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1

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2

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1

CHAPTER 4. THE MEDICAL VALUE OF MARIJUANA AND RELATED SUBSTANCES	2
Standards for evaluating clinical trials.....	3
Analgesia.....	4
Nausea and Vomiting.....	9
Wasting Syndrome and Appetite Stimulation	17
Neurological Disorders	22
Glaucoma.....	38
Summary.....	42
Other Reports on Marijuana as Medicine.....	44
References.....	46

Chapter 4. The Medical Value of Marijuana and Related Substances

Compared to most drugs, the accumulation of medical knowledge about marijuana has proceeded in reverse. Typically, during the course of drug development, a compound is first found to have some medical benefit. Following this, extensive tests are undertaken to determine the safety and proper dose of the drug for medical use. Marijuana, in contrast, has been widely used in the United States for decades.¹⁶⁵ In 1996, 68.6 million people or 32 percent of the United States population over 12 years old had tried marijuana or hashish at least once in their lifetime—although only five percent were current users.¹⁶⁵

The data on the adverse effects of marijuana are more extensive than the data on effectiveness. Clinical studies of marijuana are difficult to conduct. Researchers interested in clinical studies of marijuana face a series of barriers. Research funds are limited, and there is a daunting thicket of regulations to be negotiated at the federal (FDA and DEA) and state levels (see chapter 5). Consequently, the rapid growth in basic research on cannabinoids contrasts with the scarcity of substantial clinical studies on medical uses.

This chapter is devoted to an analysis of the therapeutic value of marijuana and cannabinoids for specific symptoms associated with a variety of conditions. The risks associated with the medical use of marijuana were discussed in chapter 3. It should be noted that THC, the primary active ingredient in marijuana, is an FDA-approved drug referred to as dronabinol and marketed under the brand name Marinol[®]. Marijuana is primarily advocated as a relief from the symptoms of disease, rather than a cure.

For the most part, the claims for medical uses of marijuana are for relief of symptoms, such as nausea, appetite loss, or chronic pain—each of which can be caused by a variety of diseases or even by the treatments for disease. Therefore, this chapter is primarily organized by symptoms rather than diseases. There are eight sections. The first six deal with specific symptoms and conditions and the last two summarize the medical benefits of marijuana and cannabinoids. The five sections on symptoms and conditions are as follows: pain, nausea and vomiting, wasting syndrome and appetite stimulation, spasticity and other neurological symptoms, and glaucoma.

The IOM study team received reports of over 30 different medical uses of marijuana, which is more than could be carefully reviewed in a report of this length; even more uses are reported elsewhere.^{66, 67} For most of the infrequently mentioned medical uses of marijuana there are only a few anecdotal reports. This report reviews only the most prominent symptoms that are reportedly relieved by marijuana. However, many of those diseases not reviewed here share common symptoms, such as pain, nausea and vomiting, and muscle spasms which might be relieved by cannabinoid drugs.

Standards for evaluating clinical trials

Before evaluating individual clinical trials concerning the efficacy and safety of medical uses of marijuana and cannabinoids, it is useful to review the general qualities of clinical trials. Clinical trials involve groups of individuals in which different treatments are compared among different cohorts, or treatment groups. Such trials measure the efficacy of a medication, and are required by the FDA for approval of any new drug or new use of a drug (discussed further in chapter 5).

The degree of assurance that the outcome of a clinical trial is due to the treatment being tested depends on how well the trial is designed. Three important factors to consider in evaluating the design of a clinical trial are: sample selection, subjective effects, and effects that are independent of the treatment. For *sample selection*, it is important to ensure that patients are allocated to different treatment groups in such a way that the cohorts are not biased towards a particular treatment outcome. For example, the health status, gender, and ages of different cohorts should be equivalent. *Subjective effects* must be controlled because they influence experimental results in two important ways. First, a patient's expectation that a treatment will be effective can influence the degree of its effect (for example, in the control of nausea). Second, the investigator's expectation can influence his or her interpretation of the treatment effect (for example, when assessing the level of pain experienced by a patient). For these reasons, double-blinding, in which neither the subject nor the person who assesses the drug's effect is aware of the subject's treatment group, is particularly important in cannabinoid drug studies. Another important control for subjective effects includes the use of placebo drugs, which are inert substances, or the use of comparison drugs that have effects similar to the experimental drug. Finally, the quality of the experimental design depends on controlling for factors unrelated to the test drug that might nonetheless influence the treatment outcome. *Sequencing effects* are one example of such factor. For example, patients might react differently to the same medication depending on whether the medication was administered after an effective or an ineffective treatment. Likewise, compared to a patient whose symptoms are initially mild, a patient whose symptoms are initially severe might react differently to the same drug treatment. Because of the psychological effects associated with cannabinoid drugs, it is particularly important to consider how such side effects might influence the therapeutic value of the treatment. Conditions such as pain and nausea are especially susceptible to subjective influences. For example, depending on the individual, THC can reduce or increase anxiety; it is important to determine to what extent this 'side effect' contributes to the therapeutic effect experienced by the patient.

While double-blind, randomized, controlled clinical trials offer the highest degree of assurance of drug efficacy; such trials are not always feasible. For safety reasons, vulnerable population, such as children, older patients, and women of child-bearing age, are often excluded from experimental drug trials. Nonetheless, such patients are part of everyday clinical practice. This challenge of integrating the ideal of standardized and rigorous processes for evaluating the effectiveness of treatments with everyday clinical practice has encouraged interest in single patient trials.⁷¹

Methods for such trials have been established and tested in a variety of clinical settings, usually under everyday conditions.^{70, 109, 162} They are particularly valuable when physicians or patients are uncertain about the efficacy of treatment for symptomatic diseases. Controls can be incorporated even in this kind of trial. Such trials can be double-blinded and can involve cross-over designs in which the patient is treated with alternating treatments, such as placebo-drug-placebo, or one drug followed by another drug. Most importantly, as with any other clinical trial, a single patient trial should be designed to permit objective comparison between treatments.

Analgesia

Pain is the most common symptom for which patients seek medical assistance.⁵ Pain associated with either structural or psychophysiological disorders can arise from somatic, visceral, or neural structures. *Somatic pain* results from activation of receptors outside the brain and is transmitted back to the brain via peripheral nerves. *Visceral pain* results from activation of specific pain receptors in the gut. It is characterized as a deep aching or cramping sensation, but the source of the pain is often experienced at sites remote from the site of receptor activation, a phenomenon known as referred pain. *Neuropathic pain* results from injury to peripheral receptors, nerves, or the central nervous system. It is typically burning and the skin feels abnormally unpleasant when gently touched (allodynia), and often occurs in an area of sensory loss—for example, post-herpetic neuralgia.

All of the currently available analgesic, or pain-relieving, drugs have limited efficacy for some types of pain. Some are limited by dose-related side effects, and some by the development of tolerance or dependence. Cannabinoids, or any new analgesic, could potentially be useful under one of the following circumstances:

- There are medical conditions or patients in which they are more effective than any currently available medication.
- They have a broad clinical spectrum of efficacy and a unique side effect profile that differs from other analgesics.
- They have synergistic interactions with other analgesics.
- They exhibit “side effects” which are considered useful in certain clinical situations.
- Their efficacy is enhanced in patients who have developed tolerance to opioids.

There have not been extensive clinical studies on the analgesic potency of cannabinoids, but data from animal studies indicate that cannabinoids could be useful analgesics. In general, cannabinoids seem to be mild to moderate analgesics. Opiates, such as morphine and codeine, are the most widely used drugs for the treatment of acute pain. But they are not consistently effective in chronic pain, they often induce nausea, and sedation and tolerance might occur in some patients. Recent research has made it clear that CB₁ receptor agonists act upon pathways that

partially overlap with those activated by opioids but through pharmacologically distinct mechanisms (see chapter 2). This means that they would likely have a different side effect profile and perhaps additive or synergistic analgesic efficacy.

In light of the solid evidence that cannabinoids can reduce pain in animals (chapter 2), it is important to carefully re-evaluate the evidence concerning analgesic efficacy in humans, and to ask, what clinical evidence is needed to help us decide whether cannabinoids have any use in the treatment of pain?

Clinical studies with cannabinoids

There have been three kinds of studies on the effects of cannabinoids on pain sensitivity in human volunteers: 1) studies of experimentally-induced acute pain, 2) studies of post-surgical acute pain, and 3) studies of chronic pain. Overall, there have been very few studies—only one since 1981—and they have been inconclusive.

Experimentally-induced acute pain

Early studies of cannabinoids in human volunteers using experimental pain models did not demonstrate consistent analgesia. In fact, three early studies testing THC on experimental pain caused by a variety of pain modalities—electrical stimulation, tourniquet pain, and thermal pain—resulted in an *increase* in pain sensitivity (hyperalgesia).^{23, 88, 112}

Other studies also failed to show an analgesic effect of THC, but they were not well-designed. Raft and coworkers¹⁵² found no evidence for THC analgesia on pain thresholds and pain tolerance following electrical stimulation and noxious pressure. But their study suffers from two major methodological problems. First, they measured only the extremes of pain sensation—*threshold* (the lowest intensity at which a particular stimulus is perceived as painful) and *tolerance* (the maximum intensity of pain that a subject can withstand). Most pain is experienced in an intermediate range, where effects on pain suppression are most detectable. Modern methods of pain assessment in humans typically use ratings of the intensity of the sensation of pain, a measure which has been found to be superior to assessing the effects of a drug on the extremes of pain.¹⁹⁶ The second problem was that they did not include a positive control; that is, they did not demonstrate the adequacy of their methodology by showing that an established analgesic, such as an opiate, was effective under their study conditions.

Clark and coworkers²³ tested smoked marijuana on thermal pain in human volunteers, and also failed to observe an analgesic effect. However, because of the study design the results are inconclusive. First, there was no positive control to demonstrate the adequacy of their methods; and second, the study subjects were habitual marijuana users. During the study they were hospitalized and allowed free access to marijuana cigarettes for a period of four weeks, consuming an average of 4 to 17 marijuana cigarettes per day. Pain was tested “approximately every one to two weeks.” Thus it is quite likely that the subjects were tolerant to THC at the time of testing.

Cancer Pain

The most encouraging clinical data on the effects of cannabinoids on chronic pain are from three methodologically sound studies on cancer pain. Cancer pain can be due to inflammation, mechanical invasion of bone or other pain sensitive structure, or nerve injury. It is severe, persistent, and often resistant to treatment with opioids. In one study, Noyes and coworkers found that oral doses of THC in the range of 5-20 mg produced analgesia in patients with cancer pain.^{141, 142} The first experiment was a double-blind, placebo-controlled study of 10 subjects using measures of both pain intensity and pain relief.¹⁴² Each subject received all drug treatments: placebo, 5, 10, 15, and 20 mg THC in pill form—each identical in appearance and given on successive days. Fifteen and 20 mg doses of THC produced significant analgesia. It is of interest that there were no reports of nausea or vomiting in this study. In fact, at least half of the patients reported increased appetite. With a 20 mg dose of THC, patients were heavily sedated and exhibited “depersonalization,” characterized by a state of dreamy immobility, sense of unreality, and disconnected thoughts. Five of 36 patients exhibited adverse reactions (extreme anxiety) and were eliminated from the study. The mean age of the patients was 51 years, so they were probably not experienced marijuana smokers. Only one patient experienced this effect at the 10 mg dose of THC. A limitation of this study is that there were no positive controls—that is, other analgesics that could provide a better measure of the degree of analgesia produced by THC.

In a subsequent larger single dose study, the same investigators reported that the analgesic effect of 10 mg of THC was equivalent to 60 mg of codeine, and 20 mg of THC was equivalent to 120 mg of codeine.¹⁴¹ (Note that codeine is a relatively weak analgesic.) The side effect profile was similar, though THC was more sedating than codeine. In a separate publication, the same authors published data indicating that patients had improved mood, a sense of well-being and less anxiety.

These studies on cancer pain are consistent with the results using a nitrogen analog of THC. Two separate trials were reported: one comparing this analog to codeine in 30 patients, and a second trial comparing it to placebo or secobarbital, a short-acting barbiturate.¹⁷⁸ For mild, moderate and severe pain, this THC-derivative was equivalent to 50 mg of codeine and superior to placebo and to 50 mg of secobarbital.

Surgical Pain

Raft and coworkers¹⁵² found no analgesic effect of THC on surgical pain, induced by tooth-extraction. However, that study suffers from several serious limitations: 1) the tooth extraction included treatment with the local anesthetic, lidocaine; 2) the pain during the procedure was assessed 24 hours later; and 3) there was no positive control. Levonantradol (a synthetic THC analogue) was tested in 56 patients with moderate to severe post-operative or trauma pain.⁹³ They were given intramuscular injections of levonantrodol or placebo 24 to 36 hours after surgery. To control for previous drug exposure, patients with a history of drug abuse or addiction, or those receiving an analgesic or anti-inflammatory drug, tranquilizer, sedative, or

anesthetic agent within 24 hours of the test drug were excluded from the study. On average, pain relief was significantly greater for the levonantradol-treated patients than for the placebo-treated patients. Because the authors do not report the number or the percent of people who responded, it is not clear whether this average represents consistent pain relief for all levonantradol-treated patients or whether some people experienced great relief and a few experienced none.

Case reports and surveys

The few case reports of clinical analgesia trials for cannabinoids are not convincing.^{89, 122} There are, however, anecdotal surveys that raise the possibility that, in certain patients with chronic pain syndromes with prominent spasticity, there might be a role for cannabinoids. A recent survey of over 100 patients with multiple sclerosis reported that a large number obtain relief from spasticity and limb pain (discussed further under section on multiple sclerosis).²⁹ Several paraplegic patients reported in an older survey that marijuana use relieved their phantom pain and headache.⁴²

Migraine Headaches

There is clearly a need for improved migraine medications. Sumatriptan (Imitrex[®]) is currently the best available medication for migraine headaches, but fails to completely abolish migraine symptoms in about 30 percent of migraine patients.^{120, 149} Marijuana has been proposed numerous times as a treatment for migraine headaches (reviewed by Russo¹⁶⁰), but there are almost no clinical data on the use of marijuana or cannabinoids for migraine. Our search of the literature since 1975 yielded only one scientific publication on the subject. This report presents three cases in which cessation of daily marijuana smoking was followed by migraine attacks, which is not convincing evidence that marijuana relieves migraine headaches.⁴⁴ In fact, the same result could have been found if migraine headaches were a consequence of marijuana withdrawal. While there is no evidence that marijuana withdrawal is followed by migraines, when analyzing the strength of reports such as these it is important to consider all the logical possibilities. Various individuals have claimed that marijuana relieves their migraines, but at this stage there are no conclusive clinical data or published surveys about the effect of cannabinoids on migraines.

There is, however, a possible link between cannabinoids and migraine which is suggested by the abundance of cannabinoid receptors in the periaqueductal gray (PAG) region of the brain. The PAG is part of the neural system that serves to suppress pain and is thought to be involved in the generation of migraines.⁵⁶ The link or lack thereof between cannabinoids and migraines might be elucidated by examining the effects of cannabinoids on the PAG. Recent results indicating that both cannabinoid receptor subtypes are involved in controlling peripheral pain,¹⁶ suggest that this might be possible. Nonetheless, the PAG offers only a weak

anatomical correlate between cannabinoid effects on the brain and their possible role in migraine relief.

Conclusions and Recommendations

Basic Pain Research

A key question to address is whether there is any receptor selectivity for the analgesic efficacy of cannabinoids. Are the unwanted side effects (amnesia and sedation) caused by the same receptors in the same brain regions as those producing the analgesia? If the answer is yes, enhancing efficacy will not solve the problem of sedation. Similarly, are the pleasant side effects due to an action at the same receptor? Can the feelings of well-being and appetite stimulation be separated by molecular design? The recent results indicating that both cannabinoid receptor subtypes are independently involved in controlling peripheral pain¹⁶ (discussed in chapter 2) suggest that this might be possible and that further research in this area is clearly warranted.

Further research into the basic circuitry underlying cannabinoid analgesia should be valuable. The variety of neural pathways that underlie the control of pain suggests that a synergistic analgesia "cocktail" might be effective. For example, Lichtman has shown the involvement of the α_2 adrenoreceptor in cannabinoid analgesia. Perhaps a combination of a CB₁ agonist and the α_2 agonist (e.g., clonidine) would provide enhanced analgesia with a lower side effect level.

Clinical Pain Research

Clinical studies should be directed at those populations of pain patients where there is a demonstrated need for improved management and where the particular side effect profile of cannabinoids holds promise of a decided benefit over current approaches. The following patient groups should be targeted for clinical studies of cannabinoids in the treatment of pain:

- Patients on chemotherapy, especially for the treatment of mucositis, nausea and anorexia.
- Postoperative pain patients as an opioid adjunct to determine whether nausea and vomiting from opioids are reduced.
- Patients with spinal cord injury, peripheral neuropathic pain, or central post-stroke pain.
- Patients with chronic pain and insomnia.
- AIDS patients with cachexia, AIDS neuropathy, or any significant pain problem.

In any patient group, an essential question to be addressed is whether the analgesic efficacy of opioids can be augmented. The strategy would be to find the ceiling analgesic effect with an opioid (as determined by pain intensity and tolerability of side effects) and then add in a cannabinoid to determine if additional pain relief can be obtained. This would begin the investigation of potential drug

combinations. As with any clinical study on analgesic drugs, it will be important to investigate the development of tolerance and physical dependence. These are not, of themselves, reasons to preclude the use of cannabinoids as analgesics, but such information is essential to the management of many drugs to which patients develop tolerance or physical dependence.

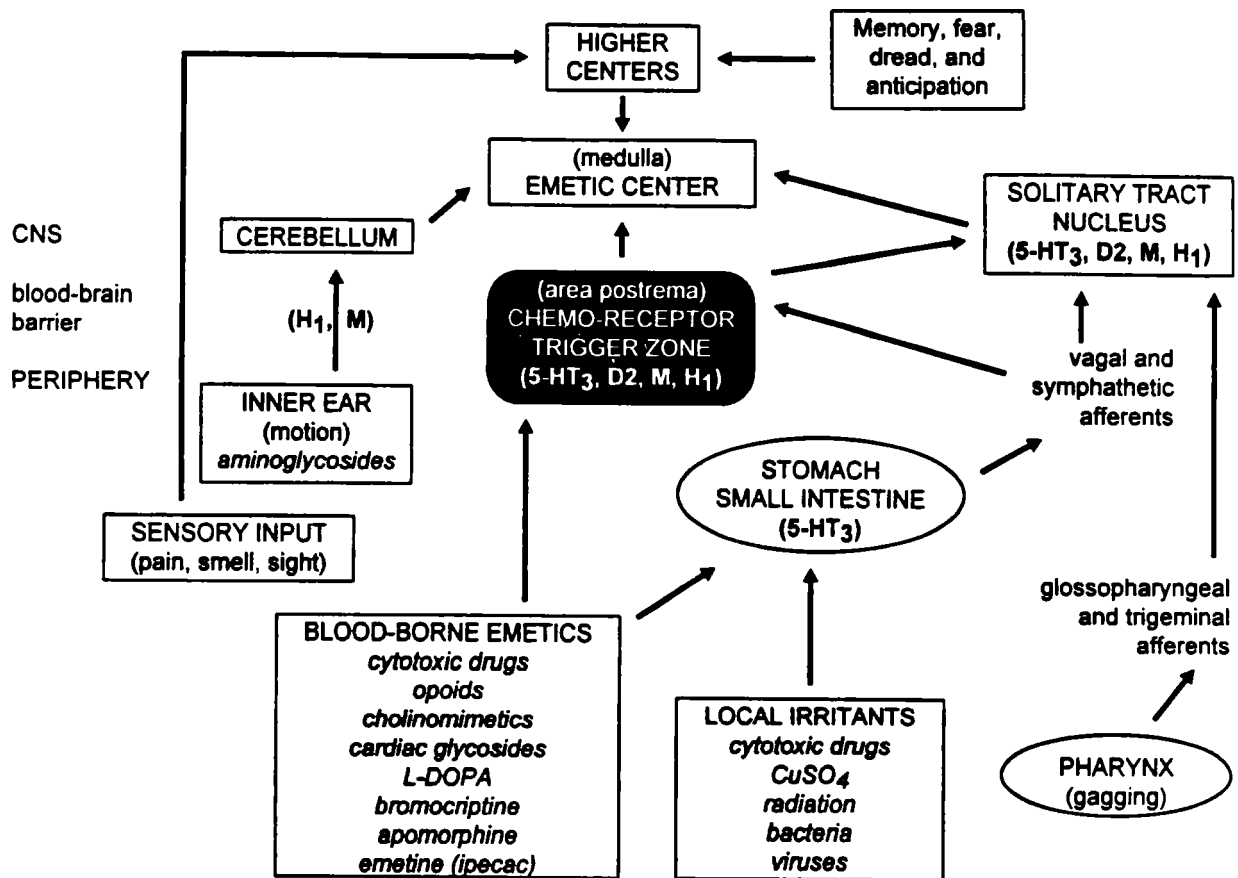
A secondary question would be to determine whether THC is the only or the best component of marijuana for analgesia. How does the analgesic effect of the plant extract compare to that of THC alone? If there is any difference, then it will be important to identify which combinations of cannabinoids are the most effective analgesics.

