

# WEINER'S PAIN MANAGEMENT

A Practical Guide for Clinicians

SEVENTH EDITION

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AMERICAN ACADEMY OF PAIN MANAGEMENT



Taylor & Francis  
Taylor & Francis Group  
Boca Raton London New York

A CRC title, part of the Taylor & Francis imprint, a member of the  
Taylor & Francis Group, the academic division of T&F Informa plc.

2006

# The Role of Cannabis and Cannabinoids in Pain Management

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## INTRODUCTION

The herb cannabis is derived from the Old World species *Cannabis sativa* L. It is generally conceived that cannabis is a monotypic species (Merzouki, 2001), but *C. afghanica* may also merit species status (Clarke, 1998). Cannabis has a history as an analgesic agent that spans at least 4,000 years, including a century of usage in mainstream Western medicine. Quality control issues and, ultimately, political fiat eliminated this agent from the modern pharmacopoeia, but it is now resurgent. The reasons lie in the remarkable pharmacological properties of the herb, and new scientific research that reveals the inextricable link that cannabinoids possess with our own internal biochemistry. In essence, the cannabinoids form a system in parallel with that of the endogenous opioids (endorphins/enkephalins) in modulating pain. More importantly, cannabis, and its endogenous and synthetic counterparts, may be uniquely effective in pain syndromes such as neuropathic pain and migraine where opiates and other analgesics fail.

Despite hundreds of supportive journal articles over the last 15 years, the news about cannabis and cannabinoids has only slowly filtered into public and even professional acknowledgment. The attendant politics remain contentious, with certain states and countries acknowledging a role for cannabis in medicine, while other governmental bodies languish in inactivity or outright opposition.

Before the previous edition of this book (E. B. Russo, 2002a), no major medical text on pain had covered this topic to the author's awareness. This chapter may then

represent a point of departure in what the author believes will be a major renaissance of interest in this plant, its healing attributes, and what it may tell us about our own internal mechanisms of analgesia. A unique set of clinical tools may be added to an armamentarium in pain management that never seems wholly adequate to the task at hand.

We examine the use of cannabis and cannabinoids historically, scientifically, and anecdotally in relation to a variety of pain syndromes. The author has previously addressed this topic with respect to migraine (E. Russo, 1998; E. B. Russo, 2001a, 2001b), chronic musculoskeletal pain (E. B. Russo et al., 2002a), obstetrics and gynecology (E. Russo, 2002b), and fibromyalgia and idiopathic bowel syndrome (E. B. Russo, 2004a). Additional history of medicinal cannabis usage is also available (E. B. Russo, 2001, 2004b).

## CANNABIS AND PAIN TREATMENT: A HISTORICAL SURVEY

### CHINA

Traditional knowledge of cannabis in China may span 5,000 years, dating to the legendary emperor and "Divine Plowman," Shên-Nung. Julien (1849) wrote of the physician Hoa-tho in the early second century and his use of a cannabis extract in surgical anesthesia (p. 197):

*He gave to the sick person a preparation of hemp (Mau-yo), and, in a few moments, he became so insensible that it were as if he was plunged into rapture of loss of*

life. Then, following this instance, he practiced some overtures, incisions, amputations, and removed the cause of the malady; then he repaired the tissues with suture points, and applied liniments. [translation EBR]

## INDIA

The *Atharvaveda* of India dates to between 1400 and 2000 B.C.E. and mentions a sacred grass, *bhanga*, which remains a modern term of usage for cannabis. Medical references to cannabis date to Susruta in the sixth to seventh centuries B.C.E. (Chopra & Chopra, 1957). Dwarakanath (1965) described a series of Ayurvedic and Arabic tradition preparations containing the herb indicated for migraine, neuralgic, and visceral pains. These ancient claims in cannabis therapeutics have almost uniformly been supported by modern experimentation (E. B. Russo, 2005).

## EGYPT

Previous scholars had thought cannabis to be absent from Ancient Egypt, but Nunn (1996) cited six supporting experts that it was utilized medicinally. These authors agree with the view of Dawson that the hieroglyphic *shemshemet* represents cannabis. Physical proof includes discoveries of hemp remnants in the tomb of Akhenaten (Amenophis IV) around 1350 B.C.E., and cannabis pollen in the tomb of Rameses II, who died in 1224 B.C.E. (Mannische, 1989). Cannabis has remained in the Egyptian pharmacopoeia since pharaonic times, administered orally, rectally, vaginally, on the skin, in the eyes, and by fumigation.

Mannische cites the following from Papyrus Ramesseum III, 1700 B.C.E. (Mannische, 1989, p. 82): "A treatment for the eyes: celery; hemp; is ground and left in the dew overnight. Both eyes of the patient are to be washed with it early in the morning." This suggests a parallel to modern use of cannabis in glaucoma treatment (Jarvinen, Pate, & Laine, 2002).

Another passage (Ebers Papyrus 821) is reminiscent of 19th century use of cannabis as an aid to childbirth (Ghalioungui, 1987, p. 209): "Another: *smsm-t* [shemshemet]: ground in honey; introduced into her vagina (*iwf*). This is a contraction." The passage E618 refers to treatment of a toenail with a bandage containing hemp resin (Ghalioungui, 1987).

## SUMER/AKKAD/ASSYRIA

Thompson (1924, 1949) documented 29 citations of use of cannabis in Assyrian medical documents, and attested to its analgesic and psychogenic effects by various methods including fumigation. The bulk of the references date to the second millennium B.C.E. and pertain to *A.ZAL.LA* in Sumerian, and *azallû* in Akkadian. Through philological arguments the author concluded (Thompson, 1924, p. 101):

The evidence thus indicates a plant prescribed in AM [Assyrian manuscripts] in very small doses, used in spinning and rope-making, and at the same time a drug used to dispel depression of spirits. Obviously, it is none other than hemp, *Cannabis sativa*, L.

Specifically, according to Thompson (1949), hemp, or *azallû*, was employed to bind the temples (possibly for headache?). Furthermore, the Sumerian texts recommended internal use for depression and staying the menses, and "for 'poison' of all limbs, dry, pound, sift, and fumigate."

## ANCIENT ISRAEL/PALESTINE/JUDEA

Physical evidence of medicinal cannabis use in Israel has been discovered (Zias et al., 1993) in a burial tomb in Beit Shemesh where the skeleton of a 14-year-old girl was found along with fourth century bronze coins. Contained in her pelvic area was the skeleton of a term fetus, of sufficient size to render a successful vaginal delivery unlikely. In her abdominal area, gray carbonized material was noted and analyzed, yielding chromatographic and nuclear magnetic resonance spectroscopy evidence of delta-6-tetrahydrocannabinol, a stable metabolite of cannabis. The authors stated (p. 215), "We assume that the ashes found in the tomb were cannabis, burned in a vessel and administered to the young girl as an inhalant to facilitate the birth process." They further remarked that cannabis retained an indication as an aid to parturition into the 19th century.

## GREEK AND ROMAN EMPIRES

In the first century of the Common Era, Dioscorides published his *Materia Medica* and described the analgesic role of cannabis (1968, 3.165, p. 390): "Cannabis is a plant of much use in this life for ye twistings of very strong ropes, ... but being juiced when it is green is good for the pains of the ears."

Pliny described additional indications for hemp (1951, Book XX, XCVII, p. 153): "The root boiled in water eases cramped joints, gout too and similar violent pains. It is applied raw to burns."

## THE ISLAMIC WORLD

In the ninth century, Sabur ibn Sahl in Persia cited use of cannabis several times in his dispensatorium, *Al-Aqrabadhin Al-Saghir* (Kahl, 1994). According to the translation and interpretation of the text by Dr. Indalecio Lozano (personal communication, 2000), ibn Sahl prescribed a compound medicine containing cannabis juice that was used to treat a variety of aching pains and migraine that was instilled into the nostril of the afflicted patient.

Also in the 12th century, Al-Biruni noted (Biruni, Said, & Hamdard National Foundation-Saydanah, 1973, p. 346): “Galen says: ‘The leaves of this plant [cannabis] cure flatus — Some people squeeze the fresh (seeds) for use in ear-aches. I believe that it is used in chronic pains.’”

Umar ibn Yusuf ibn Rasul also suggested cannabis for ear and head pains (Lewis, Menage, Pellat, & Schacht, 1971) at the end of the 13th century.

Some time later, an electuary named *bars*, or *barsh*, containing a variety of ingredients, sometimes including cannabis, became popular as an analgesic treatment in the Arab world (Lozano Camara & Arabe, 1990).

At the close of the 17th century in Indonesia, Rumphius studied cannabis use (Rumpf & Beekman, 1981) including treatment of pleuritic chest pains and hernias.

