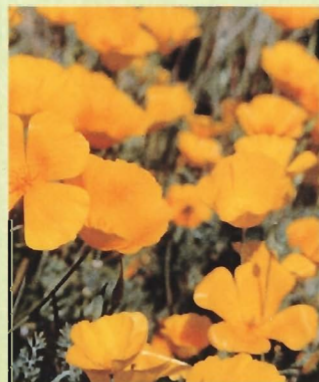




Handbook of  
**Psychotropic Herbs**

A Scientific Analysis of Herbal Remedies  
for Psychiatric Conditions



Ethan Russo, MD

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**of Psychotropic Herbs**  
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### CANNABIS: A BREED APART

*Cannabis sativa* L. and *Cannabis indica* Lam. are most recognized in our society as the recreational drug called marijuana. This agent has been employed medicinally throughout much of the world for a large variety of maladies. Although the herb remains a political pariah, the trend toward “medical marijuana” has recently revealed some important secrets about our internal chemistry. One key active component of cannabis is THC, tetrahydrocannabinol, which was synthesized in the laboratory by Raphael Mechoulam in the 1960s (Mechoulam and Burstein, 1973). The question remained regarding how this unusual chemical affected the mind of man. It was not until 1993 that Devane and colleagues (1992) discovered anandamide, an endogenous cannabinoid, which revealed that marijuana works by mimicry of our own natural chemical machinery. Though the herb has been demonized, the investigation of the cannabinoid neuromodulatory system has resulted in monthly revelations about normal neurochemistry and its perturbations. Therapeutic breakthroughs in the treatment of nausea and weight loss in AIDS and chemotherapy patients, new knowledge about the immune system, control of pain, prevention of brain damage from stroke and trauma, and many other benefits are imminent as a result of these discoveries.

Anandamide activity is highest in the hippocampus, parahippocampal cortex, thalamus, striatum, and cerebellum, suggesting, among other activities, that cannabis may modulate motor, memory, and cognitive functions (Consroe, 1998).

It has also been shown that endogenous cannabinoids and their inactive metabolites combine to enhance biochemical activities' responses (the “entourage effect”) (Mechoulam and Ben-Shabat, 1999). Considering the possible contributions of other cannabis components, such as flavonoids and essential oils, to therapeutic effects on mood (reviewed in McPartland and Pruitt, 1999), one

must readily assent to the following observation (Mechoulam and 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.

The fact is that we owe these advances in basic psychopharmacology to a plant, without which the understanding of a major biochemical system that is crucial to our well-being would have eluded our grasp for a much longer period of time.

Although cannabis represents a departure from the format of examination of commercially available therapeutic psychotropic herbs, the author feels that a reexamination of its potential benefits is warranted. Furthermore, a liberalization of legislation on medical cannabis use is occurring in many countries, if most slowly in the United States. Although this discussion will necessarily be truncated, the interested reader is referred to upcoming analyses in the *Journal of Cannabis Therapeutics* (Russo, 2000). Those concerned with the dangers of cannabis usage may be reassured by the book *Marijuana Myths, Marijuana Facts* (Zimmer and Morgan, 1997) and the Institute of Medicine Report (Joy, Watson, and Benson, 1999), as well as a recent article examining cognitive function in long-term cannabis smokers (Lyketsos et al., 1999).

Let us examine the history of this most controversial agent. The first records of medicinal use of cannabis may occur in the *Pên-tSao Ching*, the Chinese herbal based on the oral traditions passed down from Emperor Shên-nung in the third millennium B.C.E., written down in the first or second centuries. It was noted that the plant fruits “if taken in excess will produce hallucinations (literally ‘seeing devils’)” (Li, 1974, p. 446).

The *Atharva Veda* (passage 11, 6, 15), dated to between 2000 to 1400 B.C.E., provides the first mention of cannabis as a psychotropic herb under the name *bhanga*, according to G. A. Grierson (Indian Hemp Drugs Commission, 1893-1894, Appendix 3, p. 246):

We tell of the five kingdoms of herbs headed by Soma; may it and *kuca* grass, and *bhanga* and barley, and the herb *saha* release us from anxiety.

Use of cannabis in ancient Assyria has been claimed in numerous sources. Most notably, Campbell Thompson (Thompson, 1924, 1949) documented twenty-nine citations of cannabis in ancient Assyrian medical texts of Sumerian and Akkadian vintage (early second millennium B.C.E.), as well as psychogenic effects by various methods, including fumigation. Thompson stated (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.

