A Brief History of the Use of Cannabis as an Antidepressant and Stimulant

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Cannabis, Cure-Alls, and Evidence

History teaches us that we should all be wary of cure-all claims. Therefore, it is understandable that many physicians are reluctant to accept what appear, at facevalue, to be exaggerated claims made by cannabis consumers in relation to the therapeutic benefits derived from their use of the plant. This one plant and its numerous active compounds, it is claimed, seem to positively affect nearly every ailment of our minds and bodies, from mental illness to cancer. Is this possible?

In short, yes. In fact, there is no shortage of evidence to substantiate many of these claims. The last couple of decades have seen an incredible explosion of research exploring the potential therapeutic applications of cannabis and cannabis-derived medications. Today, more evidence is available in relation to the positive therapeutic applications of cannabis than is available for some of the most widely used conventional medications and therapies (Sulak, 2011).

The Endocannabinoid System

It is widely understood, although not as widely recognized by the medical community, that cannabis is both powerful and safe, and can alleviate the suffering of dozens of severe chronic and acute medical conditions. How is it possible that one plant can do so much? The answer lies in the fairly recently discovered physiologic system known as the *endocannabinoid system*, which plays a role in modulating and regulating nearly every bodily function in all vertebrates (de Fonseca et al., 2005; Gieringer, Rosenthal, & Carter, 2008; Grotenhermen, 2006a). Our bodies naturally produce five known chemical compounds called *endogenous cannabinoids*, or *endocannabinoids* (de Fonseca et al.; Grotenhermen, 2006b), similar in structure and action to the chemical compounds found most abundantly in cannabis, called *phytocannabinoids*, of which at least 85 have been identified and isolated from the plant (El-Alfy et al., 2010).

These naturally occurring compounds and their two known receptors, CB_1 and CB_2 , are found virtually everywhere in the human body, from the brain, organs, connective tissues and glands, to immune cells (Grotenhermen, 2006a, 2006b; Sulak, 2011). Despite different functions of the endocannabinoid system, which depend upon the location in the body of the receptors of interest, the goal is constant: homeostasis, or "the maintenance of a stable internal environment despite fluctuations in the external environment" (Sulak, 2011, p. 11; Melamede, 2005). In fact, cannabinoids promote homeostasis at every level of biological life, from the sub-cellular to the whole organism, and thus, the endocannabinoid system is a global homeostatic regulator (Melamede, 2005). It is estimated that the

endocannabinoid system evolved over 600 million years ago, and is now shared by all vertebrates as an essential part of adaptation to environmental changes, and thus, an essential part of life (Guzmán, 2005; Melamede, 2005; Sulak, 2011). Therefore, the endocannabinoid system is a central component of both health and healing, perhaps the most important system (Melamede, 2005; Sulak, 2011).



Depression and Fatigue

Historically, *depression* has been variously defined as an "absence of cheerfulness or hope" (Dorland, 1903a, p. 206), being "low in spirits" (Taber et al., 1952, p. D-15), an "emotional state of dejection" (Hoerr & Osol, 1952, p. 196), "the blues" (Schifferes, 1963, p. 117), and "extreme feelings of sadness, dejection, lack of worth and emptiness" (Glanze, Anderson, & Anderson, 1987a, p. 174), while *emotional depression* in one text is an "undue sadness or melancholy due to no recognizable cause" (Dorland, 1960, p. D-8).

The contemporary definition of depression, however, is more complex. Physicians, and in particular psychiatrists and psychologists, rely on the clinical definition of depression found in the American Psychiatric Association's (APA) *Diagnostic and Statistical Manual of Mental Disorders (DSM)*. Version IV, with text revisions (*DSM-IV-TR*) is the most recent release and was published in 2000. The *DSM-5*

(note: the APA dropped the roman numerals for the newest version) is scheduled for publication in 2013 (APA, n.d.). According to the **DSM-IV-TR** (APA, 2000), a diagnosis of major depressive disorder, otherwise known as clinical depression, major depression, or unipoloar depression, requires at least two major depressive episodes, characterized by depressed mood and/or loss of interest or pleasure in life activities for at least two weeks, and at least five of the following symptoms that cause clinically significant impairment in social, work, or other important areas of functioning almost every day. One of the symptoms must be either (a) depressed mood, or (b) loss of interest:

- 1. Depressed mood most of the day.
- 2. Diminished interest or pleasure in all or most activities.
- 3. Significant unintentional weight loss or gain.
- 4. Insomnia or sleeping too much (hypersomnia).
- 5. Agitation or psychomotor retardation noticed by others.
- 6. Fatigue or loss of energy.
- 7. Feelings of worthlessness or excessive guilt.
- 8. Diminished ability to think or concentrate, or indecisiveness.
- 9. Recurrent thoughts of death or suicide (with or without a plan), or an attempted suicide (APA, 2000, p. 356).

Depression is fast becoming a serious problem globally. The World Health Organization (WHO) has forecast that by 2020 depression will be the second leading cause of disability and premature death worldwide, for all ages and both sexes (WHO, n.d.). Unfortunately, current therapies fail to help approximately 30% of the depressed population (Pacher, Batkai, & Kunos, 2004), and therefore, it is imperative that any potentially beneficial interventions be pursued.