## WESTERN MEDICINE

Medicinal use of cannabis also evolved from early times involving hemp strains that in all likelihood contained cannabidiol (CBD), but no  $\Delta^9$ -tetrahydrocannabinol (THC), unlike the cannabis strains of the East. An early citation derives from the ninth century in the *Old English Herbarium Manuscript V*, translated from Anglo-Saxon (Pollington, 2000, p. 301): “For pain of the innards take the same plant [hemp], give it to drink, it takes away the pain.” Such uses persisted in England, as Gerard continued to recommend hemp for colic in 1597 (Gerard & Johnson, 1975). Similarly, in 1640 in the *Theatrum Botanicum, The Theater of Plantae* (Parkinson, Bonham, & L’Obel, 1640), Parkinson indicated (p. 598):

Hempe is cold and dry ... the Dutch as one saith doe make an Emulsion out of the seede, ... for it openeth the obstructions of the gall, and causeth digestion of choller therein: ... the Emulsion or decoction of the seede, stayeth laskes and fluxes that are continuall, easeth the paines of the collicke: and allayeth the troublesome humours in the bowels: ... The decoction, of the roote is sayd to allay inflammations in the head or any other part. the herbe it selfe, or the distilled water thereof performeth the like effect; the same decoction of the rootes, easeth the paines of the goutte, the hard tumours, or knots of the joynts, the paines and shrinking of the sinewes, and other the like paines of the hippes: it is good to be used, for any place that hath bene burnt by fire, if the fresh juyce be mixed with a little oyle or butter.

In 1758, Marcandier published his *Traité du chanvre* [Treatise on hemp] (Marcandier, 1758), which was translated into English several years later (Marcandier, 1764, pp. 24, 26):

The grain and the leaves being squeezed, while they are green, and applied, by way of cataplasm, to painful tumours, are reckoned to have a great power of relaxing and stupefying.... The root of it boiled in water, and

applied in the form of a cataplasm, softens and restores the joints of fingers or toes that are dried and shrunk. It is very good against the gout, and other humours that fall upon the nervous, muscular, and tendinous parts. It abates inflammations, dissolves tumours, and hard swellings upon the joints. Beat and pounded in a mortar, with butter, when it is still fresh, it is applied to burns, which it relieves greatly when it is often renewed.

Linnaeus acknowledged the pain-reducing properties of cannabis in his list of its medical applications in his *Materia Medica* (Linné, 1772, pp. 213–214), “narcotica, phantastica, dementans, anodyna, repellens.”

In France, Chomel (1782) noted once more the benefits of hemp seed oil on burn treatment, promoting both pain and healing.

The medical use of cannabis, or what became known as “Indian hemp” was reintroduced to the West by O’Shaughnessy in 1839 (O’Shaughnessy, 1838–1840). His treatise on the subject dealt with the apparent utility of a plant extract administered to patients suffering from rabies, cholera, tetanus, and infantile convulsions, but also a series of painful rheumatological conditions.

Shortly after Indian hemp came to England, Clendinning described his results of treatment of 18 patients (1843): three with headaches, one with abdominal pain secondary to tumor, one with pain secondary to a laceration, two with rheumatic joint pain, and one with gout. In each case, the tincture of Indian hemp provided relief, even in cases of morphine withdrawal symptoms. He observed (p. 209):

I have no hesitation in affirming that in my hand its exhibition has usually, and with remarkably few substantial exceptions, been followed by manifest effects as a soporific or hypnotic in conciliating sleep; as an anodyne in lulling irritation: as an antispasmodic in checking cough and cramp; and as a nervine stimulant in removing languor and anxiety, and raising the pulse and spirits; and that these effect have been observed in both acute and chronic affections, in young and old, male and female.

In Ireland in 1845, Donovan extensively described his own extensive trials with small doses of cannabis resin, mainly in patients with various types of neuropathic and musculoskeletal pain. Effects were fairly uniformly impressive, with few side effects. He also described the benefits of local application of hemp leaf oil on hemorrhoids and neuralgic pains.

Christison (1851) endorsed benefits of cannabis in treating tetanus, augmenting labor, and treatment of neuralgic and musculoskeletal pain.

Grigor in 1852 examined the role of cannabis in facilitating childbirth. In nine cases, little was noticeable, but in seven, including five primiparous women (p. 125), “the

contractions acquire great increase of strength ... it is capable of bringing the labour to a happy conclusion considerably within a half of the time that would other have been required." No onward effects were observed on mother or child.

Over the next decades, numerous authorities recognized cannabis as helpful for painful conditions. Sir John Russell Reynolds was eventually to become Queen Victoria's personal physician. Popular legend supports that he successfully treated her dysmenorrhea with a cannabis extract throughout her adult life. Reynolds (1868) reported on various successes with Indian hemp, theorizing (p. 160):

This medicine appears capable of reducing over-activity of the nervous centres without interfering with any one of the functions of organic, or vegetal life. The bane of many opiates and sedatives is this, that the relief of the moment, the hour, or the day, is purchased at the expense of tomorrow's misery. In no one case to which I have administered Indian hemp, have I witnessed any such results.

In 1870, Silver reported five cases in detail of menorrhagia and dysmenorrhea, all relieved nicely with cannabis. He also referred to a colleague, who had never failed in over 100 cases to control pain and discomfort in these disorders within three doses.

In 1874, a popular textbook, *Practical Therapeutics*, stated of cannabis (Waring, 1874, p. 159): "Of a good extract, gr. 1/4 to gr. 1/2, rarely gr. j, in the form of pill, is very effective in some forms of neuralgia."

In the French literature, Michel (1880) extensively reviewed and endorsed the success of cannabis in treating neuralgic afflictions.

In 1883, two letters to the *British Medical Journal* attested to the benefits of extract of *Cannabis indica* in menorrhagia, treating both pain and bleeding successfully with a few doses (Batho, 1883; Brown, 1883).

Rennie reported from India on the therapeutic value of a cannabis tincture in curing acute and chronic dysentery and its attendant pain in some dozen patients (Rennie, 1886).

In 1887, Dr. Hobart Hare published an article that dealt at length with the indications of cannabis (pp. 225–226):

CANNABIS INDICA has been before the profession for many years as a remedy to be used in combating almost all forms of pain, yet, owing to the variations found to exist as to its activity, it has not received the confidence which I think it now deserves.... I have found the efficient dose of a pure extract of hemp to be as powerful in relieving pain as the corresponding dose of the same preparation of opium.... During the time that this remarkable drug is relieving pain a very curious psychical condition sometimes manifests itself; namely, that the diminution of the pain seems to be due to its fading away in the distance, so that the pain becomes

less and less, just as the pain in a delicate ear would grow less and less as a beaten drum was carried farther and farther out of the range of hearing.

Soon after, Farlow penned a treatise on the use of rectal preparations of cannabis (1889, p. 508), "Cannabis has few equals in its power over nervous headaches such as women with pelvic troubles are subject to."

Aulde (1890) lauded the drug as follows (p. 526): "As a remedy for the relief of *supraorbital neuralgia* no article perhaps afford better prospects than cannabis."

In the French literature, Sée submitted a detailed report on use of cannabis in the treatment of various disorders producing gastric and intestinal pain (1890). He found it preferable in efficacy and side effects to other agents of the day, including opiates and bismuth that remain on the modern scene.

In the article "On the Therapeutic Value of Indian Hemp," Suckling (1891) declared (p. 12), "I have met with patients who have been incapacitated for work from the frequency of the attacks [of migraine], and who have been enabled by the use of Indian hemp to resume their employment." This echoes modern claims of clinical cannabis users who partake lightly of the drug and return to work or study.

Mattison was effusive in his praise in 1891 (pp. 270–271):

Indian hemp is not here lauded as a specific. It will, at times, fail. So do other drugs. But the many cases in which it acts well, entitle it to a large and lasting confidence. My experience warrants this statement: cannabis indica is, often, a safe and successful anodyne and hypnotic.

Mackenzie (1894) described the utility of cannabis in treating neuralgias, headache (including chronic daily headache), tabetic (syphilitic) pain, functional gastrointestinal pain (corresponding to modern idiopathic bowel syndrome), and pruritic disorders.

That year in India, among many other indications, the encyclopedic Indian Hemp Drugs Commission (1894) reported that a small piece of *charas* (hashish) placed in a carious tooth would relieve aching pain.

An 1898 American drug handbook stated the following quaint prose under "Actions and uses" for cannabis (Lilly, 1898, p. 32): "Not poisonous according to best authorities, though formerly so regarded. Antispasmodic, analgesic, anesthetic, narcotic, aphrodisiac. Specially recommended in spasmodic and painful affections."

