Of Hypes and Highs—The CBD Craze Has Arrived

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Long before governments got into the business of regulating how people get high, cannabis was recognized as a potent medicinal and psychotropic agent. The written record dates back several millennia to China, where herbalists and surgeons described its beneficial effects as an anesthetic and anxiolytic, but its use as an intoxicant and medicine undoubtedly stretch well into prehistory. Because harvesting cannabis, opium, or coca leaves does not involve the type of collective planful action needed to produce alcohol (it literally does take a village to brew a beer, and some have speculated that humans transitioned from hunter-gatherer to agrarian societies primarily to be able to transform grain into alcohol), it is quite likely that plants or fungi containing psychoactive compounds (of which there are many, including not only cannabis, opium, and coca, but ayahuasca, kava kava, kratom, betel, ephedra, nightshades, psilocin-containing mushrooms, and many more) were for millennia what humans turned to in order to induce altered states of consciousness. Some of these plants had a principally ritualistic role (drug-induced religious experiences, or the so-called ecstatic visionary shamanism, meant to provide divine guidance or inspiration), others had medicinal uses, but probably more often than not they also were used for what we quaintly call today "recreational" purposes. The use of opium can be traced to prehistoric times in what is now modern Iraq. Homer referenced it in the Iliad. That its use was for nonmedicinal purposes can be divined from its Sumerian name *hul gil*, which literally meant "plant of joy."

Often mixed with alcohol or other sedatives, cannabis also has a long history in Western medicine. Extracts of hemp were mentioned in Robert Burton's 17th century *Anatomy of Melancholy* as a potential treatment for depression; it was highly prescribed in psychiatry and medicine in the U.S. throughout the 19th and early 20th century. In combination with metallic salts like potassium bromide, alcohols like chloral hydrate, or other sedative substances, numerous cannabis-containing preparations were used as nonspecific sedatives, anxiolytics, and pain relievers, and these were a significant component of the pharmacopoeia until 1930 when a Treasury Department official named Harry Anslinger, perhaps sensing the end of Prohibition and seeking renewed job security, launched the first American "war on drugs." By the mid-1930s, cannabis had largely vanished from the U.S. pharmacopoeia, and in 1937 it was listed by the U.S. Internal Revenue Service (then the government overseer of dangerous drugs) as a "narcotic." By the time the first edition of Goodman and Gilman's classic text *The Pharmacological Basis of Therapeutics* was published in 1941, cannabis, although still clinging to a listing in the official U.S. Pharmacopoeia as a therapeutic agent, was dismissed by Goodman and Gilman: "Cannabis has no rational or indispensable uses in modern medicine. While it was formerly employed empirically in migraine, insomnia, neuralgia, and many other syndromes, it is now no longer prescribed." (p. 185 of the 1941 edition).

So there you have it. The arbiters of therapeutic drug use in the 1940s had nixed the use of cannabis as a useful drug in medicine or psychiatry, ironically for the same clinical syndromes that cannabis in the guise of "medical marijuana" is frequently used today., That is, as a nonspecific pain reliever, anxiolytic, or antidepressant. The Drug Enforcement Agency (a part of the U.S. Department of Justice) continues to list cannabis as a Schedule I drug (one that has no

medical value and has a high potential for abuse). Because the U.S. government is impervious to irony, this listing persisted even though the FDA has long approved dronabinol, a synthetic version of the psychoactive compound in cannabis, delta-9-tetrahydrocannabinol, as a prescribed agent for treating AIDS-related weight loss and chemotherapy-induced nausea and vomiting. The drug, marketed as Marinol, continues to be available today, as a Schedule III drug (one that has potential for abuse but has recognized therapeutic benefit).

Cultivation of hemp, the major source of CBD, was made legal by the 2018 Farm Bill, and this has led to an explosion in the availability of CBD in multiple formulations (CBD-containing cocktails? Order one up from your friendly neighborhood bartender). This in spite of the fact that it is technically still illegal to put CBD in food for humans or animals. Former FDA commissioner Scott Gottlieb has called for a timeout, warning that CBD remains relatively poorly studied, particularly in humans, and for most commercial claims an evidentiary base is simply not there.

