Medicinal use of cannabis: History and current status

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OBJECTIVE: To provide an overview of the history and pharmacology of cannabis in relation to current scientific knowledge concerning actual and potential therapeutic uses of cannabis preparations and pure cannabinoids.
METHODS: The literature on therapeutic uses of cannabis and cannabinoids was assessed with respect to type of study design, quality and variability of data, independent replications by the same or other investigators, magnitude of effects, comparison with other available treatments and reported adverse effects. The results of this review were also compared with those of major international reviews of this topic in the past five years.
CONCLUSIONS: Pure tetrahydrocannabinol and several analogues have shown significant therapeutic benefits in the relief of nausea and vomiting, and stimulation of appetite in patients with wasting syndrome. Recent evidence clearly demonstrates analgesic and antispasticity effects that will probably prove to be clinically useful. Reduction of intraocular pressure in glaucoma and bronchodilation in asthma are not sufficiently strong, long lasting or reliable to provide a valid basis for therapeutic use. The anticonvulsant effect of cannabidiol is sufficiently promising to warrant further properly designed clinical trials. There is still a major lack of long term pharmacokinetic data and information on drug interactions. For all the present and probable future uses, pure cannabinoids, administered orally, rectally or parenterally, have been shown to be effective, and they are free of the risks of chronic inflammatory disease of the airways and upper repiratory cancer that are associated with the smoking of crude cannabis. Smoking might be justified on compassionate grounds in terminally ill patients who are already accustomed to using cannabis in this manner. Future research will probably yield new synthetic analogues with better separation of therapeutic effects from undesired psychoactivity and other side effects, and with solubility properties that may permit topical administration in the eye, or aerosol inhalation for rapid systemic effect without the risks associated with smoke inhalation.

Key Words: *Adverse effects; Cannabinoids; Cannabis; History; Routes of administration; Therapeutic use*

Utilisation médicale du cannabis : historique et situation actuelle

OBJECTIF : Dégager une vue d'ensemble de l'historique et de la pharmacologie du cannabis en lien avec les connaissances scientifiques actuelles sur les utilisations thérapeutiques réelles et potentielles des préparations à base de cannabis et des cannabinoïdes purs.
MÉTHODE : Nous avons évalué la documentation scientifique pour ce qui est des utilisations thérapeutiques du cannabis et des cannabinoïdes selon différents critères : type d'étude, qualité et variabilité des données , répliques indépendantes d'études effectuées par les mêmes chercheurs ou non, importance des effets, comparaison avec d'autres traitements existants, effets indésirables déclarés. Les résultats de la présente étude ont aussi été comparés à ceux d'autres revues portant sur le même sujet, réalisées au cours des cinq dernières années à l'échelle internationale.
CONCLUSIONS : Le tétrahydrocannabinol pur et plusieurs autres analogues se sont avérés efficaces pour soulager les nausées et les vomissements et stimuler l'appétit chez les patients souffrant du syndrome cachectique. Des données récentes font clairement état d'effets analgésiques et antispasmodiques, qui révéleront sans doute leur utilité clinique. Quant à la diminution de la pression intraoculaire dans le glaucome et à la dilatation des bronches dans l'asthme, elles

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ne sont pas suffisamment fortes, durables ou fiables pour motiver une utilisation thérapeutique. Par contre, l'effet anticonvulsivant du cannabidiol s'avère suffisamment prometteur pour justifier la réalisation d'essais cliniques bien conçus. L'on dispose toutefois de très peu de données sur la pharmacocinétique à long terme et les interactions médicamenteuses. L'efficacité des cannabinoïdes purs, administrés par voie orale, rectale ou parentérale n'est plus à démontrer pour ce qui est des utilisations actuelles et futures probables, et ces produits sont exempts des risques d'inflammation chronique des voies aériennes et du cancer des voies respiratoires supérieures associés à l'inhalation de la fumée du cannabis brut. Cependant, l'utilisation du cannabis en inhalation pourrait être autorisée, pour des motifs de compassion, chez les patients en phase terminale, déjà habitués à cette forme de produit. La recherche permettra probablement de mettre au point de nouveaux analogues synthétiques dont les effets thérapeutiques se dissocieront davantage des effets indésirables, psychoactifs ou autres; par ailleurs, leurs propriétés de solubilité pourraient rendre possible l'administration topique dans les yeux ou l'inhalation en aérosol pour la production d'effets généraux rapides sans les risques associés à l'inhalation de la fumée de cannabis.

Despite the recent surge of interest in the potential medical use of cannabis, it is worth remembering that cannabis is not a new drug. It has a very long history of medical as well as nonmedical use in many parts of the world. In discussing possible clinical trials of cannabis or cannabinoids, there is something useful to be learned from recalling a little of that history.

HISTORICAL BACKGROUND

The cannabis or hemp plant has been known since antiquity and grows in almost all parts of the world, but has been known principally as a source of useful fibre for the manufacture of textiles and rope (1). In most fibre-producing areas, the plant was not used as a drug. Geographic and climatic factors modify the content of pharmacologically active material in the plant, and only in some regions was this content high enough to lead to the discovery that the plant, and especially its resin, had important drug actions. Knowledge of these actions appears to have arisen first in the Himalayan region of central Asia and spread gradually from there to India, Asia Minor, North Africa, and across the desert to sub-Saharan Africa and the rest of the African continent (2-4).

In India, the plant was used both medically and nonmedically (5). Its social and religious uses were related most notably to the festival of Durga Puja. On a few other occasions during the year it was also used in family celebrations such as marriages and births to induce a relaxed and sociable mood and a good appetite. Only the weaker preparations were used: 'bhang' (comparable to marijuana) was taken by mouth, and the slightly stronger preparation 'ganja' was smoked, but the most potent preparation, 'charas' (known elsewhere as hashish) was not used for these purposes. Indeed, use of charas was not socially approved for any purpose, and its devotees were regarded as 'bad characters' or outcasts.