Dixon (1899), a famed British pharmacologist, studied cannabis extensively and recognized its value "as a useful food accessory," supporting its current indications in the cachexia of cancer chemotherapy and HIV-positive patients in 1899. He also reintroduced the concept of smoking the drug to Western medicine (p. 1356):

In cases where an immediate effect is desired the drug should be smoked, the fumes being drawn through water. In fits of depression, mental fatigue, nervous headache, and exhaustion a few inhalations produce an almost immediate effect, the sense of depression, headache, feeling of fatigue disappear and the subject is enabled to continue his work, feeling refreshed and soothed. I am further convinced that its results are marvellous in giving staying power and altering the feelings of muscular fatigue which follow hard physical labour.

The same year, Shoemaker (1899) reported on a large series of patients with pain conditions, including migraine, dental neuralgia, gastralgia, enteralgia, cerebral tumor, and herpes zoster, all successfully treated with *Cannabis indica*.

As late as 1915, Sir William Osler, the acknowledged father of modern medicine stated of migraine treatment (Osler & McCrae, 1915, p. 1089): "*Cannabis indica* is probably the most satisfactory remedy. Seguin recommends a prolonged course of the drug." This statement provided support of its use for both acute and prophylactic treatment of migraine.

In 1918, *The Dispensatory of the United States of America* stated (Remington et al., 1918, p. 280), "Cannabis is used in medicine to relieve pain, to encourage sleep, and to soothe restlessness.... For its analgesic action it is used especially in pains of neuralgic origin, such as *migraine*, but is occasionally of service in other types."

In 1922, Hare still advocated use of cannabis noting (p. 181), "For the relief of *pain*, particularly that depending on nerve disturbance, hemp is very valuable."

As late as 1930, the ability of cannabis to achieve a labor with pain burden substantially reduced or eliminated, followed by a tranquil sleep, was noted (Anonymous, 1930). It was stated (p. 1165), "As far as is known, a baby born of a mother intoxicated with cannabis will not be abnormal in any way."

In 1941, despite its political disenfranchisement, Morris Fishbein, the editor of the *Journal of the American Medical Association* still advocated oral preparations of cannabis in treatment of menstrual (catamenial) migraine (Fishbein, 1942).

Cannabis remained in the British armamentarium until 1961, and was extolled above opiates and barbiturates in the treatment of the pain of hospitalized patients with duodenal ulcers (Douthwaite, 1947).

## MODERN ETHNOBOTANY OF CANNABIS IN ANALGESIA

In Tashkent in the 1930s, cannabis or *nasha* was employed medicinally, despite Soviet prohibition (Benet, 1975; pp. 46–47): "A mixture of lamb's fat with *nasha* is recommended for brides to use on their wedding night to reduce

the pain of defloration. The same mixture works well for headache when rubbed into the skin; it may also be eaten spread on bread."

In Southeast Asia, cannabis remains useful (M. A. Martin, 1975, p. 70):

Everywhere it is considered to be of analgesic value, comparable to the opium derivatives. Moreover, it can be added to any relaxant to reinforce its action. Cooked leaves, which have been dried in the sun, are used in quantities of several grams per bowl of water. This decoction helps especially to combat migraines and stiffness.

A very recent study documents the ethnobotanical uses of cannabis by the Hmong minority in the China–Vietnam border region (Gu & Clarke, 1998, p. 6): "Some older Hmong men may rarely smoke cannabis to 'relieve discomfort,' but they are not daily smokers."

In a book about medicinal plants of India (Dastur, 1962), we see the following (p. 67):

Charas is the resinous exudation that collects on the leaves and flowering tops of plants [equivalent to the Arabic *hashish*]; it is the active principle of hemp; it is a valuable narcotic, especially in cases where opium cannot be administered; it is of great value in malarial and periodical headaches, migraine, acute mania, whooping cough, cough of phthisis, asthma, anaemia of brain, nervous vomiting, tetanus, convulsion, insanity, delirium, dysuria, and nervous exhaustion; it is also used as an anaesthetic in dysmenorrhea, as an appetizer and aphrodisiac, as an anodyne in itching of eczema, neuralgia, severe pains of various kinds of corns, etc.

In Colombia the analgesic effects of a cannabis tincture were lauded (Partridge, 1975, p. 161): "the knowledge that cannabis can be used for treatment of pain is widespread." Rubin documented extensive usage of cannabis in Jamaica for a variety of conditions (V. Rubin, 1976; V. Rubin & Comitas, 1972), including headache. In Brazil, Hutchinson noted (1975, p. 180):

Such an infusion [of marijuana leaves] is taken to relieve rheumatism, "female troubles," colic and other common complaints. For toothache, marijuana is frequently packed into and around the aching tooth and left for a period of time, during which it supposedly performs an analgesic function.

## MODERN DATA ON CANNABIS AND ANALGESIA

### RECENT THEORY AND CLINICAL DATA

A popular treatise on marijuana noted medicinal effects (Margolis & Clorfene, 1969, p. 26):

You'll also discover that grass is an analgesic, and will reduce pain considerably. As a matter of fact, many women use it for dysmenorrhea or menorrhagia when they're out of Pamprin or Midol. So if you have an upset stomach, or suffer from pain of neuritis or neuralgia, smoke grass. If pains persist, smoke more grass.

Solomon Snyder (1971), the discoverer of opiate receptors, examined the pros and cons of cannabis as an analgesic commenting (p. 14):

For there are many conditions, such as migraine headaches or menstrual cramps, where something as mild as aspirin gives insufficient relief and opiates are too powerful, not to mention their potential for addiction. Cannabis might conceivably fulfill a useful role in such conditions.

Subsequent experimental studies by Noyes explored these reported analgesic effects of cannabis. One article examined pain tolerance thresholds (Milstein, MacCannell, Karr, & Clark, 1975). Both naïve (8% increase) and experienced human subjects (16% increase) noted statistically significant increases in pain threshold after smoking cannabis. Noyes (Noyes & Baram, 1974) described case studies of five patients who voluntarily employed it to treat their painful conditions.

Another study pertained to oral THC in patients with cancer (Noyes, Brunk, Baram, & Canter, 1975). Pain relief with escalating doses significant to the  $P < 0.001$  level was observed. Peak effects occurred at 3 hours with doses of 10 and 15 mg, but were delayed until 5 hours after the 20-mg oral dose.

Noyes's research group compared the analgesic effect of THC with codeine (Noyes, Brunk, Avery, & Canter, 1975). In short, 10 mg of oral THC reduced subjective pain burdens by similar decrements to 60 mg of codeine, as did 20 mg of THC versus 120 mg of codeine. The 20-mg dose was sedative and not as well tolerated in some elderly, cannabis-naïve subjects.

Hollister (1986) addressed possible cannabis indications including analgesia. He concluded that it seemed that no THC homologue would be an analgesic of choice, but that "It is too early to be sure, however" (p. 15). These were prophetic words in light of upcoming cannabinoid receptor research.

In 1991, a series of case studies on utility of cannabis in treating chronic pain were published (Randall, 1991). One pertained to Lynn Hastings, an Idaho woman with severe juvenile rheumatoid arthritis, whose symptoms of pain, spasm, and depression were resistant to standard medicine, but were effectively treated with cannabis. A state Supreme Court finding of "medical necessity" followed her initial arrest for cultivation of cannabis. Eventually, charges were dropped.

In 1993, the landmark book, *Marihuana, the Forbidden Medicine*, was first published by Grinspoon and Bakalar, and since revised (Grinspoon & Bakalar, 1997). Although criticized in some quarters as anecdotal, the book contains numerous compelling testimonials from patients and their doctors attesting to the clinical efficacy of cannabis where conventional pharmacotherapy failed. Cases of painful conditions responding to cannabis are legion: osteoarthritis, ankylosing spondylitis, pruritus from allergic dermatitis, premenstrual syndrome (PMS), menstrual cramps, labor pains, gingival pain (with local application of cannabis tincture), migraine, phantom limb pain, Crohn's disease, and "functional" gastrointestinal pain. Often these patients improved with cannabis, worsened without it, and improved once more upon its resumption. These accounts fulfill criteria of "N-of-1 studies" and have been accepted by epidemiologists as proof of efficacy in rare conditions or ones in which blinded, controlled trials are technically difficult (Guyatt et al., 1990; Larson, 1990).

The *American Journal of Public Health* issued a particularly strong plea for liberalization of laws pertaining to medical cannabis (Anonymous, 1996) in 1996, citing its activity in "decreasing the suffering from chronic pain."