In conclusion, the available evidence from both animal and human studies indicates that cannabinoids can produce a significant analgesic effect. One exception is the lack of analgesic effect in studies on experimentally-induced acute pain, but because of limitations in the design of those studies they were inconclusive. Further clinical work is warranted to establish the magnitude of this effect in different clinical conditions and to determine if the effect is maintained over time. Although the usefulness of cannabinoids appears to be limited by side effects, notably sedation, there are other effects, such as anxiolysis, appetite stimulation, and perhaps antinausea and antispasticity effects that should be studied in randomized, controlled clinical trials. It is this particular combination of effects that might warrant development of cannabinoid drugs for certain clinical populations.

Nausea and Vomiting

Nausea and vomiting (emesis) occur under a variety of conditions such as acute viral illnesses, cancer, radiation exposure, cancer chemotherapy, postoperative recovery, pregnancy, motion, and poisoning. Both are produced by excitation of one or a combination of trigger(s) located in the gastrointestinal tract, brain stem and higher brain centers (figure 4.1, Emesis-stimulating pathway).¹²⁹ There are numerous cannabinoid receptors in the nucleus of the solitary tract, a brain center that is important in the control of emesis.^{83, 84} Although the same mechanisms appear to be involved in triggering both nausea and vomiting, one can occur without the other. Much more is known about the neural mechanisms that produce vomiting than nausea, in large part because the act of vomiting is a complex behavior involving coordinated changes in the activity of the gastrointestinal tract, respiratory muscles and posture, whereas nausea is a sensation primarily involving higher brain centers and lacks a discrete observable action.^{108, 130} Most reports on the antiemetic effects of marijuana or cannabinoids are based on chemotherapy-induced emesis; they are the subject of the following section.

FIGURE 4.1 Emesis-stimulating pathways



Chemotherapy-Induced Nausea and Vomiting

The use of effective chemotherapeutic drugs has produced cures in some malignancies and retarded the growth of others. Unfortunately, nausea and vomiting are frequent side effects of these drugs. Nausea ranks behind only hair loss as a concern of patients on chemotherapy, and many patients experience it as the worst side effect of chemotherapy. The side effects can be so devastating that patients abandon therapy or suffer diminished quality of life. As a result, the development of effective strategies to control the emesis induced by many chemotherapeutic agents is a major goal in the supportive care of patients with malignancies.

The mechanism by which chemotherapy induces vomiting is not completely understood. Studies suggest that emesis is caused by stimulation of receptors in the central nervous system or in the gastrointestinal tract. This stimulation appears to be caused by the drug itself, a metabolite of the drug, or a neurotransmitter.^{6, 13, 36, 50} In contrast with an emetic like apomorphine, there is a delay between the administration of chemotherapy and the onset of emesis. This delay depends on the chemotherapy agent; emesis can begin anywhere from a few minutes after the administration of an agent like mustine to an hour for cisplatin.¹³

The most desirable effect of an antiemetic is to control emesis completely, which is currently the primary standard in testing new antiemetic agents (R. Gralla, IOM workshop). Patients recall the number of emetic episodes accurately, even with antiemetics that are sedating or that affect memory.¹⁰⁵ Thus the desired endpoint of complete control is also a highly reliable method of evaluation. The degree of nausea can be estimated through the use of established visual analog scales.^{a, 22, 59, 105}

Another consideration for antiemetic drugs is that the frequency of emesis varies from one chemotherapeutic agent to another. For example, cisplatin causes vomiting in more than 99 percent of patients who are not taking an antiemetic, with approximately 10 vomiting episodes per dose of cisplatin; whereas methotrexate causes emesis in fewer than 10 percent of patients.^{59, 86, 87} Among chemotherapy agents, cisplatin is the most consistent emetic known and has become the benchmark for judging antiemetic efficacy. To date, antiemetics that are effective with cisplatin are at least as effective with other chemotherapy agents. Lastly, controlling for factors such as the influence of prior chemotherapy and balancing predisposing factors (i.e., gender, age, and prior heavy alcohol usage) among study groups is vital for reliability. Additionally, reliable randomization of patients and blinding techniques (easier when there are no psychoactive effects) are necessary to evaluate the control of vomiting and nausea.

^a The *visual analog scale* is a continuous line representing all possible levels of a particular sensation. It is an estimation of a patient's subjective evaluation and not a true measurement. Patients select a point anywhere on the line to demonstrate the level of sensation they are experiencing, with one end representing one extreme, such as no sensations and the other end representing the opposite extreme, such as a maximum level of that sensation.

THC/Marijuana Therapy for Chemotherapy-Induced Nausea and Vomiting

Cannabinoids are mildly effective in preventing emesis in some patients receiving cancer chemotherapy. Several cannabinoids have been tested as antiemetics, including THC (both Δ^9 THC and Δ^8 THC) and two synthetic cannabinoids, nabilone and levonantradol. In addition, smoked marijuana has been examined.

Antiemetic Properties of THC

The quality and usefulness of antiemetic studies depend on adherence to the methodological considerations outlined above. Many of the cannabinoid clinical experiences reported are not based on definitive experimental methods. In studies where THC was compared to placebo, THC was usually found to possess antiemetic properties. However, the chemotherapy drug used varied in most of the trials, and some of the studies consisted of small numbers of patients. In one study, THC was found to be superior to placebo for patients receiving chemotherapy with methotrexate, an agent that is not a strong emetic.¹⁹ The same investigators found only a weak antiemetic effect of THC in a small number of patients receiving anthracyclines, chemotherapy drugs that more likely to cause emesis than methotrexate.²⁰

Other trials compared the efficacy of THC with that of prochlorperazine (Compazine®).^{145, 163} Compazine® was one of the more effective antiemetics available in the 1980s, but it was not completely satisfactory and the search for better agents continued. THC and prochlorperazine given orally showed similar degrees of efficacy, but those studies often used various chemotherapeutic agents; even when administered in combination, THC and prochlorperazine failed to stop vomiting in two-thirds of patients.⁵⁴

In a carefully controlled double-blind study comparing THC and the antiemetic drug, metoclopramide, in which no patient had previously received chemotherapy so anticipatory emesis was not a factor, all patients received the same dose of cisplatin, and the subjects were randomly assigned to each group (THC or metoclopramide). Complete control of emesis occurred in 47 percent of those treated with metoclopramide, as opposed to 13 percent of those treated with THC.⁶² Major control (two or fewer episodes) occurred in 73 percent of the patients given metoclopramide compared to 27 percent of those given THC. Despite many flaws in experimental methods, those results suggest that THC reduces chemotherapy-induced emesis.^{19, 20, 54, 164} The studies also indicate that the degree of efficacy is not high. In 1985, the FDA approved THC in the form of dronabinol for this treatment (discussed in chapter 5).

The THC metabolite, 11-OH-THC, is more psychoactive than THC but is a weaker antiemetic.¹²³ Thus it might be possible to design antiemetic cannabinoids without the psychological effects associated with marijuana or THC. Δ^8 -THC is less

psychoactive than THC¹⁵³, but was found to completely block both acute and delayed chemotherapy-induced emesis in a study of eight children, aged 3-13 years.^b Two hours before the start of each cancer treatment and every six hours thereafter for 24 hours, the children were given Δ^8 -THC as oil drops on the tongue or as a bite of bread (18 mg/m² body surface area). The children received a total of 480 treatments. The only side effects reported were slight irritability in two of the youngest children (aged 3.5 and 4 years). Based on the prediction that the THC-induced anxiety effects would be less in children than in adults, the authors used doses that were higher than those recommended for adults (5-10 mg/m² body surface area).

Antiemetic Properties of Synthetic THC Analogues

Nabilone (Cesamet[®]) and levonantradol were tested in a variety of settings, with results similar to those with THC. While efficacy was observed in several trials, no advantage emerged for these agents.^{179, 189} As with the THC trials, nabilone and levonantradol reduced emesis, but not as well as other available agents in moderately to highly emetogenic settings. Neither is commercially available in the United States.

Antiemetic Properties of Marijuana

Among the efforts to study marijuana a preliminary study was conducted in New York State on a group of 56 cancer patients who were unresponsive to conventional antiemetic agents.¹⁹² These patients were asked to rate the effectiveness of marijuana compared with results during prior chemotherapy cycles. Seventy-eight percent of patients in this survey rated marijuana as "moderately effective" or "highly effective." The authors concluded that marijuana had antiemetic efficacy, but its relative value was difficult to determine because no control group was used and the patient population was varied with respect to previous experiences, such as prior marijuana use and THC therapy.

A Canadian oncology group conducted a double-blind, cross-over, placebo-controlled study comparing smoked marijuana with THC given in pill form to 20 patients receiving a variety of chemotherapeutic drugs.¹¹¹ The degree of emetic control was similar, with only 25 percent of the patients achieving complete control of emesis. Thirty-five percent of the patients indicated a slight preference for the THC pills over marijuana. Twenty percent preferred marijuana and 45 percent expressed no preference.¹¹¹

^b Note that the authors of this study chose to use Δ^8 -THC because it is more stable and easier to produce than Δ^9 -THC; it does not follow from this particular study that marijuana, with its mixture of cannabinoids, should be a more powerful antiemetic than Δ^9 -THC.

Neither study showed a clear advantage for smoked marijuana over oral THC, but neither reported data on the time course of antiemetic control, possible advantages of self-titration with the smoked marijuana, or the degree to which patients were able to swallow the pills. Patients with severe vomiting would have been unlikely to be able to swallow or keep the pills down long enough for them to take effect. The onset of drug effect is much faster with inhaled or injected THC than it is for oral delivery.^{91, 114, 143} Although many marijuana users have claimed that smoked marijuana is a more effective antiemetic than oral THC, no controlled studies have yet been published that analyze this in sufficient detail to estimate the extent to which that is the case.

Side Effects Associated with THC/Marijuana in Antiemetic Therapy

Frequent side effects associated with THC and marijuana include dizziness, dry mouth, hypotension, moderate sedation, and euphoria or dysphoria. The side effects seen with smoking marijuana include dizziness, dry mouth, confusion, and anxiety.^{19, 20, 54, 111, 145, 163, 179, 189} Dry mouth and sedation are the least troubling side effects to patients. Perhaps the most troubling side effects are orthostatic hypotension and dizziness, which could enhance the patient's distress.

There is disagreement as to whether the psychoactive effects of THC correlate with its antiemetic activity. In the prospective double-blind trial comparing THC and metoclopramide, the authors report no relationship between the occurrence of complete antiemetic control and euphoria or dysphoria.⁶² In contrast, other investigators believe that such psychoactive effects (euphoria or dysphoria) are often associated with improved antiemetic control.¹⁶³ Nevertheless, consensus exists among most investigators that dysphoric effects are more common among patients who have not had prior experience with cannabinoids. An important and unexpected problem encountered in the New York State open trial with marijuana was the inability of nearly one-quarter of the patients to tolerate the administration of marijuana by smoking.¹⁹² This intolerance could be due to inexperience with smoking marijuana and is an important consideration.

Therapy for Chemotherapy-Induced Nausea and Vomiting

Present Therapy

New classes of antiemetics have emerged over the last ten years. They have dramatically reduced the nausea and vomiting associated with cancer chemotherapy and literally transformed the acceptance of cisplatin by cancer patients. These new antiemetics, including selective serotonin type 3 receptor antagonists, substituted benzamides, corticosteroids, butyrophenones, and phenothiazines, have few side effects when given on a short-term basis and are convenient in a variety of clinical settings.

The most effective commonly used antiemetics are serotonin receptor antagonists (i.e., ondansetron, granisetron) with or without corticosteroids.^{38, 60, 92, 147, 157} In a combination trial using dexamethasone (corticosteroid) and a serotonin

antagonist, complete control of acute cisplatin-induced emesis was observed in about 75 percent of patients. In tests where the chemotherapy was only moderately emetogenic, as many as 90 percent of the patients who received these combinations achieved complete control of emesis. Side effects of those antiemetic agents include headache, constipation and alterations in liver function, but are generally well-tolerated by most patients.¹⁴

Other commonly used antiemetics include phenothiazines (i.e., prochlorperazine [Compazine[®]], haloperidol) and metoclopramide. Metoclopramide is somewhat less effective than the serotonin antagonists, and has more side effects including acute dystonic reactions, drowsiness, diarrhea, and depression.^{14, 38} Side effects associated with phenothiazines include severe or acute dystonic reactions, hypotension, blurred vision, drowsiness, dry mouth, urinary retention, allergic reactions, and occasional jaundice.¹⁴

SIDEBAR: Attitudes of Oncologists Toward Prescribing Marijuana

In the 1990s, two groups of investigators conducted three surveys on the attitudes of clinical oncologists toward prescribing marijuana as an anti-emetic. These studies are arguably out of date, because the antiemetics that are available now are so much more effective than they were when these studies were conducted. Nonetheless, the studies merit attention because they are still frequently cited as evidence for or against the use of marijuana as an antiemetic.

The results of the two groups were contradictory. In 1994, by which time serotonin receptor antagonists (5-HT receptors) had become available, Schwartz and Beveridge¹⁷⁴ concluded that oncologists had little interest in prescribing marijuana to control emesis, whereas Doblin and Kleiman concluded in 1991 that interest was great.⁴⁰ Since 1994 the two groups have debated in the literature as to which study represents the true sentiment among oncologists.^{39, 175, 180} In fact, there are numerous methodological differences between the two studies that might explain the different results.^{39, 175} Nonetheless, ultimately these studies are irrelevant. Both studies deal with perceptions rather than pharmacological realities based on well-designed outcome studies.¹⁸⁰

The cost of effective antiemetic regimens can vary markedly depending on the agent, dose, schedule and route of administration. Overall, oral regimens cost less than intravenous regimens due to lower pharmacy and administration costs, as well as lower acquisition costs in many countries. Regimens costing (to the pharmacy) as low as \$30 to \$35 per treatment session have been shown to be effective.⁶¹ These costs reflect the treatment of acute emesis and delayed emesis, with the use of generic agents where available.

Major progress, generally not well-known to the public, in controlling chemotherapy-induced acute nausea and vomiting has been made since the 1970s. Patients receiving the most difficult to control emetic agents now have no more than a 20-30 percent likelihood of experiencing acute emesis,¹⁵⁷ whereas in the 1970s the likelihood was nearly 100 percent despite antiemetics.^{59, 90} As has been seen, most

antiemetic studies with cannabinoids present methodological difficulties and are inconclusive. If one concentrates on the well-conducted trials, the evidence indicates that cannabinoids reduce emesis in about one quarter of patients receiving cancer chemotherapy. Cannabinoids are not as effective as several other classes of agents, such as substituted benzamides, serotonin receptor antagonists and corticosteroids. The side effects associated with cannabinoid use are generally tolerable. As with cannabinoids, efficacy was apparent with smoked marijuana, but the degree of efficacy was no better than that seen with available antiemetic agents now considered to be marginally satisfactory. At present, the most effective antiemetic regimens are combinations of oral serotonin receptor antagonists with dexamethasone in single dose regimens given prior to chemotherapy. Neither multiple dose regimens nor intravenous antiemetics provide better control, and both add unnecessary costs.^{63, 85}

Future Therapy

Advances in therapy for chemotherapy-induced nausea and vomiting will require discovery of agents that work through different mechanisms than existing antiemetics, including the serotonin antagonists. Among the proposed new pathways, agents that involve the neurokinin receptors (NK-1 antagonists) appear to be the most promising.^c In animal models, agents that block the NK-1 receptor prevent cisplatin-induced emesis. At the time of this writing, clinical trials with NK-1 receptor antagonists are underway (phase II or small phase III comparison studies). Preliminary results indicate that these agents have useful activity in both acute and delayed chemotherapy-induced emesis and are safe to administer orally.^{106, 137}

It is theoretically possible, considering that the mechanism of cannabinoid action appears to be different than that of the serotonin receptor antagonists and of corticosteroids, that added to more effective regimens, THC might enhance control of emesis. Such combinations should aim to be as convenient as possible while having few added side effects. The critical issue is not whether marijuana or cannabinoid drugs might be superior to the new drugs, but rather whether there is a group of patients who might obtain added or better relief from marijuana or cannabinoid drugs.

Finally, even with the best antiemetic drugs, the control of nausea and vomiting that begins or persists 24 hours after chemotherapy remains imperfect. The pathophysiology appears different than that of acute emesis and it is more likely to occur with a strong emetic agent, but it varies from patient to patient. Treatment to prevent this emesis requires dosing after chemotherapy as well as before.¹⁰⁷

^c Neurokinin receptors are found in brain and the gut and thought to be involved in motor activity, mood, pain, and reinforcement. They may well be involved in mediating gut sensations, including nausea.

Conclusions and Recommendations: Chemotherapy-induced nausea

Most chemotherapy patients are unlikely to want to use marijuana or THC as an antiemetic. In 1998, there are more effective antiemetic agents available than were available earlier. By comparison, cannabinoids are only modest antiemetics. However, since modern antiemetics likely act through different mechanisms, cannabinoids might be effective in people who respond poorly to currently used antiemetic drugs, or cannabinoids might be more effective in combination with the new drugs than either are alone. For both reasons, studies of the effects of adjunctive cannabinoids on chemotherapy-induced emesis are worth pursuing for patients whose emesis is not optimally controlled with other agents.

While some people who spoke to the IOM study team described the mood enhancing and anxiety reducing effects of marijuana as a positive contribution to the antiemetic effects of marijuana, one-quarter of the patients in the New York State study described earlier were unable to tolerate smoked marijuana. Overall, the effects of oral THC and smoked marijuana are similar, but there are differences. For example, in the residential studies of experienced marijuana users by Haney and coworkers, subjects reported that marijuana made them feel "mellow,"⁷⁵ whereas comparable doses of oral THC did not.⁷⁴ Such differences might be due to the different routes of delivery of THC, as well as the different mixture of cannabinoids found in the marijuana plant. As of this writing, no studies have been published that weigh the relative contributions of those different factors.

