Cannabinoids and the Endocannabinoid System: Emerging Trends

Cannabis-derived therapies may offer a great opportunity to modulate the endocannabinoid system, but understanding the risks is paramount.

By Shawn Masia, MD and Ryan Zaklin, MD, MA

First reported some 5,000 years ago, the medicinal use of cannabis has since been reported anecdotally in the treatment a variety of conditions.[1] Over the last century, as many commonly prescribed modern pharmaceuticals were discovered by studying ethnobotanical traditions, 80 years of prohibition have sidelined clinical cannabis research.[2] The phytocannabinoids with physiological effects isolated in the 1960s and 1970s ultimately led to the identification of the endogenous receptors, ligands, enzymes, and transporter proteins that comprise what has been called the Endocannabinoid System (ECS).[3] In addition to pharmaceutical development and testing, 28 states and the District of Columbia (DC) have enacted medicinal cannabis access programs,[4] with over 1.2 million patients enrolled nationally.[5]

Although the US government still lists cannabis as a Schedule I drug,[6] compounds derived from cannabis (*Cannabis sativa, Cannabis indica*) have recently entered FDA clinical testing, and some are approved for use in the European Union. As these trends continue, it is useful for physicians to understand the fundamentals of the ECS and the emerging pharmaceuticals that target this system, as well as the impact of medical cannabis regulations on their patients and practice.

HISTORICAL USE AND PROHIBITION

The earliest writings on the use of medical cannabis date back to a 15th century BC Chinese Pharmacopoeia called the *RhYa*.[7] Indian Ayurvedic texts from 600 BC described cannabis use for both stimulating and calming the mind, and also as an anti-phlegmatic and an anesthetic.[8] The 700 BC Persian text the *Venidad* included over 10,000 medicinal plants and cited cannabis among the most significant.

Greek and Roman doctors prescribed cannabis for a variety of ailments, a tradition that persisted through the Renaissance.[9] Western civilization brought hemp, a common name for *Cannabis sativa*, across the Atlantic. Cannabis tincture was added to the US Pharmacopeia in 1850,[10] and was widely prescribed for a number of ailments. By 1918, US pharmaceutical firms grew over 60,000 pounds to produce tincture from the flowering tops.

During the early 20th century, growing concerns over its abuse potential drove many states to pass laws prohibiting cannabis, along with opium and alcohol. In 1936, Harry J. Anslinger, Commissioner of the newly established Federal Bureau of Narcotics, characterized marijuana as a dangerous drug and advised federal action. The American Medical Association called for further research, however Anslinger's efforts led to the 1937 Marijuana Tax Act, which greatly diminished its use. Further shaping public opinion were films such as *Reefer Madness* (1936) and a chain of anti-marijuana articles published in newspapers owned by William Randolph Hearst.[11]

With increasing associations to crime, cannabis was removed from the Pharmacopoeia in 1942. The next decades saw increasing enforcement and harsher punishment of cannabis related offenses, culminating in the Schedule I classification under the Controlled Substances

Act in 1970. Since that time, the National Institute on Drug Abuse (NIDA) regulated all clinical research conducted in the US, using cannabis grown by the University of Mississippi. Recently, though, the DEA announced that it will certify additional institutions to provide medical cannabis for research.[12]

PHYTOCANNABINOIDS AND THE ECS

Raphael Mechoulam and colleagues identified and synthesized the main psychoactive component of cannabis, delta-9-tetrahydrocannabinol (THC), along with cannabidiol (CBD) and several other constituents in 1964.[13] Subsequently, at least 113 different phytocannabinoids unique to cannabis were identified along with numerous terpenes found in other plants.[14] While some debate remains regarding the taxonomy of cannabis, plant morphology suggests that four species exist: *Cannabis sativa, Cannabis indica, Cannabis rhudarelis*, and *Cannabis kafiristanica*, with genetic confirmation of at least two original species lineages (*Cannabis sativa* and *Cannabis indica*).[15,16]

A frequent misconception within the lay literature is that *Cannabis sativ*a derived strains offer more of a stimulating effect, thus are for daytime use, while *Cannabis indica* offers more of a relaxing, narcotic effect, thus reserved for nighttime use.[17-19] This alludes to a variation in odor, texture, and physiological effect found in individual strains, which is thought to be derived from the combined effects of the various phytocannabinoids and terpenes present.[20] Hybridization and breeding towards a higher THC content has diluted the genetics and diminished the presence of higher levels of the other cannabinoids in many strains used today for medical marijuana.[21]

Ben Shabat proposed that the multiple ligands and receptors of the ECS allowed an unprecedented level of orchestrated modulation he called the entourage effect.[22,23] Some have proposed that the specific concentration of phytocannabinoids, terpenes, and other active compounds exert their activity via an analogous entourage effect upon both the ECS and non-ECS components, such as the combination of THC and CBD used in nabiximols.