Fatigue has been defined as "weariness, usually from overexertion" (Dorland, 1903b, p. 265). More contemporarily, fatigue is defined as a "feeling of weariness, tiredness, or lack of energy" (U.S. National Library of Medicine, 2011). Note that *overexertion* is left out of the current definition because fatigue may be a normal response to physical overexertion, but may also be a normal response to emotional stress, sleep deprivation, or even boredom, and may be alleviated by proper sleep hygiene, stress reducing activities such as exercise or meditation, and/or proper nutrition. However, fatigue may also be a symptom of more serious mental or physical conditions, as fatigue is also a common symptom of major depression or may be the result of diseases such as diabetes and lupus (U.S. National Library of Medicine, 2011).

Antidepressants and Stimulants

An *antidepressant* is defined as "a drug or a treatment that prevents or relieves depression" (Glanze et al., 1987b, p. 36). A *stimulant* is defined as "an agent or remedy that produces…functional activity" (Dorland, 1903c, p. 666). According to the National Institute on Drug Abuse (NIDA), stimulants "increase alertness, attention, and energy, as well as elevate blood pressure and increase heart rate, and respiration" (NIDA, 2001/2011, p. 6).



The History of the Use of Cannabis as an Antidepressant and Stimulant

Within the long history of medical literature concerning cannabis there are many differing views about the risks associated with the use of cannabis, as well as varying opinions about the causes of those risks. However, as to the effects of cannabis, its reputation as an antidepressant and stimulant has remained a constant through thousands of years of documented use, including up to the present day.

The Ancient Era

One of the first recorded benefits of cannabis use was to relieve depression. The earliest known descriptions of cannabis or hashish (note: hashish or hasheesh is a concentrated extract of whole cannabis) being used to treat depression and fatigue come from clay tablets from the 22nd century B.C.E. in Sumer. Thompson spent 50 years deciphering medical texts from the Bronze Age civilization of Assyria (Russo, 2007) and translated the tablets in 1949, revealing that cannabis was used for grief or "depression of spirits" (as cited in Fride & Russo, 2006, p. 372). Homer - circa the 8th century B.C.E. - wrote of *nepenthes*, a magical drug that could assuage grief (literally, an antisorrow drug), believed by some scholars and writers to be cannabis (Abel, 1980; Robinson, 1946). Herodotus - circa 440 B.C.E. wrote that the Scythians "...delighted, shout for joy..." from breathing in hemp (i.e., cannabis) seed vapors (Herodotus, 440 B.C.E./1994) and Democritus (460-371 B.C.E), the 'laughing philosopher', spoke of a plant called potamaugis thought to be cannabis - which was responsible for "immoderate laughter" when drunk with wine or myrrh (Emboden, 1990, p. 219; Robinson, 1996, p. 77). Galen (129-216 C.E.) wrote that cannabis was a "promoter of high spirits" (Rätsch, 1998/2001, p. 91), and described the custom of using cannabis to infuse occasions with laughter and joy by sharing cannabis with guests (Robinson, 1996). In addition, ancient Sanscrit writers speak of "Pills of Gaiety" - a preparation based on cannabis and sugar (Lewin, 1924/1998, p. 91).

Mahsati, a 12th century Persian poet wrote that eating "a little" hashish helped "against sorrow" (as cited in Rätsch, 1998/2001, p. 99), while 12th and 13th century Egyptian poets indentified *euphoria* as one of the effects of eating hashish (Clarke, 1998, p. 238). The leader of the Safaviya (Sufi Order) from 1460-1488 C.E. was the Persian monk Haider – or Haydar – who introduced his fellow monks to hashish "and were transformed from austere ascetics into jolly good fellows" (Robinson, 1925, p. 30).

In 1563, Garcia Da Orta (1563/1895, p. 56), physician, pioneer of tropical medicine, and naturalist, wrote that bangue, an Indian drink made with cannabis, allowed his servants "...not to feel work, to be very happy, and to have a craving for food". Moreover, he noted that bangue could raise a man "...above all cares and anxieties, and it makes some break into a foolish laugh" (p. 55). Captain Thomas Bowrey noted similar effects and wrote in 1680 that if a user ingested cannabis when "merry...he Shall Continue Soe with Exceedinge great laughter..." (1905/1993, p. 79). In 1689 an account of the plant from India called *Bangue*, at that time largely unfamiliar to the British, was presented before the Royal Society. Descriptions of the effects upon ingesting a dose included "...yet is he very merry,

and laughs, and sings" (Hooke, 1726, p. 210). Linnaeus (1707-1778), the father of modern taxonomy, stated that cannabis could be used for "chasing away melancholy" making the user feel "happy and funny" (Koerner, 1999, p. 41), and in 1777, Johan Friedrich Gmelin, a German botanist, wrote that "Orientals" mixed the cannabis buds with honey to "achieve a pleasant type of drunkenness" (as cited in Fankhauser, 2002, p. 41).

The Scientific Era

In the modern scientific era (i.e., mid 18th century onward), a new appreciation for and interest in the medical benefits and potential negative effects of cannabis developed. However, similar to the observations of the ancients, modern doctors wrote that the effects of cannabis were "of the most cheerful kind, causing the person to sing and dance, to eat food with great relish, and to see aphrodisiac enjoyments" (O'Shaughnessy, 1839/1973, p. 7). In 1843, Dr. Ley observed that the use of hashish produced glee and cheerfulness in warmer regions, but that "[i]n the colder climate of this country [England] the effects are much modified" (Ley, 1843, p. 487).