The goal of antiemetic medications is to prevent nausea and vomiting. Hence, antiemetics are typically given before chemotherapy, in which case, a pill is an effective form of drug delivery. However, in patients already experiencing severe nausea or vomiting, pills are generally ineffective, because of the difficulty in swallowing or keeping a pill down, and slow onset of the drug effect. Thus an inhalation (but, preferably not smoking) cannabinoid drug delivery system would be advantageous for treating chemotherapy-induced nausea.

Until the development of rapid onset antiemetic drug delivery systems, there will likely remain a subpopulation of patients for whom standard antiemetic therapy is ineffective and who suffer from debilitating emesis. It is possible that the harmful effects of smoking marijuana for a limited period of time might be outweighed by the antiemetic benefits of marijuana, at least for, patients for whom standard antiemetic therapy is ineffective and who suffer from debilitating emesis. Such patients should be evaluated on a case by case basis and treated under close medical supervision.

Wasting Syndrome and Appetite Stimulation

Wasting syndrome in acquired immune deficiency syndrome (AIDS) patients is defined by the Centers for Disease Control as the involuntary loss of more than 10 percent of baseline average body weight in the presence of diarrhea or fever of more than 30 days that is not attributable to other disease processes.¹⁸ Anorexia, which is a loss of appetite, can accelerate wasting by limiting intake of the necessary

nutrients. Both wasting (cachexia) and anorexia are common end-stage features of certain fatal diseases such as AIDS as well as metastatic cancers. In AIDS, weight loss of as little as 5 percent is associated with decreased survival, and a body weight about one-third below ideal body weight results in death.^{103, 161}

There are two forms of malnutrition: starvation and cachexia. Starvation is the deprivation of essential nutrients and results from underlying causes such as famine or poverty, malabsorption, and eating disorders (e.g., anorexia nervosa). Starvation results in metabolic adaptations that deplete body fat before losses of lean tissue. Cachexia, in contrast, results from tissue injury such as trauma, infection, or tumor, and is characterized by a disproportionate loss of lean body mass, such as skeletal muscle.⁹⁸ The key distinguishing factor between starvation and cachexia is that the effects of starvation can usually be reversed by providing food regardless of the cause of starvation, while the effects of cachexia can be reversed only through control of the underlying disease, and—at least for some patients—drugs that stimulate metabolism, such as growth hormone or androgenic-anabolic hormones.

Malnutrition in HIV-Infected Patients

By 1997, there were more than 30 million people worldwide infected with human immunodeficiency virus (HIV), and this number is predicted to increase to almost 40 million by the year 2000.^{128, 190} Malnutrition is common among AIDS patients and plays an independent and significant role in morbidity and mortality.^{99, 104, 161}

Because treatment for malnutrition depends on whether it is caused by starvation or cachexia, one needs to know what effects HIV infection has on metabolic processes. The answer depends on the clinical situation and can be either or both.⁹⁸

The development of malnutrition in HIV infection has many facets. Malnutrition in HIV-infected patients results in a disproportionate depletion of body cell mass,^d total body nitrogen, and skeletal muscle mass—consistent with cachexia.^{101, 198} Body composition studies show that the depletion of body cell mass precedes the progression to AIDS (i.e., falling CD4 lymphocyte counts), suggesting that malnutrition can be a consequence of the inflammatory response to the underlying viral infection, rather than a general complication of AIDS.¹⁴⁶ In contrast, weight loss is often episodic and related to acute complications such as febrile opportunistic infections.¹¹⁵ Mechanisms underlying wasting in HIV-infected patients vary depending on the stage of HIV infection and on specific associated complications.

There are many reasons for decreased food intake among AIDS patients. These include mouth, throat, or esophageal infections or ulcers (oropharyngeal and esophageal pathology); adverse effects of medications;²⁰⁰ diarrhea; enteric infection;

^d Body cell mass is the fat-free cellular mass. It is composed of the cells of the muscle and organs, plus circulating hematopoietic cells and the aqueous compartment of adipocytes. It is not fat, extracellular water, or extracellular solids (such as tendons, etc.).

malabsorption; serious systemic infection; focal or diffuse neurological disease; HIV enteropathy; depression; fatigue; and poverty. Nutrient malabsorption is often the result of microorganism overgrowth or infection in the gut, especially in the later stages of AIDS.^{99, 159}

Marijuana, THC, and Malnutrition in HIV-Infected Patients

Despite their frequency of use, there is little published information about the effectiveness of marijuana or cannabinoids for the treatment of malnutrition and wasting syndrome in HIV-infected patients. The only cannabinoid evaluated in controlled clinical studies is THC, or dronabinol. Short-term (6 weeks) and long-term (1 year) therapy with dronabinol was associated with an increase in appetite and stable weight, and in a previous short-term (5 weeks) clinical trial in five patients, dronabinol was shown to increase body fat by one percent.^{9, 10, 182} In 1992, the FDA approved THC, under the trade Marinol®, as an appetite stimulant for the treatment of AIDS related weight loss. Megestrol acetate^c (Megace®), an appetite stimulant, is more effective than dronabinol in stimulating weight gain, and there is no additive effect of dronabinol when used in combination with megestrol acetate.¹⁸⁷ HIV/AIDS patients are the largest group of patients who use dronabinol. However, some reject dronabinol because of the intensity of neuropsychologic effects, an inability to easily titrate the oral dose, and the delayed onset together with the prolonged duration of its action.³ There is evidence to suggest that cannabinoids modulate the immune system (see chapter 2, section on Cannabinoids and the Immune System), which might be a problem in immunologically-compromised patients. No published studies have formally evaluated the use of any of the other cannabinoids in AIDS wasting or as an appetite stimulant.

Anecdotes abound that smoked marijuana is useful for the treatment of HIV-associated anorexia and weight loss.^{24, 66} Some individuals report a preference for smoked marijuana over oral THC because it gives them the ability to titrate the effects, depending on how much they inhale. In controlled laboratory studies on normal, healthy adults, smoked marijuana was shown to increase body weight, appetite, and food intake.^{49, 121} Unfortunately, there have been no controlled studies of the effect of smoked marijuana on appetite, weight gain and body composition in AIDS patients. At the time of this writing, Donald Abrams at the University of California at San Francisco (UCSF) is conducting the first clinical trial to test the safety of smoked marijuana in AIDS patients, and the results are not yet available.

A major concern with marijuana smoking in HIV-infected patients is that they might be more vulnerable than other marijuana users to immunosuppressive effects of marijuana, or to the exposure of infectious organisms associated marijuana plant material (see chapter 3, Marijuana Smoke).

^c Megestrol acetate is a synthetic derivative of progesterone that can stimulate appetite and cause significant weight gain when given in high doses (320 to 640 mg/d) to AIDS patients.⁵⁸

Therapy for Wasting Syndrome in HIV-Infected Patients

Present Therapy

Generally, therapy for wasting in HIV-infected individuals has focused on appetite stimulants. Few therapies have proven successful in the treatment of the AIDS wasting syndrome. The stimulant studied most is megestrol acetate, which has been shown to increase food intake about 30 percent over baseline for reasons that remain unknown. Its effect in producing significant weight gain is dose-dependent, but the majority of the weight gain is fat tissue, not lean body mass. Although the findings are still preliminary, anabolic compounds, such as testosterone or growth hormone, might be useful in preventing the loss of, or help in restoring, lean body mass in AIDS patients.^{11, 46, 68, 173} Additionally, enteral and parenteral nutrition have been evaluated and shown to increase weight, but again, the increase is more due to body fat than to lean body mass.^{100, 102}

Encouraging advances in the antiviral treatment of HIV infection coupled with developments in the prophylaxis and therapy of opportunistic infections have recently changed the outlook for the long-term health of HIV-infected individuals. Death rates have halved, and the frequency of serious complications, including malnutrition, has fallen markedly.^{98, 135}

Future Therapy

The primary focus of future therapies for wasting in HIV-infected patients is to increase lean body mass as well as appetite. Active systemic infections are associated with profound anorexia which is believed to be mediated by cytokines that stimulate inflammation through their actions within and outside the brain.¹³⁴ Cytokine inhibitors such as thalidomide have been under investigation as potential treatments to increase lean body mass and reduce malnutrition. Even though cannabinoids do not appear to restore lean body mass, they might be useful as adjunctive therapy. For example, cannabinoids could be used as an appetite stimulant in patients with diminished appetite who are undergoing resistance exercises or anabolic therapy to increase lean body mass. Additionally, cannabinoids could be beneficial for a variety of effects, such as increased appetite while reducing the nausea and vomiting caused by protease inhibitors, as well as the pain and anxiety associated with AIDS.

Considering current knowledge about malnutrition in HIV infection, cannabinoids, by themselves, will not likely be a primary therapy for this condition, but might be useful in combination with other therapies. Specifically, the proposed mechanism of action of increasing food intake, would most likely be ineffective in promoting an increase in skeletal muscle mass and functional capacity, the goal in the treatment of cachexia in AIDS patients (D. Kotler, Columbia University, personal communication, 1998).

Malnutrition in Cancer Patients

Malnutrition in cancer patients compromises their quality of life and contributes to the progression of their disease. Approximately 30 percent of Americans will develop cancer in their lifetimes, of whom two-thirds will die as a result of their disease.⁵ Depending on the type of cancer, 50-80 percent of patients will develop cachexia, and up to 50 percent of these patients will die, in part, as a result of cachexia.^{12, 41} The cachexia appears to result from the tumor itself, and cytokines (proteins secreted by the host during an immune response to tumor) are likely important factors in this development. Cachexia does not occur in all cancers, but generally occurs at the late stages of advanced cancers, such as pancreas, lung, and prostate.

The only cannabinoid evaluated for treating cachexia in cancer patients is dronabinol, which has been shown to improve appetite and promote weight gain.⁵⁸ Present treatments for cancer cachexia are similar to that for cachexia in AIDS patients. These treatments are usually indicated at late stages of advanced disease, and include megestrol acetate and enteral and parenteral nutrition. Megestrol acetate stimulates appetite and promotes weight gain in cancer patients, although the gain is mostly fat mass (reviewed by Bruera 1998¹⁵). Both megestrol acetate and dronabinol result in dose-related side effects that can be troublesome for patients: megestrol acetate can cause hyperglycemia and hypertension, and dronabinol can cause dizziness and lethargy. Cannabinoids have also been shown to modulate the immune system (see chapter 2, Cannabinoids and the Immune System), which could be contraindicated for certain cancer patients (both the chemotherapy and the cancer can be immunosuppressive).

Future treatments will probably depend on the development of methods that block cytokine actions, and the use of selective β_2 -adrenergic receptor agonists to increase muscle mass.^{15, 77} Additionally, treatments for cancer cachexia will most likely need to identify the patients' individual needs, in that some patients might need only a cytokine inhibitor, while others could benefit from combined approaches, such as an appetite stimulant and β_2 -adrenergic receptor agonists. In this respect, cannabinoids such as THC might prove useful as part of a combination therapy as an appetite stimulant, antiemetic, analgesic and anxiolytic, especially for patients in late stages of the disease.

Anorexia Nervosa

Anorexia nervosa, a psychiatric disorder characterized by distorted body image and self-starvation, affects an estimated 0.6 percent of the United States population, with a greater predominance in girls than boys.⁵ The mortality rate is high, and response to standard treatments is poor.

THC appears to be ineffective in treating this disease. In one study it caused severe dysphoric reactions in 3 of 11 patients.⁶⁹ One possible explanation for the

dysphoria is that THC increases appetite and thus intensifies the mental conflict between hunger and food refusal.¹⁴ Furthermore, such patients may have underlying psychiatric disorders (schizophrenia, depression) in which cannabinoids might be hazardous (see chapter 3 Psychological Harms).

Current treatments include psychological techniques to overcome emotional or behavioral problems and dietary intervention to reverse the malnutrition.¹⁹⁹ Pharmacological treatments such as antidepressants have been used in addition to psychotherapy, but tend to lack the desired level of efficacy.³⁴ Recently, alterations in a gene for one of the serotonin receptors have been identified in some patients with anorexia nervosa.⁴⁷ The possibility of a genetic component presents a pathway for the development of new drugs to treat this disease.

Recommendations

The profile of cannabinoid drug effects suggests that they are promising for treating wasting syndrome in AIDS patients. Nausea, appetite loss, pain, and anxiety are all afflictions of wasting and all can be mitigated by marijuana. Although there are medications that are more effective than marijuana for these problems, they are not equally effective for all patients. Thus we recommend the development and clinical testing of a rapid onset (that is, within minutes) form of THC for such patients. We do not recommend smoking. The long-term harms from smoking make it a poor drug delivery system, particularly for patients with chronic illnesses.

Terminal patients raise different issues. For those patients, the medical harms of smoking are of little consequence. For terminal patients suffering debilitating pain or nausea and for whom all indicated medications have failed to provide relief, the medical benefits of smoked marijuana might outweigh the harms.

Neurological Disorders

Neurological disorders are those that affect the brain, spinal cord, or peripheral nerves and muscles in the body. Marijuana has been proposed most often as a source of relief for three general types of neurological disorders: *muscle spasticity*, particularly for multiple sclerosis patients and spinal cord injury victims; *movement disorders*, such as Parkinson's disease, Huntington's disease, and Tourette's syndrome; and *epilepsy*. Note that marijuana is not proposed as a cure for such disorders, merely that it might relieve certain associated symptoms.

Muscle Spasticity

Spasticity is the increased resistance to passive stretch of muscles and increased deep tendon reflexes. Muscles may also contract involuntarily (flexor and

extensor spasms). In some cases these contractions are debilitating and very painful, and require therapy to relieve the spasms and associated pain.

There are numerous anecdotal reports that marijuana can relieve the spasticity associated with multiple sclerosis or spinal cord injury, and animal studies have shown that cannabinoids affect motor areas in the brain—areas that might influence spasticity.^{55, 82, 132, 171}

Multiple Sclerosis

As the name implies, “multiple sclerosis” (MS) is a condition in which multiple areas of the CNS are affected. Many nerve fibers become demyelinated,^f some are destroyed, and scars form (sclerosis) resulting in plaques scattered throughout the white matter of the CNS. MS exacerbations appear to be caused by abnormal immune activity which causes inflammation and myelin destruction in the brain (primarily the periventricular area), brain stem or spinal cord. The demyelination slows or blocks transmission of nerve impulses and results in an array of symptoms such as fatigue, depression, spasticity, ataxia (inability to control voluntary muscular movements), vertigo, blindness, and incontinence. Approximately 90 percent of MS patients eventually develop spasticity. With an estimated 2.5 million MS patients worldwide, spasticity is a major concern for many patients and physicians.¹³⁶ Spasticity is variably experienced as muscle stiffness, muscle spasms, flexor spasms, or cramps, muscle pain or ache. The tendency for the legs to spasm at night (flexor spasms) can interfere with sleep.

Marijuana is frequently reported to reduce the muscle spasticity associated with this disease.^{66, 125} In a mail survey of 112 MS patients that regularly use marijuana, patients reported that spasticity was improved and the associated pain and clonus decreased.²⁹ However, a double-blind placebo-controlled study on postural responses in 10 MS patients and 10 normal volunteers indicated that marijuana smoking impairs posture and balance in MS patients as well as normal volunteers.⁶⁵ Nevertheless, the 10 MS patients felt that they were clinically improved.

The subjective improvement, while intriguing, does not constitute unequivocal evidence that marijuana relieves spasticity. Survey data do not measure the degree of placebo effect, estimated to be as great as 30 percent in pain treatments.^{124, 133} Furthermore, surveys do not separate the effects of marijuana or cannabinoids on mood and anxiety from spasticity.

The effects of THC on spasticity were evaluated in a series of three clinical trials testing a total of 30 patients.^{25, 150, 191} They were ‘open trials,’ which means the patients were informed before treatment that they would be receiving THC. Based on patient report or clinical exam by the investigator, spasticity was less severe after the THC treatment. However, THC was not effective in all patients and frequently caused unpleasant side-effects. Spasticity was also reported to be less severe in a single case study after nabilone treatment (figure 4.2).¹¹⁹

^f Myelin is the lipid covering that surrounds nerve cell fibers and facilitates the conduction of signals along nerve cells and ultimately between the brain, spinal cord and the rest of the body.

FIGURE 4.2 Effect of nabilone on multiple sclerosis symptoms

Figure 4.2 Effect of nabilone on multiple sclerosis symptoms

General wellbeing

Well
III

A = nabilone 1 mg every other day
B = placebo

Muscle spasms

Painful
Not painful

Frequency of nocturia

4
3
2
1
0

None A B A B None
Type of treatment

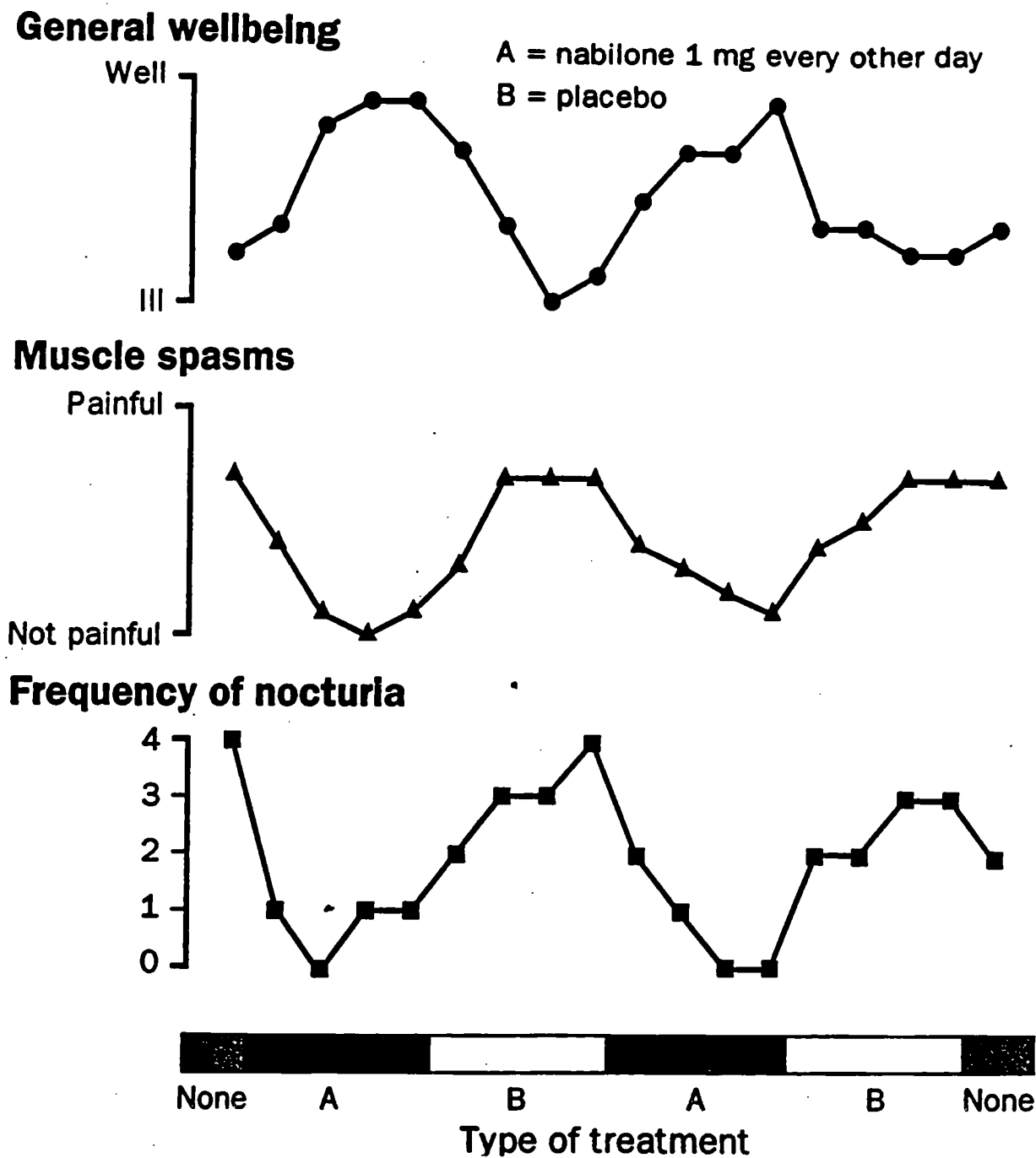


FIGURE LEGEND 4.2

Figure 4.2 shows the results of an n-of-1 trial in which a 45-year-old man with multiple sclerosis was given 4-week treatments alternately with placebo and nabilone, which he received every second day.¹¹⁹ In this study design, the patient served as both experimental subject and control; that is, his treatment sequence was: nabilone-placebo-nabilone-placebo. This pattern of alternating treatment reduces the possibility that the observed changes are unrelated to the drug and are not simply due to other factors that changed with the passage of time. The results of this study are consistent with the possibility that THC might relieve spasticity, but this study, although more rigorous than many self-report studies for psychoactive substances, still has problems.