Campbell asserted cannabis to be “an intoxicant and drug for mental exhilaration.”

Herodotus, the Greek historian (circa 450 B.C.E.), documented a funeral rite of the Scythian people. They erected tents, heated stones, and placed cannabis seeds or the flowering tops upon them to produce smoke (Herodotus, 1954, p. 95):

for when they have parties and sit round a fire, they throw some of it into the flames, and as it burns it smokes like incense, and the smell of it makes them drunk just as wine does us; and they get more and more intoxicated as more fruit is thrown on, until they jump up and start dancing and singing.

This passage lends credence to cannabis’s reputation as an “assuager of grief.”

Jābir ibn Hayyān in the *Kitab al-Sumum* in the eighth century also cited the psychoactive effects of cannabis (Lewis et al., 1971).

Cannabis also figured in the medical writings of Avicenna (ibn Sīnā) in the tenth century, wherein the inebriating effects of the plant leaves were noted (Ainslie, 1826), as they were, too, in the works of Maimonides (Moses ben Maimon) in the twelfth century (Meyerhof, 1940).

Leclerc documented various Arab authors’ experiences with cannabis, for example, he quoted Ed-Dimachky (Leclerc, 1881, p. 118), who stated that cannabis “purifies the brain if one injects its decoction in the nose” (translation E. B. R.).

Cannabis was not without controversy in the early Islamic world and has been vilified by many contemporary authors, some even claiming that it actually provoked melancholy (Lozano Camara and Instituto de Cooperación con el Mundo Árabe, 1990).

Europeans were reminded of the psychoactivity of cannabis by Garcia da Orta (1913), a Spanish Jew who explored India in the sixteenth century. The author documented sedative and appetite-stimulating properties in his 1563 book.

In Indonesia, then known as the Dutch East Indies, Georg Everard Rumpf studied the flora, writing (Rumpf and Beekman, 1981, p. 194):

The Indians [loose term for peoples of the East] deem this Fool’s-Herb to be their *Nepenthes* which serves to drive away sorrow and bring them jollity.

Robert Burton (1907) did not neglect the therapeutic benefits of cannabis (“bange”) in his encyclopedic *Anatomy of Melancholy* of 1621: “Bange is like in its effects to opium, causing a kind of ecstasy, an inclination gently to laugh” (p. 593).

In 1712, Engelbert Kaempfer published his *Amoenitatum Exoticarum Politico-Physico-Medicarum*, in which he described the psychotropic nature of cannabis as utilized in Persia and India (Dolan, 1971; Kaempfer, 1996).

In 1839, the medical use of cannabis, or Indian hemp, was re-introduced to the West from India (O’Shaughnessy, 1838-1840). He examined the effects of cannabis extract in treatment of a variety of desperate medical cases. Recoveries were documented in cases of delirium tremens (alcohol withdrawal) and tetanus. Even in rabies, which remains virtually universally fatal to this day, patients were able to attain rest, comfort, and, in terminal events, an easier passage.

In England, Clendinning (1843) used a tincture of Indian hemp to advantage in a variety of illnesses, even in cases of morphine withdrawal symptoms:

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 effects have been observed in both acute and chronic affections, in young and old, male and female. (p. 209)

The French physician Jacques-Joseph Moreau de Tours was the first to systematically examine the role of cannabis in psychiatric practice in his 1845 book *Du Hachisch et de l'Alienation Mentale: Études Psychologiques*. Moreau (1973) mused about its applications:

One of the effects of hashish that struck me most forcefully and which generally gets the most attention is that manic excitement always accompanied by a feeling of gaiety and joy inconceivable to those who have never experienced it. I saw in it a mean of effectively combatting the fixed ideas of depressives, disrupting the chain of their ideas, of unfocusing their attention on such and such a subject. (p. 211)

He went on to report that initial trials had mixed results.

Subsequently, some years later, Moreau (1857) reported in detail the case study of a young man with intractable lypemania, a sort of obsessive melancholia, and its remarkable cure with cannabis. Could the same result have occurred spontaneously? Perhaps, but subsequent evidence supports a rational basis for its efficacy.