In 1845, Dr. Moreau de Tours wrote in his book *Hashish and Mental Illness* that the effects of cannabis as hashish included "a feeling of gaiety and joy inconceivable to those who have never experienced it....It is really *happiness* [bolding added] that hashish gives, and by that I mean mental joy, not sensual joy as one might be tempted to believe" (Moreau, 1845/1973, pp. 211 and 28 respectively). He also noted that hashish could provide the means "of effectively combating the fixed ideas of depressives" (Moreau, 1845/1973, p. 211). Indeed, writers admitted they were "moved to laugh foolishly about the most unimportant matters" (von Bibra, 1885/1995, p. 153) and spoke "of exquisite lightness and airiness" (Taylor, 1855, p. 134), "unutterable rapture" (p. 138), "bliss of the gods" (p. 142), "unquenchable laughter" (p. 142), and of "a strange and unimagined ecstasy" (Ludlow, 1857, p. 24).

Starting in the late 1850s, hashish candy for medical purposes was regularly advertised in newspapers and magazines. For example, in the October 16th, 1858 edition of *Harper's Weekly*, a small advertisement for Gunjah Wallah's Hasheesh Candy promises the user "A most pleasurable and harmless stimulant – Cures Nervousness, Weakness, Melancholy &c. Inspires all classes with new life and energy" (reprinted in Ludlow, 1857/1975, p. 201). Other examples include similar advertisements in *Vanity Fair* from August 16, 1862 ("Antique cannabis medicines: Hasheesh candy", 2010).

Hasheesh Candy .- THE ARABIAN "GUNJE" OF ENCRANTMENT confectionized .- A most pleasurable and harmless stimulant .-- Cures Nervousness, Weakness, Melancholy, &c. Inspires all classes with new life and ener-A complete mental and physical invigorator. Send gy. for circular. Beware of imitations. 25 cents and \$1 per box. Imported only by the GUNJAH WALLAH CO., 476 Broadway, N. Y.

In fact, much of 19th century medical opinion of the effects of cannabis was positive and included descriptions such as: "...the face is covered in smiles....it has been proposed by M. Moreau to take advantage of this reputed action, to combat certain varieties of insanity connected with melancholy and depressing delusions" (Bell, 1857/1973, p. 42), "some inclination to laugh unnecessarily" (Polli, 1870, p. 99), "a sort of revery which is almost always very delightful...voluptuous ecstasy, usually free from a cynic element" (Trousseau & Pidoux, 1880, p. 265), "an agreeable exaltation of the mental faculties" (Lyman, 1885, p. 68), "pleasure" (Bose, 1894, p. 250), "motiveless merriment" (Stillé, Maisch, Caspari, & Maisch, 1894, p. 395), and of an effect which "allays morbid sensibility" (Pierce, 1895, p. 343, Pierce, 1918, p. 343).

Medical Indexes and Textbooks: Lying About the Risks but Telling the Truth About the High

Furthermore, many medical textbooks and drug indexes of the time made specific mention of the antidepressant effects of cannabis. For instance, the 1907 and 1930 *Merck Indexes* state that cannabis is used for "mental depression" ("Cannabis indica", 1907, p. 123; "Cannabis", 1930, p. 147), while several editions of Dock's *Textbook of Materia Medica for Nurses* indicate that cannabis indica "causes a mental state of joyous exhilaration" (e.g., Dock, 1908, p. 241, Dock, 1916, p. 245). In addition, Blumgarten's 1932 *Textbook of Materia Medica* states that cannabis produces "pleasure and exhilaration" which leaves the user "usually joyful and happy" (p. 338). Similarly, in *The British Pharmaceutical Codex, 1934*, the Pharmaceutical Society of Great Britain wrote that cannabis produces "a feeling of happiness" (1934, p. 270), and 1935's *Everybody's Family Doctor* states that users may end up "feeling very gay and pleased with everything" ("Cannabis indica", 1935, p. 130).

While inaccurate about the risks of cannabis use, such as the claims that cannabis use causes schizophrenia, cancer, and violence (please refer to the free series of informative articles at www.stressedanddepressed.ca. for more in depth

information), post-cannabis-prohibition medical textbooks (in the U.S., post-1937) continued to tell the truth about the actual effects of proper cannabis use. For example, The Dispensatory of the United States of America from 1947 states that "in some persons it appears to produce a euphoria....the euphoria produced is similar to that following alcohol but the sequelae after the acute effects have worn off are less unpleasant" (Osol & Farrar, 1947, p. 1383), while the Modern Medical *Counselor* notes that it "gives its user gay daydreams" (Swartout, 1949, p. 153), the 1950 Merck Manual of Diagnosis and Therapy lists "giggling" ("Marihuana", 1950, p. 1102) as one of the symptoms of smoking cannabis, and Solomon and Gill (1952, p. 188) in *Pharmacology and Therapeutics* describe one of the effects of cannabis use as "euphoria, a feeling of well-being accompanied by a dreamy state, The Encyclopedia of Family Health of 1959 declares exhilaration". "marihuana...cheers the spirits" and makes users "exhilarated with a sense of wellbeing" (Fishbein, p. 761). In addition, the 1977 Merck Manual describes the effects of cannabis use in a positive light, asserting, "In general, there is a feeling of well-being, exaltation, excitement, and inner-joyousness that has been termed a 'high'" (Berkow et al., 1977, p. 1515). Merck continued to use words such as euphoria in relation to cannabis use for decades, as is evidenced by its inclusion as an effect in the Merck Indexes from the 1960s (e.g., Stecher, Windholz, & Leahy, 1968, p. 201) through the new millennium (e.g., O'Neil et al., 2001, p. 292).