First, although the patient could not distinguish the treatments at the time of taking the pill, he felt sedated after the nabilone. Thus it is not possible to know how much the expectation of relief contributed to his perception of relief. Second, the study measured his perception of pain in which spasticity is an important, but not the only, factor. It is not possible to know to what extent nabilone affected the perception of pain versus the stimulus that generated the pain—in this case, involuntary muscle contractions. Because it is unaffected by conscious control, the frequency of nocturia is clearer evidence of the effect of THC, although it might also represent how well the patient slept. This single case is intriguing, but not definitive proof that THC can reliably relieve spasticity.

In general, the abundant anecdotal reports are not well-supported by clinical data (summarized in table 4.1). But this is more due to the limitation of the studies than to negative results. There are no supporting animal data to encourage clinical research in this area, but there are also no good animal models for spasticity in MS. Without an appropriate model, studies to determine how marijuana or THC might relieve spasticity cannot be conducted. Nonetheless, the survey results suggest that it would be useful to investigate the potential therapeutic value of cannabinoids in relieving symptoms associated with MS. Such research would require the use of objective measures of spasticity such as the pendulum test.⁸ Since THC is mildly sedating, it is also be important to distinguish this effect from anti-spasticity effects in any such investigations. Mild sedatives such as Benadryl® or benzodiazepines would be useful controls for studies on the ability of cannabinoids to relieve muscle spasticity. The regular use of smoked marijuana, however, would be contraindicated in a chronic condition such as MS.

⁸ The *pendulum test* is an objective and accurate measure of MS-induced spasticity. It is done by videotaping a patient who lies supine on a table with his or her leg extending off the edge. The leg is dropped and the resulting motion is mathematically analyzed by computer to provide a quantitative measure of spasticity.

Table 4.1. Studies on the Effects of Marijuana and Cannabinoids in Multiple Sclerosis

Drug and Dose	Study Design	Results	Reference
Marijuana	Mail survey 112/233 MS patients	Survey was mailed to 233 MS patients, of whom 112 (48 %) responded. 97% of respondents reported improved spasticity and reduced pain.	Consroe and coworkers, 1997
Marijuana	Clinical trial 1 MS patient	Reduction in spasticity and improved ataxia	Meinck, 1989
Marijuana	Double-blind, placebo-controlled 10 MS patients; 10 normal individuals	MS patients felt they were improved, but posture and balance were impaired.	Greenberg, 1994
Oral THC 5-15 mg 6 hourly, up to 18 hours	Open trial 8 MS patients	5 patients experienced subjective, but not objective improvement in motor coordination; objective improvement in tremor demonstrated in 2 of the 8 patients.	Clifford, 1983
Oral THC 5 and 10 mg, single doses	Double-blind, placebo controlled 9 MS patients	Spasticity was improved based on examiner ratings	Petro and Ellenberger, 1981
Oral THC 2.5 - 15 mg, once or twice daily for 5 days	Double-blind, placebo controlled, crossover 13 MS patients	Patients reported subjective decreases in spasticity at doses of 7.5 mg or greater, but no changes in objective measures of spasticity or weakness were observed.	Ungerleider, 1987
Nabilone (THC analogue)	Placebo controlled 1 MS patient	The patient reported increased well-being; less frequent nocturia, and reduced severity of muscle spasticity during nabilone treatment (Figure 4.2).	Martyn, 1995

Spinal Cord Injury

In 1990 there were approximately 15 million patients worldwide with spinal cord injury, and an estimated 10,000 new cases are reported each year in the United States alone.^{136, 140} Approximately 60 percent of these injuries are to those younger than 35 years. Most of these patients will need long-term, and some life-long care.¹¹⁸

Many spinal cord injury patients report that marijuana reduces their muscle spasms (IOM public workshop⁴²).¹¹⁶ Twenty-two of 43 respondents to a 1982 survey of people with spinal cord injuries reported that marijuana reduced their spasticity.¹¹⁶ One single case double-blind study of a paraplegic patient with painful spasm in both legs suggested that oral THC was superior to codeine in reducing muscle spasms.^{76, 122} Victims of spinal cord injury reporting at IOM workshops noted that smoking marijuana reduces their muscle spasms, while also reducing nausea and sleepless nights. The caveats described for surveys of spasticity relief in MS patients also apply here.

Therapy for Muscle Spasticity

Present Therapy

Present therapy for spasticity includes the various medications listed in table 4.2 below.

TABLE 4.2 Classes of Anti-spasticity Drugs

<u>Drug Class</u>	<u>Drug</u>
<i>GABA_B receptor agonists</i>	baclofen
<i>α-receptor agonists</i>	tizanidine
<i>non-competitive GABA_A receptor agonists</i>	benzodiazepines, including diazepam
<i>calcium blockers in skeletal muscle</i>	dantrolene

Baclofen and tizanidine, the most commonly prescribed anti-spasticity drugs, relieve spasticity and spasms with varying degrees of success. The benefit of these agents is generally only partial. Their use is complicated by the side effects of drowsiness, dry mouth, and increased weakness.

Future Therapy

The discovery of agents that work through different mechanisms than existing anti-spasticity drugs will be an important advance in the treatment of spasticity. The aim of these new treatments will be to relieve the muscle spasticity and pain without significantly increasing muscle weakness in conditions that result in spasticity. The treatment for MS itself will likely be directed toward immunomodulation. Various immunomodulating agents, such as beta-interferon and glatiramer acetate, have been shown to reduce the frequency of symptomatic attacks, the progression of disability, and the rate of appearance of demyelinated lesions as detected by MRI.⁵

Conclusion

Basic animal studies described in chapter 2 have shown that cannabinoid receptors are particularly abundant in areas of the brain that control movement, and cannabinoids affect movement and posture in animals, as well as humans. The observations are consistent with the possibility that cannabinoids have anti-spastic effects, but they do not offer any direct evidence that cannabinoids affect spasticity, even in animals. The available clinical data are too meager to either accept or dismiss the suggestion that marijuana or cannabinoids relieve muscle spasticity. But the few positive reports of the ability of THC and related compounds to reduce spasticity, together with the prevalence of anecdotal reports of the relief provided by marijuana suggests that carefully designed clinical trials testing the effects cannabinoids on muscle spasticity should be considered (see chapter 1).^{26, 66} Such trials should be designed to assess the degree to which the anxiolytic effects of cannabinoids contribute to any observed anti-spastic effects.

Spasticity occurring at night can be very disruptive to sleep. Thus a long-lasting medication would be especially useful for MS patients at bedtime—when drowsiness would be a beneficial rather than an unwanted side effect, and mood-altering effects would be less of a problem. One caution is the effects of THC on the stages of sleep architecture, which should be evaluated in MS patients who have sleep disturbances. If THC is proven to relieve spasticity, then a pill might be the preferred route of delivery for nighttime use because of its long duration of action. Compared to the currently available therapies, the long half-life of THC might allow for a smoother drug effect throughout the day. The intensity of the symptoms resulting from spasticity, particularly in MS, can rapidly increase in an unpredictable fashion such that the patient develops an ‘attack’ of intense muscle spasms lasting minutes to hours. An inhaled form of THC (if it were shown to be efficacious) might be appropriate for those patients.

Movement Disorders

Movement disorders are a group of neurological conditions caused by abnormalities in the basal ganglia and its subcortical connections through the thalamus with cortical motor areas. This dysfunction within the brain ultimately results in abnormal skeletal muscle movements in the face, limbs, and trunk. The movement disorders most often considered for marijuana or cannabinoid therapy are dystonia, Huntington's disease, Parkinson's disease, and Tourette's syndrome. Movement disorders are often transiently exacerbated by stress and activity and improved by factors that reduce stress, which is of particular interest since—for many people—marijuana is an anxiolytic (anxiety reducer).

Dystonia

Dystonia can be a sign of other basal ganglia disorders, such as Huntington's disease or tardive dyskinesia, or can be a primary basal ganglia disorder. Primary dystonias are a heterogeneous group of chronic, slowly progressive, neurological disorders characterized by dystonic movements—slow, sustained involuntary muscle contractions often resulting in abnormal postures of limbs, trunks, and neck. Dystonias can be confined to one part of the body, such as spasmodic torticollis (neck),^{h, 45} or Meige's syndrome (facial muscles), or may affect many parts of the body, such as dystonia musculorum deformans. Dystonia can cause mild to severe disability and sometimes pain secondary to muscle aching or arthritis. Some dystonias are genetic; others are caused by drugs. The specific neuropathological changes in these diseases have not been determined.

No controlled study of marijuana in patients with dystonia has been published, and the only study on cannabinoids was a preliminary open trial using cannabidiol which suggested modest dose-related improvements in the five dystonic patients studied.³¹ In mutant dystonic hamsters, however, the cannabinoid receptor agonist, WIN 55,212-2, can produce antidystonic effects.¹⁵⁵

Huntington's Disease

Huntington's disease is an inherited degenerative disease usually appearing in middle age, and results in atrophy or loss of neurons in the caudate nucleus, putamen and cerebral cortex. This disease is characterized by arrhythmic, rapid muscular contractions (chorea), emotional disturbance, and dementia (impairment in intellectual and social ability). Animal studies suggest that cannabinoids might have anti-choreic activity, presumably due to stimulation of CB₁ receptors in the basal ganglia.^{131, 171}

Based on positive results in one of four Huntington's disease patients, cannabidiol (CBD) and placebo (sesame oil) were tested in a double-blind, cross-

^h Spasmodic torticollis is defined by contractions of the neck and shoulder muscles, producing recurrent head turning, head extensions and, in some cases, shoulder elevations.

over study on 15 Huntington's disease patients who were not taking any neuroleptic drugs. The symptoms neither improved nor worsened with CBD treatment.^{28, 167}

The effects of other cannabinoids on patients with Huntington's disease are largely unknown. THC or other CB₁ agonists are more likely candidates than CBD, which does not even bind to the CB₁ receptor, that is densely distributed on the very neurons that perish in Huntington's disease¹⁵⁴. Thus far there is little evidence to encourage clinical studies of cannabinoids in Huntington's disease.

Parkinson's Disease

This late-in-life degenerative disease affects about one million Americans over the age of 50 years.⁵⁷ Parkinson's disease is characterized by bradykinesia (slowness in movement), akinesia (abrupt stoppage of movement), resting tremor, muscular rigidity, and postural instability.

Theoretically, cannabinoids could be useful for treating Parkinson's patients because cannabinoid agonists specifically inhibit the subthalamo-nigral pathway, and probably also the subthalamopallidal pathway.^{168, 172} The latter effect was not directly tested, but is consistent with what is known about these neural pathways. Hyperactivity of the subthalamic neurons, observed both in Parkinson's patients and in animal models of Parkinson's disease, is hypothesized to be a major factor in the debilitating bradykinesia associated with the disease.³⁷ Furthermore, although cannabinoids oppose the actions of dopamine in intact rats, they augment dopamine activation of movement in an animal model of Parkinson's disease, suggesting the potential for adjunctive therapy with cannabinoid agonists.^{168, 169, 170, 172}

At the time of this writing, we could find only one published clinical trial evaluating marijuana in five cases of idiopathic Parkinson's disease.⁵¹ The trial was prompted by a patient's report that smoking marijuana reduced tremor, but the investigators found no improvement in tremor after the patients smoked marijuana—although all five subjects benefited from the administration of standard medications for Parkinson's disease (levodopa and apomorphine).⁵¹ Although new animal data might someday indicate a use for cannabinoids in treating Parkinson's disease, current data do not recommend clinical trials of cannabinoids in patients with Parkinson's disease.

Tourette's Syndrome

Tourette's syndrome usually begins in childhood, and is characterized by motor and vocal tics (involuntary, rapid repetitive movements or vocalizations). It has been suggested that these symptoms might be mediated by a reduction in the activity of limbic-basal ganglia-thalamocortical circuits (shown in figure 2.4).⁴³ These circuits, while not well-understood, appear to be responsible for translating a person's intentions to move into actual movements. Damage to these structures leads to either involuntary increases in movement (as in Huntington's) or the inability to make voluntary movements (as in Parkinson's). The nature of the deficit in Tourette's is unknown.

No clear link has been established between symptoms of Tourette's and cannabinoid sites or mechanism of action. Pimozide and haloperidol, two widely used treatments for Tourette's, inhibit effects mediated by the neurotransmitter, dopamine, whereas cannabinoids can increase dopamine release.^{156, 184} The physiological relevance, if any, of these two observations has not been established.

The clinical reports consist of four case histories indicating that marijuana use can reduce tics in Tourette's patients.^{79, 166} In three of the four cases, the investigators suggest that beneficial effects of marijuana might have been due to anxiety-reducing properties of marijuana rather than to a specific anti-tic effect.¹⁶⁶

Therapy for Movement Disorders

There are a variety of drugs available, listed in table 4.3, to treat the different movement disorders. Common side effects of many of these drugs include sedation, lethargy, school and work avoidance, social phobia, and increased risk of parkinsonism and tardive dyskinesia.ⁱ With some of these medications, like those used for dystonia, efficacy is lacking in as much as 50 percent of the patients. In addition to medications, surgical interventions such as pallidotomy and neurosurgical transplantation of embryonic substantia nigra tissue into the patient's striatum have been tried in Parkinson's patients. Surgery is generally palliative, and is still considered to be in the developmental phase.

ⁱ Dyskinesia is the development of irreversible, involuntary dyskinetic movements.

TABLE 4.3 Drugs Used to Treat Movement Disorders

<i>Huntington's chorea</i>	<i>Parkinson's disease</i>
reserpine	levodopa/carbidopa combination ^j
tetrabenazine	amantadine
haloperidol	bromocriptine
	pergolide
	pramipexole
	ropinirole
	selegiline
<i>Dystonia</i>	trihexyphenidyl
benzodiazepines	benztropine
tetrabenazine	
intramuscular botulinum toxin	
anticholinergics	<i>Tourette's Syndrome Tics</i>
baclofen	pimozide
	clonidine
	haloperidol

Summary

The abundance of CB₁ receptors in basal ganglia and animal studies showing the involvement of cannabinoids in the control of movement suggest that cannabinoids might be useful in treating movement disorders in humans. Marijuana or CB₁ receptor agonists might provide symptomatic relief from chorea, dystonia, some aspects of parkinsonism, and tics. However, clinical evidence is largely anecdotal with no well-controlled studies of adequate numbers of patients. Further, non-specific effects may confound interpretation of studies. For example, the anxiolytic effects of cannabinoids might make patients feel that their condition is improved, despite the lack of any measurable change in the condition.

Compared to the abundance of anecdotal reports concerning the beneficial effects of marijuana on muscle spasticity, there are relatively few claims that marijuana is useful for treating movement disorders. This might reflect a lack of effect or a lack of individuals with movement disorders who have tried marijuana. In any case, while there are a few isolated reports of individuals with movement disorders who report a benefit from marijuana, there are, as yet, no published surveys indicating that a substantial percent of patients with movement disorders find relief from marijuana. Existing studies involve too few patients from which to draw conclusions. The most promising reports involve symptomatic treatment of spasticity. If the reported neuroprotective effects of cannabinoids discussed in chapter 2 prove to be therapeutically useful, this could benefit patients with

^j Tablet contains both drugs = combination therapy.

movement disorders—although, at this point, such is highly speculative. Since stress often transiently exacerbates movement disorders, it is reasonable to hypothesize that the anxiolytic effects of marijuana or cannabinoids might be beneficial to some patients with movement disorders. However, chronic marijuana smoking is a health risk that could increase the burden of chronic conditions such as movement disorders.

Cannabinoids inhibit both major excitatory as well as inhibitory inputs to the basal ganglia. This suggests that a cannabinoid agonist could produce opposite effects on movement, depending on the type of transmission (excitatory or inhibitory) that is most active at the time of drug administration. This property could be used to design treatments in basal ganglia movement disorders such as Parkinson's disease where either the excitatory subthalamic input becomes hyperactive or the inhibitory striatal input becomes hypoactive. The dose employed would be a major factor in designing therapeutic uses for cannabinoids in movement disorders; low doses should be desirable while higher doses could be expected to further aggravate pathological conditions. Thus, there is a clear reason to recommend pre-clinical studies; that is, animal studies to test the hypothesis that cannabinoids play an important role in movement disorders.

With the possible exception of multiple sclerosis, the evidence to recommend clinical trials of cannabinoids in movement disorders is relatively weak. Ideally, clinical studies would follow animal research that provided stronger evidence than is currently available indicating a potential therapeutic value of cannabinoids in the treatment of movement disorders. Unfortunately, there are no good animal models for these disorders. Thus we recommend double-blind, placebo controlled clinical trials of isolated cannabinoids that include controls for relevant 'side effects.' Such effects include anxiolytic and sedative effects, which might either mask or contribute to the potential therapeutic effects of cannabinoids.

Epilepsy

Epilepsy is a chronic seizure disorder that affects about two million Americans and 30 million people world wide.¹⁵⁸ It is characterized by recurrent, sudden attacks of altered consciousness, convulsions, or other motor activity. A seizure is the synchronized excitation of large groups of cells. These abnormal electrical events have a wide array of possible causes, including trauma or injury to the brain and chemical changes derived from metabolic faults of exposure to toxins.¹⁵⁸

Seizures are classified as partial (focal) or generalized. Partial seizures are associated with specific sensory, motor or psychic aberrations that reflect the function of part of the cerebral cortex from which the seizures arise. Generalized seizures are usually the result of pathology at brain sites that project to widespread regions of the brain. Such pathology can produce petit mal seizures or major grand mal convulsions.

Cannabinoids in Epilepsy

There are anecdotal and individual case reports that marijuana controls seizures in epileptics (reviewed in BMA 1997 report¹⁴), but there is no solid evidence to support this belief. While there are no studies indicating that either marijuana or THC worsen seizures, there is no scientific basis to justify such studies.

In the only known case-controlled study that was designed to evaluate illicit drug use and the risk of first seizure, Ng and coworkers¹³⁹ concluded that marijuana is a protective factor for first-time seizures in men but not for women; that is, men who used marijuana reportedly had fewer first-time seizures than men who did not use marijuana. This was based on a comparison of 308 patients who had been admitted to a hospital after their first seizure with a control group of 294 patients. The control group was made up of patients who had not had seizures and were admitted for emergency surgery (such as appendicitis, intestinal obstruction, acute cholecystitis). Compared to men who did not use marijuana, the odds ratio of first seizure for men who had used marijuana within 90 days of hospital admission was 0.36 (95% confidence interval=0.18-0.74). An odds ratio of less than one is consistent with the suggestion that marijuana users are less likely to have seizures. The results for women were not statistically significant. However, this was a weak study. The study did not include measures of health status prior to hospital admissions for their serious conditions, and differences in their health status might have influenced their drug use rather than—as suggested by the authors—that differences in their drug use influenced their health.