Cannabis also formed part of the therapeutic armamentarium of traditional Indian medicine, and many of the uses were similar to those for which it is currently advocated in our own society. Among its claimed benefits were sedative, relaxant, anxiolytic and anticonvulsant actions – all of which also made it useful in the treatment of alcohol and opiate withdrawal – analgesia, appetite stimulation, antipyretic and antibacterial effects, and relief of diarrhea (6).

The introduction of the drug effects of cannabis into Europe in the 19th century followed different routes for the medical and nonmedical uses. In France, interest centred on the nonmedical application of the psychoactive effects, whereas in England the interest was primarily medical. During the Napoleonic invasion of Egypt in 1798, De Sacy and Rouyer, two French scholars who accompanied the army, described the plant, and the practice and effects of hashish smoking, and they collected samples of the material to take back to France for further study (4). The famous French psychiatrist Moreau de Tours made further observations of its effects on mood during his North African travels in the 1830s. He later described in detail the mental effects of high doses of hashish, and advanced the hypothesis that dreams, insanity and drug intoxication involve similar mechanisms. He proposed the use of hashish to produce a 'model psychosis' for scientific study (7,8), a full century before this concept was proposed in North America in connection with the hallucinogens lysergic acid diethylamide and mescaline. In Paris, the 'Club des Haschichins' flourished in the 1850s, with such members as the poets and authors Baudelaire, Gautier and Dumas. They served as subjects for Moreau's experiments and popularized hashish in their writings as a claimed route to esthetic self-realization, as Ginsberg and others did in the United States over a century later.

In the United Kingdom, on the other hand, interest in cannabis was aroused by the medical and scientific writings of O'Shaughnessy (9), a British physician working in India as Professor of Chemistry and Materia Medica in Calcutta. He observed the use of cannabis in Indian traditional medicine, for the treatment of spastic and convulsive disorders such as 'hydrophobia' (rabies), tetanus, cholera and delirium tremens. He sent supplies of the material to a pharmaceutical firm in London for analysis and clinical trials. The extracts of cannabis were adopted into the British Pharmacopoeia and later into the American Pharmacopeia, and were widely used in the English-speaking world as sedative, hypnotic and anticonvulsant agents in the late 19th and early 20th centuries (10,11).

Yet, by the time that cannabis was dropped from the British Pharmacopoeia in 1932 and the American Pharmacopeia in 1941 (12), its clinical use had virtually disappeared and its formal banishment evoked little or no protest. Among the reasons for this loss of favour were that the plant material was too variable in composition, its shelf-life was too short and unpredictable (13), and it had been increasingly replaced by pure opiates and more reliable new

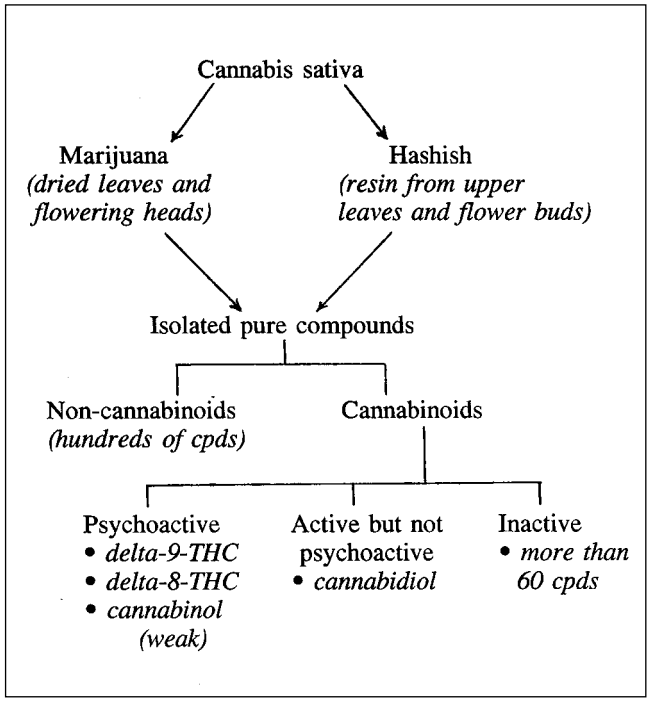

Figure 1) Relationships between crude cannabis products and pure cannabinoids. cpds Compounds; THC Tetrahydrocannabinol

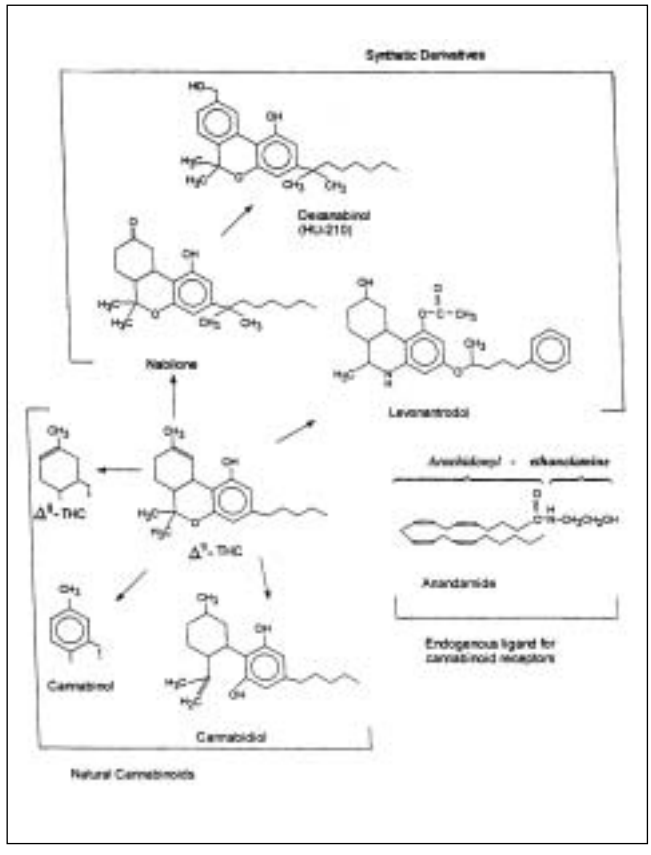

Figure 2) Structures of the major cannabinoids, including naturally occurring compounds, synthetic analogues or derivatives, and endogenous cannabinoid-like compounds in the mammalian organism. Arrows indicate closest resemblances, not actual lines of synthesis

synthetic drugs invented in the early part of the 20th century (2,11). Therefore, cannabis would have to be substantially improved as a drug if it were to regain clinical interest.