Government Reports

Despite the preceding positive reports about the effects of cannabis, concerns about the potential negative effects of cannabis upon the physical and mental well-being of its consumers and society have also been part of the historical records. Thus, due to the controversy surrounding the use of cannabis, several countries' governments have commissioned large-scale reports, on multiple occasions, to investigate the impacts of cannabis use on society and individuals. These comprehensive studies date back to over 100 years, have each typically taken several years to complete, and have included panels of experts from every discipline of study conceivably impacted by the use of cannabis. From the first government-commissioned report in 1894 up to the present day, all have noted the antidepressant effects of cannabis use.

For example, in 1894 the British-initiated *Indian Hemp Drugs Commission Report* noted that to devotees, bhang (the Indian drink made with cannabis, noted previously as bangue) is "the Joy-giver, the Sky-flier, the Heavenly-guide, the Poor Man's Heaven, the Soother of Grief..." (Campbell, 1894, ¶ 10). Moreover, the Commission also found that cannabis had beneficial stimulating properties, as it was used as a tonic to effectively increase stamina (Mikuriya, 1998).

Fifty years later, the *La Guardia Committee Report*, the first in-depth investigation of smoked cannabis in the U.S., specifically looking at what was happening in New York, reported effects such as "...a sense of well-being and contentment, cheerfulness and gaiety..." (Mayor's Committee on Marihuana, 1944, p. 37). The British conducted their own investigation and in 1968 published what is commonly known as the *Wootton Report*, which mentioned *elation* and *euphoria* as two of the effects (U.K. Home Office, 1968). Canada soon followed, and in 1972 published what is commonly called the *Le Dain Commission*, which came to similar conclusions, reporting in the interim report of 1970 that "Cannabis is an intoxicant and a euphoriant, and it generally acts as a relaxant" (LeDain, 1970, p. 202). Nearly simultaneously, then U.S. president Richard Nixon commissioned a report to study cannabis abuse in the U.S., commonly referred to as the *Shafer Commission*, which reported that "[a]t low, usual 'social' doses, the intoxicated individual may experience an increased sense of well-being; initial restlessness and hilarity followed by a dreamy, care-free state of relaxation" (Shafer, 1972, p. 68).

The Canadian Senate Special Committee on Illegal Drugs more recently reported that "[l]ow doses generally produce the effects that cause people to like smoking pot. They include mild euphoria, relaxation, increased sociability and a non-specific decrease in anxiety" (Nolin, Kenny, Banks, Maheu, & Rossiter, 2002, p.

137). Thus, to date, every country that has commissioned an expertly conducted study of the effects of cannabis use has come to the same conclusion: Cannabis, when used at proper doses, has antidepressant properties.

Cross-Cultural Use

Humans brought cannabis with them wherever they migrated (Robinson, 1996). Von Bibra (1855/1995, p. 150) wrote that hashish confections eaten by the Turks caused them to become "cheerful, to sing, laugh, and to make all kinds of merry follies". In India, the antidepressant effects of cannabis are some of the most well-known, and the plant has been used in central Asia as an antidepressant for centuries (Rubin, 1976).

According to researchers studying users in Jamaica, cannabis "makes you feel happy" (Rubin & Comitas, 1976, p. 127). Working class males in Jamaica note an energizing effect (Rubin, 1976), as do the Iroquois, who use cannabis as a stimulant – they claim "this plant will get you going" (Moerman, 1998, p. 136). Carter wrote in 1980 (as cited in Fride & Russo, 2006, p. 374) that in Costa Rica smokers use cannabis as a remedy for depression and malaise, as do the Shamans of Nepal who continue to use cannabis as an antidepressant to this day (Rätsch, 1998/2001, p. 18). Schnelle, Grotenhermen, Reif, and Gorter (1999) reported in a study of 128 German-speaking medical cannabis users that depression was the most common reason (12%) cited for self-medicating with cannabis. Swift, Gates, and Dillon (2005) found similar, but even stronger results in an Australian study of 128 medical cannabis users. They reported that 56% of their participants used cannabis for depression.

These kinds of results substantiate what the overall historical and global evidence tell us. After a massive review of the historical and cross-cultural evidence of the medicinal use of cannabis, Rätsch (1998/2001, p. 178) writes; "Around the world, hemp is particularly valued as an antidepressant. From a medical perspective, this mood-enhancing ability may be hemp's most important effect". Dr. Tod Mikuriya, psychiatrist and world-renowned cannabis expert, came to the same conclusion based on the evidence and his own clinical practice, calling cannabis' ability to fight depression "…perhaps its most important property" (as cited in Gieringer et al., 2008, p. 83).