Hollister (2000) reviewed indications for cannabis, "for exploratory purposes, any patient with pain unrelieved by conventional analgesics should have access to smoked marijuana if they so desire" (p. 5).

## CANNABINOID AND ENDOCANNABINOID NEUROCHEMISTRY

In recent years, scientists have provided elucidation of the mechanisms of action of cannabis and THC, the primary psychoactive component, with the discovery of an endogenous cannabinoid (endocannabinoid) ligand, arachidonylethanolamide, nicknamed anandamide, from the Sanskrit word *ananda*, or "bliss" (Barinaga, 1992; Devane et al., 1992; Marx, 1990; Matsuda, Lolait, Brownstein, Young, & Bonner, 1990). Anandamide inhibits cyclic AMP mediated through G protein coupling in target cells, which cluster in nociceptive areas of the CNS (Herkenham, 1993). Early testing of its pharmacological action and behavioral activity indicate similarity to THC (Fride & Mechoulam, 1993), although anandamide differs from THC in some respects. Pertwee (1997) has examined the pharmacology of cannabinoid receptors in detail. CB<sub>1</sub> receptors are mainly confined to the CNS, while CB<sub>2</sub> receptors are found in the periphery, often in conjunction with immune mechanisms.

Further research has elucidated analgesic mechanisms of cannabinoids, which will be examined system by system.

## Cannabinoids and Serotonergic Systems

Serotonergic mechanisms are implicated in many pain conditions, especially migraine and cluster headaches. THC reduces serotonin release from the platelets of human migraineurs (Volfe, Dvilansky, & Nathan, 1985). Cannabis has been observed to stimulate 5-HT synthesis, its brain content, decrease its synaptosomal uptake, while stimulating its release (Spadone, 1991). Anandamide and other cannabinoid agonists inhibit rat serotonin type 3 (5-HT<sub>3</sub>) receptors (Fan, 1995) that mediate emetic and pain responses. The recent advent of alosetron, a 5-HT<sub>3</sub> blocker employed in treatment of irritable bowel syndrome (Letter, 2000), would seem to support claims of the efficacy of cannabis in that disorder on the basis of this mechanism.

Recently, Boger and his group have demonstrated an 89% relative potentiation of the 5-HT<sub>1A</sub> receptor response, and a 36% inhibition of the 5-HT<sub>2A</sub> receptor response by anandamide (Boger, Patterson, & Jin, 1998). Similar effects by THC are likely, supporting efficacy for cannabinoids in acute symptomatic migraine treatment due to agonistic activity at 5-HT<sub>1A</sub> or 5-HT<sub>1D</sub>, and in prophylactic treatment of chronic headache due to antagonistic activity at 5-HT<sub>2A</sub> (Peroutka, 1990a, b).

Kimura et al. (Kimura, Ohta, Watanabe, Yoshimura, & Yamamoto, 1998) showed that high concentrations of anandamide decreased serotonin and ketanserin binding (a 5-HT<sub>2A</sub> antagonist). 11-OH-delta 8-THC and 11-oxo-delta 8-THC metabolites of cannabis were also observed to modify serotonin receptor binding.

Ultimately, this author and colleagues have shown that essential oil components of cannabis demonstrate potent serotonin receptor activity (E. B. Russo, Macarah, Todd, Medora, & Parker, 2000) that supports putative synergism with THC in the modulation of analgesia. Similarly, CBD seems to harbor similar activity that would help to explain prophylactic benefits of cannabis in migraine (Hall et al., 2004).

## Dopaminergic Systems

The importance of dopaminergic mechanisms in treatment of migraine and other types of pain has received recent emphasis (Peroutka, 1997). However, existing neuroleptics are significantly sedating. Ferri et al. (Ferri, Cavicchini, Romualdi, Speroni, & Murari, 1986) were able to demonstrate that 6-hydroxydopamine, which causes degeneration of catecholamine terminals, was able to block THC antinociception. In a review article (Mechoulam, Fride, & Di Marzo, 1998, p. 12), a number of studies were reviewed as demonstrating that cannabinomimetic drugs cause "inhibition of the dopaminergic nigrostriatal system."

Müller-Vahl and her colleagues cited Maillieux (Maillieux & Vanderhaeghen, 1992) in their discussion of

cannabinoid interactions with the dopaminergic system (Müller-Vahl, Kolbe, Schneider, & Emrich, 1998) stating, "Cannabinoid receptors were found to be co-localized both with dopamine D<sub>1</sub> receptors on striatonigral dynorphin/substance-P-containing neurones and with dopamine D<sub>2</sub> receptors on striatopallidal enkephalinergic neurones" (p. 504).

Carta et al. demonstrated that antinociceptive effects of THC are mediated by CB<sub>1</sub> and dopamine D<sub>2</sub> receptors, and that combination of the agents improved analgesic effects in rats (Carta, Gessa, & Nava, 1999).

## Inflammatory Mechanisms

Modern authors (S. Burstein, 1992; A. T. Evans, Formukong, & Evans, 1987; Formukong, Evans, & Evans, 1988, 1989) have examined the relationship between cannabinoids and inflammation. McPartland (2001a) provides an excellent summary and analysis of the subject.

Burstein et al. demonstrated that THC and other cannabinoids inhibit prostaglandin E<sub>2</sub> synthesis (S. Burstein, Levin, & Varanelli, 1973). In 1979, experiments showed that smoked cannabis reduced platelet aggregation (Schaefer, Brackett, Gunn, & Dubowski, 1979).

In 1981, cannabichromene was demonstrated to be a more effective anti-inflammatory agent than phenylbutazone in carrageenan-induced rat paw edema and the erythrocyte membrane stabilization method (Turner & ElSohly, 1981). The authors stated, "The activity of cannabichromene through the oral route, its safety and its lack of behavioral-type (psychotomimetic) activity characteristic of THC(I) indicate its therapeutic potential for the treatment of inflammatory diseases" (pp. 288S–289S).

Evans stated (1991, p. S65). "Experiments involving oral administration of THC suggested that THC was 20 times more potent than aspirin and twice as potent as hydrocortisone." Cannabidiol (CBD) functioned as a dual cyclooxygenase and lipoxygenase inhibitor in various assays.

Klein noted that THC had variable effects on tumor necrosis factor (TNF- $\alpha$ ) production depending on the cells and culture system selected (Klein, Friedman, & Specter, 1998).

In 1998, Jaggar et al. issued two reports addressing visceral and inflammatory pain in rats (Jaggar, Hasnie, Sellaturay, & Rice, 1998; Jaggar, Sellaturay, & Rice, 1998). The endocannabinoid anandamide, a CB<sub>1</sub> ligand, prevented and reduced viscerovisceral hyperreflexia (VVH) in the inflamed bladder. In contrast, palmitylethanolamide, a presumptive endogenous CB<sub>2</sub> ligand that accumulates in inflamed tissues and reduces edema by downmodulating mast cells, only reversed VVH once previously established. The authors posited the possibility of development of non-sedating analgesic anti-inflammatory drugs based on CB<sub>2</sub> receptor agonism.

In a 1999 review, Fimiani et al. note, "Delta-9-THC blocks the conversion of arachidonic acid into all metabolites derived by cyclooxygenase activity, whereas it stimulates lipoxygenase, resulting in an increase in lipoxygenase products" (p. 27). Clinically, no increased incidence of gastric ulceration was reported in chronic cannabis users (New York [City] Mayor's Committee on Marijuana, Wallace, & Cunningham, 1973; V. D. Rubin & Comitas, 1975; Stefanis, Dornbush, & Fink, 1977). In 1978, cannabis was felt to reduce gastric acidity in humans (Nalin et al., 1978), while another group demonstrated THC to have antiulcer effects in rats (Sofia, Nalepa, Harkal, & Vassar, 1973). In fact, one essential oil sesquiterpene component of cannabis, caryophyllene, has recently been demonstrated to have a gastric cytoprotective effect (Tambe, Tsujiuchi, Honda, Ikeshiro, & Tanaka, 1996).

The above authors (Fimiani et al., 1999) also observed that the morphine-cannabinoid system modulates the eicosanoid cascade and its proinflammatory cytokine activity through induction of nitric oxide synthesis, averting damaging effects on tissues. They state in summary, "Thus, we can surmise cannabinoid-morphine systems are down-regulators of inflammatory processes in an attempt to restore homeostasis" (p. 30).

A recent report has demonstrated the efficacy of oral cannabidiol (CBD), a minimally psychoactive cannabis component, at a dose of 5 mg/kg/day in treating mice against collagen-induced arthritis, a model for human rheumatoid arthritis (Malfait et al., 2000). Benefits were produced through a combination of immunosuppressive effects (diminished CII-specific proliferation and interferon-gamma production) and anti-inflammatory effects (decreased release of tumor necrosis factor by synovial cells).