Many judged Moreau's efforts to be an ultimate failure, but not all. In 1926, Professor E. Perrot of the *Faculté de Pharmacie de Paris* stated:

The Indian hemp, to take but one example, quite cheated the hopes of Moreau de Tours, but it would be imprudent to affirm that it will not be better utilized by the psychiatry of tomorrow! (Rouhier, 1975, p. IX) (translation E. B. R.)

In 1853, François Allemand, a French physician, wrote a utopian treatise, *Le hachych*, which was published in Paris. In it, a fictional Dr. Lebon speaks of hashish's psychotropic effects, when asked about its benefits:

What pleasure? Without hashish, I should have died of melancholy a hundred times. . . .

The most constant and remarkable property of hashish is to exalt the dominant ideas of the person who has taken it, to make him see in the clearest way his most complicated plan come to fruition without difficulty, his dearest project realized without obstacle, to furnish him with the precise intuition he seeks. Finally, it lets him taste in thought the absolute possession of everything according to his wishes, and habitual passions, and according to the direction of his thoughts at the moment the hashish acts on him. (Kimmens, 1977, pp. 117-118)

A physician in Ohio reported a notable therapeutic success with cannabis in the treatment of "hysterical insanity," a case that we would currently recognize as bipolar disease (manic depression) (McMeens, 1860). Concluding an extensive review of cannabis therapeutics, the author stated:

In those mixed and indefinable paroxysms of an hysterical nature, I have found no remedy to control or curtail them with equal promptness and permanency. . . . In sleeplessness, where opium is contraindicated, it is an excellent substitute. . . . As a calmative and hypnotic, in all forms of nervous inquietude and cerebral excitement, it will be found an invaluable agent, as it produces none of those functional derangement or sequences that render many of the more customary remedies objectionable. (McMeens, 1860, p. 95)

John Russell Reynolds, who was to become personal physician to Queen Victoria, initially reported on various successes with an extract of cannabis in depression, lassitude, and senile restlessness (Reynolds, 1868).

In 1870, a Professor Polli of Milan documented at length another fascinating case of a young widow with an advanced melancholia with obsessional features and anxiety. She was successfully treated over ten days with *dawamesk*, an Egyptian confection composed of hashish (Polli, 1870, p. 99):

with a steady and progressive amelioration of all the phenomena; the nights became tranquil, the intelligence just, the affec-

tions natural. There only remained for a few days a little loquacity, some inclination to laugh unnecessarily, and a slight muscular feebleness.

Some months afterwards this lady was perfectly well, lively, and in flourishing health. The cure was permanent.

Indian hemp proved to be a useful agent in treatment of delirium tremens (alcohol withdrawal) and for treating opiate addiction. One author, citing his experience and that of his colleagues, stated, "the effect was marvellous" (Tyrell, 1867, p. 244).

Referring to *Cannabis indica*, it was said (Strange, 1883, p. 14):

in cases of melancholia, and, indeed, in all cases of mental depression with sleeplessness, I have found a valuable and almost certain ally in this drug.

By 1890, Reynolds had employed cannabis medicinally for almost forty years. As a treatment for senile insomnia, he wrote, "in this class of cases, I have found nothing comparable in utility to a moderate dose of hemp" (Reynolds, 1890, pp. 637-638). He related its effectiveness over long periods of time without resort to escalating dosages.

The same year, the treatment of delirium tremens was described (Aulde, 1890, p. 526):

In all probability the first dose will be sufficient to arrest the vomiting, and, if the drug is pushed, the patient will gradually fall in to a natural-like sleep, and awake several hours after greatly refreshed and entirely free from the threatening symptoms presented a few hours previously.

Suckling reported successes with Indian hemp in the treatment of mania and melancholia, in quaint prose that would raise eyebrows nowadays for its misogyny:

almost a specific in that form of insanity peculiar to women, caused by mental worry or moral shock. (1891, p. 12)

Mattison (1891) reviewed cannabis therapy in detail. One indication he advocated was treatment of addiction to cocaine, chloral

hydrate, and opiates. He stated, "In these, often, it has proved an efficient substitute for the poppy." He concluded with a flourish:

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. (p. 271)

At the turn of the twentieth century, a British pharmacologist touted smoking cannabis (Dixon, 1899, 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.

