Cerebrum, April 2016

David Casarett's *Stoned: A Doctor's Case for Medical Marijuana*

Review by Bradley E. Alger, Ph.D.

Editor's Note: With legal cannabis sales at $5.4 billion in 2015 and expected to rise by another billion this year in the United States, legalization and marijuana's impact on health is a hot topic of national debate. Casarett, a physician at the University of Pennsylvania, immerses himself in the culture, science, and smoke of medical marijuana in order to sort out the truth behind the buzz. Our reviewer, who has authored more than 120 research papers and reviews on the regulation of synaptic inhibition and endocannabinoids, tell us what the author got right, but also overlooked on his journey to learn more about a complex and controversial subject.

David Casarett was a palliative care doctor with an Archie-Bunkereseque level of skepticism regarding medical marijuana. He doubted that marijuana was a medicine, or indeed that it was good for anything, but finally had to admit that he didn't know enough to advise patients who asked about it. Does marijuana "work?" Is it safe? Effective?

This book chronicles Casarett's foray into the world of medical marijuana. It is an engaging, lively, thought-provoking tour seen from the street, not the laboratory; the walk-in clinic, not the ivory tower. The doctor wants to know not only the subject, but also how to explain it to his patients (and readers) in terms that they will understand; how to give them a voice in their own care and be informed medical consumers. In trying to accomplish this, he covers a lot of ground.

Casarett discusses a range of maladies for which marijuana is said to be beneficial—including insomnia, nausea, cachexia, pain, and cancer—in vignettes that begin with an arresting anecdote or personal story of a patient (including himself in one case). He establishes a largely jargon-free scientific/medical context for understanding how marijuana might act in a given case, and sums up his impressions of the evidence. This is advice such as you'd get from a neighbor (who happens to be a doctor) over a beer after a game of golf: many "possibles" and "maybes," a few numbers, but no charts and graphs; and only a couple of firm answers.

The uncertainty and caveats are unsurprising because many of the experimental studies available are small and not well controlled. Marijuana "seems to be" effective in treating neuropathic pain, "definitely" works for nausea, "probably" improves appetite, and reduces insomnia; it "might be" helpful for anxiety and PTSD; "maybe, someday" we'll know whether it does anything for cancer, but now, nothing. The reader, who may be frustrated by the indefiniteness of his verdicts, is reminded that the scarcity of hard data results from the benighted federal drug policy that still classifies marijuana as a Schedule I drug (dangerous and of no medical value), significantly worse than morphine, cocaine, or amphetamines, which are on the less restrictive Schedule II.

Usually Casarett gives us enough scientific background to clarify his opinions without overdoing it. His accounts of why marijuana affects different people differently, and how the storage of THC (the psychoactive chemical in cannabis) in body fat can modulate its effects, are two good examples among many. But the book is as much sociology as medicine. Casarett often goes undercover to capture the experience of the individual patient peering in at the medical marijuana subculture. At one point he gets a tutorial in the psychoactive subtleties of marijuana varieties that is as nuanced as the wine recommendations of a sommelier at a tony New York restaurant (Casarett takes it all in, but is a noncustomer.)

He reviews the panoply of forms and delivery methods of cannabis products—besides the standard joints, there are pills, vaporizers ("vape pens"), oils, resins, oral sprays, potables (cannabis-infused beer and wine), and edibles from gummy bears to brownies—and weighs their pros and cons. He recounts his own attempt to treat chronic back pain by smoking a joint on his back porch: it is neither transformative nor a complete nightmare, although one doubts that he'll go there again. He does answer a commonly asked question: why smoke if you can get cannabinoids in FDA-approved pills, or edibles? In a nutshell: control. Because of the rapid transit time for THC to go from the lungs to the brain (tens of seconds), an experienced user can titrate his intake to produce just the desired level of symptomatic relief. Taken by mouth, THC has to pass through the GI tract (tens of minutes, with times dependent on what food was eaten and when, etc.) and undergo variable absorption into the blood stream; no wonder the effects of ingested marijuana are less predictable. Couple this lack of control with the disinclination of severely nauseated patients to swallow anything, and one appreciates the appeal of smoking.

Despite the book's subtitle ("a Doctor's Case for Medical Marijuana") this is not a tale of advocacy; the author shuttles evenly between doubt and sympathy. A hilarious visit to a sketchy marijuana clinic/dispensary that will confirm the worst suspicions of die-hard opponents who see the entire medical marijuana movement as a scam, is counterbalanced by moving stories of people who, having tried conventional medications (including morphine) without success, depend on the comfort that they get from marijuana to live a normal life.

