 18 times over 5 months. Codeine and THC alleviated pain to a similar degree and were better than placebo, but the THC had an additional benefit on spasticity. Frankel *et al.* [55] compared cannabis smoking with other drugs in five patients with Parkinson's disease and found that it produced no beneficial results. Among schizophrenic patients misusing cannabis, such use is associated with a greater severity of psychotic symptoms and earlier and more frequent relapses. More recently, Schnelle *et al.* [56] carried out a survey directed at determining the incidence and nature of the medical use of cannabis and cannabinoids in Germany, Austria and Switzerland. They reported that only five of the 128 patients surveyed took δ-9THC by prescription and the remainder used natural cannabis products. Among a range of claimed therapeutic indications were multiple sclerosis, back pain, spasticity and spinal cord injury. Notcutt *et al.* [57] reported the clinical outcomes of giving Nabilone orally to 60 patients, including 16 with multiple sclerosis. Of these 16, six experienced analgesia, muscle relaxation and sleep improvement after Nabilone. The other 10 obtained no useful benefit from the drug. A large proportion of patients experienced drowsiness and dysphoria of sufficient severity to cause many to discontinue the drug in spite of obtaining a benefit. Some symptoms of multiple sclerosis or spinal cord injury may be worsened by cannabinoids. Thus, in a double-blind randomised placebo-controlled study, Greenberg *et al.* [58] found that although cannabis cigarettes smoked by 10 multiple sclerosis patients produced a subjective feeling of clinical improvement, they caused a subtle impairment of posture and balance as measured by dynamic posturography. On present evidence, it appears that cannabinoids could be helpful for particular symptoms in some patients, possibly as adjuvants to other drugs.

Pain

The number of published human trials on the use of cannabis in acute and chronic pain is limited and the results are equivocal. Noyes *et al.* [59, 60] carried out two double-blind placebo-controlled studies with THC. In the first study, 10 patients with cancer pain received oral THC 5, 10, 15 and 20 mg and placebo in random order. Significant pain relief was obtained with the two higher doses compared with placebo. Pain relief peaked at 3 h and was still near maximum 6 h after THC administration. In the second study, oral THC 10 mg and 20 mg was compared with oral codeine 60 mg and 120 mg in 36 patients with cancer pain. Tetrahydrocannabinol 20 mg and codeine 120 mg gave significant pain relief compared with placebo. Jain *et al.* [61], in another controlled study, reported significant pain relief compared with placebo in 56 patients with postoperative pain given the synthetic cannabinoid levonantradol intramuscularly in four doses (1.5, 2.0, 2.5 and 3.0 mg). There was no clear dose−response effect but analgesia with the higher doses persisted for well over 6 h. In contrast, Raft *et al.* [62] found no significant analgesic effects from two doses of intravenous THC in 10 healthy patients undergoing wisdom teeth extraction. A negative result was also reported by Lindstrom *et al.* [63] in 10 patients with

chronic neuropathic pain. In a survey by Dunn & Davis [52], four respondents reported improvement in phantom limb pain after taking cannabis, and there are anecdotal reports of the analgesic effects of cannabis in one patient with a brain tumour and one patient with migraine. Holdcroft *et al.* [64] found that oral administration of a cannabis extract decreased the requirement of morphine in a patient suffering from chronic abdominal pain. The efficacy of THC appears to be approximately equivalent to codeine and an adjunctive role seems to be the most promising use of cannabinoids in the management of pain.

Anti-emetic use
Cannabinoids have been used in the prevention of nausea and vomiting caused by anticancer drugs. Nabilone and dronabinol (THC in sesame oil) have been shown to be as effective or more effective than phenothiazines, metoclopramide and domperidone for this indication, although they have not been tested against the 5-HT$_3$ antagonist ondansetron [65, 66]. Nabilone is usually given in a dose of 4–8 mg per day in divided doses for a few days during cancer chemotherapy. There is a high incidence of adverse effects and 50–100% of patients experience drowsiness, dizziness and lethargy [66].

Appetite stimulation
Cannabinoids stimulate appetite and may have a use in palliative care for anorexia caused by opioids, antiviral drugs, AIDS-related illnesses or terminal cancer [67]. Nabilone given in small doses may be effective in stimulating appetite, although clinical experience is lacking.

Epilepsy
Cannabinoids have complex actions on seizure activity and exert both anticonvulsant and proconvulsant effects. In one single case report and two anecdotal reports, smoking cannabis appeared to alleviate seizures in patients with generalised, partial or absence seizures. With scanty human data, the role of cannabinoids in epilepsy remains speculative. Cannabidiol may have a therapeutic potential, as it does not interact with cannabinoid receptors and has a different profile of anticonvulsant activity in animal models [68].