The potential anti-epileptic activity of cannabidiol (CBD) has been investigated, but is not promising. Three controlled trials were conducted in which cannabidiol was given orally to patients with generalized grand mal seizures or focal seizures (table 4.4). Two of these studies were never published, but information about one study was published in a letter to the South African Medical Journal, the other was presented at the Marijuana 1990 International Conference on Cannabis and Cannabinoids.¹⁸⁸

Even if CBD had anti-epileptic properties, these studies were likely too small to demonstrate efficacy. Proving efficacy of anticonvulsants generally requires large numbers of patients followed for months because the frequency of seizures are highly variable and the response to therapy varies depending on seizure type.^{4, 53}

Table 4.4 Clinical Trials of Cannabidiol in Epileptics

Study Design	Results	Reference
<i>Double-blind placebo-controlled trial</i> - 8 epileptic patients were given 200-300 mg CBD/day in conjunction with standard antiepileptic therapies.	Four out of 8 remained almost free of convulsions. Three of the 4 were partially improved for up to 4.5 months.	Cunha et al. ³⁵
<i>Double-blind placebo-controlled study</i> - 12 epileptic patients were given 200-300 mg CBD/day along with standard antiepileptic drugs.	CBD had no effect on seizure frequency.	Ames ⁴
<i>Double-blind placebo-controlled, add-on cross-over trial</i> - 10 epileptic patients were given 300 mg. CBD/day for 6 months. <i>Open trial</i> - 1 patient was given 900-1200 mg. CBD/day for 10 months.	CBD had no effect on seizures. Seizure frequency was reduced in the patient.	Trembly et al. ¹⁸⁸ (reviewed in Consroe, 1992 ³⁰)

Therapy for Epilepsy

Present Therapy

Standard pharmacotherapy for partial and generalized seizures, listed in table 4.5, involve a variety of anticonvulsant drugs.

TABLE 4.5 Anticonvulsant Drugs for Various Types of Seizures⁵

<i>Generalized grand mal</i>	<i>Partial (focal)</i>
carbamazepine	carbamazepine
valproate	phenytoin
phenytoin	valproate
phenobarbital	phenobarbital
	clonazepam
<i>Generalized petit mal</i>	gabapentin
ethosuximide	lamotrigine
clonazepam	tiagabine (as adjunct
valproate	therapy)

These drugs suppress seizures completely in approximately 60 percent of patients with chronic epilepsy and improve seizures in another 15 percent of patients. All of the above mentioned anticonvulsants present side effects, some of the more common ones being drowsiness, mental slowing, ataxia, tremor, hair loss, increased appetite, headache, insomnia, and rash. Nevertheless, recurrent seizures create a physically dangerous and emotionally devastating environment, and preventing them outweighs the undesirable side effects seen with anticonvulsant drugs.

Future Therapy

The goal in epilepsy treatment is to halt the seizure attacks completely with minimal or no side effects, followed by efforts to eradicate the cause whenever possible. Most of the anticonvulsant research with cannabinoids was conducted before 1986. Since then, many new anticonvulsants have been introduced and cannabinoid receptors have been discovered. At present the only biological evidence that cannabinoids might have antiepileptic properties is that CB₁ receptors are abundant in the hippocampus and amygdala. Both regions are involved in partial seizures, but are better known for their role in functions unrelated to seizures.²⁷ While basic research might reveal stronger links between cannabinoids and seizure activity, this is not likely to be as fruitful an area of cannabinoid research as others. At this stage of knowledge, clinical studies of cannabinoids in epileptics are not indicated.

Alzheimer's Disease

Food refusal is a common problem in patients suffering from Alzheimer's type dementia. The causes of anorexia in demented individuals is not known, but may be a symptom of depression. Antidepressants improve eating in some, but not all, patients with severe dementia. Eleven Alzheimer's patients with dementia were treated for 12 weeks on an alternating schedule of dronabinol and placebo (six weeks

of each treatment). The dronabinol treatment resulted in significant weight gains and declines in disturbed behavior.¹⁹⁴ No serious side effects were observed. One patient had a seizure and was removed from the study, but it is not clear that this was due to the dronabinol. Recurrent seizures develop without any precipitating events in 20 percent of patients with advanced dementia of the Alzheimer's type.¹⁹³ Nevertheless, these results are encouraging enough to recommend further clinical research with cannabinoids.

The patients in the study discussed above were in long-term institutional care, and most were severely demented with impaired memory. Although short-term memory loss is a common side effect of THC in healthy patients, it was not a concern in this study. However, the effect of dronabinol on memory in Alzheimer's patients who are not as severely disturbed as those in the above study would be an important consideration.

Glaucoma

After cataracts, glaucoma is the second leading cause of blindness in the world and almost 67 million people are expected to be affected worldwide by the year 2000¹⁵¹ (for an excellent review, see Alward 1998²). The most common form of glaucoma, primary open-angle glaucoma (POAG), is a slowly progressive disorder that results in loss of retinal ganglion cells and degeneration of the optic nerve, causing deterioration of the visual fields and, ultimately, blindness. The mechanisms behind this disease are not understood, but three major risk factors are known: age, race and elevated intraocular pressure (IOP). POAG is most prevalent among the elderly, with 1 percent affected in those older than 60 years of age and more than 9 percent affected in those older than 80 years.⁷ For African-Americans older than 80 years there is more than a 10 percent chance of having the disease.¹⁸⁶ Older African-Caribbeans (who are less racially mixed than African -Americans) have a 20 - 25 percent chance of having the disease.¹¹⁰

The eye's rigid shape is normally maintained, in part, by IOP which is regulated by the circulation of a clear fluid, called the aqueous humor,^k between the front of the lens and the back of the cornea. Because of impaired outflow of aqueous humor from this anterior chamber of the eye, an elevated IOP is a risk factor for glaucoma, but the mechanism by which it damages the optic nerve and retinal ganglion cells remains unclear.¹⁷⁷ The two leading possibilities suggest that elevated IOP interferes with 1) the nutrient blood flow to the region of the optic nerve, and 2) the transport of nutrients, growth factors and other compounds within the optic nerve axon (P. Kaufman, IOM workshop). If this interference continues, both the retinal ganglion cells and optic nerve will permanently atrophy with

^k The cornea and lens of an eye must be optically clear, which means there cannot be blood circulation in these tissues. The aqueous humor is a clear fluid that functions as alternative circulation across the rear of the cornea and to the lens to provide nutrients and remove waste from these tissues.

consequent blindness.⁷² Because elevated IOP is the only known major risk factor that can be controlled, most treatments have been designed to reduce IOP. Unfortunately, reducing IOP does not always arrest or slow the progression of visual loss.^{21, 113}

Marijuana and Cannabinoids in Glaucoma

Both marijuana and THC have been shown to reduce IOP by 24 percent on average in people with normal IOP that have visual field changes.^{80, 81} In a number of studies on normal adults and glaucoma patients, IOP was reduced by an average of 25 percent after smoking a marijuana cigarettes that contained approximately 2 percent THC, a reduction as good as that observed with most other medications available today.^{1, 17, 33, 80, 81, 127, 197} Similar responses have been observed when marijuana is eaten or THC was given in pill form (10 - 40 mg) to normal, healthy adults or glaucoma patients.^{80, 95} But the effect lasts only about 3 to 4 hours. Elevated IOP is a chronic condition and must be controlled continuously.

Intravenous administration of $\Delta 9$ -THC, $\Delta 8$ -THC, or 11-OH-THC to normal adults significantly decreased IOP, whereas cannabinal (CBN), CBD and β -OH-THC had little effect.^{32, 148} The cause for the reduction in IOP remains unknown, but the effect appears to be independent of the frequently observed drop in arterial systolic blood pressure (Keith Green, personal communication).

Three synthetic cannabinoids were investigated, BW29Y, BW146Y and nabilone. These were given orally to patients with elevated IOP. BW146Y and nabilone turned out to be as effective as ingesting THC or smoking marijuana, but again with a very short duration of action, while BW29Y was ineffective.^{138, 185}

Topical treatments of cannabinoids have been ineffective in reducing IOP. When $\Delta 9$ -THC was applied topically as an eye drop, whether as a single dose or multiple doses, whether once or four times a day, there was no decrease in IOP.^{64, 94} Suspensions of lipophilic THC tended to be irritating to the eye.

In summary, cannabinoids or marijuana can reduce IOP when administered orally, intravenously, or by inhalation, but not when administered topically. Even though a reduction in IOP by standard mediations or surgery clearly slows the rate of glaucoma symptom progression, there is no direct evidence to support the benefits of cannabinoids or marijuana on the natural progression of glaucoma, visual acuity, or optic atrophy.^{96, 117}

In addition to lowering IOP, marijuana reduces blood pressure and has many psychological effects. Merritt and coworkers reported hypotension, palpitations and psychotropic effects in glaucoma patients after inhaling marijuana.¹²⁷ Cooler and coworkers³² also reported increased anxiety and tachycardia with an intravenous infusion of THC (1.5 - 3 mg). All of these side effects are problematic, particularly for elderly glaucoma patients with cardiovascular or cerebrovascular disease. The reduction of blood pressure can be substantial, and might adversely affect blood flow to the optic nerve.¹²⁶ Many people with systemic hypertension have their blood

pressure reduced to manageable and acceptable levels through medication, but this does not seem to affect IOP. In contrast, there is evidence that reduction in blood pressure below normal levels (considerably below) will influence IOP, and particularly ocular blood flow.^{48, 78, 144} Hence, an eye with elevated IOP, or an optic nerve in poor condition with susceptibility to increased IOP, reduced blood flow to the optic nerve could compromise a functional retina and be a factor in the progression of glaucoma.

Because it is not known how these compounds work, it is also not known how they might interact with the other drugs used to treat glaucoma. If the mechanism involves a final common pathway, the effects of cannabinoids may not be additive and might even interfere with effective drugs.

Therapy for Glaucoma

Present Therapy

There are currently six classes of drugs used to treat glaucoma, all of which reduce IOP (table 4.6).⁹⁷

TABLE 4.6 *Classes of Glaucoma Drugs*

<i>Cholinergic Agonists</i> pilocarpine	<i>Carbonic Anhydrase Inhibitors</i> acetazolamide dorzolamide (Trusopt®)
<i>β₂-Adrenergic Agonists</i> epinephrine dipivefrin	<i>Prostaglandin-F_{2α} Analogs</i> latanoprost unoprostone
<i>β₂-Adrenergic Antagonists</i> timolol betaxolol (Betoptic®)	
<i>α₂-Adrenergic Agonists</i> aproclonidine brimonidine	

In the late 1970s when early reports of the effects of marijuana on IOP surfaced, only cholinomimetics, epinephrine, and oral carbonic anhydrase inhibitors were available. None are popular today because of their side effects such as pupil constriction or dilation, brow ache, tachycardia and diuresis, and all been superseded by the other classes of drugs.⁹⁷ Additionally, there are surgical options available today to lower IOP, including laser trabeculoplasty, trabeculectomy/sclerostomy, drainage implants, and cyclodestruction of fluid-forming tissues.¹⁷⁶ Thus, there are many effective options to choose from today to slow the progression of glaucoma by reducing IOP.

One important factor in slowing the progression of glaucoma via medications that reduce IOP is patient compliance with dosing regimens. For compliance purposes, the ideal glaucoma drug is one that is applied at most twice a day (P. Kaufman, IOM workshop). If the dose must be repeated every 3 - 4 hours, patient compliance becomes a serious issue and for this reason marijuana and the cannabinoids studied thus far would not be highly satisfactory treatments for glaucoma. Additionally, present therapies, especially combinations of approved topical drugs, can control IOP when administered once or twice a day, at a cost of about \$60 per month.

Future Therapy The next generation of glaucoma therapies will in all likelihood deal with neural protection, neural rescue, neural regeneration, or blood flow where the optic nerve and neural retina are treated directly, rather than just lowering IOP (P. Kaufman, IOM workshop). There is some evidence that a synthetic cannabinoid, HU-211, might have neuroprotective effects *in vitro*, which presents a potential approach having nothing to do with IOP.²⁰¹ HU-211 is commonly referred to as a cannabinoid, because its chemical structure is similar to THC; however, it does not bind to cannabinoid receptor.

It is known that cannabinoids lower IOP fairly substantially, but not how. No one has tested whether the effect is receptor-mediated (B. Martin, IOM workshop). To do so, one could test whether a receptor antagonist blocked the effects of THC or other cannabinoids. If the decrease were shown to be receptor-mediated, then it would be important to know whether it was through CB₁, which mediates central nervous system effects, or CB₂ receptors, which are not involved in CNS effects. If the latter were true, then it might be possible to reduce IOP without the CNS side effects. Finally, it is not known if the endogenous cannabinoid system is a natural regulator of IOP.

Summary

Although glaucoma is one of the most frequently cited medical indications for marijuana, the data do not support this indication. High intraocular pressure (IOP) is a known risk factor for glaucoma and can, indeed, be reduced by cannabinoids and marijuana. However, the effect is too short-lived, requires too high doses, and there are too many side effects to recommend lifelong use in the treatment of glaucoma. The potential harmful effects of chronic marijuana smoking outweigh its modest benefits in the treatment of glaucoma. Clinical studies on the effects of smoked marijuana are unlikely to result in improved treatment for glaucoma.

Future research might reveal a therapeutic effect of isolated cannabinoids. For example, it might be possible to design a cannabinoid drug with longer-lasting effects on IOP and with less psychoactivity than THC.

Summary

Advances in cannabinoid science of the last 16 years have given rise to a wealth of new opportunities for the development of medically useful cannabinoid-based drugs. The accumulated data suggest a variety of indications, particularly for pain relief, antiemesis, and appetite stimulation. For patients, such as those with AIDS or undergoing chemotherapy, who suffer simultaneously from severe pain, nausea, and appetite loss, cannabinoid drugs might thus offer broad spectrum relief not found in any other single medication. The data are weaker for muscle spasticity, but moderately promising. The least promising categories are movement disorders, epilepsy, and glaucoma. Animal data are moderately supportive of a potential for cannabinoids in the treatment of movement disorders and might eventually yield stronger encouragement. The therapeutic effects of cannabinoids are most well established for THC, which is the primary psychoactive ingredient of marijuana. But it does not follow from this that smoking marijuana is good medicine.

Although marijuana smoke delivers THC and other cannabinoids to the body, it also delivers harmful substances, including most of those found in tobacco smoke. In addition, plants contain a variable mixture of biologically-active compounds and cannot be expected to provide a precisely defined drug effect. For those reasons, there is little future in smoked marijuana as a medically-approved medication. If there is any future in cannabinoid drugs, it lies with agents of more certain, not less certain composition. While clinical trials are the route to developing approved medications, they are also valuable for other reasons. For example, the personal medical use of smoked marijuana—regardless of whether or not it is approved—to treat certain symptoms is reason enough to advocate clinical trials to assess the degree to which the symptoms or course of their diseases are affected. Trials testing the safety and efficacy of marijuana use are an important component to understanding the course of disease, particularly for diseases such as AIDS where marijuana use is prevalent. The argument against the future of smoked marijuana for treating any condition is not that there is no reason to predict efficacy, but that there is risk. That risk could be overcome by the development of a nonsmoked, rapid-onset delivery system for cannabinoid drugs.

There are two caveats to following the traditional path of drug development for cannabinoids. The first is timing. Patients who are currently suffering from debilitating conditions unrelieved by legally available drugs, and who might find relief with smoked marijuana, will find little comfort in a promise of a better drug ten years from now. In terms of good medicine, marijuana should rarely be recommended unless all reasonable options had been eliminated. But then what? It is conceivable the medical and scientific opinion might find itself in conflict with drug regulations. This presents a policy issue that must weigh—at least temporarily—the needs of individual patients against broader social issues. Our

assessment of the scientific data on the medical value of marijuana and its constituent cannabinoids is but one component of attaining that balance.

The second caveat is a practical one. Although most scientists who study cannabinoids would agree that the scientific pathways to cannabinoid drug development are clearly marked, there is no guarantee that the fruits of scientific research will be made available to the public. Cannabinoid-based drugs will only become available if either there is enough incentive for private enterprise to develop and market such drugs, or if there is sustained public investment in cannabinoid drug research and development. The perils along this pathway are discussed in chapter 5. Although marijuana is an abused drug, the logical focus of research on the therapeutic value of cannabinoid-based drugs is the treatment of specific symptoms or diseases, not substance abuse. Thus, the most logical research sponsors would be the several institutes within the National Institutes of Health or organizations whose primary expertise lies in the relevant symptoms or diseases.

CONCLUSION: Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily THC, for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however, is a crude THC delivery system that also delivers harmful substances.

RECOMMENDATION: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.

RECOMMENDATION: Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should be approved by institutional review boards; involve only short-term marijuana use (less than 6 months); be conducted in patients with conditions for which there is reasonable expectation of efficacy; and collect data about efficacy.

RECOMMENDATION: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:

- **failure of all approved medications to provide relief has been documented;**
- **the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs;**
- **such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness;**
- **and involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.**

Until a non-smoked, rapid-onset cannabinoid drug delivery system becomes available, we acknowledge that there is no clear alternative for people suffering from *chronic* conditions that might be relieved by smoking marijuana, such as pain or AIDS wasting. One possible approach is to treat patients as n-of-1 clinical trials, in which patients are fully informed of their status as experimental subjects using a harmful drug delivery system, and in which their condition is closely monitored and documented under medical supervision, thereby increasing the knowledge base of the risks and benefits of marijuana use under such conditions. We recommend these “n-of-1” clinical trials using the same oversight mechanism as that proposed in the above recommendations.

Other Reports on Marijuana as Medicine

Since 1996, five important reports pertaining to the medical uses of marijuana have been published, each prepared by deliberative groups of medical and scientific experts (appendix D). They were written to address different facets of the medical marijuana debate, and each offers a somewhat different perspective. With the exception of the report by the Health Council of the Netherlands, each concluded that marijuana can be moderately effective in treating a variety of symptoms. They also agree that current scientific understanding is rudimentary; indeed, the sentiment most often stated is “more research is needed.” And these reports record the same problem with herbal medications as noted here: the uncertain composition of plant material makes for an uncertain, and hence often undesirable, medicine.

The 1996 report by the Health Council of the Netherlands concluded that there is insufficient evidence to justify the medical use of marijuana *or* THC, despite the fact that the latter it is an approved medication in the United States and Britain.

THE MEDICAL VALUE OF MARIJUANA AND RELATED SUBSTANCES

However, that committee addressed only whether there was sufficient evidence to warrant the prescription of marijuana or cannabinoids, not whether the data are sufficient to justify clinical trials. Conclusions of the Health Council of the Netherlands contrast with that country's tolerance of marijuana use. The Health council's report noted that marijuana use by patients in the terminal stages of illness is tolerated in hospitals. It also said that they did "not wish to judge patients who consume marihuana (in whatever form) because it makes them feel better"

In contrast, the American Medical Association House of Delegates, National Institutes of Health (NIH), and the British Medical Association recommend clinical trials of smoked marijuana for a variety of symptoms. The NIH report, however, was alone in recommending clinical studies of marijuana for the treatment of glaucoma—and even then there was disagreement among the panel members (William T. Beaver, *chair*, NIH Ad Hoc Expert Panel on the Medical Use of Marijuana, personal communication).