EARLY AND MODERN CHEMICAL STUDIES

The very high lipid solubility of the materials responsible for the drug effects of cannabis was known in North Africa, where a common practice was to heat the leaves and flowering tops of the plant in a mixture of butter and water (10). The active drug materials concentrated in the butter phase and, as the mixture cooled, the butter could be separated from the water and used in preparations to be taken by mouth to produce the desired effects. In 1857, the Smith Brothers of Edinburgh prepared a nonalkaloidal fraction with a high level of drug activity, and alcoholic extracts or the dry residues obtained from them were later standardized for their biological activity, forming the basis of the pharmacopoeial preparations. In 1899, Wood, Spivey and Easterfield attempted to isolate the active agents from such preparations, but their 'cannabinol' had very little pharmacological activity and proved to be a mixture rather than a single compound (cited by Todd [14]).

It was not until the 1930s and 1940s that Todd et al (15) in the United Kingdom and Adams et al (16) in the United States isolated pure cannabidiol and various tetrahydrocannabinols (THC), and showed that the latter were responsible for the psychoactive effects. The relationship of crude cannabis preparations (marijuana and hashish) to pure cannabinoids is shown schematically in Figure 1. Of the numerous chemical compounds isolated from cannabis, only three have the typical psychoactive effects for which cannabis is used nonmedically: Δ^9-THC, Δ^8-THC and (very weakly) cannabinol (17,18). A fourth natural cannabinoid, cannabidiol, has other types of pharmacological activity but is not psychoactive.

Finally, Mechoulam et al (19) in Israel, and Claussen and Korte (20) in Germany achieved the complete synthesis of the pure compounds, established their molecular structures and began the study of their structure-activity relationships. This work led to the synthesis of new cannabinoid derivatives and analogues that do not exist in nature. Armed with these pure and potent chemicals, Devane et al (21) identified specific binding sites (cannabinoid receptors) in the brain, and showed that the receptor-binding affinities of the different compounds paralleled their respective potencies of biological activity. Because cannabinoids themselves do not exist in the brain, the existence of the receptors implied that some other endogenous material in the brain normally binds to them. Devane et al (22) later reported the isolation of anandamide (arachidonyl-ethanolamine), a lipid material related to the prostaglandins, that is formed locally in the brain and binds to the receptors, exerting actions similar to those of the cannabinoids but less potent. Arachidonyl-glycerol and several other such materials have been identified subsequently.

The cannabinoid receptors were found to be of at least two different types (3,23), the CB1 receptors present mainly in various parts of the brain (cerebral cortex, cerebellum, basal ganglia, limbic system, hypothalamus, hippocampus), and the CB2 receptors present exclusively in peripheral tissues such as the immune system, bone marrow, lung, pancreas and smooth muscle. Both receptor types are linked to the inhibitory G protein, through which they act to inhibit adenylyl cyclase activity, preventing the activation of various calcium ion channels in the cell membrane, while increasing potassium ion influx (3,23). The functional results vary in different types of neurons. Inhibitory neurons are activated, with increased GABA release (24), while in motor neurons, cell excitability and neurotransmitter release are decreased. Isolation of the different types of receptor has made it possible to develop wholly synthetic compounds with high selective affinity for one or other type, some acting as agonists and others as antagonists (23). The availability of these receptor-specific ligands has permitted rapid advances in analyzing the cellular mechanisms underlying various pharmacological effects of the cannabinoids. The structures of some of the main natural and synthetic cannabinoids are shown in Figure 2, and their relative affinities for CB1 and CB2 receptors in Table 1.

TABLE 1
Relative affinities of various cannabinoids for CB1 and CB2 cannabinoid receptors

	CB1	CB2
Agonists		
Δ^9-THC, Δ^8-THC	+++	+++
Nabilone	++++	++++
Levonantrodol	++++	++++
WIN 55,212	++	++++
Cannabinol	+	++
Anandamide	++	+
Antagonists		
SR 141716A	++++	–
SR 144528	–	++++

+, ++, +++ and ++++ indicate the relative strengths of the binding affinity; – indicates no binding affinity. THC Tetrahydrocannabinol

PHARMACOKINETICS

Cannabinoids can be administered by a variety of routes. Because of their high lipid solubility, topical administration is possible in such locations as the eye or the nasal mucosa. However, this has been of very limited applicability, because preparations of THC available in the past tended to be irritating (25) to the eye. However, newer vehicles that permit lipid-soluble materials to be applied to the eye in aqueous solution may make this route of greater interest again (26). In theory, percutaneous absorption, as from a drug-impregnated skin patch, should be possible, but the absorption would be very slow and not clinically useful.

Oral administration results in a slow and variable absorption, with a bioavailability of 10% to 20%, and usually less than 15% (3,27-29). There is also a high hepatic uptake from the portal venous blood, and an active first-pass metabolism in the liver. Nevertheless, this does not result in a loss of pharmacological activity, because the major first-pass metabolite, 11-hydroxy-THC, is at least as potent a psychoactive agent as THC itself (3). THC can also be converted to a hemisuccinate and administered as a rectal suppository (30). Absorption is quite good by this route, with much higher bioavailability than after oral administration. In addition, rectal absorption delivers the drug directly into the systemic circulation, thus avoiding the first-pass metabolism.