Recent Studies

Modern scientific studies continue to substantiate the observations of ancient cultures, while showing a more nuanced interaction between the consumer and the plant. A World Health Organization (WHO) study included the following

statement: "There are also reports of an anti-depressant effect, and some patients may indeed use cannabis to 'self-treat' depressive symptoms, but these need to be better evaluated" (WHO, 1997, p. 28). These findings were bolstered by Grant and Pickering (1998) in a U.S. epidemiological study investigating the relation between levels of cannabis use and cannabis abuse and dependence, commenting "...cannabis might be used to self-medicate major depression" (p. 255). Gieringer et al. (2008, p. 83) assert that "[m]any psychiatric patients who do not respond well to standard treatment find marijuana beneficial for depression". In addition, multiple studies fail to find an association between cannabis use and depression, despite rigorous design, statistical power, and methodology (see Denson & Earleywine, 2006 for the studies).

However, a study of 17 subjects at Duke University found that cannabis smoking actually increased depression - but only among inexperienced users (Mathew, Wilson, & Tant, 1989). A follow-up study (Mathew, Wilson, Humphreys, Lowe, & Wiethe, 1992) did not produce any adverse effects. The authors argue that this is likely because adverse effects are most often associated with novice users, and although the participants were infrequent users, they did have experience. In addition, dose plays a role in the positive versus negative effects of cannabis, as do age of first use and level of use. For example, Degenhardt, Hall, and Lynskey (2003) did find a modest association between cannabis use and depression in a review of the literature, but only among problematic and heavy users. Degenhardt et al. (2003) also found a modest association in several studies between early onset use, regular use, and later depression, even when potential confounding variables were controlled for. Hayatbakhsh et al. (2007) found that the association between age of onset, level of use, and later depression was strongest for those who initiated use before age 15. A more recent epidemiological study using more than 85,000 participants from 17 countries found a similar association (de Graaf et al., 2010).

However, it is important to note that at least one longitudinal study following participants from preschool through age 18 found that those who experimented with drug use during their adolescence (up to once a month, almost exclusively with cannabis), were the best adjusted, both psychologically and socially, compared to both frequent users and abstainers (Shedler & Block, 1990). It is also important to keep in mind that correlation does not equal causation. In fact, emerging evidence suggests that accounting for childhood traumas such as sexual abuse may diminish the association between cannabis use and psychosis, and therefore, researchers investigating the association between cannabis use and psychiatric disorders should adjust their analyses to account for this potentially confounding variable (Houston, Murphy, Shevlin, & Adamson, 2011).

A recent review of the literature by Fride and Russo (2006) demonstrated the complexity of the topic, reporting that cross-sectional studies tend to show that depression leads to the use of cannabis while longitudinal studies tend to show the converse and that in non-clinical samples, either weak or no associations are found between several measures of depression and cannabis smoking. Furthermore, although a significantly higher number of suicide attempts was reported in cannabis smokers in one study, once several confounding factors were controlled for, the association disappeared. Thus, the authors conclude that, "...taken together, the epidemiological evidence does not support a causative or precipitating role for cannabis in chronic depression or anxiety" (Fride & Russo, 2006, p. 376).



Indeed, the opposite may be true. Importantly, a study of 79 psychotics found that those who used cannabis recreationally reported less anxiety, depression, insomnia and physical discomfort (Warner et al., 1994). In fact, emerging evidence strongly suggests that *cannabidiol*, one of the other most well-known cannabinoids, is a potent antipsychotic. For example, a phase II clinical trial on the effects of cannabidiol in schizophrenia and schizophreniform psychosis revealed that cannabidiol was as effective as amisulpride, a standard antipsychotic in Europe and Australia and available in Canada through the Special Access Program but not available in the United States, in reducing acute psychosis symptoms, but with far fewer negative side effects (Canadian Agency for Drugs and Technologies in Health, 2011; Kaplan, 2004; Lecrubier et al., 2001; Leweke et al., 2005). Other

studies substantiate these findings (e.g., Zuardi et al., 2006; Zuardi & Guimaraes, 1997).

Researchers have identified the cannabinoid delta-9-tetrahydrocannabinol (THC) as a primary source of the stimulating, euphoric, and antidepressant effects of cannabis (Rätsch, 1998/2001, p. 6), and after investigating the potential effects of cannabinoids on depression, Musty (2002) reported participants had feelings of euphoria, but no anxiety from the use of cannabis. Furthermore, an internet survey of 4,400 adults by researchers at the University of Southern California found that cannabis users reported less depressed mood and more positive affect than nonusers (Denson & Earleywine, 2006). In fact, evidence is mounting that major depression, along with other psychiatric disorders, may be associated with a dysfunctional endocannabinoid system (e.g., Ashton & Moore, 2011; Pacher et al., 2006), and therefore, it is not surprising that studies continue to find that depression is one of the leading reasons cited for the use of cannabis (e.g., Swift et al., 2005). There is also a well-known association between chronic illness and depression, such as the development of depression due to pain caused by Multiple Sclerosis, and that the alleviation of the pain also leads to the alleviation of depression. For instance, a recent Canadian study concluded, "...results support the claim that smoked cannabis reduces pain, improves mood and helps sleep" (Ware et al., 2010, p. E701).

Further support for the antidepressant effects of cannabis and the cannabinoids comes from a surprising source. In 2007, rimonabant, a CB₁ receptor blocker developed as an anti-obesity drug by French company Sanofi-Aventis under the trade name Acomplia[®], was denied FDA approval by the U.S. because it was linked to increased depression, suicidal thoughts, suicide attempts, suicide events, anxiety, and insomnia (Badawi, n.d.; Gieringer et al., 2008). Considering the evidence strongly suggesting the antidepressant effects of cannabis, as well as the known mechanisms of action of the cannabinoids and the homeostatic role the endocannabinoid system plays, it should not be surprising that blocking one of the main receptors for the cannabinoids would lead to these adverse events.

