# Contents

Foreword by Lester Grinspoon, M.D. ........................................... xi
Introduction ............................................................................. 1

**PART ONE**

**An Overview of Cannabis**

Introduction to Part One ...................................................... 6

1. The Subjective Effects of Cannabis ................................. 9
   *Matthew G. Kirkpatrick and Carl L. Hart, Ph.D.*

2. Early/Ancient History ..................................................... 17
   *Chris Bennett*

3. Recent History .............................................................. 27
   *David Malmo-Levine*

4. The Botany of *Cannabis* ................................................ 35
   *Lyle E. Craker, Ph.D., and Zoë Gardner*

5. Cannabis Grow Revolution ............................................. 44
   *Danny Danko*

6. The Endocannabinoid System ......................................... 52
   *Gregory L. Gerdeman, Ph.D., and Jason B. Schechter, Ph.D.*

7. Anandamide and More ................................................... 63
   *Raphael Mechoulam, Ph.D., and Lumír Hanuš*

8. Cannabis Laws in the United States ............................... 73
   *Allen St. Pierre*

9. On Ending Prohibition ..................................................... 130
   *Ethan Nadelmann, J.D., Ph.D.*
PART TWO
Risks of Use and Harm Reduction

Introduction to Part Two

10 Medical Risks and Toxicology
William Holubek, M.D.

11 Pulmonary Harm and Vaporizers
Mitch Earleywine, Ph.D.

12 Cannabis and Cognition
Caroline B. Marvin and Carl L. Hart, Ph.D.

13 Mental Health Risks Associated with Cannabis Use
Cheryl Corcoran, M.D.

14 How Real Is the Risk of Addiction?
Ryan Vandrey, Ph.D., and Margaret Haney, Ph.D.

15 Driving Under the Influence
Paul Armentano

16 Arrest Statistics and Racism
Harry G. Levine, Ph.D.

17 Getting Busted Is Not So Funny
An Interview with Tommy Chong
Julie Holland, M.D.

18 The Collateral Consequences of Cannabis Convictions
Richard Glen Boire, J.D.

19 Harm Reduction Psychotherapy
Andrew Tatarsky, Ph.D.

PART THREE
The Clinical Use of Cannabis

Introduction to Part Three

20 The Clinical Applications of Medical Marijuana
An Interview with Andrew Weil, M.D.
Julie Holland, M.D.
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Medical Marijuana Research An Interview with Donald Abrams, M.D.</td>
<td>252</td>
</tr>
<tr>
<td></td>
<td><em>Julie Holland, M.D.</em></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>MAPS and the Federal Obstruction of Medical Marijuana Research</td>
<td>261</td>
</tr>
<tr>
<td></td>
<td><em>Rick Doblin, Ph.D.</em></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>The Government’s Pot Farm An Interview with Mahmoud A. ElSohly, Ph.D.</td>
<td>266</td>
</tr>
<tr>
<td></td>
<td><em>Julie Holland, M.D.</em></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Cannabinoids and Psychiatry</td>
<td>282</td>
</tr>
<tr>
<td></td>
<td><em>Julie Holland, M.D.</em></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Cannabinoids and Neuroprotection</td>
<td>295</td>
</tr>
<tr>
<td></td>
<td><em>Sunil K. Aggarwal, M.D., Ph.D., and Gregory T. Carter, M.D.</em></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Cannabis and HIV/AIDS</td>
<td>311</td>
</tr>
<tr>
<td></td>
<td><em>Mark A. Ware, M.D., and Lynne Belle-Isle</em></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Multiple Sclerosis and Spasticity</td>
<td>318</td>
</tr>
<tr>
<td></td>
<td><em>Denis J. Petro, M.D.</em></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Pain Management</td>
<td>328</td>
</tr>
<tr>
<td></td>
<td><em>Mark S. Wallace, M.D., and Ben Platt, M.D.</em></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>Sativex</td>
<td>336</td>
</tr>
<tr>
<td></td>
<td><em>William Notcutt, M.D., F.R.C.A., F.F.P.M.R.C.A.</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>PART FOUR</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Cannabis Culture</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Introduction to Part Four</td>
<td>344</td>
</tr>
<tr>
<td>30</td>
<td>What to Tell the Children</td>
<td>349</td>
</tr>
<tr>
<td></td>
<td><em>Marsha Rosenbaum, Ph.D.</em></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Pot, Parenting, and Outing Myself</td>
<td>361</td>
</tr>
<tr>
<td></td>
<td><em>Neal Pollack</em></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>Cannabis: Stealth Goddess</td>
<td>366</td>
</tr>
<tr>
<td></td>
<td><em>Doug Rushkoff</em></td>
<td></td>
</tr>
</tbody>
</table>
33 Gardener’s Rights, Forgetting, and Co-Evolution  373
   An Interview with Michael Pollan
   Julie Holland, M.D.