Intravenous injection or infusion is possible, but because of the very low water solubility of cannabinoids, a special formulation must be used, such as a complex of the cannabinoid with plasma protein, or a solution in a water-miscible organic solvent. Without such formulations, almost no active material can be delivered, and intravenous toxicity is due essentially to injection of insoluble particulate material (31). Intravenous administration of suitable preparations gives a very rapid onset of action, but because of dosage limitations to avoid excessive intensity of the peak effect, the duration of action is short.

Smoking is undoubtedly the best-known method of administration, and is the typical manner of using crude marijuana, as opposed to pure cannabinoids. Much of the total THC in crude cannabis is not free THC but tetrahydrocannabinolic acid (32). The heat just ahead of the advancing zone of combustion in a cigarette or pipeful of cannabis converts the THC acid to free THC (33), and volatilizes the THC so that it can be inhaled with the smoke, deep into the lung. The high lipid-solubility of the THC allows it to cross the alveolar membrane rapidly, entering the blood in the pulmonary capillaries. From here it is carried rapidly to the heart and pumped directly to the brain, so that the onset of action is at least as rapid as with intravenous injection. The bioavailability of THC by this route ranges from 18% to 50% in different studies. Much of the variation is due to individual differences in smoking technique, relating to volume of the 'draw', depth of inhalation into the lungs and duration of retention of the smoke in the alveoli (34,35). Both the peak plasma THC level and the intensity of subjective effects are directly proportional to the puff volume and frequency (34). The time course of action of smoked cannabis is very similar to that of intravenous THC, with rapid onset, high peak intensity and short duration.

Like other highly lipid-soluble drugs, THC in the plasma is largely transported as a loosely bound complex with plasma protein. This complex dissociates readily, so that the free THC rapidly crosses cell membranes and enters the tissues in proportion to their respective blood flow rates. Not surprisingly, therefore, the time course of THC concentrations in the different tissues is very much like that of thiopental (36,37). The plasma THC concentration curve after cannabis smoking is, therefore, triphasic: a rapid

absorption phase with a half-time of 50 s, a slower tissue distribution phase with a half-time of 40 to 80 min, and a much slower metabolic elimination phase with a half-life that varies considerably in different studies (3,28), but is most typically about two to three days. A variety of metabolites appear in the urine and feces, but the major one in urine is 11-nor-9-carboxytetrahydrocannabinol. The 72 h cumulative excretion of total metabolites, expressed as a percentage of the administered dose, amounts to 13% to 17% in the urine and 25% to 30% in the feces after intravenous injection or smoking, but the fecal excretion increases to 48% to 53% after oral ingestion (27).

Chronic use appears to produce little or no increase in the rate of metabolism (ie, no appreciable shortening of the half-time of the third phase) (38); therefore, there is a potential risk of cumulative increase in the tissue concentrations over time, in daily users.

PHARMACOLOGICAL EFFECTS

Acute effects

Both crude cannabis and pure THC have a wide range of pharmacological effects, only some of which are of potential therapeutic interest.

Central nervous system: Cannabis acts essentially as a central nervous system (CNS) depressant (3,39,40); therefore, its main acute effects in many ways resemble those of alcohol. It produces drowsiness and decreased alertness, being synergistic with alcohol, barbiturates and other CNS depressants in this respect (2,41,42). Similarly, although THC has minimal respiratory depressant effect by itself, it may be synergistic with other depressants. Cognitive effects include impairment of short term memory, slowed reactions, decreased accuracy of psychomotor task performance and decreased selectivity of attention (greater interference by extraneous stimuli). Motor coordination and muscle tone are also decreased, resulting in ataxia (43,44). As a result of all of these effects, it causes poorer performance in simulated driving (45) or flying (46) tasks. However, the risk for real life driving may be less than with equivalent levels of alcohol intoxication because the cannabis users appear to be more cautious and less aggressive (45).

Low doses of cannabis typically induce mild euphoria, relaxation, increased sociability and decreased anxiety. However, high doses often result in dysphoria, increased anxiety and panic reactions, especially in inexperienced users. Similarly, low doses tend to increase sensory acuity, often in a pleasurable way, whereas high doses may cause sensory distortion, hallucinations and even an acute toxic psychosis that is usually of short duration after the drug is discontinued (47).

Pain perception is diminished, and pain tolerance increased, by a central action of THC that is separate from that of opioid analgesics (48-51). It is exerted at CB1 receptors in the central grey matter, and local injection of THC or its synthetic analogues at this site is effective in alleviating pain (52). However, there also appear to be spinal cord sites (53) and peripheral sites (54) that contribute to the analgesic action. The CB1 receptor blocker SR 141716A prevents the analgesic effect of THC but not of morphine (55), whereas naloxone blocks the morphine analgesia but not the analgesia produced by THC or its analogues (23).

The antinauseant and antiemetic effects of THC, nabilone and other cannabinoids have been well demonstrated (12,56). These effects appear to be due mainly to action in the CNS, although they may be partly of peripheral origin also. There is also a well demonstrated increase in appetite, which results in increased food intake (57-59), although the preference is for sweet foods, ie, carbohydrate rather than protein, and much of the observed weight gain appears to be fluid retention.

All of the foregoing effects are produced by cannabinoid actions on the CB1 receptors.

In contrast, an anticonvulsant effect of THC (60,61) does not appear to be produced via CB1 receptors, because cannabidiol (which does not bind to the CB1 receptor) is at least as effective as THC in preventing or suppressing seizures (62-64). Both drugs have electrophysiological effects similar to those of phenytoin in experimental animal models of epilepsy.

Neuromuscular system: Apart from the centrally mediated effect on skeletal muscle tone, there appears to be a more peripherally mediated antispasticity action. It is not clear whether this is exerted in the spinal cord or at peripheral sites such as the nerve-muscle junction (65).