Of particular importance in this discussion is the fact that the federal Medical Marihuana Access Regulations in Canada already allow for the use of cannabis for depression, among other psychiatric conditions, so long as the appropriate form (i.e., Form B2) is completed by a qualified medical professional (Health Canada, 2005, 2007). The situation in the United States is a little bit more complicated because they do not have a federal medical cannabis program. However, to date sixteen states and the District of Columbia have enacted their own laws to legalize cannabis for medical purposes, and of those, thirteen leave room for the use of

cannabis for depression and/or other psychiatric conditions by including medical conditions whose primary symptoms include depression, such as Post Traumatic Stress Disorder, by allowing the use of cannabis for any chronic or persistent medical condition that limits a person's ability to perform one or more major life activities or if not alleviated, could cause serious mental or physical harm to the patient, or by allowing the use of cannabis for any number of unspecified medical conditions upon the approval of the various state Departments of Health (California Senate Bill 420, 2003; ProCon.org, 2011).

However, despite the evidence and both federal and state programs allowing for the use of cannabis for depression, it is acknowledged that treating "...depression with cannabis may be difficult because of differences in individual makeup, need for continuous dose levels, expense, availability, and illegality" (Mikuriya, 1998).



Comparisons With Synthetic Medicines

Lester Grinspoon, retired Harvard Medical professor and world-renowned cannabis expert who specialized in the study and treatment of schizophrenia, reported that cannabis compares favorably in both efficacy and safety to many pharmaceutical antidepressants (Grinspoon & Bakalar, 1993). Moreover, numerous independent assessments of the safety, efficacy, and dependence potential of cannabis clearly indicate that cannabis and cannabis-based medications are well-tolerated, nontoxic, cannot lead to death by overdose, and are unlikely to lead to dependence in the vast majority of patients. For instance, the Institute of Medicine's 1999 report, *Marijuana and Medicine: Assessing the Science Base*, in relation to the safety of cannabis, noted: "The side effects of cannabinoid drugs are within the acceptable risks associated with approved medications" (Joy, Watson, & Benson, 1999, p. 127). In addition, in 1988 the Drug Enforcement Agency's Chief Administrative Law Judge, Francis Young, after two years of hearing expert testimony and reviewing thousands of documents concluded:

A smoker would theoretically have to consume nearly 1,500 pounds of marijuana within about 15 minutes to induce a lethal response. In practical terms, marijuana cannot induce a lethal response as a result of drug-related toxicity....In strict medical terms marijuana is far safer than many foods we commonly consume. For example, eating 10 raw potatoes can result in a toxic response. By comparison, it is physically impossible to eat enough marijuana to induce death. Marijuana in its natural form is one of the safest therapeutically active substances known to man. By any measure of rational analysis marijuana can be safely used within the supervised routine of medical care. (pp. 57-59)

Sadly, the same safety and efficacy profile cannot be said to exist for the majority of pharmaceutical antidepressants, with well-known court cases and science establishing the very real and dangerous side-effects of drugs like the commonly prescribed Serotonin Specific Reuptake Inhibitors (SSRIs) (Degroot, 2008; Kauffman, 2009). For instance, it is well established that during the early stages of treatment with SSRIs that anxiety is actually likely to increase, and that certain populations are at increased risk of suicide or self-harm (Degroot, 2008; Kauffman, 2009). As a result, to reduce these potential side effects, early treatment with SSRIs is often combined with the use of drugs like benzodiazapines (which have a list of their own serious negative side effects) (Degroot, 2008; Longo & Johnson, 2000). Furthermore, along with a host of physical and psychological complaints (Degroot, 2008; Kauffman, 2009), the potential side effects of SSRIs may include homicide and suicide (Kauffman, 2009). In fact, case precedence has established that murder and suicide are potential side effects of SSRI use and the manufacturer can be, and has been, held liable (Kauffman, 2009; see http://ssristories.com/index .php for a list of violent incidents and court cases associated with SSRI use). Neither of these outcomes has been shown to be causally associated with the use of cannabis (Price, Hemmingsson, Lewis, Zammit, & Allebeck, 2009; Reiss & Roth, 1993).

To compound the problem, it may very well be that millions of patients are not only being prescribed a more dangerous medication than cannabis, but that most of them are deriving no benefit while shouldering substantial risks. For example, Kirsch, Moore, Scoboria, and Nicholls (2002) analyzed both published and unpublished clinical trials submitted to the U. S. Food and Drug Administration (FDA) on the six most commonly prescribed SSRIs and found that placebo control groups duplicated about 80% of the response to medication. In 2008, Kirsch, Deacon, et al. conducted a meta-analysis on data submitted to the FDA on four new-generation antidepressant medications. They found that the medications were ineffective in treating patients with moderate and even severe depression, with only minor clinical improvements in the most severely depressed.