34 Cannabis, Business, and Philanthropy  383
   An Interview with Peter Lewis
   Julie Holland, M.D.

35 Thots on Pot  387
   Jeremy Wolff

PART FIVE
Steps in the Right Direction

36 Patients Out of Time  399
   An Interview with Al Byrne, L.CDR. (retired), and
   Mary Lynn Mathre, R.N., C.A.R.N.
   Julie Holland, M.D.

37 Prescribing Cannabis in California  416
   Jeffrey Hergenrather, M.D.

38 Canadian Compassion Clubs  432
   N. Rielle Capler, M.H.A.

39 Dutch Drug Policy  441
   Mario Lap

40 A Cost-Benefit Analysis of Legalizing Marijuana  447
   Jeffrey Miron, Ph.D.

41 The Marijuana Policy Project  454
   Bruce Mirken

42 The ACLU and Cannabis Drug Policy  462
   An Interview with Graham Boyd, J.D.
   Julie Holland, M.D.

Resources  473
References  483
Contributors  534
Index  544
Introduction

I didn’t start out editing this book as an expert on cannabis. I felt more comfortable editing my last book, on MDMA (Ecstasy), because I had been studying its potential use in psychiatry for fifteen years prior to its publication. This time, I knew very little going in. And so, feeling a bit over my head, I amassed a group of experts on cannabis to help explain what I could not. Both books are nonprofit ventures; proceeds from sales of the books will fund clinical research on their respective drugs. Please see ThePotBook.com to learn more as well as to find other articles on cannabis.

I am editing this book for many of the same reasons that inspired my last book. Cannabis, like MDMA, is considered both a drug and a medicine. Both drugs are widely used recreationally but also have therapeutic potential.

As most people know, the status of medical cannabis at the federal level is different from its status at the state level. With the introduction of the Controlled Substances Act of 1970, marijuana was classified as a Schedule I drug, the strictest classification, on par with heroin, LSD, and Ecstasy; and as such, it was outlawed. However, cannabis is deemed a prescription medication in nearly a third of the United States, where it is recommended for the treatment of nausea, pain, diminished appetite, muscle spasms, insomnia . . . the list goes on. Fourteen states and the District of Columbia have legalized medical marijuana: Alaska, California, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Jersey, New Mexico, Oregon, Rhode Island, Vermont, Washington, and Washington, D.C. In Maryland, if it can be proven that cannabis is a medical necessity, reduced penalties apply. California, Colorado, New Mexico, Maine, Rhode Island, and Montana are currently the only states to utilize dispensaries to sell medical cannabis.

With regard to drug use around the globe, when nations are compared, the World Health Organization finds clear differences across different
regions of the world, with the United States having among the highest levels of legal and illegal drug use of all the countries surveyed. Drug use does not appear to be related to drug policy, however, as countries with more stringent policies (e.g., the United States) do not have lower levels of illegal drug use than countries with more liberal policies (e.g., the Netherlands) (Degenhardt et al. 1988).

It’s important to look at these numbers. Forty-three percent of Americans have tried pot, as opposed to 20 percent of the Dutch, despite their more lenient policies (MacCoun and Reuter 2001). (In Holland, possession and production for personal use are considered misdemeanors, punishable by a fine only.) Also, interestingly, after California opened up its medical marijuana program, teen cannabis use fell (MPP 2008), proving that making a drug more available in a specific framework does not necessarily yield rampant abuse of that drug.

Cannabis is the most popular illicit drug in the world. An estimated 162 million adults worldwide, 52 million in Asia, and somewhere between 11 and 20 million Americans are regular users (United Nations 2006). According to the most recent available data, 3.5 million U.S. citizens report smoking marijuana daily or near-daily, 14.5 million report smoking the drug at least once a month, and more than 100 million have tried it at least once in their lives (Substance Abuse and Mental Health Services Administration 2008). That’s nearly 43 percent of the American population aged twelve years and older admitting to the federal government about their illegal drug use. The numbers are most likely much higher.

Because millions of people around the world are using cannabis, the sensible course of action is to find ways to minimize its harmful impact. Most useful medications have recommended doses and toxic doses, as well as methods of ingestion that minimize harm and maximize therapeutic results. Harm-reduction strategies should include not only utilizing vaporizers to diminish pulmonary disease, but also a careful reexamination of our drug laws. It is illogical that the most harmful consequence of cannabis use is a blow delivered by our legal system. There’s a great Jimmy Carter quote I love: “Penalties against possession of a drug should not be more damaging to an individual than the use of the drug itself.”

Yet somehow we persist in punishing the pot smokers, adding them to the heap of imprisoned Americans. Our nation now leads every other country on the planet in one thing: more prisoners. One percent of American adults are in jail. Both per capita and in absolute terms, we put more of our
own nation in prisons than any other. In 2009, half of all federal prisoners in the United States were serving sentences for drug offenses (Mendoza 2010). U.S. spending on the drug war tops $100 billion annually. Each prisoner costs $45,000 per year. That is very expensive public housing.