Glaucoma
Several studies have shown that smoked or orally administered cannabis and intravenous infusions of THC can decrease intraocular pressure (IOP) in normal subjects. Only two double-blind controlled trials of THC in patients with glaucoma have been reported. Merritt *et al.* [69] studied 18 patients who inhaled THC 2%. He observed a significant decrease in IOP but also noted hypotension, palpitations and psychotropic effects. These effects occurred with such frequency as to militate against the routine use of cannabis in this way. Tolerance to the IOP-decreasing effect develops rapidly and the place of cannabinoids in the treatment of glaucoma remains to be established.

Bronchial asthma
Acute administration of cannabis and THC exert a definite bronchodilator effect on the small airways of the lungs [32]. Tashkin *et al.* [70] studied 14 asthmatic volunteers and compared smoked cannabis (THC 2%), oral THC (15 mg) and a standard bronchodilator (isoprenaline 0.5%). They found that smoked cannabis and oral THC produced significant bronchodilation for at least 2 h. However, smoking cannabis is not a therapeutic option because of the other smoke constituents

Mood disorders, psychiatric conditions
Cannabis and cannabinoids have been advocated as antidepressants, anxiolytics, sedatives, hypnotics and as treatment for alcohol and opiate withdrawal syndromes. There is no convincing evidence that they are superior to existing drugs for these conditions. Animal work and some anecdotal reports suggest that THC and cannabinol can inhibit many of the signs of opioid withdrawal by a non-opioid mechanism [71]. This possibility may be worth pursuing in clinical studies to assist patients detoxifying from opiates.

Other uses
In addition, cannabinoid receptor agonists have potential as neuroprotective agents through CB$_1$ receptor-mediated inhibition of glutamate release [18] in the treatment of dyskinesia that is produced by L-DOPA in patients with Parkinson's disease [72]. Potential therapeutic applications have also been suggested for CB$_1$ receptor antagonists/ inverse agonists. These include the management of acute schizophrenia [73] and the amelioration of cognitive and memory dysfunctions associated with disorders such as Alzheimer's disease [74].

Adverse effects of cannabinoids
The acute toxicity of cannabinoids is very low and no deaths have been directly attributable to their recreational or therapeutic use. Some of the adverse effects commonly observed during the clinical setting are given below.

Sedation
Drowsiness, dizziness and lethargy are common and the incidence approaches 50–100%.

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Psychological effects
Euphoria, dysphoria, anxiety, feeling of loss of control, mental clouding, impaired memory, depersonalisation, fear of dying, paranoia, hallucinations, depression and altered time perception.

Physical symptoms and signs
Dry mouth, ataxia, blurred vision, incoordination, muscle weakness, tremor, slurred speech, palpitations, tachycardia and hypotension.

Impairment of psychomotor and cognitive performance
These include slowed reaction time and impaired attention. These effects combine with the sedative effects to cause deleterious effects on driving ability or operation of machinery [75]. Additive effects are known to occur with other depressants, including alcohol, benzodiazepines and opiates.

Effects of chronic dosage with cannabinoids

Tolerance to many of the pharmacological effects of cannabinoids can be induced rapidly in animals and man, and this appears to be largely pharmacodynamic in nature. These include effects on mood, heart rate, blood pressure, IOP, psychomotor performance and anti-emetic effects. Tolerance can develop within weeks with repeated dosage, although not at the same rate or degree for different effects [76]. Tolerance can be an advantage in decreasing unwanted effects, e.g. dry mouth and dysphoria, but a disadvantage if a desired effect is involved.

Dependence and withdrawal effects

Dependence is unlikely to present a problem with clinically prescribed doses for patients in therapeutic settings, but withdrawal effects may be undesirable. As well as psychological effects (restlessness, anxiety and insomnia, tremor), there may be a rebound increase in IOP, nausea, diarrhoea and other physical symptoms [77]. Withdrawal symptoms are usually short-lived in experimental subjects but they may be more severe in recreational users.

The cannabinoid most likely to be prescribed for clinical use in the UK is Nabilone. It is advised that prescribed Nabilone should not be identified as a cannabinoid and that patients should be warned to keep it in a place inaccessible to others, especially children and adolescents.