Cannabis seed also has dietary benefits as an anti-inflammatory agent. It yields linolenic acid, which promotes formation of anti-inflammatory metabolites, and gamma-linolenic acid, which inhibits the formation of proinflammatory products from arachidonate (Conrad, 1997; Haines et al., 2000; Wirtshafter, 1997).

Flavonoid and terpenoid essential oil components of cannabis demonstrate anti-inflammatory effects at physiologically appropriate levels (McPartland & Russo, 2001). Cannflavin A and B inhibited prostaglandin E<sub>2</sub> production in human rheumatoid synovial cells 30 times more potently than aspirin (Barrett, Scutt, & Evans, 1986).

The cannabis flavonoid apigenin has anti-inflammatory actions on interleukin, TNF- $\alpha$ , and carrageenan-induced edema and by inhibition of upregulation of cytokine-induced genes (Gerritsen et al., 1995). Quercetin, another flavonoid in cannabis, serves as an antioxidant, and inhibits hydrogen peroxide-mediated nuclear factor (NF)-kappa B activity (Musonda & Chipman, 1998). Burstein et al. have demonstrated eugenol to be a potent prostaglandin inhibitor (S. Burstein, Varanelli, & Slade,

1975). Subsequently, both the alpha-pinene and caryophyllene components of cannabis have proved to demonstrate anti-inflammatory activity in the rat hindpaw edema model (S. Martin et al., 1993).

### Cannabinoid Interactions with Opiates and Endogenous Opioids

THC experimentally increases beta-endorphin levels (Wiegant, Sweep, & Nir, 1987). Depletion of endorphins has been measured in the cerebral spinal fluid of migraineurs during attacks (Fettes, Gawel, Kuzniak, & Edmeads, 1985) and theoretically contributes to migraine effects such as hyperalgesia and photophobia. Early exposure to THC in rat pups boosted adult levels of beta-endorphins in specific brain areas (Kumar et al., 1990).

Mailleux and Vanderhaeghen (1994) have also demonstrated that THC regulates substance P and enkephalin mRNA levels in the basal ganglia. Manzanares et al. (1998) have shown THC is able promote increases in beta-endorphin in rats. Meng and his group demonstrated that THC is involved in an analgesic brainstem circuit in the rostral ventromedial medulla that interacts with opiate pathways (Meng, Manning, Martin, & Fields, 1998).

Cichewicz and her group examined the enhancement of opioid antinociception by oral THC in rodents (Cichewicz, Martin, Smith, & Welch, 1999). THC (20 mg/kg) preceding morphine rendered it significantly more analgesic with an ED<sub>50</sub> dropping from 28.8 to 13.1 mg/kg. For codeine, the ED<sub>50</sub> dropped phenomenally from 139.9 to 5.9 mg/kg, with enhancement also noted for oxymorphone, hydromorphone, methadone, diacetylmorphine (heroin), and meperidine. This THC enhancement was decreased by naloxone, but not by other opiate-blockers, suggesting an effect on  $\mu$ -opiate receptors.

In a subsequent study, Cichewicz, Haller, and Welch (2001) demonstrated that continued low doses of THC and morphine in mice produce no behavioral tolerance to the opioid, and that the combination circumvented the expected downregulation of opioid receptor protein in the mouse midbrain observed in tolerant animals. Extension of this work (Cichewicz & McCarthy, 2003) demonstrated that oral doses of THC with either morphine or codeine produced synergistic increases in analgesia.

Perhaps the most exciting development from this group surrounds the suggestion that THC blocks opiate withdrawal effects and prevents the development of opiate tolerance (Cichewicz & Welch, 2003). Such tolerance in chronic opioid-treated mice was circumvented with nonanalgesic doses of oral THC, while THC also significantly reduced naloxone-precipitated withdrawal effects in such mice. Substantiation is thus provided for 19th century claims of utility of cannabis in treatment of opiate addiction, suggesting a new indication for clinical trials.

Finally, Cichewicz presented findings indicating that late administration of THC will restore opioid analgesic effects after low doses or ones that had previously worn off (Cichewicz, Rubo, & Welch, 2003), thus scientifically verifying the anecdotal reports of cannabis-opiate alternation from the 19th century.

Welch and Eads (1999) note cannabinoid-induced analgesia produced antinociception through spinal dynorphin release with synergistic effects with opiates. They state, however, "THC, in comparison to the morphine derivatives, has a greater therapeutic range" (p. 188).

Many analgesic effects of cannabinoids cannot be reproduced by opiates, however, particularly in cases of neuropathic pain (Hamann & di Vadi, 1999). Nicolodi (1998) examined opiate aggravation of migraine. Manzanares (Manzanares et al., 1999) cited that chronic cannabinoid administration could similarly promote hypothalamic production of beta-endorphin.

Strangman and Walker (1999) demonstrated that a cannabinoid antagonist was able to decrease wind-up in spinal nociceptive neurons producing hyperalgesia and allodynia in chronic pain states. A similar group (Walker et al., 1999) showed that cannabinoids selectively affect nociceptive neurons in the spinal cord and ventroposterolateral nucleus of the thalamus in a manner that promotes antinociception without anesthesia. In all, seven sites in the CNS involved in pain processing produced effects after microinjections of cannabinoids, effecting a circuit that mediates the descending pain suppressing effects of opiates.

### Cannabinoids and the Periaqueductal Gray Area

In 1996, researchers demonstrated antinociceptive effects of delta-9-THC and other cannabinoids in the periaqueductal gray (PAG) matter in rats (Lichtman, Cook, & Martin, 1996). The PAG is a putative migraine generator area (Goadsby & Gundlach, 1991; Raskin, 1988) and has received a lengthy analysis (Behbehani, 1995) citing its importance in the processes of ascending and descending pain pathways. A detailed review of effects of the PAG and cannabinoids in migraine is contained in Russo (E. B. Russo, 2001a).

Manzanares (Manzanares et al., 1998) suggested that cannabinoid-mediated antinociception in the PAG is produced by activation of endogenous opioids, supported by the fact that subchronic THC administration elevates proenkephalin gene expression in the area.

Walker, Huang, Strangman, Tsou, and Sanudo-Pena (1999) demonstrated that electrical stimulation of PAG in the rat stimulated anandamide release and CB<sub>1</sub> receptor-mediated analgesia. The system seemed to be tonically active, and cannabinoid antagonists produced hyperalgesia. The authors posited that this cannabinoid-modulated

pain system would support the prospect of approaches with cannabinoids to opiate-resistant syndromes.

### NMDA and Glutamate

A trigeminovascular system, which has long been implicated as subserving pain, inflammatory and vascular effects, has again been reviewed (E. B. Russo, 2001a).

In 1996, Shen et al. elucidated basic mechanism of cannabinoids in glutamatergic systems (Shen, Piser, Seybold, & Thayer, 1996). Through G protein coupling, cannabinoid receptors inhibit voltage-gated calcium channels, and activate potassium channels to produce presynaptic inhibition of glutamate release. Subsequently, it has been shown (Shen & Thayer, 1999) that THC is a partial agonist acting presynaptically via CB<sub>1</sub> to modulate glutamatergic transmission through a reduction without blockade.

Hampson and colleagues demonstrated a 30 to 40% reduction in delta-calcium-NMDA responses by THC (Hampson, Bornheim et al., 1998), which was eliminated by a cannabinoid antagonist. THC and CBD components of cannabis act as neuroprotective antioxidants against glutamate neurotoxicity and cell death mediated via NMDA, AMPA, and kainate receptors (Hampson, Grimaldi, Axelrod, & Wink, 1998). Effects are independent of cannabinoid receptors. The natural cannabinoids were more potent in their antioxidant effects than either alpha-tocopherol or ascorbate.

Italian researchers Nicolodi and Sicuteri have recently elucidated the role of NMDA antagonists in eliminating hyperalgesia in migraine, chronic daily headache, fibromyalgia, and possibly other mechanisms of chronic pain (Nicolodi & Sicuteri, 1995, 1998; Nicolodi, Del Bianco, & Sicuteri, 1997; Nicolodi, Volpe, & Sicuteri, 1998). Gabapentin and ketamine were suggested as tools to block this system and provide amelioration. Given the above observations and relationships, it is logical that prolonged use of THC prophylactically may exert similar benefits, as was espoused in cures of chronic daily headache claimed in the 19th century with regular use of extract of Indian hemp (Mackenzie, 1887).