But rather than focusing on legal constraints, let's look at some more practical aspects of CBD usage. In general, CBD use is probably unwise at present, simply because there are no regulatory mechanisms in place to ensure that what you consume is actually CBD (which it very well may not be) and if it is, how much of it you're getting. Like most herbal or alternative medicines, regulatory processes are sketchy, and many if not the majority of herbal agents do not contain what the label says they do. Absent government oversight, the ability to detect adulterants or contaminants in the manufacturing process simply doesn't exist. Readers are likely familiar with a well-known DNA analysis that found even in well-established commercial venues in the U.S. and Canada less than 50% of the supplements for sale contained the authentic product, over 60% had incorrect labels, and substitutions, contaminants, and undeclared fillers were common. Since the publication of that study, herbal marketing groups have promised to improve their practices, and perhaps they did, but without effective regulatory control there is no way of verifying this.

Perhaps more importantly, at the present time we really don't have a clear picture of what CBD actually does, in part because the government's classification of cannabis as a dangerous substance with no therapeutic value has severely limited our ability to research its actions and effects. In a nutshell, though, CBD has been claimed to lack the psychotropic effects of THC, but is said to be useful as an anxiolytic, potential antidepressant, antiseizure, and anti-inflammatory agent. (As a not-too-technical aside, please note that while CBD has been claimed to lack *psychotropic* properties, if it is an anxiolytic/antidepressant it is by definition a psychotropic agent. It may not be psychogenic, but that is a discussion for another time.)

Bear with me, because to understand all this a little bit of science is needed: Humans, like many if not most living creatures, have endogenous cannabinoid receptors (even invertebrates as basic as sea squirts possess some type of cannabinoid receptor). Since endogenous cannabinoid receptors are so highly evolutionarily conserved, it makes sense that they play some kind of role in regulating essential but incompletely understood homeostatic processes. Humans possess two known cannabinoid receptors, CB1 and CB2 receptors. CB1 receptors seem to be where THC binds and exerts most of its activity. CB2 receptors, like CBD, are less well understood (for a great, if technical review of endocannabinoid receptors see Bow & Rimoldi, 2016, who noted that CB2 has been called a "receptor with an identity crisis".

CBD does appear to have lesser affinity for CB1 receptor binding, and its action at CB2 receptors may suggest an anti-inflammatory action, among others. While its mechanism of action is incompletely understood, CBD may serve as a competitive antagonist at CB1 receptor binding sites, and its role in epilepsy has been ascribed to a down-regulation of excitatory neural activity.

CBD in prescription form exists. Epidiolex was approved 2018 to treat Lennox-Gastaut or Dravet syndrome—two very rare seizure disorders that appear in infancy or early childhood. Dravet syndrome is generally marked by febrile seizures and is associated with hyperactivity and deficits in motor, speech, and social functioning. It may progress to status epilepticus. Likewise, cognitive, motor, and social difficulties are often present in Lennox-Gastaut syndrome, which generally begins ages 3–5 and is associated with tonic (muscle contraction) seizures.

So if you have read this far, you can see that our story is full of ironies (an undeclared filler in this column). Adding to the ironic quotient, if someone wants to consume a cannabinoid, rather than using nonprescription CBD they are far better off seeking out plain old cannabis in a state that has legalized the use of medical or recreational marijuana, because those states have regulatory mechanisms to determine things like total THC content and growing and sales of cannabis have some degree of oversight. Of course there are plenty of good reasons to use cannabinoids that are free of the psychoactive or intoxicant actions of THC. But until we have a better understanding of exactly what CBD does, it's likely better to use it only for the purposes that have been best studied. And like all herbal substances, unless we really know what we (and the substance itself) are doing, it's probably best that we recommend patients don't use them.