An interesting description of cannabis intoxication provided by Lewis in 1900 is telling in its potential for therapeutic effects:

A feeling of joyful anticipation of some unknown yet great pleasure is experienced, and there seems to be an end of all trouble and care. Without taking cognizance of the fact, past events and details grow very unimportant and the most pressing obligations are forgotten. The mind seems wholly taken up with the thoughts of the moment. Very frequently a great inexplicable sense of relief is felt, the sensation many times being identical with that experienced by one who suddenly awakes from a horrible dream to the feeling of gratitude which is always felt at its unreality. (p. 247)

Although cannabis use was essentially outlawed in the United States in the late 1930s, it has remained an agent of ethnobotanical importance around the world. In a treatise titled *Indigenous Drugs of India*, Chopra and Chopra (1957, p. 91) stated, "cannabis is used in medicine to relieve pain, to encourage sleep, and to soothe restlessness."

In another book about medicinal plants of the subcontinent, the author asserted (Dastur, 1962, 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.

Similarly, cannabis retains many uses in the folk medicine of Southeast Asia, including smoking and ingestion as a tonic for chronic illness, after childbirth, as a soporific, and as a relaxant (Martin, 1975). In Vietnam, a use of cannabis seed was observed: "The preparation (*sac thuoc*) is used to combat loss of memory and mental confusion" (Martin, 1975, p. 172).

Despite cannabis prohibition in most countries, investigation has continued in modern times to some degree. In 1944, the LaGuardia Commission published an in-depth examination of marijuana and found its dangers vastly overstated. Therapeutic applications were even advanced (Mayor's Committee on Marihuana, 1944, p. 147): "the typical euphoria-producing action . . . might be applicable in the treatment of various types of mental depression."

As part of the study (Mayor's Committee on Marihuana, 1944), fifty-six inmates with morphine or heroin addiction were examined. A group treated with THC (tetrahydrocannabinol, the main psychoactive cannabinoid)

had less severe withdrawal symptoms and left the hospital at the end of the treatment period in better condition than those who received no treatment or who were treated with Magendie's solution. The ones in the former group maintained their appetite and in some cases actually gained weight during the withdrawal period. (p. 147)

Efforts continue in a similar vein to treat withdrawal with cannabis and have been spearheaded by Tod Mikuriya, who has reported

on a successful use of cannabis in the treatment of alcoholism (Mikuriya, 1970). Current governmental constraints in the United States have recently rendered formal clinical studies with cannabis an extreme rarity.

A clinical study in 1976 revealed statistically significant results (Regelson et al., 1976, p. 775):

Delta-9-THC in cancer patients at acceptable dosage (0.1 mg/kg tid, orally) had the effect of a tranquilizer and mild mood elevator, clearly without untoward effects on cognitive functioning and apparently without untoward effect on personality or emotional stability—at least as can be measured by psychological tests.

Thousands of cancer survivors have anecdotally supported similar personal observations.

Cannabis use has often been cited as an implicated etiological or aggravating factor in the development of psychosis (schizophrenia). A recent study found otherwise (Warner et al., 1994). Among the findings, psychotic patients who used marijuana had lower hospitalization rates than those who abused other substances, and they had lower rates of activation symptoms. Patients reported beneficial effects on depression, anxiety, insomnia, and pain.

Cannabis may improve night vision, according to reported observations of night fishermen in Jamaica, as reported in the journal *Nature* (West, 1991). This proposition could be scientifically verified by the use of ERG (electroretinography) testing in volunteers.

Any pharmacological discussion of cannabis is complicated by the fact that, as with any herb, it is subject to quality control issues. Cannabis is a mixture of myriad cannabinoids and essential oils that may contribute to its physiological effects. In addition, ratios of tetrahydrocannabinol (THC) and cannabidiol (CBD) are critical in observed medicinal activity. THC is primarily responsible for euphoric effects but may aggravate anxiety. CBD, in contrast, is less psychoactive, more sedative, and ameliorates anxiety. It also serves to modulate the "high" produced by THC. These relationships between cannabis components have been extensively studied in Brazil by Zuardi and colleagues (Zuardi et al., 1981, 1982, 1993, 1995; Zuardi, Guimaraes, and Moreira, 1993; Zuardi and Karniol, 1983;

Zuardi, Rodrigues, and Cunha, 1991). Although these results are not easily summarized, and the interested reader is urged to examine the source material, a good review of CBD activity is available (Zuardi and Guimaraes, 1997).

CBD had a significant effect on anxiety in normal subjects in an experimental protocol, and without significant sedation (Zuardi, Guimaraes, and Moreira, 1993).