Recent reviews that have received extensive attention from those who follow the medical marijuana debate have been written by strong advocates *for* (Grinspoon and Bakalar 1993⁶⁶ ; Zimmer and Morgan 1997²⁰²) or *against* (Voth and Schwartz 1997¹⁹⁵) the medical use of marijuana. Those reports represent the individual views of their authors, and they are not reviewed here but have been reviewed in major scientific journals.^{8, 73, 181, 183}

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THE MEDICAL VALUE OF MARIJUANA AND RELATED SUBSTANCES

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CANNABINOID DRUG DEVELOPMENT

DEVELOPMENT OF CANNABINOID DRUGS	2
FEDERAL DRUG DEVELOPMENT POLICY	3
THE DEVELOPMENT AND MARKETING OF MARINOL®	12
MARKET OUTLOOK FOR CANNABINOIDS	17
MARIJUANA: REGULATION AND MARKET OUTLOOK	23
CONCLUSIONS	28
REFERENCES	29

DEVELOPMENT OF CANNABINOID DRUGS

Medicines today are expected to be of known composition and quality. Even in cases where marijuana can provide relief of symptoms, the crude plant mixture does not meet this modern expectation. The future of medical marijuana lies in classical pharmacological drug development, and indeed there has been a resurgence of scientific, as well as public, interest in the therapeutic applications of cannabinoids. After an initial burst of scientific activity in the 1970s, today's renewed interest has been fueled by major scientific discoveries discussed in previous chapters: the identification and cloning of endogenous cannabinoid receptors, the discovery of endogenous substances that bind to these receptors, and the emergence of synthetic cannabinoids that also bind to cannabinoid receptors. These scientific accomplishments have propelled interest in developing new drugs that can treat more effectively or more safely the constellation of symptoms for which cannabinoids might have therapeutic benefit (see chapter 4). Through the process of what is referred to as "rational drug design", scientists manipulate the chemical structures of known cannabinoids to design better therapeutic agents. Several new cannabinoids are being developed for human use, but none has reached the stage of human testing in the United States.

The purpose of this chapter is to describe the process of and analyze the prospects for development of cannabinoid drugs. It first discusses the regulatory hurdles that every new drug encounters en route to market. It then proceeds to describes the regulatory and market experiences of dronabinol (tetrahydrocannabinol, or THC, in sesame oil), the only approved cannabinoid in the United States. These sections serve as a road map to determine whether the therapeutic potential of cannabinoids is likely to be exploited commercially to meet patient needs. Finally, the chapter describes what would be needed to bring marijuana to market as a medicinal plant.

The term cannabinoids is used in this chapter to refer to a group of substances that are structurally related to THC—by virtue of a tricyclic chemical structure—or that bind to cannabinoid receptors, such as the natural ligand anandamide. From a chemist's point of view, this definition encompasses a variety of distinct chemical classes. But because the purpose of this chapter is to explore prospects for drug development, both chemical structure and pharmacological activity are important; therefore, the broader definition of cannabinoids is used.

FEDERAL DRUG DEVELOPMENT POLICY

Like controlled substances, cannabinoids developed for medical use encounter a gauntlet of public-health regulatory controls administered by two federal agencies: the Food and Drug Administration (FDA) of the Department of Health and Human Services (DHHS) and the Drug Enforcement Administration (DEA) of the Department of Justice. FDA regulates human testing and the introduction of new drugs into the marketplace, whereas DEA determines the schedule of and establishes production quotas for drugs with potential for abuse to prevent their diversion to illicit channels. DEA also authorizes registered physicians to prescribe controlled substances. Some drugs, such as marijuana, are labeled Schedule I drugs in the Controlled Substance Act (CSA), and this adds considerable complexity and expense to their clinical evaluation. It is important to point out that Schedule I status does not necessarily apply to all cannabinoids.

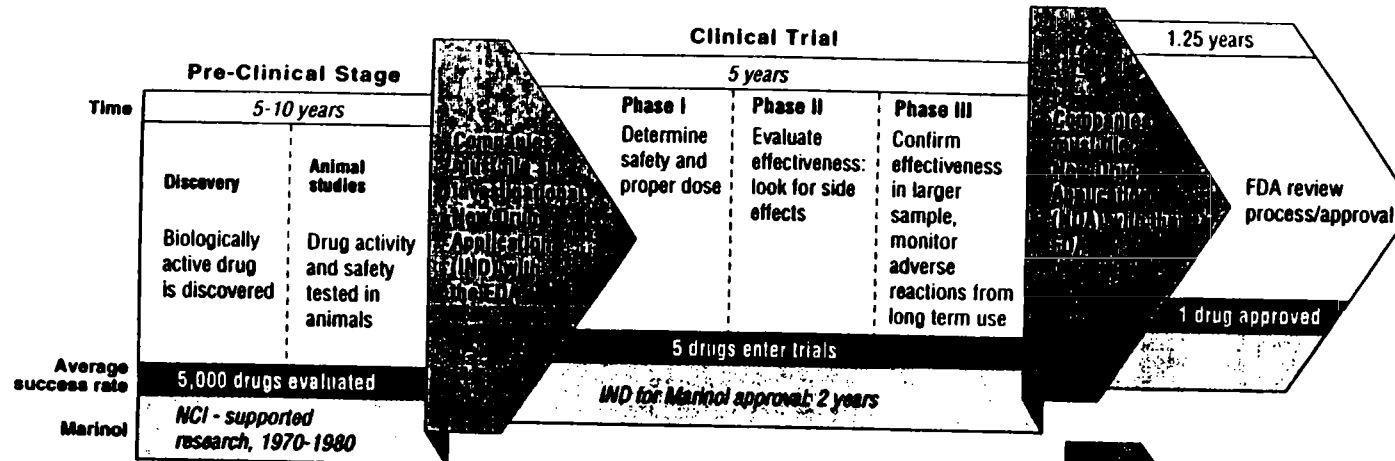
Food and Drug Administration

Under the Federal Food, Drug, and Cosmetic Act, the FDA approves new drugs for entry into the marketplace after their safety and efficacy are established through controlled clinical trials conducted by the drugs' sponsors.²³ FDA's approval of a drug is the culmination of a long, research-intensive process of drug development, which often takes well over a decade.^{19, 44} Drug development is performed largely by pharmaceutical companies, but some targeted drug development programs are sponsored by the National Institutes of Health (NIH) to stimulate further development and marketing by the private sector. The NIH's drug development programs—including those for AIDS, cancer, addiction, and epilepsy—have been instrumental in ushering new drugs to market in collaboration with pharmaceutical companies.³³ In fact, as noted later, most of the preclinical and clinical research on dronabinol was supported by NIH.

Drug development begins with discovery, that is, the synthesis and purification of a new compound with expected biological activity and therapeutic value. The next major step is the testing of the compound in animals to learn more about its safety and efficacy and to predict its utility for humans. Those early activities are collectively referred to as the preclinical phase. When evidence from the preclinical phase suggests a promising role in humans, the manufacturer submits an Investigational New Drug application (IND) to the FDA. The IND submission contains a plan for human clinical trials and includes the results of preclinical testing and other information.²⁰ Absent FDA objection, the IND becomes effective after 30 days, allowing the manufacturer to conduct clinical testing (testing in humans),

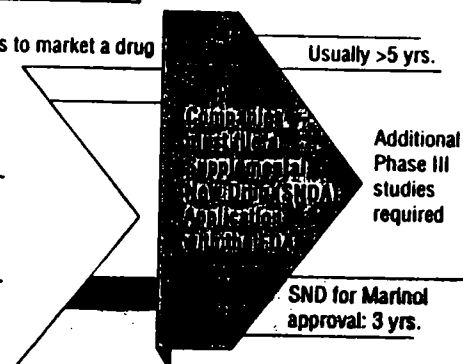
which generally involves three phases (see figure 5.1). The three stages of clinical testing are usually the most time-consuming phases of drug development, lasting five years on average.²² The actual time depends on the complexity of the drug, availability of patients, duration of use, difficulty of measuring clinical end points, therapeutic class, and indication (the disease or condition for which the drug has purported benefits).³¹

Figure 5.1 Stages of Clinical Testing



Average cost to develop a drug:	\$200-300 million
Average cost of a SND Application:	\$10-40 million
Cost to develop Marinol:	Unimed estimates that approximately 75% of the pre-clinical and clinical research on THC that led to FDA's 1985 approval was supported by the National Cancer Institute (NCI)
Cost of supplemental indication for Marinol:	\$5 million (treatment of anorexia associated with weight loss in AIDS)

When a company wants to market a drug for a new indication



Durg development is a long and financially risky process. For every drug that ultimately reaches clinical testing through an IND, thousands of drugs are synthesized and tested in the laboratory. And only about one in five drugs initially tested in humans successfully secures FDA approval for marketing through a new drug application.¹⁹

The manufacturer submits an NDA to FDA to gain approval for marketing clinical testing is complete. An NDA is a massive document, the largest portion of which contains the clinical data from Phase I-III testing. The other technical sections of an NDA include chemistry, manufacturing, and controls; nonclinical pharmacology and toxicology; and human pharmacokinetics and bioavailability.²³ In the case of a new cannabinoid, an abuse liability assessment would also probably be part of an NDA submission. In 1996, the median time for FDA review of an NDA, from submission to approval, was 15.1 months, a review period considerably shorter than that in 1990, when the figure was 24.3 months.²² The shortening of approval time is an outgrowth of the Prescription Drug User Fee Act of 1992, which authorized FDA to hire additional review staff with so-called user fees paid by industry, and imposed clear deadlines for FDA action on an NDA. With respect to the cost of a single drug's development, a number of recent studies have provided a range of estimates of about \$200-300 million, depending on the method and year of calculation.^{33, 44}

With FDA approval of an NDA, the manufacturer is permitted to market the drug *for the approved indication*. At that point, although any physician is at liberty to prescribe the approved drug for another indication (an "off-label use"), the manufacturer cannot promote it for that indication unless the new indication is granted separate marketing approval by the FDA.^a To obtain such approval, the manufacturer is required to compile another application to the FDA for what is known variously as an "efficacy supplement," a "supplemental application", or a "supplemental new drug application". Those terms connote that the application is supplemental to the NDA. In general, collecting new data for FDA approval of an efficacy supplement is not as intensive a process as that for an NDA; it generally requires the firm to conduct two additional Phase III studies, although under some circumstances only one additional study of the drug's efficacy is needed.²⁴ The preclinical studies, for example, ordinarily need not be replicated. The average cost to the manufacturer for obtaining approval for the new indication is typically about \$10-40 million.³³ The review time for FDA approval of the new indication can be considerable; a recent study of supplemental indications approved by FDA in 1989 - 1994 found the approval time to exceed that for the original NDA,¹⁸ a reflection, in part, of the lower priority FDA accords to the review of efficacy supplements as opposed to new drugs.²³

^aFDA policies for off-label use are being transformed as a result of the Food and Drug Administration Modernization Act of 1997, which, FDA recently promulgated new rules to give manufacturers greater flexibility to disseminate information about off-label uses (FDA, 1998b). As of this writing, however, court decisions have left the status of the new rules somewhat unclear.

The manufacturer also must apply to the FDA to receive marketing approval for a new formulation of a previously approved drug. A new formulation is a new dosage form, which may include a new route of administration. One example of such a new formulation would be an inhaled version of dronabinol, which is currently approved only in oral capsule form. The manufacturer is required to establish bioequivalence, safety, and efficacy of the new formulation. The amount of evidence required for approval is highly variable, depending on the similarities between the new formulation and the approved formulation. Each new formulation is evaluated on a case-by-case basis by the FDA. In the case of dronabinol, for example, an inhaled version is likely to require not only new studies of efficacy, but also new studies of abuse liability (see below). There appear to be no published, peer-reviewed studies of the average cost and time to approval of a new formulation.

Two other FDA programs may be relevant to the potential availability of new cannabinoids. One program is authorized under the Orphan Drug Act of 1983, which provides incentives to manufacturers to develop drugs to treat orphan (i.e., rare) diseases. Orphan diseases, defined in a subsequent amendment to the Act, are those affecting 200,000 or fewer people in the U.S.^b The Act's most important incentive is a period of exclusive marketing protection for seven years, during which time FDA is prohibited from approving the same drug for the same indication.^{5, 6} Some of the medical conditions for which cannabinoids are being considered—Huntington's disease, multiple sclerosis, and spinal cord injury (see chapter 4)—may meet the definition of an orphan disease, thus enabling manufacturers to take advantage of the Act's financial incentives to bring the product to market. If the disease affects more than 200,000, then the manufacturer sometimes subdivides the patient population into smaller units in order to qualify. For example, while a drug for the treatment of Parkinson's disease is not likely to receive an orphan designation because its prevalence exceeds 200,000 patients, orphan designations have been accorded to drugs for a subset of Parkinson's patients, e.g., those suffering from early-morning motor dysfunction in the late stages of the disease.²⁵

The other program is the "Treatment IND" program which was established by regulation in 1987 (and codified into law in 1997) to allow patients with serious and life-threatening diseases to obtain experimental medications, such as marijuana, before their general marketing.^c Treatment INDs may be issued during Phase III studies to patients who are not enrolled in clinical trials, provided there is no comparable alternative drug available, among other requirements.^{22, 32, 33} Thus, the treatment IND program may provide a mechanism for some patients to obtain a promising new cannabinoid before its widespread commercial availability, if it were to reach the late stages of clinical testing for a serious or life-threatening disease.

^b An orphan designation also can be granted by FDA for drugs intended for conditions affecting larger populations as long as the manufacturer's estimated expenses are unlikely to be recovered by sales in the U.S. (Public Law 98-551).

^c Marijuana cigarettes were available under a special FDA-sponsored Compassionate Investigational New Drug Program for desperately ill patients until March 1992, when the program was terminated for new participants.⁴⁸

Drug Enforcement Administration

The Drug Enforcement Administration (DEA) is responsible for scheduling controlled substances, i.e., drugs and other agents that possess a potential for abuse. Abuse is generally defined as nonmedical use that leads to health and safety hazards, diversion from legitimate channels, self-administration, and other untoward results.^{15,}

²¹ The legislation that gives DEA the authority to regulate drugs of abuse is called the Controlled Substances Act (CSA), which was first passed in 1970 and amended several times thereafter. The overall purpose of the CSA is to restrict or control the availability of drugs to prevent their abuse.

Under the CSA, DEA places each drug with abuse potential into one of five categories. The five categories, referred to as schedules I-V, carry different degrees of restriction. Schedule I is the most restrictive, covering drugs with “no accepted medical use in the U.S. and a high abuse potential.” The definitions of each category and examples of scheduled drugs are listed in appendix B. Each schedule is associated with a distinct set of controls affecting manufacturers, investigators, pharmacists, practitioners, patients and recreational users (among others). These controls, which vary by schedule, include registration with DEA, labeling and packaging, production quotas, security, recordkeeping, and dispensing.¹⁵ For instance, patients with a legitimate medical need for drugs in Schedule II, the most restrictive schedule for drugs use, can neither refill their prescriptions nor have them telephoned to the pharmacy (except in an emergency).

The scheduling of substances under the CSA is handled on a case-by-case basis. It may be initiated by the DEA, by the Department of Health and Human Services (DHHS), or by petition from an interested party, including the drug’s manufacturer or a public interest group.¹⁵ The final decision for scheduling rests with DEA, but for this purpose the Secretary of DHHS is mandated to provide a recommendation. The Secretary’s recommendation^d to DEA is based, in part, on results from abuse liability testing that FDA, an agency of DHHS, requires of the manufacturer seeking a new drug approval. Abuse liability testing is not a single test; it is a compilation of several *in vitro* human and animal studies, some of the best known being drug self-administration and drug discrimination studies.^{21, 34} The Secretary’s recommendation for scheduling is formally guided by eight legal criteria, including the drug’s actual or relative potential for abuse; scientific evidence of its pharmacological effect; risk to public health; and its psychic or physiological dependence liability (21 U.S.C. § 811 (b), (c)). Once DEA receives a scheduling recommendation, its scheduling decision, including the requirement for obtaining

^dFDA and the National Institute of Drug Abuse, two agencies of DHHS, work jointly to develop the medical and scientific analysis that is forwarded to the Secretary, who, in turn, makes a recommendation to the Administrator of DEA (DEA, 1998).

public comment, usually takes weeks to months.³³ In practice, DEA usually adheres to the recommendation of the Secretary.^e Beyond the DEA, there are a variety of State scheduling laws that also affect the manufacture and distribution of controlled substances.^{33, 50}

Under the CSA, marijuana and THC^f are in Schedule I, the most restrictive schedule. The scheduling of any other cannabinoid under this Act first hinges upon whether it is found *in the plant*. All cannabinoids in the plant are automatically in Schedule I. That is because they fall under the Act's definition of marijuana (21 U.S.C. § 802 (16)). In addition, under DEA's regulations, synthetic equivalents of the substances contained in the plant and "synthetic substances, derivatives, and their isomers" whose "chemical structure and pharmacological activity" are "similar" to THC also are automatically in Schedule I (21 CFR § 1308.11(d)(27)). Based on the examples listed in the regulations, the word "similar" probably limits the applicability of the regulation to isomers of THC, but DEA's interpretation of its own regulations would carry significant weight in any specific situation.

Prompted by a 1995 petition from the National Organization for the Reform of Marijuana Laws (NORML), to remove marijuana and THC from Schedule I, DEA gathered information which was then submitted to DHHS for a medical and scientific recommendation and scheduling recommendation, as required by the CSA. For the reasons noted above, any changes in scheduling of marijuana and THC would also affect other plant cannabinoids. However, for the present, any cannabinoid found in the plant is automatically controlled in Schedule I.

Investigators are affected by Schedule I requirements, even if their research is being conducted *in vitro* or on animals. For example, researchers studying cannabinoids found in the plant are required under the CSA to submit their research protocol to DEA, which issues a registration contingent upon FDA's evaluation and approval of the protocol (21 CFR § 1301.18). DEA also inspects the researcher's security arrangements. However, the regulatory implications are quite different for cannabinoids *not found in the plant*. Such cannabinoids appear to be unscheduled unless (1) FDA or DEA decide they are sufficiently similar to THC to be placed automatically into Schedule I under the regulatory definition outlined above, or (2) FDA and/or the manufacturer deem them to have potential for abuse, thereby triggering the *de novo* scheduling process noted above. Thus far, the cannabinoids most commonly used in pre-clinical research (table 5.1) appear to be sufficiently distinct from THC that they are not currently considered controlled substances by definition (F. Sapienza, DEA, personal communication, 1998). Since no new cannabinoids other than THC have yet been clinically tested in the United States, scheduling experience is limited. It is possible that, as research progresses, the

^eUnder the CSA, "The recommendations of the Secretary to the Attorney General shall be binding on the Attorney General as to such scientific and medical matters, and if the Secretary recommends that a drug or other substance not be controlled, the Attorney General shall not control the drug or other substance." (21 U.S.C. § 811 (b))

^fTechnically, the CSA and the regulations use the term "tetrahydrocannabinols."

unscheduled status of some cannabinoids may change. Results from early clinical research may lead the manufacturer to proceed with, or the FDA to require, abuse liability testing. Depending on the results of such studies, DHHS may or may not recommend *de novo* scheduling to DEA, which makes the final decision on a case-by-case basis.

Will newly discovered cannabinoids be subject to scheduling? This is a complex question. The answer depends entirely on each new cannabinoid—whether it is found in the plant, its chemical and pharmacological relationship to THC, and its potential for abuse. Those novel cannabinoids with strong similarity to THC are likely to be scheduled at some point before marketing; whereas, those with weak similarity may not be. The manufacturer's submission to FDA, which contains its own studies and its request for a particular schedule, can also shape the outcome. Cannabinoids found in the plant are automatically in Schedule I until the manufacturer requests, and provides justification for, rescheduling. The CSA does permit DEA to reschedule a substance (move it to a different schedule) and to deschedule a substance (remove it from control under the CSA), according to the scheduling criteria (see appendix E) and process outlined above.