Anaesthesia and cannabinoids

Up to 10–20% of people aged 18–25 years may take cannabis weekly or more often. As a result of its slow elimination, these compounds may be present in the tissues of users for weeks, and they may interact with a number of anaesthetic agents. Animal work has shown additive effects and/or cross-tolerance with barbiturates, opioids, benzodiazepines and phenothiazines [75, 76]. There are very few published human data, but such interactions are thought to be possible [5]. Cannabis smoking is associated with an impairment of lung function similar to that associated with tobacco smoking. There is one case report of cannabis smoking causing uvular oedema and airway obstruction in a patient undergoing tympanomastoidectomy who smoked cannabis 4 h before surgery [78]. The authors caution that elective operations should not be performed on patients who have recently been exposed to cannabis smoke. As a result of its cardiovascular effects, cannabis may interact with other drugs affecting heart rate or blood pressure, such as β-blockers, anticholinergics and cholinesterase inhibitors [5]. It is also possible that adverse psychiatric and autonomic reactions to cannabis, including withdrawal effects, may interfere with the induction of anaesthesia and postoperative recovery. Hence, it is prudent to enquire about the drug history of young patients and to be aware of the potential interactions between cannabis and anaesthetic agents.

Conclusions and future prospects

There have been significant advances in our understanding of the basic science of cannabinoids in recent years and the stage is set for these to be translated into clinical practice. Further scientific advances should lead to the elucidation of the roles of CB_1 and CB_2 receptors in both health and disease, as well as the role of other cannabinoid receptors. It will also be important to determine the structural features that determine the efficacy and affinity of cannabinoid receptor agonists and inverse agonists. The role of anandamide transporter inhibitors needs to be examined. One important issue, which needs to be resolved before cannabinoids can be introduced widely into clinical practice, is the need for better formulations and modes of administration. It may be possible to deliver cannabinoids by aerosol inhalation, buccal absorption, rectal suppository, skin patch, intravenous injection or even direct application, e.g. to the eye and spinal cord [79]. The recent synthesis of the water-soluble cannabinoid O-0157 may facilitate such developments.

Although cannabinoids have been shown to decrease signs and symptoms of multiple sclerosis and spinal cord injury in terms of spasticity, rigidity, tremor and pain, much more information from controlled studies is required before the place of these compounds in clinical

practice can be determined. Practical difficulties confronting the organisation of clinical trials include the dearth of sensitive and reliable objective measures of spasticity and the problem of devising an adequate placebo control for drugs that produce such marked and characteristic psychotropic effects. In addition, because of their high lipophilicity, cannabinoid elimination from the body is rather slow, necessitating lengthy washout periods between treatments if a crossover design is to be used. In practice, it may be better to use a pragmatic randomised, controlled trial approach rather than the more traditional explanatory randomised, controlled trial. The pragmatic approach endeavours to take account of all aspects of a treatment, e.g. psychotropic effects in this situation, and to compare it with another treatment, rather than trying to eliminate all non-pharmacological differences by providing a blinded placebo. Whatever methods are used, it is essential that scientifically rigorous trials are conducted in order to establish the efficacy of these agents in different clinical situations.

Another important area for future research is the development of strategies that maximise separation between the sought-after therapeutic effects of cannabinoids and the unwanted effects of these drugs, particularly their psychotropic effects. This could be either by pharmacological, pharmaceutical or therapeutic means. The psychotropic effects are mediated largely by CB_1 receptors within the brain, and one possibility would be to deliver a CB_1 agonist near to the spinal cord – perhaps by the epidural route. Another strategy would be to design a CB_1 receptor agonist that does not readily cross the blood–brain barrier, as an agonist of this kind might be able to produce analgesia by acting on the CB_1 receptors that are located on nociceptive neurones outside the brain and spinal cord. A third strategy would be to focus on CB_2 selective agonists, as there is evidence from animal experiments that cannabinoids can act through CB_2 or CB_2-like receptors to relieve inflammatory pain and reduce the spasticity of multiple sclerosis [17]. It may be worth exploiting the synergistic interactions that occur between cannabinoids and opioids for antinociception, or between cannabinoids and benzodiazepines or baclofen for inhibition of motor function [79]. Finally, it may be possible to use drugs that activate the endogenous cannabinoid system indirectly by increasing extracellular levels of cannabinoids through inhibition of their membrane transport or enzymic hydrolysis. Drugs of this kind are available [12, 14]. The potential for a useful extension of the therapeutic armamentarium of both the pain management specialist and those who treat acute postoperative pain is apparent, and awaits continued basic scientific advance accompanied by careful clinical evaluation.

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