CBD also improved symptoms of psychosis in one patient, without induction of parkinsonian symptoms, as commonly occurs with standard antipsychotic agents. Improvement did not occur with addition of haloperidol to CBD (Zuardi et al., 1995).

Dr. Lester Grinspoon, a psychiatrist at Harvard University, has pioneered and spearheaded the medical use of marijuana. His writings have frequently included personal case studies of patients whose psychiatric illnesses have been successfully treated through cannabis use (Grinspoon and Bakalar, 1997). Although critics have derided testimonials of this type as anecdotal, many of the patients failed miserably on standard pharmaceuticals but successfully alleviated their symptomatology with cannabis. How much scientific verification do the patients themselves require?

Many of these accounts document the manner in which patients were relieved on cannabis, worse without it, and helped once more upon its resumption. This represents an "N-of-1 trial" (patient acts as own control and notes effects on and off the drug) that has been widely accepted as a valid research technique in pharmacological study of conditions that are extremely rare, or in which true double blinding is impossible, as is clearly the case for cannabis.

Dr. Grinspoon recently published another series of case studies of cannabis in the treatment of bipolar disease (manic depression) (Grinspoon and Bakalar, 1998). This author believes that these accounts are extremely compelling in supporting efficacy for cannabis in this most difficult clinical problem.

Consroe (1998) has nicely reviewed the topic of brain cannabinoids in neurological disease and points out that the effect of cannabis to impair short-term memory suggests the potential utility of cannabinoid *antagonists* in treatment of dementia. Interestingly, and contrary to logic, recent reports indicate that dronabinol (synthetic THC) actually decreased the severity of disturbed behavior in

a dozen patients with Alzheimer's disease (Volicer et al., 1997). Cohen-Mansfield Agitation Inventory scores, expressed as a percentage of baseline, were diminished significantly ( $p = 0.05$ ), while negative affect in the dronabinol group also decreased over placebo ( $p = 0.004$ ). Dronabinol also produced weight gain in these previously anorexic subjects ( $p = 0.006$ ). The results were sufficiently compelling to cause the drug's manufacturer to seek out a formal indication for its use in Alzheimer's disease from the FDA.

Finally, cannabis has been reported as effective in treatment of Tourette's syndrome (TS) (Hemming and Yellowlees, 1993; Moss et al., 1989; Müller-Vahl, Kolbe, and Dengler, 1997; Müller-Vahl et al., 1998, 1999; Sandyk and Awerbuch, 1988). This entity consists of a combination of involuntary movements, or tics, and pervasive features of obsessive-compulsive disorder (OCD). Cannabinoid receptors are heavily represented in the basal ganglia (Herkenham et al., 1990; Herkenham, 1993), and it has been hypothesized that this is the pathologically impaired site in TS patients.

Efficacy has been demonstrated anecdotally (Müller-Vahl et al., 1998) with cannabis in 82 percent of surveyed TS patients on both tics and OCD symptoms. The same was confirmed experimentally in one patient with dronabinol (Müller-Vahl et al., 1999). A few patients of this book's author report similar findings.

Such results have important implications. OCD represents one of the most recalcitrant disorders in psychiatry. Before 1980, no standard pharmaceuticals were significantly effective in its treatment. Nowadays, high, and sometimes massive, doses of clomipramine (a TCA) or SSRIs (Prozac and others) are required for its control.

Whereas a disorder of serotonin expression has been implicated as etiological in OCD, the necessity of these massive doses undermines that theory and, rather, supports the prospect that the current therapeutic drugs are producing secondary effects in another neurotransmitter system. What if OCD actually represents a disorder of the cannabinoid neurotransmitter system? After all, depression may be due to serotonin or norepinephrine deficiency, anxiety to GABA abnormalities, dementia to acetylcholine deficiency, and schizophrenia to dopamine excess. Conceivably, OCD and other illnesses (e.g., migraine and idiopathic bowel disease) may eventually be tied to a clinical cannabinoid deficiency state.



OCD is marked by an insurmountable preoccupation with fixed ideas (e.g., if I walk on the lawn, I will step on worms and something very bad will happen), no matter how preposterous, that withstand the patient's best efforts to submerge them through the application of logic. Cannabis, as no other substance yet discovered, allows a person to forget, and to laugh, even at one's own obsessions and compulsions. For OCD, it sounds like just what the doctor ordered.

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