The possibility of scheduling is a major determinant of whether a manufacturer proceeds with drug development.³³ In general, pharmaceutical firms perceive scheduling to be a deterrent because it limits their ability to achieve market share for the following reasons: restricted access; physician disinclination to prescribe scheduled substances; stigma; the additional expense for abuse liability studies; and costly delays in reaching the market due to Federal and State scheduling processes.³³ Empirical evidence to support these widely held perceptions is difficult to find; however, at least one large survey of physicians found them to have moderate concerns about prescribing opioids because of actual or perceived pressure from regulatory agencies—such as the DEA.⁵⁷ On the basis of a legal analysis and widespread complaints from researchers and pharmaceutical executives, the IOM (1995)³³ recommended changes to the CSA to eliminate the Act's barriers to undertaking clinical research and development of controlled substances, a position supported in a subsequent report on marijuana.⁴⁰

**Table 5.1 Cannabinoids and Related Compounds Commonly
Used in Research**

Agonists

THC
WIN 55212-2
CP-55940
HU-210
Anandamide (natural ligand)
2-arachidonylglycerol (natural ligand)

Antagonists

SR 141716A
SR 144528

Sources: Felder and Glass, 1998, Mechoulam et al., 1998.

THE DEVELOPMENT AND MARKETING OF MARINOL®

The following material is based on the published literature (where cited), workshops sponsored by the IOM, and an interview with Dr. Robert Dudley, senior vice-president of Unimed Pharmaceuticals, Inc., the manufacturer of Marinol® and the holder of the NDA. Unimed jointly markets Marinol® with Roxane Laboratories, Inc.

Marinol® (dronabinol) is the only cannabinoid with approval for marketing in the U.S.* The following description covers its development, regulatory history, pharmacokinetics, adverse events, abuse liability and market growth. The experience with dronabinol may serve as a bellwether for the regulatory and commercial fate of new cannabinoids being considered for development.

Development and Regulatory History

Dronabinol is an oral capsule containing THC in sesame oil. It was approved by FDA in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy. In 1992, FDA approved the marketing of dronabinol for a second indication, the treatment of anorexia associated with weight loss in patients with AIDS.⁴⁵ The pre-clinical and clinical research on THC that culminated in FDA's 1985 approval was primarily supported by the National Cancer Institute (NCI), whose research support stems back to the 1970s. The NCI's contribution appears pivotal, considering that Unimed, the pharmaceutical company that holds the NDA, estimates its contribution to have been only about 25 percent of the total research effort. FDA's review and approval time for dronabinol took approximately two years after submission of the NDA, according to Unimed. In order to obtain approval for dronabinol's second indication (i.e., through an efficacy supplement, see above), FDA required two more relatively small Phase III studies. The studies lasted three years and cost \$5 million to complete.

*The only cannabinoid licensed outside of the U.S. is nabilone (Cesamet®), which is an analog of THC available in the U.K. for the management of nausea and vomiting associated with cancer chemotherapy (Pertwee, 1997a).

Physical Properties, Pharmacokinetics, and Adverse Events

Dronabinol is synthesized in the laboratory rather than extracted from the plant. Its manufacture is complex and expensive because of the numerous steps in the manufacturing process needed for purification. Since dronabinol is highly lipophilic, its poor solubility in aqueous solutions together with its high first-pass metabolism in the liver are responsible for its poor bioavailability; only 10-20 percent of the original oral dose reaches the systemic circulation.^{45, 60} The onset of action is slow, with peak plasma concentrations attained 2-4 hours after dosing.^{45, 56} By contrast, inhaled marijuana is rapidly absorbed. In a study comparing THC administered via oral, inhaled and intravenous routes, plasma levels peaked almost instantaneously for both inhaled and intravenous forms, whereas oral THC was the slowest to reach the circulation, most participants' peak plasma levels occurring at 60 or 90 minutes, although the average time to reach peak levels was about 2 hours. Variation in individual responses is highest for oral THC and bioavailability is lowest.⁴²

Dronabinol's most common adverse events are associated with the central nervous system (CNS): anxiety, confusion, depersonalization, dizziness, euphoria, dysphoria, somnolence, and thinking abnormality.^{8, 9, 45, 59} In two recent clinical trials, CNS adverse events affected about one-third of patients, but only a small percentage discontinued the drug due to adverse events.^{8, 9} Lowering the dose of dronabinol can minimize side effects, especially dysphoria (i.e., disquiet or malaise).⁴⁷

Abuse Potential and Scheduling

Upon its commercial introduction in 1985, dronabinol was placed in Schedule II. This schedule, the second most restrictive category, is reserved for medically-approved substances with "high potential for abuse" (21 U.S.C. § 812 (b) (2)). Unimed did not encounter any delays in marketing as a result of the scheduling process because the scheduling decision was made by DEA prior to FDA's approval for marketing. Nor did Unimed encounter any marketing delays as a result of State scheduling laws. Unimed was not specifically asked by the FDA to perform abuse liability studies for the first approval, presumably because such studies had been conducted earlier.

Unimed later petitioned DEA to reschedule Marinol® from Schedule II to Schedule III, the next less restrictive category reserved for medically-approved substances with some potential for abuse (21 U.S.C. § 812 (b) (3)). To buttress its request for rescheduling, Unimed supported an analysis of Marinol's® abuse liability by researchers at the Haight Ashbury Free Clinic of San Francisco, which treats a significant number of cannabis-dependent patients as well as people with HIV/AIDS. This study found no evidence of abuse or diversion of Marinol® after a literature analysis and surveys and interviews of addiction medicine specialists, oncologists, researchers in cancer and HIV treatment, and law enforcement. The authors attribute

Marinol®'s low abuse potential to its slow onset of action and dysphoric effects, among other factors.¹² On November 5, 1998, the DEA announced a proposal to reschedule Marinol® to Schedule III.¹⁷ As of this writing, no formal action on that proposal has been taken.

The rescheduling of a drug from Schedule II to Schedule III is considered to be a very important step because it lifts some of the restrictions to availability. For example, Unimed anticipates a sales increase of approximately 15-20 percent as a result of rescheduling. In its judgment, and that of many other pharmaceutical companies,³³ scheduling limits market penetration, with progressively greater limitations at the more restrictive schedules. The reasons are (1) physicians and other providers are reticent to prescribe Schedule II drugs; (2) patients are deterred from seeking prescriptions because of Schedule II prohibition of refills, unlike the case for any other commercially available scheduled substances; (3) the existence of additional restrictions imposed by several States, such as quantity restrictions (e.g., 30-day supply limits) and triplicate prescriptions;⁵⁰ and (4) the exclusion of some Schedule II drugs from hospital formularies because of onerous security and paperwork requirements under Federal and State controlled substances laws.

Market Growth and Transformation

The annual sales of Marinol® currently are estimated at \$20 million, according to Unimed. The composition of Marinol®'s patient population is 80 percent for HIV, 10 percent for cancer chemotherapy, and about 5-10 percent for other purposes. The latter group is thought to consist of Alzheimer's patients drawn to the drug by a recently published clinical study indicating dronabinol's promise for the treatment of their anorexia and disturbed behavior.⁵⁸ As noted earlier, Unimed cannot promote Marinol® for this unlabelled indication, but physicians are free to prescribe it for such an indication. Unimed is conducting additional research in pursuit of FDA approval of a new indication for Marinol® in the treatment of Alzheimer's disease (see below).

The 1992 approval of Marinol® for the treatment of anorexia in AIDS patients marked a major transformation in the composition of the patient population. Prior to that, Marinol®'s use was restricted to oncology patients. The oncology market for Marinol® gradually receded as a result of the introduction of newer medications, including serotonin antagonists such as ondansetron, which are more effective (see chapter 4, section on Nausea and Vomiting) and are not scheduled. Much of the recent growth of the market for Marinol®, at approximately 10 percent annually, is attributed to its increasing use in HIV patients being treated with combination anti-retroviral therapy. Marinol® appears to have a dual effect, not only in stimulating appetite, but also in combating the nausea and vomiting associated with combination therapy. Unimed is presently supporting a Phase II study to examine this combined effect, and with promising results, plans to seek FDA approval for this new indication.

Unimed possesses two forms of market protection for Marinol®. In December 1992, Marinol® was granted by FDA seven years of exclusive marketing

under the Orphan Drug Act. The market exclusivity relates to Marinol®'s use in anorexia associated with AIDS. With a designated orphan indication, the active ingredient, THC, cannot be marketed by another manufacturer for this same indication until December 1999 (see earlier section). Other pharmaceutical manufacturers are not constrained from manufacturing and marketing THC for its *other* indication (i.e., antiemesis for cancer chemotherapy); however, none appear to be interested in what is, by pharmaceutical company standards, a small market. In addition to market exclusivity, Unimed secured in June 1998 a "use patent" for dronabinol for the treatment of disturbed patients with dementia. This confers patent protection to Unimed for this use for 20 years from the date of filing the application^b, assuming that this indication eventually gains approval from FDA.

The following are considered to be the rate-limiting factors in the growth of the current market for Marinol®, according to Unimed: the lack of physician awareness of the drug's efficacy; its adverse effects (see earlier section); and its restricted availability as a result of placement in Schedule II. Unimed perceives only a small percentage of its market to be lost to "competition" from marijuana itself, but there are, admittedly, no reliable statistics on the number of people that have chosen to treat their symptoms with illegally obtained marijuana, despite their ability to obtain Marinol®.

New Routes Of Administration

It is well recognized that Marinol®'s oral route of administration hampers its effectiveness due to slow absorption and to patients' desire for more control over dosing. A drug delivered orally first is absorbed from the stomach and small intestine and then is passed through the liver, where it undergoes some metabolism before being introduced into the circulation. To overcome the deficiencies of oral administration, Unimed activated an IND in 1998 as a step toward developing new formulations for Marinol®. Four new formulations are under study in Phase I clinical studies being conducted in conjunction with Roxane Laboratories. These formulations seek to deliver Marinol® more rapidly and directly to the circulation: deep lung aerosol, nasal spray, nasal gel, and sublingual preparation. The first two fall under inhalation as a route of administration. Inhalation is considered to be the most promising method owing to the rapidity of onset of its effects and potential for better titration of the dose by the patient, but it might also carry an increased potential for abuse. The abuse of a drug is correlated with its rapidity of onset (G. Koob, IOM workshop). The sublingual route of administration also affords rapid absorption into the circulation, in this case from the oral mucosa. Other researchers are pursuing the delivery of THC through rectal suppositories, but this slower route

^bA use patent—also known as a process patent—is one type of patent that accords protection for a method of using a composition or compound. A use patent is not considered as strong as a product patent, which prohibits others from manufacturing, using, or selling the product for all uses, rather than for a specific use defined in a use patent.

may not be acceptable to many patients. A transdermal route of administration, which is best suited to a hydrophilic drug, is precluded because of the lipophilicity of THC. Thus, the choice of routes of administration heavily depends on the physicochemical characteristics of the drug as well as safety, abuse liability, and tolerability.

Unimed anticipates that it will be required by FDA to conduct studies of the bioavailability, efficacy, and possibly the abuse liability of any new formulation it seeks to market. Any formulation that expedites Marinol®'s onset of action, as noted above, is thought to carry greater possibility for abuse. The cost of developing each new formulation is estimated by Unimed at \$7-10 million.

Unimed and Roxane are developing, or considering development of, five new indications for Marinol®: (1) treatment of disturbed behavior in Alzheimer's disease; (2) treatment of nausea and vomiting in HIV patients receiving combination therapy; (3) the treatment of spasticity in multiple sclerosis; (4) the treatment of intractable pain; and (5) stimulating appetite in patients with cancer and renal disease.

Cost of Marinol® vs. Marijuana

During the IOM public workshops held during the course of this study, many people commented that an important advantage of using marijuana for medical purposes is that it is much less expensive than Marinol®. But this comparison is deceptive. While the direct costs of marijuana are relatively low, the indirect costs can be prohibitive. Individuals who violate federal or state marijuana laws risk a variety of costs associated with engaging in criminal activity, ranging from increased vulnerability to theft and personal injury legal fees to long prison terms. In addition, when purchasing illicit drugs there is no guarantee that the product purchased is what the seller claims it is, or that it is not contaminated.

The price of Marinol® for its most commonly used indication, anorexia in AIDS, is estimated at \$200 dollars per month. The less commonly used indication—nausea and vomiting with cancer chemotherapy—is not as costly because use is not chronic. Yet regardless of indication, patients' out-of-pocket expenses tend to be much less, often minimal, because of reimbursement through public or private health insurance. For indigent patients who are uninsured, Roxane sponsors a patient assistance program to defray the cost.

The street value of marijuana is, according to DEA's most recent figures, about \$5-10 per bag of loose plant.¹⁶ At the California buyers' clubs, the price ranges from 2-16 dollars per gram, depending on the grade of marijuana. The cost to a patient using marijuana will vary according to the number of cigarettes smoked on a daily basis, their THC content, and the duration of use. Insurance does not cover the cost of marijuana. In addition, it is possible for a person to cultivate marijuana privately with little financial investment.

Thus, Marinol® appears to be cheaper than marijuana for patients with health insurance or with financial assistance from Roxane. Yet, if the full cost of

¹⁶ The DEA did not provide an estimate for the weight of marijuana per bag.

CANNABINOID DRUG DEVELOPMENT

Marinol® is borne out-of-pocket by the patient, the cost comparison is not so unambiguous. In this case, the daily cost in relation to marijuana varies according to the number of cigarettes smoked: If the patient smokes two or more marijuana cigarettes a day, Marinol® may be cheaper than marijuana; if the patient smokes only one marijuana cigarette a day, dronabinol may be more expensive than marijuana, according to an analysis submitted to the DEA by Unimed. These cost comparisons will vary according to fluctuations in the retail price and street value of dronabinol and marijuana, respectively, and will vary if marijuana were to become commercially available.

In summary, this section has described Marinol's® scientific, regulatory, and marketing milestones. Marinol® has been on the US market since 1985. Its commercial development was heavily reliant upon research supported by the NIH. Marinol's® market has grown over time to reach \$20 million in sales. Further market growth is anticipated, yet is still constrained by lack of awareness, adverse effects, oral route of administration (conferring low bioavailability and slow onset), and by restrictions imposed by drug scheduling. As mentioned above, the absence of evidence for abuse or diversion of dronabinol to illicit channels recently has resulted in a proposal to reschedule it to a less restrictive schedule. The manufacturer is proceeding with research on new forms of delivery to overcome the problems associated with oral administration. The manufacturer also is proceeding with research on a spectrum of new indications for Marinol®.

MARKET OUTLOOK FOR CANNABINOIDS

The potential therapeutic value of cannabinoids is extremely broad. It extends well beyond antiemesis for chemotherapy and appetite stimulation for AIDS, the two indications for which the FDA has approved dronabinol (Marinol®). Chapter 4 of this report assessed the possible wider therapeutic potential of marijuana and THC in neurological disorders, glaucoma, and analgesia, all conditions for which clinical research has been underway in order to fulfill unmet patient needs. New therapeutic areas are being explored in pre-clinical research. For any of these therapeutic indications, will novel cannabinoids reach the market to satisfy the medical needs of the patients?

Economic Factors in Drug Development

The outcomes of pre-clinical and clinical research determine whether a drug is sufficiently safe and effective to warrant FDA approval for marketing. But the decisions to launch pre-clinical research and to proceed to clinical trials, when early results are promising, are largely dictated by economic factors. A pharmaceutical company must decide whether to invest in what is universally regarded as a lengthy and risky research path. For any given drug, the question is: will there be an adequate return on investment? The "investment" in this case is the high cost of developing a drug (noted earlier). The expectation of high financial returns on investment is what drives drug development.^{44, 53}

Market analyses are undertaken to forecast whether a drug can be expected to reap a significant return on investment. The market analysis for a cannabinoid is likely to be shaped by the following factors. On the cost side, the average cost of developing a cannabinoid is likely to be higher than that for other drugs if its clinical indication falls under the therapeutic categories of neuropharmaceutical or nonsteroidal antiinflammatory drug, the two therapeutic categories associated with the highest research and development costs.¹⁹ One reason for higher costs is the need to satisfy DEA's regulatory requirements related to drug scheduling.

On the "market return" side are a multiplicity of factors. A market analysis examines the expected returns from the possible markets for which a cannabinoid could be clinically pursued. The financial size of each market is calculated mostly on the basis of the current and projected patient prevalence (i.e., for a given clinical indication), sales data (if available), and competition from other products. The duration of use is also factored in—a drug needed for long-term use in a condition with an early age of onset is desirable from a marketing perspective. Other factors that can augment or diminish market return include patentability and other forms of market protection, reimbursement climate, restrictions in access due to drug scheduling, social attitudes, adverse effect profile, and drug interactions.^{33, 53} New cannabinoids generally can receive product patents, giving the patent holder 20 years of protection against others seeking to manufacture or sell the same product. According to U.S. patent law, the product must be novel and "nonobvious" in relation to prior patents.²⁸

Cannabinoids under Development

From publicly available sources, the IOM was able to identify several cannabinoids being developed for human use (table 5.2). All of these compounds, with the exception of dronabinol and marijuana, are in the pre-clinical phase of testing in the U.S. This list may not be comprehensive, since other compounds may well be under development, but that information is proprietary.^d This table does not list the full complement of cannabinoids, both agonists and antagonists, being used in research as tools to understand the pharmacology of cannabinoids (for more comprehensive lists of cannabinoids, see Felder and Glass, 1998²⁶; Mechoulam et al, 1998³⁶; Howlett et al, 1995³⁰; Pertwee 1997⁴⁶). Nor does it list cannabinoids once considered for development, but later discontinued. An 18-year survey of analgesics in development from 1980-1998 found that over half of the nine cannabinoids under development for analgesia were either discontinued or undeveloped,⁴⁹ * but most of these were halted before 1988 when the first endogenous cannabinoid receptor was discovered (chapter 3).

There are three points to be made from this table. The first is that virtually all of the listed cannabinoids are being developed by small pharmaceutical companies or by individuals. In general, this implies that their development is considered especially risky from a commercial standpoint, since small companies frequently are willing to assume greater development risks than are larger, more established firms (Schmidt, W., personal communication, 1998). Without the benefit of sales revenues, small companies are able to fund their research through financing from venture capital, stock offerings, and relationships with established pharmaceutical companies.⁴³

^dInformation about the existence of an IND is confidential, and can only be confirmed by the manufacturer, not by the FDA.

^eDiscontinuations: levonantradol, nabitan, nantradol, pravadoline. Undeveloped: CP-47497, CP-55244.

Table 5.2 Cannabinoids Under Development for Human Use

Name of Drug	Investigator	Stage of Development	Pharmacology	U.S. FDA Status	Possible Indication(s)
HU-211	Pharmos Corp.	Clinical Phase II in Israel	NMDA receptor Antagonist	None	Neuroprotection (Neurotrauma, stroke, Parkinson's, Alzheimer's)
CT-3	Atlantic Pharmaceuticals	Pre-clinical	Nonpsychoactive	None	Antiinflammatory Analgesia
THC	Unimed Roxane Labs	Clinical Phase I	Cannabinoid Receptor Agonist	IND	[see text]
<i>Marijuana Plant</i>	HortaPharm GW Pharmaceuticals	Clinical in England*	Cannabinoid mixture	None	Multiple Sclerosis
	Donald Abrams, M.D.	Clinical Phase I	Cannabinoid mixture	IND	HIV-related appetite stimulation
	Ethan Russo, M.D.		Cannabinoid mixture	IND pending	Migraine

*Clinical trials are to proceed in the next few years under a license from the British Home Office¹⁰

Sources: Glain, 1998²⁷; Atlantic Pharmaceuticals, 1997⁷; Striem et al, 1997⁵⁵; Nainggolan, 1997³⁷; Zurier et al, 1998⁶¹; D. Abrams and E. Russo, personal communications, 1998; R. Dudley, personal communication, 1998; Pharmaprojects Database, 1998.