This concept is bolstered by examination of another series of articles by Richardson and her group. One study examined peripheral mechanisms (Richardson, Kilo, & Hargreaves, 1998), wherein cannabinoids acted on CB<sub>1</sub> to reduce hyperalgesia and inflammation via inhibition of neurosecretion of calcitonin gene-related peptide (CGRP) in capsaicin-activated nerve terminals.

At the spinal level, her group noted an antihyperalgesic effect of cannabinoids (Richardson, Aanonsen, & Hargreaves, 1998a), mediated by the CB<sub>1</sub> receptor. Additionally, experimental cannabinoid receptor blockade induced a glutamate-dependent hyperalgesia, suggesting a tonic activity of cannabinoids in averting such a development. The authors suggested the clinical use of cannabinoids in

disorders, "characterized by primary afferent barrage" (p. 152). An increased potency of cannabinoids observed in hyperalgesia "may mean that there are dosages of cannabinoids that would be effective as antihyperalgesic agents but sub-threshold for the untoward psychomimetic effects" (p. 152). This is akin to Dixon's observations of patients able to return to work after having treated their headaches with a few inhalations of cannabis (Dixon, 1899).

Elaborating on these themes, Richardson noted that a decrease in lumbar cannabinoid receptor numbers correlated with hyperalgesia (Richardson, Aanonsen, & Hargreaves, 1998b) and could provide an etiology for certain chronic pain states, especially those unresponsive to opiates.

In another study (Li et al., 1999), the synthetic cannabinoid agonist WIN 55,212-2 was employed to block capsaicin-induced hyperalgesia in rat paws much as has been observed for THC in formalin treatment. Ko and Woods (1999) examined local THC administration and its activity on capsaicin-induced pain in rhesus monkeys. THC effectively reduced pain, which was blocked by a CB<sub>1</sub> antagonist and was effective at a parenteral dose that produced no behavioral change or sedation.

Maneuf, Nash, Crossman, and Brotchie (1996) examined similar issues at higher CNS levels and were able to show a tonic activation of the cannabinoid system serving to reduce GABA uptake in the globus pallidus.

These tonic endocannabinoid systems subserving analgesic pathways are strongly suggestive that certain pain disorders long conceived as at least partially "psychogenic," including migraine, fibromyalgia, idiopathic bowel syndrome, complex regional pain syndromes, and others may be attributable to a "clinical endocannabinoid deficiency" (CECD). This concept is explored elsewhere in depth (E. B. Russo, 2004a).

### Synergism and the Entourage Effect

Palmitylethanolamide (PEA) is another endogenous cannabinoid with analgesic effects, released from a phospholipid in conjunction with anandamide (Calignano, La Rana, Giuffrida, & Piomelli, 1998). In ensemble, the two substances effect a 100-fold synergism on CB<sub>1</sub> type peripheral receptors in cutaneous tissues.

Endocannabinoids and their inactive metabolites combine to boost physiological responses (the "entourage effect"; Mechoulam & Ben-Shabat, 1999). Given the likely contributions of cannabis flavonoids and essential oils to therapeutic effects on mood, inflammation, and pain reviewed in McPartland and Russo (2001), one may readily accept Mechoulam's quotation (Mechoulam & Ben-Shabat, 1999, p. 136): "This type of synergism may play a role in the widely held (but not experimentally based) view that in some cases plants are better drugs than the natural products isolated from them."

## PRACTICAL APPLICATION OF CANNABINOIDS TO ANALGESIA

### MARINOL (DRONABINOL): PROS AND CONS

Marinol,<sup>®</sup> developed by Unimed Pharmaceuticals, is a synthetically derived THC dissolved in sesame oil. It is available in capsules of 2.5, 5, and 10 mg and is marketed in the United States, Canada, Australia, and some areas in Europe (Grotenhermen, 2001a). Until 1999, Marinol was a Schedule II drug in the United States with close scrutiny to its usage, which was restricted to indications of AIDS-associated anorexia and cancer chemotherapy. After safety studies revealed a low potential for abuse or diversion (Calhoun, Galloway, & Smith, 1998), dronabinol was "down-scheduled" to Schedule III in 1999, allowing refill prescriptions for up to 6 months, and its "off-label" administration for any indication.

Clinicians have used Marinol only to a limited degree. Its bioavailability is only 25 to 30% of an equivalent smoked dose of THC (Association, 1997). Additional problems include the first pass effect of hepatic metabolism, which results in the production of a possibly more psychoactive metabolite 11-hydroxy-THC, and its considerable cost, which may exceed U.S. \$600 per month for the lowest dosage of 2.5 mg TID. Considerable anecdotal data supports preference by patients of herbal cannabis over dronabinol (Grinspoon & Bakalar, 1997; E. B. Russo et al., 2002).

Reports of dronabinol use in painful clinical conditions are few, but it has had some variable success in migraine prophylaxis (Mikuriya, 1997; E. Russo, 1998; E. B. Russo, 2001a).

Maurer et al. demonstrated efficacy of analgesia of 5 mg per oris THC to 50 mg codeine in treatment of pain in a young paraplegic patient after removal of a spinal tumor (Maurer, Henn, Dittrich, & Hofmann, 1990). However, THC also limited spasticity whereas codeine and placebo did not.

Holdcroft et al. (1997) were able to demonstrate an analgesic benefit ( $p < 0.001$ ) of THC 50 mg per day in five split doses in a patient with relapsing familial Mediterranean fever in a double-blind, placebo-controlled trial.

### NABILONE

Nabilone is a synthetic cannabinoid said to be pharmacologically similar to THC, but more potent, less apt to produce euphoria, and possessing lower "abuse potential" (Association, 1997). It is produced by Eli Lilly Company as Cesamet<sup>®</sup> and is available in the United Kingdom, Canada, Australia, and certain countries in Europe (Grotenhermen, 2001a) as an agent for nausea in chemotherapy. Some scattered reports have noted benefit on spasticity in multiple sclerosis (MS) and effects on dyskinesias.

Lethal toxicity in dogs has been noted with chronic use (Mechoulam & Feigenbaum, 1987).

A group in the United Kingdom recently assessed analgesic effects of nabilone in patients including some with neuropathic pain (Notcutt, Price, & Chapman, 1997). Side effects of drowsiness and dysphoria were troubling. Several patients claimed improved pain relief and fewer side effects with smoked cannabis and preferred it to this legal alternative. Nabilone's cost was also estimated to be 10 times higher than cannabis even at black market rates.

#### LEVONANTRADOL

Levonantradol is a synthetic cannabinoid developed by Pfizer. In 1981, levonantradol was studied in double-blind fashion versus placebo with single intramuscular exposures in acute postoperative or trauma pain (Jain, Ryan, McMahon, & Smith, 1981). Various doses were analgesic for up to 6 hours compared with placebo ( $P < 0.05$ ), but no dose-response effect was evident, and side effects were prominent with levonantradol (57 vs. 12.5%), including prominent drowsiness with less degrees of dry mouth, dizziness, "weird dreams," mild hallucinations, and anxiety. These adverse events were labeled "unacceptable" according to the British Medical Association (Association, 1997).

#### AJULEMIC ACID (CT3)

Ajulemic acid is a synthetic derived from delta-8-THC that does not bind to cannabinoid receptors. CT3 was developed by Atlantic Pharmaceuticals. It has shown analgesic and anti-inflammatory properties in animal models without COX-1 inhibition side effects (S. H. Burstein, 2000, 2001). It has shown strong analgesic and anti-inflammatory properties in animal models of arthritis without COX-1 inhibition side effects such as ulcer production, and is in advanced clinical trials (S. H. Burstein 2000, 2001). Ajulemic acid binds to the peroxisome proliferator-activated receptor gamma, part of the nuclear receptor superfamily involved in inflammatory processes (Liu, Li, Burstein, Zurier, & Chen, 2003), and also suppresses human monocyte interleukin-1beta production *in vitro* (Zurier, Rossetti, Burstein, & Bidinger, 2003). Ajulemic acid may represent a valuable addition to cannabinoid pharmaceuticals used for anti-inflammatory and analgesic effects.

#### DEXANABINOL (HU-211)

Dexanabinol is a synthetic cannabinoid agent developed at Hebrew University from  $\Delta^8$ -THC. It is a nonpsychoactive enantiomer of the extremely potent cannabis agonist, HU-210 (Pop, 2000). It has several interesting properties including antioxidant and anti-inflammatory effects, as well as suppression of TNF- $\alpha$  production. Additionally,

it reduced damage in experimental focal ischemia, as may be associated with closed head injury (Lavie, Teichner, Shohami, Ovadia, & Leker, 2001). In one human Phase II clinical trial of 67 patients with closed-head injury, dexanabinol reduced intracranial pressure and perfusion significantly with few adverse events (Knoller et al., 2002). Improvements in clinical outcome scales were seen after 3 and 6 months, but were relatively subtle.