Cardiovascular effects: One of the most consistent and reliable signs of acute action of cannabis is tachycardia, with increased cardiac output and correspondingly increased myocardial oxygen requirement. These effects are generally mild and of no pathological significance, but the increased myocardial workload could in theory become dangerous in an individual with some degree of coronary insufficiency (66). The tachycardia may possibly be a compensatory reaction to cannabis-induced vasodilation, which is often revealed as orthostatic hypotension.

Respiratory system: One of the manifestations of smooth muscle relaxation by cannabis or THC is bronchodilation, with resulting decrease in airway resistance. This is an acute effect, but with chronic use it tends to be offset by bronchial irritation caused by the particulate fraction of cannabis smoke (67). Because cannabis smoke is similar in most respects (other than cannabinoid content) to tobacco smoke, the consequences of chronic exposure to cannabis smoke are similar to those of tobacco smoke (67).

Eye: Cannabis and THC have been shown repeatedly to lower the intraocular pressure (IOP) by a mechanism that is not yet understood (26). This effect can be produced by systemic administration at doses that also produce the characteristic CNS effects, and rather inconsistently by local application to the eye.

Immune system: In vitro exposure to very high concentrations of THC results in decreased function of macrophages, lymphocytes and natural killer cells (68). In vivo, however, the observations are highly variable in different studies, and it is not yet clear whether smoking cannabis significantly

affects immune functions. Experimental studies in mice have suggested that resistance to legionella infection may be decreased by THC (68). The risk of pulmonary aspergillosis is increased in patients with acquired immune deficiency syndrome (AIDS) (68-71), but it is difficult to know whether cannabis acts as an immunosuppressant or simply as the source of the fungal contaminant (72). In any case, the in vitro effects on immune cells are probably not produced via CB1 receptors because they are also produced by cannabinoids that lack the psychoactivity of THC.

Chronic effects

In contrast to the potential therapeutic interest in the acute effects described above, changes in these effects that may occur with chronic use are linked mainly to the production of adverse effects that may limit the therapeutic usefulness of cannabinoids.

CNS: Prolonged daily use of cannabis has been linked to a variety of cognitive changes, including poor memory, vagueness of thought, decreased verbal fluency and learning deficits that are not always fully reversible when use of the drug is stopped (47). High-dose, daily use can give rise to a chronic intoxication syndrome, characterized by apathy, confusion, depression and paranoia. Cannabis dependence that meets the *Diagnostic and Statistical Manual of Mental Disorders, 3rd edn, revised* (DSM-III-R) (73) criteria has been well documented in regular heavy users (74-76). Among the components of this dependence are increased tolerance to most of the effects of cannabis, and physical dependence in the form of a relatively mild spontaneous withdrawal syndrome or a more severe one precipitated by the CB1 antagonist SR 141716A (3,76-80). This precipitated withdrawal is analogous to the reaction provoked by naloxone in a dependent opiate user. Cannabis use has also been reported to precipitate clinical relapse in compensated schizophrenics, producing a picture that differs from that of spontaneous relapse in which cannabis use may be merely a symptom (43,81-83). Finally, the offspring of women who smoke cannabis during pregnancy have been reported to show subtle but apparently permanent cognitive and personality changes (impulsiveness, poor memory, decreased verbal fluency and verbal learning) when they reach school age (84,85).

Respiratory system: Two relatively large scale studies of pulmonary function in chronic cannabis and tobacco smokers have given contradictory findings with respect to chronic obstructive pulmonary disease (COPD). One study, using a 'convenience sample' (ie, recruited through advertisements) of young chronic smokers of tobacco, marijuana or both, as well as nonsmokers, found a clear linkage of COPD to tobacco smoking, but not to marijuana smoking (86). In contrast, a larger study using a systematic population sample subjected to very similar pulmonary function tests found a significant link between COPD and marijuana smoking, as well as an additive effect of tobacco and marijuana (87). The reason for the difference between the findings of the two studies is not yet entirely clear, but the two agreed that chronic inflammatory changes were definitely increased in cannabis smokers.

Chronic inflammatory chest disease has been reported to be present in over 60% of long term daily smokers of cannabis, in some studies (67,74,75,88). Precancerous changes in bronchial epithelial cells have been described in such users, and there are a number of case reports of upper airways malignancy or premalignant changes in young smokers of cannabis (aged less than 30 years, ie, much younger than is typical of tobacco-induced bronchial carcinoma) (67,88-91). Although one prospective study of a large clinic population found no apparent increase in risk of lung cancer in cannabis users compared with that of nonusers (92), this study is flawed by its inclusion, in the group of cannabis users, of individuals who had used it as little as six times in their life. A much better designed recent case-control study of patients with proven upper airways cancer indicated a significant increase in risk among cannabis smokers, even after correction for concurrent tobacco use, and the increase in risk was proportional to the frequency and duration of cannabis use (93). The authors of the latter study systematically considered possible sources of error, such as selection bias, misclassification of cannabis exposure, low power and precision, etc, but were able to discard these by appropriate statistical comparisons of the control group with the general population. They recognized the need for larger scale comparisons as more long term cannabis smokers become available for study, but their findings point to a significant risk. This is consistent with the experimental demonstration of mutagenicity of cannabis smoke in the Ames test, which is probably not an effect of THC but of the particulate fraction of the smoke (88).

Other systems: Heavy smokers of cannabis have shown various endocrine changes, including decreased testosterone levels and reduced sperm counts in males, and decreased luteinizing hormone and prolactin levels in the luteal phase of the menstrual cycle in females, resulting in shorter periods and more anovulatory cycles. However, the clinical importance of these changes is uncertain, because tolerance to these effects of cannabis may develop. Decreased levels of thyroxine and corticosteroids have been found in experimental animals receiving high doses of cannabinoids, but such changes have not been clearly demonstrated in humans (94). Similarly, high doses of THC have been found to impair protein and nucleic acid synthesis in rats, but the significance of these findings for humans remains unclear. Tolerance also develops to the acute cardiovascular effects of cannabis, and chronic use has not been shown to cause any significant harm to the cardiovascular system.