As long as cannabis is illegal, there will be a black market for its sale and distribution. And underground means unregulated. Despite intensive eradication efforts, domestic marijuana production has increased tenfold over the past twenty-five years, from 2.2 million pounds in 1981 to 22 million pounds in 2006. American gang members are the primary retail distributors of most illegal drugs, and they have increased their ranks to nearly 1 million, growing 20 percent from 2005 to 2008, according to the Justice Department (2009), which reports that gangs are responsible for up to 80 percent of the crime in many communities. Mexican drug cartels make 70 percent of their profits from marijuana sales. There is no question in anyone’s mind that the Mexican gangs and the warfare that is waged on both sides of our borders is primarily marijuana-driven. Legalize cannabis, and this mess most likely goes away.

The other important issue here is children’s access to pot. All surveys of teenagers show that it is getting easier for them to acquire marijuana as time goes on; teens have an easier time buying it than purchasing cigarettes or alcohol. Dealers don’t card. Liquor stores do. Also, dealers may interest kids in purchasing other drugs besides marijuana. What the Netherlands figured out a long time ago is that if you separate cannabis from the harder drugs, you can have an impact on which drugs teenagers end up using. In Holland, they have one quarter as many cocaine users as we have in America. Less than 2 percent of the adult population has ever used cocaine. Lifetime cannabis use in the Dutch population aged twelve years and over is less than half of what it is in America (Degenhardt et al. 2008). (For more on the Dutch, please see chapter 39.) It is quite possible that a harm-reduction-based drug policy could keep our country healthier.

What I hope to outline in the pages that follow is a comprehensive assessment of cannabis, its risks and benefits, including the ramifications of our current drug policy. I have gathered experts from around the world to come together and teach what I could not, to share their knowledge with you all. I hope you learn as much as I learned in the process of editing this book.
The study of cannabis and cannabinoids could be enormously beneficial to the field of psychiatry. Cannabis has been used as a treatment for depression, anxiety, inattention, malaise, and insomnia for thousands of years. Millions of people around the world are using marijuana to “self-medicate” these symptoms and others. For these two reasons alone, it would behoove us to have a better understanding of the medicinal properties of this plant.

Specific to the field of psychiatry, we have much to learn about the brain’s endogenous cannabinoid system. To study THC, CBD, and other cannabinoids is to better understand ourselves, our brain chemistry, the brain’s response to injury, and the underlying pharmacology of mind states such as paranoia and panic. Understanding the chemistry and physiology of the cannabinoid molecules could potentially help us create analogues and antagonists to treat other symptoms and diseases. (For example, the cannabinoid antagonist rimonabant can help curb appetite, or stop the “munchies,” but, interestingly, it was rejected by the FDA due to concerns surrounding its ability to induce depression, anxiety, and suicidal thoughts.)

In my private practice, I see and treat many pot smokers. Some of them note that smoking marijuana helps them fall asleep or relax, and they tend to smoke at the end of their day. Others find it helps them focus, be creative, or become more meticulous and obsessive; these patients tend to use
marijuana before starting a project. I have patients with attention deficit disorder (ADD) who feel it helps them pay attention to minute details. I also hear from a fair number of people with depression that it can reliably lift their spirits and create a much-longed-for sense of euphoria and hopefulness. Then there are my anxious or panicky patients who feel that pot makes their symptoms worse; they become more self-conscious and hyperaware, and they are not at all comfortable with marijuana’s effects. On the other hand, I have some anxious patients who swear by it as an aid to relaxation. Any reasonable clinician should be intrigued by this phenomenon: Why are so many patients having such vastly different effects and experiences?

The joke I always make about cannabis with my patients is that it is a “mixed bag.” Because there is such tremendous genetic diversity in cannabis, every strain is unique. Each time someone makes a purchase, they are getting a different medicine, so to speak. Hybrids abound in New York City as they do in the rest of the world, and it is nearly impossible to know just what the mix will be. If they buy an indica-predominant strain, they may become sleepier, more relaxed, and possibly less motivated. A sativa-predominant strain may help energize or focus their thoughts. Both strains seem to induce appetite, which may be a nuisance for some users, but a blessing for those patients made nauseated and anorectic by their medications or illnesses. Some strains might trigger paranoia, perhaps due to a high THC content, while another strain might have an opposite effect if it is CBD-heavy (see below).

Our brains, in particular the cortex where higher thinking and planning are performed, are full of receptors for cannabis. An interconnected network, the cannabinoid system, makes use of our own endogenously made cannabis-like molecules, which are called endocannabinoids. In much the same way as endorphins stimulate our opioid receptors, our bodies make anandamide to activate our cannabinoid receptors. Much like the human race and the opium poppy, we have been co-evolving on this planet with the cannabis plant since our beginnings. Cannabis was likely one of the first plants to be domestically cultivated.