Dexanabinol is currently in Phase III clinical trials. Parenteral injection of dexanabinol is required.

#### HU-308

HU-308 is another agent emerging from the research of Raphael Mechoulam's laboratories in Israel. It is a synthetic and specific CB<sub>2</sub> agonist demonstrating no cannabinoid behavioral effects in laboratory animals (Hanus et al., 1999). Its pharmacological properties include inhibition of forskolin-stimulated cyclic AMP production, blood pressure reduction, inhibition of defecation, and production of peripheral analgesia with anti-inflammatory effects. An important therapeutic role for HU-308 as a peripherally acting agent may eventuate on further testing.

#### CANNABIS PROPER

Use of cannabis for pain conditions is extensive in the United States and some European nations. A survey of patients attending the Oakland Cannabis Buyers' Club revealed (Gieringer, 2001):

By far the largest category of patients interviewed by Mikuriya use cannabis for analgesia to treat conditions including: migraines and neuralgias; arthritis and rheumatism; spinal, skeletal and back disorders due to injury, deformity, or degenerative disease; inflammatory gastrointestinal disorders, and a host of miscellaneous diseases.

Analysis of the totals revealed that at least 1,133 of 2,480 patients or 46% sought cannabis for analgesia in treatment of chronic pain conditions.

Cannabis is traditionally employed therapeutically by smoking, ingestion, or vaporization. Each has advantages and disadvantages. Grotenhermen has produced an excellent summary of "Practical Hints" (Grotenhermen, 2001b), as have Brazis and Mathre (1997). Dosing of therapeutic cannabis must be titrated to the patient's need. In general, 5 mg of THC represents a threshold dose for noticeable effects in the average adult. While tolerance to cardiovascular effects (tachycardia) and psychoactive effects ("high") are achieved after some days to weeks of chronic usage, observed clinical and "anecdotal" reports support retention of analgesic efficacy over the long term. Occasionally, upward dose titration is necessary, as is true for any agent.

Allergies to cannabis are rare, although some may experience rhinitis symptoms, particularly when exposed to the smoke of the unrefined product.

More severe psychiatric conditions present a relative contraindication to use of cannabis, while many milder emotional afflictions may benefit from the drug (Grinspoon & Bakalar, 1997; Grinspoon, Bakalar, & Russo, 2005; E. B. Russo, 2001c). Although concerns have been raised about subtle neuropsychological sequelae in children born to mothers employing cannabis in pregnancy, other studies have shown no significant abnormalities (Dreher, 1997). Certainly, no mutagenic or teratogenic potential has been demonstrated in humans (E. Russo, 2002b).

Concerns about our youth employing cannabis are often well intentioned. However, there is some evidence that very young children may be relatively resistant to its psychoactive properties. A research group in Israel examined the antiemetic effects of delta-8-tetrahydrocannabinol (a natural isomer) in a series of children undergoing chemotherapy (Abrahamov & Mechoulam, 1995). Excellent efficacy and tolerance was observed at doses that would be expected to produce significant psychoactivity in adults. People employing cannabis therapeutically must be warned of the usual caveats assigned to any potentially sedative drug: due care with operation of machinery, motor vehicles, etc.

Acute overdoses of cannabis are self-limited, and most frequently consist of panic reactions. These are uniquely sensitive to reassurance (“talking down”) and are quite unusual once a patient becomes familiar with the drug. Cannabis has a unique distinction of safety over four millennia of analgesic usage: No credible deaths due to direct toxicity of cannabis have ever been documented in the medical literature. An extremely detailed review of chronic cannabis effects in a medical context is available (E. B. Russo et al., 2002).

Some cannabis–drug interactions are apparent, but are few in number or consequence. Additive sedative effects with other agents, including alcohol, may be observed. Similarly, however, additive or synergistic antiemetic and analgesic benefits may accrue when combining dopamine agonist neuroleptics and cannabis (Carta et al., 1999). Cannabis may accelerate metabolism of theophylline, while slowing that of barbiturates. Anticholinergic-induced tachycardia may be accentuated by cannabis, while this effect is countered by beta-blockers (Grotenhermen, 2001b). Indomethacin seems to reduce slightly the psychoactive and tachycardic effects of cannabis (Perez-Reyes, Burstein, White, McDonald, & Hicks, 1991). As discussed above, synergistic analgesic benefits may accrue with concomitant usage of cannabis and opioids (Cichewicz et al., 1999; Hare, 1887).

Crude cannabis contains most of its THC in the form of delta-9-THC acids that must be decarboxylated by heating to be activated. This occurs automatically when can-

nabis is smoked, whereas herbal cannabis that is employed orally should be heated to 200 to 210°C for 5 minutes prior to ingestion (Brenneisen, 1984).

Contrary to political opinion in the United States, average cannabis potency has varied little over the last three decades (ElSohly et al., 2000; Mikuriya & Aldrich, 1988). It is true that the *maximum* potency has increased through applied genetics, cultivation, and harvesting techniques. This goal is achieved through production of clonal cultivation of the preferred female plants and maximization of the yield of unsterilized flowering tops known as *sinsemilla* (Spanish for “without seed”). In this manner a concentration of stalked trichomes where THC and therapeutic terpenoids are produced is effected. Resultant yields of THC may exceed 20% by weight. This is potentially advantageous, particularly if smoked, because a therapeutic dosage of THC is obtained with fewer inhalations, thereby decreasing lung exposure to tars and potential carcinogens.

A considerable concentration of THC, other cannabinoids, and terpenoids may also be achieved through some simple processing of crude dried cannabis. Techniques for sieving or washing of cannabis to isolate the trichomes to produce hashish are well described (Clarke, 1998; Rosenthal, Gieringer, & Mikuriya, 1997), and may produce potential yields of 40 to 60% THC. Clarke demonstrates a simple method of rolling the resultant powdery material into a joint of pure hashish, termed “smoking the snake” (Clarke, 1998), providing a relatively very pure product for inhalation.

Cultivation techniques are beyond the scope of this review, but are freely available through a variety of guidebooks (Clarke, 1981; Rosenthal et al., 1997), magazines such as *Cannabis Culture* or *High Times*, or via the Internet to those who live in jurisdictions where this endeavor is legal. Outdoor, indoor, or hydroponic techniques are possible. Recent reviews outline good agricultural practice in cultivation of cannabis (Anonymous, 2003), its husbandry for medical usage in an industrial setting (Potter, 2004; E. B. Russo, 2003), and a primer on cannabis genetics (E. P. de Meijer et al., 2003). Emphasis should focus on potent medicinal strains, scrupulous organic cultivation of female plants, clonal selection and augmentation, and appropriate processing, all combined with best available techniques of harm reduction.

### Oral Use of Cannabis

A variety of issues attend this mode of cannabis administration. The most important one concerns bioavailability. Oral absorption of cannabinoids is slow and erratic at best, often requiring 30 to 120 minutes. In HIV-positive or chemotherapy patients and in acute migraine, nausea and emesis may preclude oral usage altogether. Additionally, oral THC is subject to the “first pass effect” of hepatic

metabolism yielding 11-hydroxy-THC, which may be more psychoactive than THC itself. Thus, some patients clearly become “too high” even on low doses of medicine, such as 2.5 mg of THC as dronabinol.

Advantages of oral usage are its avoidance of lung exposure in those who are immunosuppressed or have impaired pulmonary function, and its prolonged half-life. This may be of advantage for nocturnal complaints where sedation is less of an issue.

Grotenhermen suggests dose titration beginning with 2.5 mg of oral THC bid with increases as needed and tolerated (Grotenhermen, 2001b). For cannabis of 5% THC content, this would represent 50 mg of herb per dose. For 10% THC cannabis, only 25 mg of plant material would be required. Most painful clinical conditions require tid dosing of cannabis.

THC, CBD, and terpenoids are all highly lipophilic. Gastrointestinal absorption is markedly enhanced by inclusion of lipids in the cooked preparations. Traditional Indian cannabis cookery makes good use of *ghee*, or clarified butter. When cannabis tea is employed, added cream will enhance clinical benefits. Therapeutic tincture extraction in alcohol is also possible.