The ECS is a ubiquitous signaling system present throughout human tissues. Its function has been summarized as playing a major role in our ability to, "relax, eat, sleep, forget, and protect."[24] In 1990, Herkenham and colleagues discovered endogenous receptors for a synthetic THC analog showed high densities in basal ganglia, hippocampus, and cerebellum, but with paucity in the brainstem respiratory centers, a pattern preserved within numerous mammalian species.[25] These so-called CB1 (Cannabinoid 1) receptors proved to be the most numerous g-protein coupled receptors[26] in the CNS.[27]

Soon thereafter, Devane, Hanus, and Mechoulam (who identified THC in 1964), discovered an endogenous arachidonic acid derivative with strong affinity for the newly isolated CB1 receptors. They called it N-arachidonoylethanolamine (AEA) or anandamide, named after "ananda," a Sanskrit word for "bliss."[28] THC and AEA were found to additionally activate a second g-protein coupled receptor expressed in peripheral tissues, called CB2 (Cannabinoid 2). The principal expression of the CB2 receptor in peripheral tissues, such as immune cells and gastrointestinal cells, suggested roles far removed from the psychoactive effects of the plant that led to its discovery.[29] An additional ligand known as 2-arachidonoylglycerol (2AG) was subsequently isolated from canine gut and showed affinities for both CB1 and CB2.[30] These main putative ligands are postsynaptic, membrane bound, fatty acid precursors with complex and varied synthetic pathways, and are released in response to depolarization (AEA)[31] and increased postsynaptic calcium (2AG).[32]

AEA has a rapid half-life due to the activity of fatty acid amide hydrolase (FAAH),[33] whereas 2AG has a longer half-life and is terminated by monoacylglycerol lipase (MAGL).[34] Multiple other ligands and receptors are thought to be involved in the ECS, in addition to transporter proteins that shuttle the lipophilic ligands to their presynaptic targets.[35]

The presence of presynaptic receptors co-localized with postsynaptic ligands suggested a homeostatic role. Preclinical and clinical studies further indicate ECS involvement in embryogenesis, driving suckling in neonates, learning and memory, emotional processing, hunger and satiety, inflammation, pain, and carcinogenesis.[36]

Ethnobotanical traditions, preclinical and pharmacological studies, and the increasingly available clinical data suggest that modulation of the ECS may be useful for the treatment of diverse disorders, such as painful peripheral neuropathy, pain associated with cancer, stimulation of appetite in AIDS wasting and chemotherapy treatment, irritable bowel syndrome, fibromyalgia, migraine, depression, epilepsy, heart disease, and many other diseases.[37-40] AEA and 2AG, along with the putative modulatory constituents N-palmitoylethanolamide and N-oleoylethanolamide, have been found in decreased levels in the cerebrospinal fluid of MS patients.[41-43] Additional interventions such as acupuncture, massage, and lifestyle

PRACTICAL POINTER

Physicians who certify patients within medical cannabis programs should familiarize themselves with the applicable state-specific regulations and confirm appropriate coverage with their malpractice insurance carrier.

Risks and Adverse Reactions to Cannabis Use

While cannabis-derived compounds have shown potential benefits in the management of neurological conditions, it is important to consider the potential risks and adverse reactions. Here is a brief list:

RISKS

- Addiction
- Driving impairment
- Cardiopulmonary complications associated with smoked cannabis
- Carcinogenesis
- Complications during pregnancy

ADVERSE REACTIONS

- Cognitive dysfunction
- Paranoia
- Tachycardia
- Orthostatic hypotension

modifications such as diet and exercise also play a role in balancing the ECS.[44]