It has been used as a medicine since the third century BCE, and it has a long history of being used to treat psychiatric complaints as well as physical ones (please see chapter 2 by Chris Bennett). The Atharva Veda (around 2000 BCE) tells of using bhanga to “release us from anxiety” (International Hemp Drugs Commission 1893). In ancient Assyrian medical texts, smoking is mentioned as a way to “dispel depression of spirits” (Thompson 1924).
People of the Dutch East Indies noted that cannabis “serves to drive away sorrow and bring them jollity” (Rumpf and Beekman 1981). In Burton’s *Anatomy of Melancholy*, he describes the intoxication of cannabis as a “kind of ecstasy, an inclination gently to laugh.” In England, in the mid-1800s, a tincture of hemp was used to treat morphine withdrawal, inducing “sleep; as an anodyne in lulling irritation . . . a nervine stimulant in removing languor and anxiety” (Clendinning 1843).

In France, the physician Jacques-Joseph Moreau de Tours first wrote of cannabis’s potential for treating psychiatric patients in his book *Du hachisch et de l’alienation mentale: Etudes psychologiques* (“Of hashish and insanity: Psychological studies”), noting that hashish produced “manic excitement always accompanied by a feeling of gaiety and joy inconceivable to those who have never experienced it. I saw in it a means of effectively combating the fixed ideas of depressives, disrupting the chain of their ideas, un-focusing their attention on such and such a subject.” And in America, an Ohio physician, reporting on a case he identified as “hysterical insanity,” wrote of cannabis, “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 . . . . 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 derangements or sequelae that render many of the more customary remedies objectionable” (McMeens 1860).

The English physician John Russel Reynolds, best known as the personal physician to Queen Victoria, had a long career of using and championing cannabis as medicine. Early reports of success treating depression, lassitude, and senile restlessness (Reynolds 1868) paved the way for forty years of successful practice. About the treatment of senile insomnia, he wrote, “I have found nothing comparable in utility to a moderate dose of hemp” (Reynolds 1890).

A British pharmacologist suggested, “In cases where an immediate effect is desired, [cannabis] should be smoked, the fumes being drawn through water, for fits of depression, mental fatigue, nervous headache, and exhaustion, a few inhalations produce an almost immediate effect, the sense of depression, headache, feelings of fatigue disappear and the subject is enabled to continue his work, feeling refreshed and soothed” (Dixon 1899).

Lewis, in 1900, described the effects of cannabis: “The mind seems wholly taken with thoughts of the moment. Very frequently a great inexplicable sense
of relief is felt, the sensation 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.” In Southeast Asia, cannabis was used as a tonic in chronic illness, to induce sleep, and as a relaxant. In Vietnam, a preparation of cannabis seeds was used to “combat loss of memory and mental confusion” (Martin 1975).

Cannabis was used to treat delirium tremens (withdrawal from alcohol dependence) and addiction to cocaine and opiates. Mattison (1891) concluded, “In these, often, it has proven efficient substitute for the poppy. . . . My experience warrants this statement: cannabis indica is often a safe and successful anodyne and hypnotic.” Cannabis has been used to treat opiate addiction (Mayor’s Committee on Marijuana 1944) and alcoholism (Mikuriya 1970; O’Shaughnessy 2007) with good results. A study of THC in cancer patients reported positive psychological effects 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” (Regelson et al. 1976).

A survey of California clinicians working with cannabis revealed psychiatric symptoms to be a common indication for a prescription. (Nearly every patient coming to these clinicians had already been using cannabis to treat their symptoms, so a more appropriate term for what these physicians offer may be “approval,” as opposed to “recommendation.”) From Jeffrey Hergenrather: “In my opinion, there is no better drug for the treatment of anxiety disorders . . . ADHD, obsessive compulsive disorder, and Post Traumatic Stress Disorder” (O’Shaughnessy 2007).

Doctors responding to the survey reported that many of their patients were able to decrease their use of other psychiatric medications, like antidepressant, antianxiety, and sleeping medications, or else they used cannabis to treat their side effects of jitteriness or gastrointestinal problems in order to stay on their medications.

THE PSYCHOACTIVE EFFECTS OF CANNABIS
The psychoactive effects of cannabis are mediated primarily through the CB1 receptors (Pertwee 1997). (Please see chapter 12 on cognition for a review, as well as chapter 6 on the endocannabinoid system.)

The CB1 antagonist rimonabant has been shown to block the subjective effects of marijuana (Huestis et al. 2001) as well as induce depression. It is postulated that dysregulation of the endocannabinoid system is involved in
the emotional processing of stressful events. In a study with mice, impaired CB1 receptor signaling interfered with stress-coping behavior (Steiner et al. 2008). In mice bred to have no CB1 receptors, many abnormalities were seen, taken as a whole to support an “increased susceptibility to develop an anhedonic state” (Martin et al. 2002).