MEDICAL USES OF MARIJUANA AND CANNABINOIDS

The history of drug therapy has been to a large extent one of progressive movement away from natural products of unknown or variable composition and potency, toward the use of pure active compounds of precisely known composition, stability, dosage and pharmacology. In light of the rea-

sons why cannabis fell out of favour as a medication nearly a century ago, and the great advances in chemistry and pharmacology of cannabinoids in recent years, the current revival of interest in clinical trials of smoked marijuana for therapeutic purposes may seem like a backward step. Does it have any valid scientific basis? The following section explores what arguments can be raised for and against it.

Of the acute effects of cannabis and cannabinoids described above, the following appear to offer possible therapeutic applicability:

- low-dose euphoriant and anxiolytic effects, as possible treatment for depression and anxiety;
- anticonvulsant action, as an adjuvant therapy for epilepsy;
- analgesia;
- antinauseant and antiemetic action in the treatment of patients receiving radiation therapy or chemotherapy for AIDS or cancer;
- appetite stimulation in patients with anorexia and wasting syndromes;
- reduction of IOP in the treatment of glaucoma;
- bronchodilation in the treatment of asthma; and
- immunosuppressant action in the treatment of autoimmune diseases or to prevent rejection of transplanted organs or tissues.

Of these possibilities, the antinauseant, antiemetic and appetite-stimulating effects have already been reviewed in detail elsewhere (12) and approved as indications for the therapeutic use of pure THC in patients with AIDS or cancer. The potential antidepressant and anxiolytic actions so far have not been supported by sufficient experimental evidence, in either laboratory animals or humans, to warrant the effort and expense of full-scale clinical trials. As mentioned above, the bronchodilatory effect does not appear to be sufficiently long lasting to be of potential interest in the treatment of asthma, and there is insufficient evidence to justify clinical trials of the immunosuppressant action in autoimmune disease or transplant rejection. Currently, therefore, the most interesting possibilities for clinical exploration are probably analgesia, relief of muscle spasm, reduction of IOP and anticonvulsant action.

In most potential therapeutic applications, the psychoactive effects – ie, the 'high' – constitute an undesirable side-effect, interfering with the patient's ability to carry out a variety of normal psychomotor functions. It then becomes important to see whether the desired therapeutic effects can be separated from the undesired psychoactive effects at appropriate doses, and to select the most appropriate routes of administration to achieve this goal. The current status of the relevant research is considered below in relation to the four major potential uses identified above.

Analgesia

Although earlier studies failed to confirm a consistently useful degree of analgesia with intravenous THC, oral cannabinoids or smoked cannabis (49), short term trials in humans have demonstrated the ability of oral or parenteral THC, levonantrodol and cannabis extract to decrease postoperative (95), dental (96), cancer (97) and visceral (98) pain. The latter was a double-blind, placebo controlled crossover subacute study in a single patient with chronic gastrointestinal pain due to familial Mediterranean fever. A marked reduction of pain was achieved with oral administration of a cannabis extract at a dose providing 50 mg of THC daily (98). However, there is still a need for controlled studies of its efficacy in chronic pain such as musculoskeletal, arthritic and cancer-induced pain. A recent animal study has described the efficacy of a synthetic cannabinoid in an experimental model of neurogenic pain (99), but there is only sparse anecdotal evidence for its ability to relieve migraine (100). Nevertheless, the modern neuropharmacological studies cited above leave no doubt that there is an analgesic action at appropriate doses. Because the mechanisms of opioid-induced and cannabinoid-induced analgesia differ, there is interest in the possibility that a combination of the two drugs, at lower doses than would be used for either alone, might result in improved analgesia with lower risk of the typical side effects of each drug (50).

In open-label, uncontrolled studies, both smoked cannabis and oral cannabinoids have been reported to be effective analgesics (101). The onset of action is more rapid with smoking, but there are few situations in which this is an important consideration. In chronic pain, for example, the therapeutic objective is to maintain consistent and continuous analgesia, so that successive doses are timed to have overlapping effects, and the difference in speed of effect would apply only to the first dose. Indeed, the less intense and more prolonged effect of oral THC appears to offer an advantage over the more intense but shorter lasting effect of smoked cannabis. Moreover, for long term use in chronic painful disorders, such as musculoskeletal problems, the pulmonary complications of smoking would be a distinct disadvantage.

Some of the new synthetic derivatives or analogues of THC may offer improved possibilities for therapeutic use. Water-soluble esters of the THC acids appear to have both analgesic and anti-inflammatory action, without the undesired psychoactive effects of THC itself. Because they do not produce gastric irritation, they might be useful substitutes for the current nonsteroidal anti-inflammatory agents (102,103).

Relief of muscle spasticity

Numerous claims have been made for the ability of cannabis to relieve muscle spasms, especially in multiple sclerosis, but most of these claims consist of unverified subjective reports, rather than controlled studies. A case report of one patient described the suppression of pendular nystagmus by the smoking of cannabis (104). A self-report study, based on

interviews with 112 multiple sclerosis patients in the United Kingdom and the United States who smoked marijuana, found that the main benefits claimed by the users were decreased spasticity and pain, but other claimed benefits included decreased bladder spasm, and improved balance and walking (105). However, the known pharmacology of cannabis makes it difficult to see how this drug could improve balance. Indeed, an experimental study of 10 multiple sclerosis patients and 10 healthy control subjects, each smoking one marijuana cigarette, found that marijuana caused worse posture and balance in both groups, but more so in the patients than in the control subjects (106). Nevertheless, several controlled studies with objective measures of spasticity as well as subjective self-reports have shown improvement after oral and rectal administration of THC or nabilone (107-110). To date, there have been no controlled studies comparing the antispasticity effects of smoked marijuana and oral THC in the same patients, and no controlled comparisons with other drugs currently used for the relief of spasm.