Casarett's authorial instinct for the captivating image occasionally leads him astray: he repeats a story of some cannabis-dependent soldiers in the 1940s and their lurid and sometimes violent behavior when compelled to go cold-turkey during assignment to a cannabis-free environment. This anecdote, seemingly right out of the *Reefer Madness* handbook, is used to dramatize the withdrawal symptoms that might accompany cessation of marijuana use, although Casarett acknowledges that this case is atypical (and hardly a controlled study). He is alarmed that nine percent of marijuana users meet the clinical definition of addiction (as compared with 12 percent of alcohol users and 15 percent of heroin users), and takes it as a given that any addiction is bad.

The discussion would have benefited from a more critical analysis. For instance, given the numbers, shouldn't we promote marijuana use as a way of reducing the overall heroin addiction rate? Or consider what he doesn't stress: that overdoses of opiates or alcohol are often fatal. In 2014 opiates caused 25,000 deaths (DrugAbuse.gov), and alcohol-poisoning causes 2,200 deaths each year (CDC website), whereas, as Casarett notes, deaths from marijuana overdose are essentially unknown (DrugWarFact). Finally, alcohol consumption was implicated in 10,076 deaths from car crashes in 2013 (CDC website). Despite the presence of millions of recreational users in the US, there is no evidence that marijuana causes anything like that level of carnage. Nobody is recommending marijuana use as a public health safety measure—you shouldn't operate cars or heavy machinery when stoned—but these are some of the societal complexities that the book skirts.

Given his cautious conclusion that marijuana can be beneficial in some instances, it may come as a surprise that Casarett is not bullish on marijuana's future as a medicine (he considers it an "herbal remedy"), arguing that major pharmaceutical companies are working overtime to find drugs that will be better at treating the disorders that medical marijuana treats, and will not have marijuana's side effects. He cites the case of glaucoma, for which marijuana used to be recommended, but which is now controlled effectively by conventional medications. On the other hand, the discovery of the opioid receptor many years ago prompted confident predictions that opiate drugs would soon be available that would selectively relieve pain without causing euphoric or addictive side-effects. The current epidemic of prescription opiate-drug addiction (and rebound heroin use) in the US is enough to give one pause. Will Big Pharma have better luck in replacing marijuana?

Casarett's engrossing narrative stance, basically as a physician playing the role of educated layman, perhaps leads him to overemphasize the interactions of the chemicals in marijuana, e.g., THC, CBD (a non-psychoactive extract) with the major cannabinoid receptors, CB1 and CB2, for understanding marijuana's actions. Different drug-receptor interactions do contribute to marijuana's assortment of behavioral effects, but this narrow focus fosters the misperception that "the future of marijuana research" is in the hands of chemists who are tweaking the THC molecule and producing variants ("synthetic cannabinoids") that also activate the CB1/CB2 receptors. In fact, these variants will potentially interact with a large number of other molecular targets. As a case in point, anandamide, the classic natural CB1 activator ("endocannabinoid") in the body ("the THC inside all of us"), activates a non-cannabinoid receptor, the TRP receptor, more efficiently than it does CB1! We will need to know much more about the molecular targets of synthetic cannabinoids before assigning them a leading role in medical marijuana-type therapies.

More significantly, Casarett skips over the myriad issues associated with the highly variable distribution of CB1 receptors across brain regions and functional classes of brain cells. Admittedly, this is a complicated subject, yet understanding it and figuring out how to target the cannabinoids correctly to carefully defined subregions will, I believe, ultimately be more relevant for developing marijuana-based therapies, than refining drug-receptor match-ups. Finally, Casarett barely scratches the surface of the exploding field of the endocannabinoid system, exploitation of which will surely be a major direction for the future of medical marijuana. Why worry about exogenous cannabinoids if we can harness the ones we already have on board?

By and large, however, such lapses do not detract from my enthusiasm for the book. It accomplishes what it sets out to do, giving patients and care-givers a balanced, insightful view of medical marijuana in an entertaining, straight-talking way. I found it an enjoyable read and highly recommend it.

Bio

Bradley E. Alger, Ph.D., is a professor emeritus in the Department of Physiology at the University of Maryland School of Medicine. He received his Ph.D. in experimental psychology from Harvard University in 1977, and taught and did research at Maryland from 1981 to 2013. In the early 1990s, Alger and Thomas Pitler characterized the first signaling process ultimately found to be mediated by endocannabinoids in the brain. Alger has authored over 120 research papers and reviews, focusing in the past two decades on the regulation of synaptic inhibition and endocannabinoids.