As delineated in chapter 12 by Carl Hart, the subjective effects of cannabis depend on dosage, route of administration, and, most crucially, the set (expectations) and setting (environment). Also important is the person’s familiarity with cannabis. Many of my patients have told me that they didn’t get “high” the first time they smoked pot. Some theorize that this is because they didn’t know what “high” was and couldn’t recognize it when it was upon them. Others believe there is some sort of priming mechanism involved, the way one would have to prime the pump of a well. Not becoming intoxicated the first time one smokes cannabis is a curious, though not universal, phenomenon that deserves more study.

ANTI-PSYCHOTIC EFFECTS OF CBD: CANNABIS AND SCHIZOPHRENIA

While cannabis has frequently been implicated in causing or exacerbating psychosis, there are actually promising leads in using cannabidiol CBD as an antipsychotic medication. (Please see chapter 13 for more on this.) Unlike THC, CBD is a noneuphoriant, anti-inflammatory analgesic that does not bind well to the CB1 or CB2 receptors. Zuardi and colleagues (1997) have proposed that the ratio of THC to CBD is crucial in determining the effects of cannabis on psychosis, and these two components have been studied extensively. Currently, it is widely believed that cannabis strains that are higher in THC are more apt to produce paranoia and other symptoms reminiscent of psychosis, while those higher in CBD are less likely to do so. This is likely the problem with the strains known as “skunk,” which have much higher ratios of THC to CBD. This may also end up being an issue with “Spice,” a synthetic cannabinoid also known as K2 (made up of certain psychoactive chemicals such as JWH-018, JW-073, JWH-250, HU-210, and a homologue of CP-47, 497, that are, as of this writing, not yet scheduled; please check ThePotBook.com for more on this), which acts as a full, potent agonist at the CB1 receptor, as opposed to THC, which is a weak partial agonist.

While THC is responsible for the euphoric and anxiety-inducing effects of cannabis, CBD may modulate these effects, causing sedation and diminishing anxiety (Zuardi and Guimaraes 1997). Thus, strains with higher THC/CBD
ratios may be more paranoia-inducing or anxiety-provoking, than those strains with higher levels of CBD. More importantly, CBD may actually diminish psychotic symptoms in patients who have them, such as those with schizophrenia (Zuardi et al. 1995). CBD was also found to reduce psychotic symptoms in a group of patients with Parkinson’s disease (Zuardi et al. 2009).

In a 1994 study by Warner, psychotic patients who used marijuana had lower rates of hospitalization than those who abused other substances. They were also found to have lower activation symptoms such as psychomotor agitation. These patients reported beneficial effects on depression, anxiety, insomnia, and pain. In a review of twenty-three studies of schizophrenics using cannabis, fourteen studies reported that cannabis users had better cognitive performance than nonusers. Eight reported no difference, and only one study reported better cognitive performance in the schizophrenics who did not use cannabis. The authors say this meta-analysis confirmed their own experiences with cannabis-using patients (Løberg and Hugdahl 2009).

Negative symptoms of schizophrenia (thinking and talking less, having less motivation and activity) are particularly stubborn symptoms to ameliorate with antipsychotic medications. Bersani and colleagues (2002) noted a subgroup of schizophrenics who used cannabis to decrease their negative symptoms. On the other hand, Verdoux (2003) noted a significant association between cannabis use and the negative symptoms of schizophrenia. It is crucial that CBD be carefully studied to determine if it may have a place in psychiatry as an antipsychotic, potentially not only quieting the positive symptoms of schizophrenia (namely the paranoia and hallucinations), but also ameliorating the very difficult-to-treat negative symptoms of amotivation, depression or blunted affect, and talking and thinking less.

The prefrontal cortex is a particular area of interest in schizophrenia research. It is one of the parts of the brain known to be dysfunctional in people with schizophrenia, and many antipsychotics exert some of their beneficial effect there (Thierry et al. 1978). A high density of CB1 receptors can be found in the prefrontal cortex (Herkenham et al. 1990). The primary neurotransmitter abnormalities in schizophrenia involve dopamine, which interacts with the cannabinoid system. THC enhances the flow and utilization of dopamine in the prefrontal cortex (Chen et al. 1990) and, conversely, activation of dopamine receptors (D2) causes an increased outflow of anandamide (Giuffrida et al. 1999).

A 2009 study using receptor tracers and PET (positron emission tomography) scans showed that THC induces dopamine release in the human striatum. This implies that the endogenous cannabinoid system is
involved in regulating striatal dopamine. This is important for two reasons. Not only is there dopamine dysfunction in this area in schizophrenia, but also drugs of abuse are often enhancers of dopamine levels, thus creating pleasure, excitement, and possibly an increased risk of addiction through this “reward pathway” (Bossong et al. 2009).