Glaucoma

In about 65% of both normal subjects and patients with glaucoma, THC has been shown to reduce the IOP, and both oral THC and smoked cannabis are effective (26). After smoking marijuana, the fall in IOP reaches its peak in about 2 h and is gone by 3 to 4 h. The therapeutic objective of preventing retinal and optic nerve damage in glaucoma requires a continuously sustained fall in IOP. To produce such a sustained effect with marijuana, it would be necessary to smoke it eight to 10 times a day (26). The effect of oral THC is more prolonged, and fewer doses a day would be required, but it is still not possible to avoid the psychoactive effects at THC doses that would provide a useful reduction of IOP.

Potential future developments will rest on synthetic analogues with a superior separation of effects. For example, Dexanabinol (CH211) lowers the IOP but appears to be devoid of psychoactivity at ophthalmologically useful doses (26). Other synthetic analogues with higher water solubility than THC itself are under development. Such compounds might permit topical use as eye drops, without need for the irritating solvents used as vehicles for THC itself.

Anticonvulsant use

As noted above, numerous animal experiments have demonstrated that both THC and cannabidiol have phenytoin-like effects in models of grand mal seizures, but tolerance develops rapidly to this action of THC (61). One well designed but unfortunately rather small scale, double-blind controlled study (111) has been carried out in epileptics who did not have adequate therapeutic benefit with conventional agents, despite apparently good compliance. When oral capsules of cannabidiol were added as a supplement to their regular treatments, their seizure frequency was significantly less than when they received supplementary placebo capsules. Two other double-blind, placebo controlled clinical trials of cannabidiol in epileptics that have been carried out since then are said to have shown no therapeutic effect (112,113), but unfortunately these have not been published in detail. No comparison of the efficacy of smoked marijuana versus oral cannabinoids has been reported. Because cannabidiol is not psychoactive and its oral use does not carry the pulmonary risks of smoking cannabis, it seems worthwhile for cannabidiol to be made available for more extensive clinical trials.

Problems in the design of clinical trials of cannabis

Almost all of the data on the pharmacokinetics of cannabinoids are derived from acute single-dose studies, and very little is known about possible changes in pharmacokinetics during long term chronic use. The long elimination half-life of THC means that there is a potential risk of accumulation of the drug in the body during chronic therapy, so that there is a need to monitor residual levels regularly during chronic studies. This problem is complicated by the very high lipid-solubility of THC, which means that the drug passes very rapidly from the plasma to the tissues, where it accumulates. Thus, the plasma level cannot be used as a measure of the tissue levels for more than the first few minutes after administration of THC (114,115), and the degree of disparity differs with different routes of administration. The slower the rate of absorption, the lower is the plasma level relative to the tissue levels of THC. For this reason, the usual methods of estimating bioavailability may not be valid, especially for comparing bioavailability by different routes.

Another potential problem is that cannabidiol is an effective inhibitor of cytochrome P450 activities when given acutely (116), and an inducer when given chronically (117). The same is true of the polycyclic hydrocarbons in cannabis smoke, as in tobacco smoke. There is thus a significant risk of drug interactions, both acutely and chronically, including a metabolic interaction between cannabidiol and THC itself (118). This consideration applies to the use of smoked marijuana, but to a much smaller degree to that of pure THC (116). The variability of this effect with different preparations, and with acute versus chronic administration, may account for the widely differing findings concerning interaction between THC and cannabidiol. Cannabidiol has been found to enhance the effects of THC in some studies (118-120), to reduce or abolish them in others (121-126) and to produce no change in still others (127,128). This marked variability of interaction illustrates one of the advantages of using single pure cannabinoids.

Many of the potential therapeutic uses of cannabis would be chronic or lifelong. Therefore, it is necessary for clinical trials to be of long enough duration to assess the quantitative impact of tolerance on the desired therapeutic effect. Consideration must also be given to the risks of pulmonary damage from smoking cannabis and the risk of dependence on THC by any route.

As with any drug, clinical trials of cannabis or cannabinoids must consider whether the potency and selectivity of their pharmacological effects provide an acceptable risk to

benefit ratio for clinical use. Unfortunately, very few trials in the literature have used more than two or at most three dose levels, and the effects that have been measured have consisted principally of subjective 'high', heart rate, and one or two other convenient physiological or psychomotor functions. There is thus a great need for thorough dose-response studies with respect to both the proposed therapeutic uses and a broad range of potential adverse effects to define the safety factor or 'margin of safety'. As much as possible, the measures should be objective and quantifiable, rather than subjective or of the yes/no type. Some of the potential applications, such as relief of pain or spasm, are clearly subject to the effects of suggestion and expectancy, so that the design of the trial is extremely important for ruling out the placebo effect or the influence of bias either for or against the use of cannabis.

For some of the possible applications, the numbers of available subjects may be too small to permit useful trials at single locations, so that multicentre studies may be required. Finally, for some of the potential therapeutic applications, cannabis or cannabinoids are less potent and less effective than some of the existing therapies, and would, therefore, be added to these rather than replace them. There is then the problem of how to evaluate the contribution of each drug to the final outcome, and this clearly requires statistical input to the design of the study, rather than merely to the evaluation of the results.

Practical issues in the use of crude cannabis versus pure cannabinoids

A number of differences in the manner of use of marijuana, and of pure THC and other cannabinoids also affect the design of comparative clinical trials. The first difference is the route of administration: marijuana can be used only by inhalation of smoke or by mouth (eg, in brownies), whereas pure cannabinoids can be used by almost all routes. For therapeutic trials, one would want to use the most effective route for each drug, and these are different. Therefore, in double-blind comparison trials, it may be necessary to include a placebo control for each route used, eg, smoked marijuana plus a placebo capsule, versus smoked placebo plus a THC capsule. A second issue is the choice of doses for each agent being compared. It is not sufficient to use the same dose of THC in each form because the route of administration, as already noted, affects the pharmacokinetics, resulting in different rates of absorption, different peak concentrations in plasma and different time courses of action. Therefore, it is necessary to use dosages that produce equivalent peak effects rather than identical amounts.