While cannabis derived therapies may offer a great opportunity to modulate the ECS, understanding the risk obviously becomes prudent. Underreporting of adult use and research regulation frustrate attempts to quantify the health risks of acute and chronic cannabis use. Some of these potential risks may include addiction,[45] driving impairment,[46] cardiopulmonary complications associated with smoked cannabis,[47,48] carcinogenesis,[49] and complications during pregnancy.[50] Adverse reactions are common, and may include cognitive dysfunction, paranoia, tachycardia, and orthostatic hypotension.[51] A paradoxical cannabinoid hyperemesis syndrome, associated with chronic cannabis abuse, has been reported.[52] Of note, drug-drug interactions may prove concerning, as cannabis use is associated with significant inactivation of cytochrome p450.[53]

PHARMACEUTICALS

Phase 3 studies of the botanical compound Epidiolex (cannabidiol) showed a reduction in frequency and severity of seizures in patients with Lennox Gastaut Syndrome and separately in Dravet syndrome with good tolerability and low incidence of adverse reactions.[54-55] Multiple possible mechanisms including CBD affinity at non-cannabinoid receptor targets are proposed.[56-58] A botanical compound of THC and CBD derived from cannabis known as Sativex (nabiximols) is approved in the EU for treatment of painful spasms associated with multiple sclerosis and FDA trials are ongoing for pain associated with cancer.[59]

Synthetic cannabimimetic compounds have shown mixed results. For example, Marinol (dronabinol) is synthetic THC indicated for cachexia and anorexia in patients with AIDS, as well as for nausea and vomiting associated with cancer chemotherapy.[60]

Cesamet (nabilone) is a synthetic cannabinoid that is chemically similar to naturally occurring THC and is approved for treatment of nausea and vomiting associated with cancer chemotherapy when other drugs have failed.[61] Some have suggested that dronabinol and nabilone are not as effective as botanical extracts of cannabis due to removal of the active and inactive matrix of compounds found in whole plant extracts.[62]

Some of this is attributed to the increased psychoactive effects from orally ingested cannabis and cannabis-derived products, large in part to the conversion of Delta9THC to 11HydroxyTHC, a longer acting, more potent psychoactive derivative.[63-64]

Rimonabant (Acomplia, Zimulti), a selective CB1 antagonist, was approved in the EU for weight loss in obese patients with other complications such as dyslipidemia or diabetes. It was suspended due to severe psychiatric side effects, including increased risk of suicide, and thus was never approved by the FDA.[65] Synthetic cannabinoids have side effects and risks that far exceed those of cannabis or cannabis extracts and there is great concern over the safety, unregulated proliferation, and abuse of these compounds.[66]

MEDICAL-LEGAL ISSUES

Significant variations exist amongst medical cannabis programs in each of the 28 states and DC, as well as the 16 states with CBD-specific laws and three states that had medical marijuana on the ballot for 2016.[67-69] Thus, physicians who certify patients within medical cannabis programs should familiarize themselves with the applicable state specific regulations, and confirm appropriate coverage with their malpractice insurance carrier. Proper documentation, including the specific indication(s) for certification, as well a discussion of potential risks is necessary.[70]

Unique liabilities present risk for certifying physicians. For example, despite provisions in the California legislation that called for protection for physicians who certified patients according to regulations, the Clinton administration in 1997 announced that any physicians who recommended or prescribed cannabis would face losing their DEA registration.[71] However, a successful lawsuit raised by California physicians concerned their First Amendment rights to discuss the literature with their patients[72] and the DEA did not proceed. Cases in Ohio,[73] Massachusetts,[74] and Colorado[75] have shown that physicians who do not follow state guidelines face penalties, suspension, and even revocation of their licensure.

CONCLUSIONS

Emerging evidence suggests important roles for the ECS in central and peripheral tissues and diseases, thus it is beneficial to keep apprised of ongoing developments. The further identification of multiple ECS components heralds the potential for multiple new treatment options, including whole plant and molecular-based pharmaceutical products that will follow traditional FDA approval pipelines.

Concomitantly, a body of literature concerning the clinical use of whole plant cannabis and its derivatives for a large variety of medical conditions continues to expand. Given the increasing numbers of patients certified for cannabis use, it is important for physicians caring for patients utilizing medical cannabis to understand the common side effects, risks, and alternative methods of ingestion. ■

Shawn Masia, MD is a board certified neurologist and clinical Neurophysiologist. He provides evidence-based, patient-centered care via telemedicine platforms at hospitals across the country.

Ryan D Zaklin, MD, MA is a board certified Internal Medicine physician practicing north of Boston. His focus on Integrative Medicine and Mind-Body Medicine has led to his interest in Endocannabinoid Medicine and Cannabis-based Therapeutics.

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