In a clinical case series, four chronic, treatment-refractory schizophrenic patients (who had reported improvement in their symptoms when they smoked cannabis) were administered oral THC (dronabinol). Three of the four showed significant improvement in core psychotic symptoms. The results would suggest “that the role of cannabinoids in psychosis may be more complex than previously thought. They open a possible new role for cannabinoids in the treatment of schizophrenia” (Schwarz et al. 2009).

**DEPRESSION**

As reviewed above, there is abundant clinical lore, both ancient and recent, that cannabis can help lift one’s mood. In my private practice, it comes up fairly often: my patients use marijuana to feel better. In an Internet survey of over 4,400 respondents (Denson and Earleywine 2006), those who use cannabis had lower levels of depressive symptoms than those who had never tried cannabis. Weekly and daily users of cannabis had less depressed mood and more positive affect than nonusers.

In an exquisitely complicated review paper (Hill 2005), melancholic depression was compared to an endogenous cannabinoid deficiency. Further, the author makes an excellent case for using the cannabinoid system as a target for future antidepressant development. In a follow-up paper, Hill and colleagues (2008) measured one of the endogenous cannabinoids, 2-AG, in depressed patients. Serum 2-AG content was significantly decreased in patients diagnosed with major depression, and the 2-AG content was progressively lower the longer the depressive episode.

In an overview by Mangieri and Piomelli (2007) of the cannabinoid system and depression, the authors state, “The overlap between the physiological functions altered by depression and those affected by cannabinoid receptor signaling is striking.” They continue, “changes in levels of the cannabinoid CB1 receptor or the endogenous CB1 receptor ligands, anandamide and 2-AG, are observed both in humans suffering from depression and in animal models of depression, and experimental manipulation of CB1 receptor signaling has also been shown to affect emotional reactivity in rodents.” CB1 receptors may be up-regulated in suicide victims suffering from depression, as was shown in a
study of postmortem brains (Vinod and Hungund 2006). This may suggest a hypofunctioning cannabinoid system in depressed or suicidal patients.

**BIPOLAR DISORDER**

In a short review article (Ashton et al. 2005), several points were laid out. Though there are no placebo-controlled trials of cannabinoids in bipolar illness, there exist many anecdotal reports of patients experiencing relief of both the depressed and manic phases of their illness. CB receptors are plentiful in areas of the brain thought to be affected by bipolar illness. Patients may experience psychosis or a manic episode due to cannabis use, or they may be more sensitive to its effects than the general population. THC and CBD may have different effects on the various symptoms of bipolar illness.

The take-home message from this article is simple: more research needs to be performed so psychiatrists can ascertain whether cannabinoids, and CBD in particular, might have a role in the treatment of bipolar illness, although Zuardi did not see symptom improvement in two manic patients with trials of CBD (Zuardi et al. 2010). Some of my bipolar patients feel that cannabis destabilizes them, and one study by Strakowski and colleagues (2007) reported that cannabis use was associated with more time spent in affective episodes (depressed or manic phases of illness) and with rapid cycling.

Lester Grinspoon, in his 1998 article, gave multiple case reports of bipolar patients who had experienced marked relief from their symptoms with the use of cannabis, and who believed it to be more effective than standard medications. Others used cannabis to fight the side effects of their psychiatric medications, thus allowing them to remain on effective dosages. Dr. Grinspoon encourages clinical research to follow up on these convincing anecdotal histories and laments the “present social circumstances” that make “such studies almost impossible.”

**POST-TRAUMATIC STRESS DISORDER AND OTHER ANXIETY DISORDERS**

In many self-reports, relaxation and stress relief are benefits that cannabis consumers report. In animal and human studies, cannabinoids have been shown to reduce anxiety (Rubino et al. 2008; Musty 1984). The endocannabinoid system is found in many brain circuits believed to be involved in stress reactions, the extinction of fear, and emotional regulation (Jankord and Herman 2008; Akirav and Maroun 2007).

The endocannabinoid system is linked with the hormonal system known
as the HPA (hypothalamic-pituitary-adrenal) axis and is thought to exert a basal level of inhibition. After someone has been emotionally stressed, it is possible that endocannabinoids help bring the HPA axis back to baseline (Viveros et al. 2007). The endocannabinoid system is also thought to be involved in the learned extinction of the conditioned fear response (Moreira and Lutz 2008). Because cannabis helps you forget, this has implications for the novel treatment of anxiety disorders as well as post-traumatic stress disorder.

CBD in particular seems to have antianxiety effects. In an experiment with college students in a public-speaking model of anxiety, CBD achieved significant improvement (compared with placebo) in subjective anxiety equivalent to diazepam (Valium) and ipsapirone, two medications (anxiolytics) known to decrease anxiety (Zuardi and Guimaraes 1997). Also, dronabinol (Marinol; THC) was found to relieve the symptoms of two patients with treatment-refractory obsessive-compulsive disorder (Schindler et al. 2008).