A related dosage problem is that absorption is quite variable, both for smoking and for oral ingestion. Smoking techniques can be standardized by adequate training of experimental subjects, with respect to frequency, volume of draw, depth of inhalation and duration of retention of smoke in the chest, but it is questionable whether this can be done satisfactorily in ill patients. No such training is possible at all, with respect to absorption after oral ingestion.

INTERNATIONAL PERSPECTIVE ON MEDICAL USE OF MARIJUANA

A number of major reviews of the possible therapeutic uses of cannabis and cannabinoids have been carried out in several countries in the past seven years. A report of the Royal Pharmaceutical Society of Great Britain (129) dealt with actual protocols for proposed multicentre clinical trials of smoked marijuana versus oral THC for the treatment of postoperative pain and of muscle spasm in multiple sclerosis. The other reports, however, presented more general coverage of the nature of cannabis and cannabinoids, their potential therapeutic uses and their limitations. It is, therefore, informative to review their conclusions briefly, to see what measure of agreement or disagreement there is among them.

The report of the National Drug Strategy of Australia (43) concluded that there is good evidence of the effectiveness of THC as an antiemetic, reasonable evidence for the potential therapeutic use in glaucoma, and suggestive evidence for possible use as an analgesic, an antiasthmatic agent, an anticonvulsant and an antispasticity agent in multiple sclerosis. It called for properly controlled trials dealing with these potential indications, as well as with the wasting syndrome and depression in patients with human immunodeficiency virus/AIDS. However, all of these recommendations dealt with pure synthetic cannabinoids, and not with clinical trials of smoked marijuana.

The British Medical Association Report (130) recommended further clinical research to establish suitable methods and routes of administration and optimal dosage for therapeutic use in nausea and vomiting (including well controlled comparisons with ondansetron and other 5-hydroxytryptamine$_3$ antagonists); chronic refractory spastic disorders; chronic, terminal and postoperative pain; poorly controlled epilepsy; strokes and CNS degenerative disorders; and glaucoma. It also recommended further study of cannabinoid effects on the immune system, not with respect to possible use as an immunosuppressant, but rather to see whether cannabinoids are safe to use in patients with already compromised immune systems. It specifically rejected the idea of therapeutic use of smoked marijuana or of unstandardized herbal preparations of cannabis, and points out the potential problems of cannabis tolerance and dependence in patients requiring long term therapy.

The report of a Select Committee of the British House of Lords (131) recommended clinical trials of cannabis treatment in multiple sclerosis and chronic pain "as a matter of urgency", but urged further research on alternative methods of administration, such as sublingual, rectal or aerosol-type inhalation, for rapid absorption without the adverse effects of smoking. It also pointed out the risks of acute intoxication, dependence and chronic health problems caused by cannabis itself and suggested that clinical trials of smoked marijuana should be considered only under special circumstances (of unspecified type). It suggested that one of the objectives of clinical trials should be to compare crude cannabis with pure THC, using doses that provide the same

amount of THC by the same route, to see whether other constituents of cannabis add anything to the therapeutic effect.

The report of the United States Institute of Medicine (113) found good evidence for a useful analgesic action, complementary to that of opioids. It also found good evidence for a moderate antinauseant and antiemetic effect, again useful mainly as a supplement to conventional treatment. The appetite stimulation effect was considered promising, again mainly as a supplement to megestrol acetate. It recommended clinical trials of possible relief of muscle spasticity, but considered that oral THC might be superior to inhalation because of the longer duration of action. It did not consider movement disorders, epilepsy or glaucoma to be promising areas for clinical studies with cannabis. Finally, it recommended further research on the development of safe, reliable alternative delivery systems that could provide rapid onset of action; trials of smoked marijuana should be limited to short term use, and only for those indications for which present evidence suggests a probable beneficial effect.

The conclusions set out in these reports have some important similarities and differences. All of them consider smoking to be an undesirable method of administering cannabis for therapeutic purposes, and recommend research on alternative methods of administration for rapid onset without the risks associated with smoking. All of them accept the antinauseant, antiemetic, appetite-stimulating, analgesic and antispasticity effects as worthy of further clinical trials. All of them recommend precise comparison of cannabis with pure THC or other cannabinoids. They disagree about the justification for clinical trials of cannabinoids for the treatment of asthma, epilepsy and glaucoma. Most of them accept the validity of clinical trials of smoked marijuana under special circumstances, primarily in terminally ill patients or for a limited time only in others. However, the Australian report refers only to pure cannabinoids, and a report of the Netherlands Health Council (132) rejected completely the idea of any clinical use of crude cannabis, a view shared in a recent nongovernmental review in the United Kingdom (12).

CONCLUSIONS

Although cannabis has a long history of therapeutic use, in both traditional and Western medicine, it fell into disuse almost a century ago, when it was superseded by more stable, reliable and effective new synthetic medications. The isolation and synthesis of pure cannabinoids, including more potent synthetic derivatives, and the discovery of cannabinoid receptors and their endogenous ligands, have renewed the interest in potential medical uses. This has also been stimulated by the claims of many cannabis smokers that their use of marijuana is for therapeutic rather than hedonic purposes.

Pure THC is already approved for the relief of nausea and vomiting, and for the stimulation of appetite. The major claims for other uses include relief of pain, muscle spasm, epilepsy and glaucoma. Both animal experiments and clinical observation provide varying degrees of support for these claims, but most of the controlled clinical observations have been with pure cannabinoids given by mouth, rather than with smoked cannabis. Properly designed, controlled, double-blind trials are needed to establish the efficacy for most of these claimed applications, to compare the relative potencies and benefits of crude cannabis versus pure cannabinoids for each, to compare both with existing therapies, to identify all the potential adverse effects and to assess alternative delivery methods, such as inhalers or low-heat noncombustive volatilizers to deliver measured doses of cannabinoids for rapid onset of action without the pulmonary hazards of cannabis smoke. Until much of this information is available, it is premature to recommend general use of cannabis or cannabinoids for these indications.

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