The second point is that, with the exception of THC and the marijuana plant itself, no constituents of the plant appear to be undergoing development by pharmaceutical companies. A number of plant compounds have been tested in experimental models and humans. For example, the antiemetic properties of Δ^8 -THC were demonstrated, along with negligible side effects, in a clinical trial of children undergoing cancer chemotherapy,¹ but no sponsor was interested in developing Δ^8 -THC for commercial purposes (R. Mechoulam, personal communication, 1998). The absence of plant cannabinoids under development implies that the specter of automatic scheduling in Schedule I under the CSA is a significant deterrent, even though rescheduling would occur prior to marketing.^a The point from the earlier discussion is that automatic, as opposed to *de novo*, scheduling appears to cast a pall over development of a cannabinoid found in the plant. Another impediment is that a cannabinoid extracted from the plant is not likely to fulfill the criteria for a product patent, although other forms of market protection are possible. Dronabinol, for example, was accorded orphan drug status and obtained a use patent.

The third point is that cannabinoids are being developed for therapeutic applications that extend beyond those discussed earlier in both this chapter and in chapter 4. One of the most prominent new applications of cannabinoids is for "neuroprotection," i.e., the rescue of neurons from cell death associated with trauma, ischemia, and neurological diseases.^{29, 36} Cannabinoids are thought to be neuroprotective—through receptor-dependent,⁵¹ as well as receptor-independent pathways; both THC, which binds to CB₁ receptors, and CBD, which does not, are potent antioxidants (antioxidants are effective neuroprotectants because of their ability to reduce the toxic forms of oxygen [free radicals] that are formed during cellular stress).²⁹ The synthetic cannabinoid HU-211 (dexanabinol) is an antioxidant and an antagonist of the NMDA receptor, rather than an agonist at the cannabinoid receptor.⁵² Earlier research demonstrated that HU-211 protects neurons from neurotoxicity induced by excess concentrations of the excitatory neurotransmitter glutamate. Excess release of glutamate, which acts by binding to the NMDA receptor, is associated with trauma and disease.⁵⁴ As an NMDA antagonist, HU-211 blocks the damaging action of glutamate and other endogenous neurotoxic agents.^{52, 55} After having been studied in the U.K. in Phase I clinical trials, HU-211 progressed to Phase II clinical trials in Israel for the treatment of severe closed head trauma (Pharmaprojects Database, 1998).³⁵

^a As a result of FDA's approval of an NDA, the drug would be, at a minimum, rescheduled in Schedule II. Depending on abuse liability data supplied by the manufacturer and FDA's recommendation, the drug could be rescheduled to a less restrictive schedule or be descheduled entirely.

Market Prospects for Cannabinoids

It is difficult to gauge the market prospects for new cannabinoids. There certainly appears to be scientific interest, particularly in the discovery area, but whether this interest can be sustained commercially through the arduous course of drug development is an open question. Research and development experience is limited; only one cannabinoid, dronabinol, is commercially available, and most of its research and development costs were shouldered by the federal government. Further, the size of dronabinol's market (at about \$20 million) is modest by pharmaceutical company standards. None of the other cannabinoids in development has reached clinical testing in the U.S. Their scientific, regulatory and commercial fates are likely to be very important in shaping future investment patterns. Experience with the drug scheduling process also is likely to be watched very carefully. If these early products are heavily regulated in the absence of strong abuse liability, future development may be deterred. For the present, what seems to be clear from the dearth of products in development and the small size of the companies sponsoring them is that cannabinoid development is seen as especially risky.

One scenario is that cannabinoids will be pursued for lucrative markets for which there is large unmet medical need. Of the therapeutic areas for which cannabinoid receptor agonists have been tested, analgesia is by far the largest. The annual U.S. prescription and over-the-counter analgesic market in 1997 was \$4.4 billion.⁴⁹ Given the long-standing need for less addictive, safer, easier to use, and more effective drugs for acute and chronic pain, it would not be surprising to see cannabinoids developed to treat some segments of the current analgesic market, were their safety and effectiveness clearly established in clinical trials.

In addition to cannabinoid receptor agonists, there are other classes of cannabinoid-related drugs that might prove therapeutically useful: cannabinoid antagonists and inverse agonists, compounds that bind to receptors but produce effects opposite to those of agonists. Neither would be subject to the same scheduling concerns as cannabinoid agonists, because they are not found in marijuana and would be highly unlikely to have any abuse potential. Another set of cannabinoid-related drugs, such as those that affect the synthesis, uptake, or inactivation of endogenous cannabinoids might, however, have abuse potential because they would influence the signal strength of endogenous cannabinoids.

The development of specific cannabinoid antagonists, like SR141716A for CB₁ receptors and SR144528 for CB₂ receptors, has provided a significant impetus in understanding cannabinoid actions. Those compounds block many of the effects of THC in animals, and their testing in humans has just begun. Cannabinoid antagonists have physiological effects on their own, in the absence of THC. They might have significant therapeutic potential in a variety of clinical situations. For example, since THC reduces short-term memory, it is possible that a CB₁ antagonist like SR141716A could act as a memory enhancing agent. Similarly, for conditions under which cannabinoids decrease immune function (presumably by binding to CB₂

receptors in immune cells), a CB₂ antagonist might be useful as an immune stimulant.

Cannabinoid inverse agonists would exert the opposite effects of THC and might thus cause appetite loss, short-term memory enhancement, nausea, or anxiety. Those effects could possibly be separated by molecular design, in which case inverse agonists might have some therapeutic value. One report has been published suggesting that the CB₁ receptor antagonist, SR141617A,¹¹ is an inverse agonist, and there will likely be others.

MARIJUANA: REGULATION AND MARKET OUTLOOK

Marijuana is not a legally marketed drug in the United States.^b No sponsor has ever sought from the FDA marketing approval for medical use of marijuana. One sponsor has an IND for a clinical safety study on HIV anorexia (D. Abrams, personal communication, 1998). Another has an IND pending for the treatment of migraine headaches (E. Russo, personal communication, 1998). Since 1970, marijuana's manufacture and distribution have been tightly restricted under the CSA, which places marijuana in Schedule I. This schedule is reserved for drugs or other substances with: 1) "a high potential for abuse," 2) "no currently accepted medical use" and 3) "lack of accepted safety for use...under medical supervision" (21 U.S.C. § 812 (b)(1)).

Marijuana has remained in Schedule I despite persistent efforts at rescheduling since the 1970s by advocacy groups, such as NORML. Through petitions to DEA, advocacy groups contend that marijuana does not fit the legal criteria for a Schedule I substance owing to its purported medical uses and lack of high abuse liability.^{3, 4, 48} Another rescheduling petition, which was filed in 1995, presently is being evaluated by FDA and DEA.

Marijuana Availability for Research

To use marijuana for research purposes, researchers must register with DEA, as well as adhere to other relevant requirements of the CSA and other federal statutes, such as the Food, Drug, and Cosmetic Act. The National Institute on Drug Abuse (NIDA), one of the institutes of the National Institutes of Health, is the only organization in the U.S. licensed by DEA to manufacture and distribute marijuana for research purposes. NIDA performs this function under its Drug Supply Program.^c

^bUnder the CSA, its only legal use is in research under strictly defined conditions.

^cThis is also the program through which several patients receive marijuana under a compassionate use program monitored by FDA. For history and information on this effort, see CRS, 1993.⁴⁸

Through this program, NIDA arranges for marijuana to be grown and processed through contracts with two organizations, the University of Mississippi and the Research Triangle Institute. The University of Mississippi grows, harvests, and dries the marijuana, whereupon the latter processes it into cigarettes. A researcher can obtain marijuana free-of-charge from NIDA in one of two ways: through an NIH-approved research grant to investigate marijuana or through a separate protocol review.³⁹ Research grant approvals are handled through the conventional NIH peer review process for extramural research, a highly competitive process with success rates in 1997 of 32 percent of approved NIDA grants.⁴¹ Through the separate protocol review, in which the researcher funds the research independent of an NIH grant, NIDA submits the researcher's protocol to several external reviewers who evaluate the protocol on the basis of scientific merit and of its relevance to the mission of NIDA and NIH.

Through these two avenues, marijuana has been supplied to several research groups, most of those who apply. While there has been much discussion of NIDA's alleged failure to supply marijuana for research purposes, we are unaware of recent cases in which they failed to supply marijuana to an investigator with an NIH-approved grant for research on marijuana. Donald Abrams' difficulty in obtaining research funding and marijuana from NIDA has been much discussed,² but the case of a single individual should not be presumed to be representative of the community of marijuana researchers. Failure of investigators who apply to NIH for marijuana research grants to receive funding is hardly exceptional: in 1998, less 25 % of *all* first time investigator-initiated grant applications (known as RO1's) to the NIH were funded.³⁸

To import marijuana under the CSA for research purposes, the procedures are more complex. Under DEA regulations, marijuana can be imported provided that the researcher is registered with DEA and has approval for marijuana research (21 CFR § 1301.11, .13, and .18), has a DEA-approved permit for importation (21 CFR § 1312.11, .12, and .13), and the exporter in the foreign country has appropriate authorization by the country of exportation. Importation would enable U.S. researchers to conduct research on marijuana grown by HortaPharm, a company that has developed unique strains of marijuana. However, no U.S. researcher has imported HortaPharm's marijuana because of refusal by the Dutch authorities to issue an export permit, despite the issuance of an import permit by the DEA (D. Pate, HortaPharm, personal communication, 1998).⁴

HortaPharm, which is located in the Netherlands, grows marijuana as a raw material for the manufacture of pharmaceuticals. Through selective breeding and controlled production, HortaPharm has developed marijuana strains that feature single cannabinoids, e.g., THC, cannabidiol, etc. The plants contain a consistently

⁴It may be eventually possible to import HortaPharm's marijuana from England, where HortaPharm is growing its marijuana strains for research use in clinical trials for multiple sclerosis (Boseley, 1998). England, as the country of origin, would have to provide appropriate authorization for export of the strains to the U.S. Permission to export for research purposes is part of the basis for HortaPharm's participation in this project with GW Pharmaceuticals through a special set of licenses with the British Home Office (Dr. David Pate, HortaPharm, personal communication, 1998).

“clean” phytochemical profile and a higher level of THC (16 percent) or other desired cannabinoids than seized marijuana. Marijuana seized in the U.S. in 1996 had a THC content averaging about 5 percent.¹⁶ Consistency of THC content is desirable because it overcomes the natural variability due to latitude, weather, and soil conditions. Product consistency is a basic tenet of pharmacology because it enables standardized dosing for regulatory and treatment purposes.

The difficulties of conducting research on marijuana also were noted in the 1997 NIH report, which recommended that NIH facilitate clinical research by developing a centralized mechanism to promote design, approval, and conduct of clinical trials.

Regulatory Hurdles to Market

For marijuana to be marketed legally in the U.S., a sponsor with sufficient resources would be obliged to satisfy the regulatory requirements of both the Food, Drug, and Cosmetic Act and the CSA.

Under the Food, Drug, and Cosmetic Act, a botanical product like marijuana *theoretically* might be marketed in oral dosage form as a dietary supplement;^c however, as a practical matter, only a new drug approval is likely to satisfy the provisions of the CSA, which require prescribing and distribution controls on drugs of abuse that also have an “accepted medical use.” (The final paragraphs of this section clarify the criteria for “accepted medical use.”)

Bringing marijuana to market as a new drug is uncharted terrain. The route is fraught with uncertainty for at least three pharmacological reasons: marijuana is a botanical product; it is smoked; and it is a drug with abuse potential. In general, botanical products are inherently more difficult to bring to market than are single chemical entities because they are complex mixtures of active and inactive ingredients. Concerns arise about product consistency, potency of the active ingredients, contamination, and stability of both active and inactive ingredients over time. These are among the concerns that the sponsor would have to overcome in order to meet the requirements for a new drug application, especially those relating to safety and to chemistry, manufacturing, and control (noted earlier).

There are a handful of botanical preparations on the market, but none received a formal new drug approval by today’s standards of safety and efficacy (FDA, Center for Drug Evaluation and Research, personal communication, 1998). The three marketed botanical preparations are older drugs that came to market years before safety and efficacy studies were required by legislative amendments in 1938 and 1962, respectively, and before modern chemistry and manufacturing controls came into being. One of these botanical preparations is the prescription product digitalis. Because it came to market prior to 1938, it is available today because it was “grandfathered” under the law, but does not necessarily meet contemporary standards for safety and effectiveness.²⁰ Two other botanical preparations, psyllium

^c Inhaled products may not lawfully be marketed as dietary supplements

and senna, came to market between 1938 and 1962. Drugs entering the market during this period for over-the-counter use were later required to be evaluated by FDA in what is known as the over-the-counter drug review process.²⁰ Through this process, psyllium and senna were found to be generally recognized as safe and effective and thus were allowed to remain on the market as over-the-counter drugs.^f While no botanical preparations have been approved as new drugs, it is important to point out that a number of individual plant constituents, either extracted or synthesized *de novo*, have been approved (e.g., taxol and morphine). But these drug approvals were for single constituents rather than botanical preparations *per se*. FDA is in the process of developing guidance to industry to explain how botanicals are reviewed as new drugs, but the final document might not be available before 1999.

The fact that marijuana is smoked might pose an even greater regulatory challenge. The risks associated with smoking marijuana are described in Chapter 2. FDA would have to weigh these risks along with marijuana's therapeutic benefits in order to arrive at a judgment about whether a sponsor's new drug application for marijuana met the requirements for safety and efficacy under the Food, Drug, and Cosmetic Act. Marijuana delivered in a novel way that avoids smoking would overcome some, but not all, of the regulatory concerns. Vaporization devices that permit inhalation of plant cannabinoids without the carcinogenic combustion products found in smoke are under development by several groups; such devices would also require regulatory review by FDA.

The regulatory hurdles to market posed by the CSA are formidable, but not insurmountable. If marijuana received market approval as a drug by the FDA, it would most likely be rescheduled under the CSA, as was the case for dronabinol. That is because a new drug approval satisfies the "accepted medical use" requirement under the CSA for manufacture and distribution in commerce.¹³ But a new drug approval is not the *only* means to reschedule marijuana under the CSA.¹⁴ For years, advocates for rescheduling have argued that marijuana does enjoy "accepted medical use," even in the absence of a new drug approval. Although advocates have been unsuccessful in rescheduling efforts, their actions prompted DEA to specify the criteria by which it would determine whether a substance had "accepted medical use." In DEA's 1992 denial of a rescheduling petition, it listed these elements as constituting "accepted medical use": 1) the drug's chemistry must be known and reproducible; 2) there must be adequate safety studies; 3) there must be adequate and well-controlled studies proving efficacy; 4) the drug must be accepted by qualified experts; and 5) the scientific evidence must be widely available.¹⁴

Assuming all of these criteria were satisfied, marijuana could be rescheduled, but into which schedule? The level of scheduling would be dictated primarily by a medical and scientific recommendation to DEA made by the Secretary of DHHS.⁸ As noted earlier, this recommendation is determined by the five scheduling criteria

^f Over-the-counter monographs for these products have been issued as tentative final monographs (proposed rules), but have not yet been issued in final form as final rules (FDA, Center for Drug Evaluation and Research, personal communication, 1998).

⁸ At present, there is no practical mechanism for generating such a recommendation outside the new drug approval process, although such a mechanism could, theoretically, be developed.³³

listed in the CSA (noted above). However, scheduling in a category less restrictive than Schedule II may be prohibited by international treaty obligations. The Single Convention on Narcotic Drugs, a treaty that was ratified by the United States in 1967, imposes on the plant and its resin minimum placement in Schedule II.¹³

Market Outlook for Marijuana

The market outlook for the development of marijuana as a new drug, based on the foregoing analysis, is not favorable for a host of scientific, regulatory, and commercial reasons.

From a scientific point of view, research is difficult due to the rigors of obtaining an adequate supply of legal, standardized marijuana for study. Further scientific hurdles to overcome relate to satisfying the exacting requirements for FDA approval of a new drug. These hurdles are even more exacting for a botanical product due to inherent problems with purity, consistency, and other factors (noted above). Finally, the health risks associated with smoking represent another barrier to FDA approval, unless a new, smoke-free route of administration is demonstrated to be safe. Depending on the route of administration, an additional overlay of regulatory requirements may have to be satisfied.

From a commercial point of view, uncertainties abound. The often-cited cost of new drug development, about \$200-300 million (cited earlier), may not fully apply but there are likely additional costs needed to satisfy FDA's requirements for a botanical product. As noted above, no botanical products have ever been approved as new drugs by FDA under today's stringent standards for safety and efficacy. Satisfying the legal requirements of the CSA also will add significantly to the cost of development. On the positive side, so much research already has been done that some development costs will be lower. The cost of bringing dronabinol to market, for example, was curtailed dramatically as a result of clinical trials supported with government funding. Nevertheless, for these reasons it is impossible to estimate the cost of developing marijuana as a new drug. Estimating return on investment is similarly difficult. A full-fledged market analysis would be required for the indication being sought. Such an analysis would take into account the market limitations resulting from drug scheduling restrictions, stigma, and patentability.

The plant does not constitute patentable subject matter under US patent law because it is unaltered from what is found in nature. So-called 'products of nature' are not generally patentable.²⁸ New marijuana strains, on the other hand, could be patentable in the U.S. under a product patent or a plant patent because they *are* altered from what is found in nature. (A product patent prohibits others from manufacturing, using, or selling each strain for 20 years; whereas, a plant patent carries somewhat less protection.) Thus far, HortaPharm has not sought any type of patent for its marijuana strains in the U.S., but it has received approval for a plant registration in Europe (David Watson, HortaPharm, personal communication, 1998).

In short, the development of the marijuana plant is beset by significant scientific, regulatory, and commercial obstacles and uncertainties. The prospects for its development as a new drug are unfavorable, unless return on investment is not a driving force. It is noteworthy that no pharmaceutical firm has sought to bring it to market in the U.S. The only interest in its development appears to be in England by a small pharmaceutical firm (see Boseley, 1998¹⁰) and in the U.S. from physicians without formal ties to pharmaceutical firms (D. Abrams and E. Russo, personal communications, 1998).

CONCLUSIONS

Cannabinoids are an interesting group of compounds with potentially far-reaching therapeutic applications. There is a surge of scientific interest in their development as new drugs. But the actual road to market for any new drug is expensive, long, and risky. It is studded with scientific, regulatory, and commercial obstacles. Experiences with the only approved cannabinoid, dronabinol, may not illuminate the pathway because of the government's heavy contribution to research and development, dronabinol's scheduling history, and its small market size.

There appear to be only two novel cannabinoids actively being developed for human use, but they have yet to be tested in humans in the U.S. Their experiences are likely to be more predictive of the marketing prospects for other cannabinoids. It is simply too early to forecast the prospects for cannabinoids, other than to note that their development at this point in time is considered to be especially risky, judging by the paucity of products in development and the small size of the pharmaceutical firms sponsoring them.

The market outlook in the U.S. is distinctly unfavorable for the marijuana plant and for cannabinoids found in the plant. Commercial interest in bringing them to market appears nonexistent. Cannabinoids in the plant are automatically placed in the most restrictive schedule of the Controlled Substances Act, thereby serving as a significant deterrent to development. The plant itself is not only subject to the same scheduling strictures as are individual plant cannabinoids, but development of marijuana also is encumbered by a constellation of scientific, regulatory, and commercial impediments to availability.

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