**ADHD**

Attention deficit hyperactivity disorder is characterized by impulsivity, difficulty sustaining attention, increased activity, and poor planning. The Internet is full of testimonials from doctors and patients alike suggesting that cannabis may have a legitimate place among other treatment options, the gold standard being stimulants such as amphetamine. A case report (Strohbeck-Kuehner, Kopp, and Mattern 2008) asserts that individuals suffering from ADHD may benefit from cannabis treatment in that “it appears to regulate activation to a level which may be considered optimum for performance. There was evidence that the consumption of cannabis had a positive impact on performance, behaviour and mental state of the subject.”

In animal studies, Adriani and colleagues (2003) showed that a cannabinoid agonist reduced hyperactivity and normalized behavioral impulsivity in a spontaneously hypertensive rat strain, which is regarded as a validated animal model for ADHD. Also interesting in this animal model was the decreased density of cannabinoid receptors in the rats’ prefrontal cortex (an area of the brain thought to be involved in executive functions such as planning and organizing). In another animal model of ADHD, Viggiano and colleagues (2003) showed that by enhancing endogenous cannabinoid levels in maternal rats, he could correct the chemical imbalance and improve the hyperactivity of the offspring in “high excitability rats.”

It is not uncommon in patients with ADHD for them to “self-medicate” with caffeine, nicotine, cocaine, or speed. In one survey (O’Shaughnessy
most clinicians who recommended cannabis for their patients agreed that it was preferable to the abuse of other illicit stimulants. In a study of cocaine-dependent patients with ADHD, there was significantly better treatment retention among moderate users of cannabis compared to abstainers or heavy users (Aharonovich et al. 2006).

MEMORY

The endocannabinoid system is involved in memory formation, consolidation, and modulation. Forgetting is an important part of natural brain functioning, and endogenous cannabinoids help to perform this function. Cannabinoids have been shown to interfere with long-term potentiation (the electrochemical basis for memory creation) in the hippocampus, one region of the brain felt to be crucial for memory formation (Riedel and Davies 2005). Animal studies with the CB1 antagonist rimonabant showed improved memory retention for social recognition involving olfactory cues (Terranova et al. 1996). Current theories on how cannabis interferes with memory function implicate the glutamate system and GABAergic axon terminals (see Mackie and Katona 2009 for a review). It is quite possible that cannabinoid antagonists could be a treatment for dementias such as Alzheimer’s disease, and this is an area that deserves further study.

One particular aspect of memory that cannabis affects in animal and human studies is working memory. Rehearsing a phone number you’ve just heard before you dial it, or remembering your train of thought as you speak are two examples of working memory. A common stoner question: “Uh . . . what was I just saying?” Because disruptions in working memory are present in a cannabis-induced state and also in schizophrenia, cannabinoid antagonists may be helpful in ameliorating this symptom.

PRUNING AND LATE ADOLESCENCE

During my initial evaluation of a new patient, I always ask about prior experiences with psychoactive substances, and I have heard one story repeatedly: marijuana was enjoyable in the teen years, reliably causing giddiness or elation, but for many of my patients, when they smoked pot in their late teens or early twenties, they got more paranoid and self-conscious. Many of my patients, especially women, tell me that they simply gave up and stopped smoking at this time. But, in those who went back and tried it again after several years, this unpleasant reaction seemed to subside, and people found they could again enjoy getting high later in their twenties or thirties. (These
patients have a wide array of ages, so I can’t blame the quality of marijuana that was available in the eighties, for example.

It is a curious coincidence that at the same time the brain is vulnerable to a first psychotic break—schizophrenia and manic episodes often begin in the late teens or early twenties, when the brain is undergoing pruning and reorganizing—is also when many people find they cannot tolerate cannabinoids. I would be delighted if there were more research into this particular phenomenon, or to learn if other clinicians are seeing this as well.

**ADDITION**

Although the risk of becoming addicted to cannabis does exist (please see Vandrey and Haney’s chapter 14), it is significantly lower than the risk associated with many other drugs, both legal and illegal. Compare the dependency risks in an Institute of Medicine report (1999): cigarettes (32 percent), heroin (23 percent), cocaine (17 percent), alcohol (15 percent), and marijuana (9 percent). It should also be noted that withdrawal from cannabis use is typically short-lived and mild, as opposed to potentially life-threatening (with alcohol) or nearly insurmountable (cigarettes). Although the numbers of people seeking treatment for marijuana dependence are higher than one might think, this may be due to changing drug laws and policies, where compulsory treatment instead of jail time requires enrolling in a rehab or drug program.