It is important to note that emerging evidence demonstrates that many patients are turning to cannabis to safely and effectively reduce and/or replace synthetic antidepressants after having grown tired of the negative side effects associated with their use. For example, in examinations of 2,480 California patients, Dr. Mikuriya found that 27% reported using cannabis for "mood disorders" and another 5% used cannabis as a substitute for more toxic drugs (Gieringer, 2002). A recent survey of doctors in California found "that many of their patients were able to decrease their use of...antidepressant, antianxiety, and sleeping medications, or else they use cannabis to treat their side effects of jitteriness or gastrointestinal problems in order to stay on their medications" (Holland, 2010, p. 285). Currently, the most comprehensive study ever conducted in Canada investigating the barriers medical cannabis users encounter while trying to gain access to their medication of choice is underway (see https://www.surveymonkey.com/s/CannabisSurvey). The survey includes several questions about cannabis as a substitute for both illicit drugs and prescribed pharmaceuticals.

Cannabis as Preventive Medicine

Those studying the plant and its uses throughout world cultures, as well as human history, have observed the ability of cannabis and the cannabinoids to prevent illness, and not just treat symptoms, for some time. For instance, in 1845 in relation to the use of hashish and its effects, Moreau wrote, "I report them here only to call attention to the *prophylactic action* [emphasis added] of a substance that could offer valuable therapeutic resources" (Moreau, 1845/1973, p. 213).

More recently, after an extensive review of the then extant literature, Mikuriya (1969) made a list of the medical uses for cannabis, under the title of *Possible Therapeutic Applications of Tetrahydrocannabinols and Like Products*. The list included "*Prophylactic* [emphasis added] and treatment of the neuralgias,

including migraine and tic douloureux....*Antidepressant-tranquilizer* [emphasis added]" (p. 39). Even more recently, Dr. Dreher, nurse, anthropologist, and dean of nursing at Rush University Medical Centre, in an interview about her research into prenatal exposure to cannabis and neonatal outcomes in Jamaica had the following to say about the importance of cultural context and the preventive properties of cannabis:

American drug use often takes place without cultural rules and in an unsupervised context. The Jamaican women we studied had been educated in a cultural tradition of using marijuana as a medicine. They prepared it with teas, milk and spices, and thought of it as a *preventive and curative substance* [emphasis added]....Some of these women were in dire socioeconomic straits, and they found that smoking ganja *helped allay feelings of worry and depression* [emphasis added] about their financial situation. (Brady, 1998, "Is it possible that American women...")

Rätsch (1998/2001), writing about the use of cannabis in Jamaica amongst Rastafarians noted that:

[h]emp tea is a popular drink for *preventive use* [emphasis added] and is also consumed therapeutically for almost all ailments. Hemp preparations are often ingested for *prophylactic purposes* [emphasis added]. The frequent use does not just protect from diseases, but also gives courage and strength...(p. 140).

It is important to note that one can also infer the preventive medicine properties of cannabis by taking a step back and, instead of focusing on one or two narrow medical conditions for which cannabis may be used, recognizing the sheer volume of and widely disparate chronic and acute medical conditions and/or symptoms for which cannabis has already been proven effective in treating, for which accumulating evidence strongly suggests cannabis is effective in treating, and for which preliminary research shows cannabis is potentially effective in treating. These varied and serious medical conditions and symptoms include, but are not limited to, nausea and vomiting, wasting syndromes associated with AIDS and cancer, multiple sclerosis, amyotrophic lateral sclerosis, spinal cord diseases and injuries, epilepsy and other seizure disorders, a variety of chronic pain conditions (e.g., migraine, fibromyalgia, rheumatoid arthritis, neuropathy), a variety of movement disorders, glaucoma, a variety of psychiatric disorders, a variety of inflammatory diseases, and various cancers (e.g., Fride & Russo, 2006; Grinspoon, Bakalar, & Russo, 2005; Guzmán, 2003; Health Canada, 2010; Russo, 2001). A rational analysis of the body of evidence demonstrating the ability of a single substance, cannabis, to treat or potentially treat such a wide variety of medical

conditions and symptoms through its actions on the endocannabinoid system, which acts as a bodily homeostatic regulator, very strongly suggests that cannabis likely plays a role in delaying the progression of and/or preventing many illnesses when used properly.

However, perhaps the most powerful evidence of the preventive properties of cannabis and the cannabinoids comes from the U.S. government itself. In 2003 the government, as represented by the Department of Health and Human Services, was awarded patent number 6630507, entitled *Cannabinoids as Antioxidants and Neuroprotectants*. The abstract states, in part, that cannabinoids are "…useful in the *treatment and prophylaxis* [emphasis added] of wide variety of oxidation associated diseases, such as ischemic, age-related, inflammatory and autoimmune diseases" (Hampson, Axelrod, & Grimaldi, 2003, Abstract section).

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Tablets Cannabis Extract 1/4 gr., Squibb

T. T. Per 1000 Per 500 Per 100 Cannabis has been employed as a Sedative, Anodyne and Hypnotic, in cases where opium does not agree with the patient. Unlike the latter, it causes neither nausea nor constipation. It produces at first a mental stimulation, which is later followed by a calmer mood and finally by sleep. It is used in acute

Tablets

Licey

Cannabis Indica, Extract, 1/10 gr.; 1/8 gr.; 1/4 gr. Physiologically tested. Antispasmodic, anodyne and hypnotic. Used in neuralgia, migraine, hysteria, delirium tremens, melancholia, insomnia, etc. Dose -1/10 to 1 gr.