### Smoked Cannabis

Techniques of smoking cannabis are legion, and include marijuana cigarettes (“joint,” “reefer,” etc.), pipes, waterpipes (“hookahs”), bongs etc. Pharmacodynamically, smoking might seem a reasonable administration of clinical cannabis, but for its attendant pulmonary sequelae, lack of standardization, risks of intoxication, and illegality in most jurisdictions (E. B. Russo et al., 2002). Clinical effects are noted within seconds to minutes after smoking. Inhalation avoids the first pass effect that hampers oral use and allows effective dosage titration. Doses as low as 5 mg of THC equivalent may provide relief of clinical symptoms, while anecdotal evidence claims the ability to continue work or study with unimpaired effectiveness. When symptoms return, repeat dosage may be achieved quickly and easily. Overdosage is possibly avoidable.

In chronic usage of smoked cannabis, isolated cases of upper airway carcinogenesis have been noted (Tashkin, 2001). Precancerous cytological changes in the airways of heavy cannabis smokers have been observed via bronchoscopy but do not seem to lead to emphysematous deterioration (Tashkin, Simmons, Sherrill, & Coulson, 1997). There still has never been a documented case of a pulmonary malignancy in a cannabis-only smoker. That notwithstanding, smoked cannabis is unlikely to be a vehicle that can achieve FDA approval as a prescription medicine, due to the irritant effects, lack of standardization, quality control, and similar issues herein discussed.

The “amotivational syndrome” has been largely relegated to the dustbin of drug war propaganda (Zimmer & Morgan, 1997). In fact, the interested reader may wish to seek out three rare books of the past generation on chronic usage that are remarkable for their careful documentation of the few distinguishing features between chronic cannabis smokers and age-matched controls (Carter, Coggins, Doughty, University of Florida Center for Latin American Studies, & National Institute on Drug Abuse, 1976; V. D. Rubin & Comitas, 1975; Stefanis et al., 1977). These are hardly ever mentioned in alarmist reviews of the dangers of cannabis.

Some old myths die hard. Traditional smoking techniques in the United States make prolonged holding of a marijuana “toke” *de rigueur*. From a dose–response standpoint, this is unnecessary. Inhaled THC is well absorbed after a very brief interval, and subjective high and serum THC levels do not increase beyond a maximum 10-second inhalation (Azorlosa, Greenwald, & Stitzer, 1995). Furthermore, prolonged breath holding under pressure increases the potential for hypoxia or pneumothorax (Tashkin, 2001).

Contamination of herbal cannabis by pesticides, herbicides, and bacterial or fungal agents is possible and may represent a threat to the smoker, especially immunosuppressed patients (McPartland, 2001b; McPartland & Pruitt, 1997; Tashkin, 2001). Scrupulous cultivation techniques avoid some of these issues. McPartland recommends pasteurization of herbal cannabis by heating in an oven of 150°C for 5 minutes (McPartland, 2001b).

Waterpipes and bongs are popular techniques for cooling smoke. While they may reduce particulate matter as well, THC content and pharmaceutical efficiency also seem to be compromised (Gieringer, 1996a, b). Surprisingly, the unfiltered “joint” seems to represent a relatively efficient means for conventional smoking, although use of hashish in a pipe (without tobacco) was not examined.

### Vaporizers for Cannabis Administration

Vaporization of herbal cannabis may allow THC and terpenoid components below the flash point of the leaf, thereby reducing exposure to smoke, tar, and carcinogens. The technology has been hampered in its development by paraphernalia laws. Initial investigations of available second-generation devices were quite disappointing in their results (Gieringer, 1996a, b), but additional studies with the Volcano® vaporizer are more promising (E. B. Russo & Stortz, 2003). In a recent assay of the device, there was reasonable preservation of available THC, and a reduction, *but not elimination*, of potential carcinogens down to 5% of yield (Gieringer, St. Laurent, & Goodrich, 2004). A clinical trial of the Volcano vs. smoked cannabis was approved by the FDA in late 2003.

## Rectal Administration

Suppository preparations of cannabis were employed in the 19th century and may be an acceptable alternative route of administration for some conditions. The first pass effect is largely avoided, although the ability for close dose titration is lost. THC suppositories as a hemisuccinate have proved to be twice as bioavailable as oral THC (Brenneisen, Egli, ElSohly, Henn, & Spiess, 1996; Broom, Sufka, ElSohly, & Ross, 2001; ElSohly et al., 1991; Mattes, Engelman, Shaw, & ElSohly, 1994). No studies have examined use of this preparation with respect to analgesia, but one might expect comparison with dronabinol at least with regard to the spectrum of activity. Synergistic combinations of cannabis components may be more valuable. Additionally, suppositories are not a popular method of drug delivery in the United States.

## Transdermal Administration

The American Cancer Society has received a large grant to examine the use of a THC skin patch. Limited pharmacokinetic data are currently available to ascertain whether transdermal THC administration is a viable option (Brenneisen, 2001; Challapalli & Stinchcomb, 2002), but results to date have fallen far short of goals. Additionally, the gradient required to drive THC through the skin necessitates a large residual would remain in the patch that could represent a danger of diversion.

## Sublingual/Oro-Mucosal Tincture of Cannabis

The oro-mucosal method of administration was first used in the 19th century, wherein Marshall described symptoms of cannabis intoxication after 45 minutes, as opposed to 4 hours after oral ingestion of a cannabis extract (Marshall, 1897). It has been under investigation by GW Pharmaceuticals in the United Kingdom employing combinations of specific strains of cannabis that are rich in THC or CBD. Terpenoids and other minor components that may be important to therapeutic effects of cannabis are retained in this fashion (Whittle & Guy, 2001; Whittle, Guy, & Robson, 2001). Dose-metered sublingual/oromucosal sprays are currently in Phase I to III clinical trials for a variety of indications, and approval as a prescription medicine for Sativex®, a whole cannabis extract with equal proportions of THC and CBD, was confirmed for central neuropathic pain in multiple sclerosis in Canada in 2005, and is expected for other indications in the United Kingdom, European Union, and British Commonwealth nations subsequently.

Further data on the raising of the plant material through application of Mendelian genetics are available (E. de Meijer, 2004; E. P. de Meijer et al., 2003), as is further information on its organic husbandry (Potter, 2003; E. B. Russo, 2003), processing with supercritical carbon dioxide extraction and production of cannabis-based med-

icine extracts (CBME; E. B. Russo, 2003; Whittle & Guy, 2003; Whittle, Guy, & Robson, 2003).

Phase I pharmacokinetic data on the material are available (Guy & Flint, 2003; Guy & Robson, 2003a, b). Clinical studies support good bioavailability, patient tolerance, and clinical effects. A Phase II clinical study in England with 24 patients with MS and intractable pain was performed as a consecutive series of double-blind, randomized, placebo-controlled single-patient cross-over trials with oro-mucosal CBME (Wade, Robson, House, Makela, & Aram, 2003). Pain scores on visual analogue scales were significantly improved over placebo with both high THC and high CBD CBME. Subjectively, spasm was significantly improved with high THC and THC:CBD fixed ratio extracts. Spasticity was also subjectively improved with the high THC CBME. All three extracts significantly improved objective measures of spasticity, while the high THC and THC:CBD fixed ratio CBME significantly improved objective measures of spasm (all improvements were  $P < 0.05$ ).

In 34 patients with intractable pain in England (Notcutt et al., 2004), 7 experienced substantial improvement over best available conventional treatment with CBME, 13 moderate, and 8 some benefit. Many extended the range of their activities of daily living with acceptable levels of adverse effects.

Preliminary results of four Phase III clinical trials of CBME by GW Pharmaceuticals have revealed highly significant benefits ( $P < 0.01$ ) in neuropathic pain in MS, pain and sleep disturbance in MS and other neurological diseases, multiple symptoms in MS, and neuropathic pain in brachial plexus injury. Most patients attained good symptomatic control with minimal side effects. Results are available online at [http://www.gwpharm.com/news\\_pres\\_05\\_nov\\_02.html](http://www.gwpharm.com/news_pres_05_nov_02.html).

## Aerosol THC Preparations

Cannabis has a long history of use in asthma, even as a smoked preparation. A pure THC aerosol has been attempted numerous times in the past. Physical and delivery issues have been challenging, but more interestingly, pure THC seems to have an irritating and even bronchoconstrictive effect when employed in isolation (Tashkin et al., 1977). This author believes that anti-inflammatory effects of concomitant terpenoid and flavonoid administration are necessary for full effects and tolerance in pursuit of the pulmonary route. Further research is under way by GW Pharmaceuticals, Inhale Therapeutic Systems, and possibly others. Preliminary Phase I data from GW Pharmaceuticals indicate that very rapid effects within seconds to minutes are produced, comparable with those from smoking cannabis (Guy & Flint, 2003). Although this rapid onset is not necessary for most chronic pain condition treatments, it may be of value in paroxysmal disorders

such as treatment of trigeminal neuralgia, or for breakthrough pain or spasm.

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