More clinically relevant to the field of psychiatry is the use of cannabis as a substitute for other drugs of abuse like cocaine, heroin, and alcohol. Multiple California clinicians responded to the O’Shaughnessy survey (2007) with tales of patients with prior out-of-control addictions who became stabilized on small amounts of cannabis. One physician reported more than 90 percent of his patients had reduced their alcohol consumption by using cannabis. From a medical and psychiatric perspective, the substitution of cannabis for other more toxic and addictive drugs is a good example of harm reduction.

A recent examination of postmortem brains of alcoholics showed alterations in endogenous cannabinoid levels in key brain areas thought to be implicated in alcoholism (Lehtonen et al. 2010). As more studies are performed, it is my belief that abnormalities in the endocannabinoid system will be found in many more patient populations.
TRUSTING PATIENTS TO ADJUST THEIR DOSE
We have all been warned repeatedly that the cannabis available today is more potent than what was available decades ago. While there is some debate about how crucial this is (some compare it to the difference between wine and beer, others to beer and whiskey), there is some uniformity about the pot-smoker’s response: They smoke less of the good stuff. One of the advantages of smoking cannabis, as opposed to taking oral preparations, is that experienced smokers learn quickly how to adjust their dosages depending on how strong their marijuana is. Because the onset of action is minutes instead of hours, dosage can be easily regulated. Many clinical studies have shown that smokers are quite good at regulating their “high” with different types of cannabis (Heishman, Stitzer, and Yingling 1989; Herning, Hooker, and Jones 1986), using a mixture of more air and smaller or fewer “puffs” for a more potent strain of cannabis.

THE CANNABINOID AND OPIOID SYSTEMS
There seems to be some sort of synergy or overlap between the cannabinoid and opioid systems (Cichewicz 2004). Patients who use both opioids and cannabis notice a synergism between these two drugs (Welch and Eads 1999). More important, what I have heard repeatedly from caregivers is that patients who use cannabis to manage their pain typically require less opioid pain medications. The relative toxicity of these two medicines, as well as their side effect profiles, typically favors cannabis. Randomized, double-blind, placebo-controlled trials are needed to substantiate these claims.

Moderate cannabis use was associated with improved retention in a study of naltrexone treatment (an opioid antagonist) for opiate-dependence (Raby et al. 2009). Researchers noted that experimental studies are needed to directly test the hypothesis that cannabinoid receptor agonists exert a beneficial pharmacological effect on naltrexone maintenance, and to better understand the mechanism involved.

DEHABITUATION
Smoking cannabis often fills one with a sense of wonder, of childlike awe at one’s surroundings. What is habitually seen and ignored suddenly becomes captivating, eliciting renewed attention and appreciation. This is especially evident when someone who is altered finds himself or herself out and about in nature. In talking about using cannabis to treat psychiatric
complaints, it is worthwhile to consider the spiritual aspects of its use, the soul-feeding effects.

Many people who are depressed feel overwhelmed and defeated, their souls crushed as they “suffer the slings and arrows” of daily life. Certainly my patients in New York City are weighed down by a barrage of constant worries delivered around the clock via e-mail, voicemail, and to-do lists. If cannabis creates a sense of respite from all that, an oasis of sorts, might that be therapeutic in and of itself? Separating what is therapeutic from what is recreational can become quite murky with regard to treating depression. The euphoria or giddiness that may come from “recreational” use of cannabis may be just what the doctor ordered when the target symptoms are a depressed mood and a pessimistic outlook.

Think of the Dove bar commercial: “My moment. My Dove.” Or the Starbucks’s Frappuccino ad: “It’s ‘You’ Time.” What is being marketed here is the delineation of time, creating a marked boundary, a timeout, giving you permission to relax, perhaps to be alone, where no one can get to you, and there are no responsibilities or chores to be done. Meditation—sitting still, breathing deeply, and clearing the mind—is a therapeutic activity with myriad benefits for mental health and wellness. An herbal medicine to assist “going within,” to facilitate psychospiritual exploration, to allow solitude, and, more importantly, comfort in that solitude may likewise have a positive impact on mental health.

CONCLUSION

Mental health disorders, like most physical ailments, are multifactorial. Psychiatric ailments have their basis in a triad of psychological, sociological, and biological underpinnings. If an herbal remedy can offer substantial relief, it makes sense to take advantage of that first and foremost, either as a substitute for other psychiatric medications, or as a complement to allow lower doses or enhanced compliance with a current regimen.

The bottom line is that we need to know more. More research needs to be performed so we can all adequately understand whether cannabis can be a useful adjunct to psychiatric healing and another “weapon in the armamentarium” of psychopharmacologists to combat psychiatric illnesses. This observation by Marian Fry, M.D. (quoted in O’Shaughnessy 2007), sums it up nicely: “Health is a state of mind, body, and spirit. By restoring their connection to nature, cannabis helps patients on all three levels.”