Beginning to Understand the Nuances of Cannabis Medicine

Cannabis has paradoxical effects, having for instance both relaxing and stimulating effects. However, these effects are based upon many factors, including the strain of cannabis, the quality, potency, and purity of the strain, number of types and ratios of cannabinoids, number of types and ratios of terpenes (compounds that produce the unique aromas and tastes of individual strains, but which have their own proven therapeutic properties and which act synergistically with the cannabinoids),

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dose, and the health, setting, mindset, and diet of the user, as well as the user's experience with and tolerance to the various cannabinoids (e.g., Gieringer et al., 2008; McPartland & Russo, 2006; Russo, 2011).

These factors, influencing the effects of cannabis upon its consumers, have been known for quite some time. For instance, in *The National Dispensatory* of 1894, it is written that "the plants richest in resin grow at an altitude of 1800 to 2400 m" (Stillé et al., p. 393) and that the effect of cannabis "varies with the individual's temperament" (Stillé et al., p. 395). In Cushny's 1906 *Pharmacology and Therapeutics or the Actions of Drugs* the effects of cannabis are described as:

...a mixture of depression and stimulation...its action...seems to depend very largely on the disposition and intellectual activity of the individual. The preparations used also vary considerably in strength, and the activity of even the crude drug seems to depend very largely on the climate and season in which it is grown, so that great discrepancies occur in the account of its effects. (p. 232)

One text notes that "[p]reparations made from plants grown in warm climates are usually better" (Blumgarten, 1932, p. 338). Another notes that after two years of storage "...it had lost about half its potency" (Osol & Farrar, 1947, p. 1382). Still another notes that "[m]any of the psychological effects seem related to the setting in which the drug is taken" (Holvey et al., 1972, p. 1415). One even noted "...an occasional panic reaction has occurred, particularly in naive [sic] users, but these have become unusual as the culture has gained increasing familiarity with the drug" (Berkow et al., 1982, p. 1427). Another noted that cannabis' effects are dependent upon "the dose of the drug and the underlying psychological conditions of the user" (Venes et al., 2001, p. 1242).

Unfortunately, the prohibition of cannabis had a negative effect on its medicinal reputation. Textbooks began to remark upon the "completely unpredictable" nature of the drug (Faddis, 1943, p. 153), or its unreliability in providing consistent results ("Cannabis", 1952; Dilling, 1933) – blaming the drug itself for the researchers' and cultivators' lack of understanding of the proper cultivation, storage, and transportation of cannabis for medicine, the various strains, their types and ratios of cannabinoids and the effects of each on the user, and the importance of the subject's mindset and setting within which cannabis is consumed. Some textbooks then began omitting entirely any mention of cannabis in their later editions (e.g., Blumgarten, 1940; Pierce, 1935). Others began to falsely blame whole-plant cannabis for the effects experienced by one of its isolated, synthesized, and concentrated cannabinoids, particularly THC (Gieringer et al., 2008; Wade & Reynolds, 1977). This is of particular importance because the evidence is mounting

that several cannabinoids, as well as the terpenoids and flavonoids present in whole-cannabis, are important, and they act synergistically to enhance some of the positive effects and to reduce some of the negative effects of cannabis use, such as the cognitive impairment associated with THC (e.g., Gieringer et al., 2008; Russo, 2011; Russo & Guy, 2006; Russo, Guy, & Robinson, 2007).

Still, the special relationship between cannabis' prohibition and its reputation as a dangerous or unpredictable drug was accurately assessed in the 1987 *Merck Manual of Diagnosis and Therapy*: "...the chief opposition to the drug rests on a moral and political, and not a toxicological, foundation" (Berkow et al., 1987, p. 1490). The numerous studies and commissioned reports conducted since 1987, some of which call for the outright legalization and regulation of cannabis (e.g., Senate Special Committee on Illegal Drugs of 2002), but which have been ignored, only reinforce this conclusion.

What About the Smoke?

We understand that many health-care professionals are reluctant to recommend cannabis to their patients due to the potential pulmonary damage from smoking whole cannabis. However, despite what many believe about harms associated with smoking cannabis, the best available evidence strongly suggests that it does not lead to lung cancer. In fact, the evidence strongly suggests that the cannabinoids offer a protective factor against the development of several kinds of cancer (see for example Guzmán, 2003). For more detailed information about this topic, as well as other cannabis myths, please refer to the free series of informative articles at www.stressedanddepressed.ca.

That being said, the harms associated with smoking cannabis can be mitigated or eliminated through harm reduction techniques such as vaporizing or ingesting cannabis (see for example Earleywine & Van Dam, 2010). For more detailed information about this, please refer to the free series of informative articles at www.stressedanddepressed.ca.

Conclusion

Thus, despite current fears that the use of cannabis leads to depression, when all the evidence is considered together and taken in context, it is clear that cannabis has been used safely and effectively as an antidepressant and mild stimulant for thousands of years, continues to be used for those purposes by many cultures all over the world, and modern science corroborates those uses, when used properly. Therefore, it can be asserted that cannabis has antidepressant and stimulant properties. If, after reviewing the evidence surrounding its safety, cannabis is found to pose an acceptable risk for medical use, it should be considered by physicians as a legitimate treatment option for those who are currently dealing with depression and/or fatigue, as well as for those who wish to avoid – or, in the case of current users, continue to avoid – these serious conditions.



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