Cannabinoids and Mental Health, Part 1 The Endocannabinoid System and Exogenous Cannabinoids

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Cannabinoids and Mental Health, Part 1

The Endocannabinoid System and Exogenous Cannabinoids

ABSTRACT

The increasing public acceptance of cannabis and the proliferation of cannabis products in the marketplace has coincided with more patients using the drug as a substitute for psychiatric medications or as an adjunctive treatment modality for psychiatric conditions, despite limited evidence of efficacy. With a goal of furthering harm-reduction efforts in psychiatric nursing, the current article reviews the fundamentals of the endocannabinoid system in humans and the exogenous phytocannabinoids that act on this regulatory neurotransmitter system. The basics of cannabis botany are also reviewed to help nurse clinicians understand the heterogeneous nature of cannabis products. This foundational knowledge will help improve clinical interactions with patients who use cannabis and provide the necessary understanding of cannabinoids needed to undertake further scientific query into their purported benefits in psychiatric disease states. [*Journal of Psychosocial Nursing and Mental Health Services, 57*(9), 7-10.]

Psychosocial nursing has, at its core, a belief in meeting patients "where they are." This tradition of partnership requires understanding of the ecosystem in which both the person and a behavior reside. Regarding the phenomenon of substance use, the context in which the use occurs and the substance itself and how it interacts with the body must be understood.

Regarding cannabis, most nurses have not received sufficient education about this plant to meet patients who use it where they are. Depending on one's generation, cannabis was a semi-innocuous presence in the youth culture of the 1960s and 1970s; a mind-wrecking drug that one was told to "Just Say No" to by Nancy Reagan; or a vague panacea for all manner of ills in an anecdotally based pseudo-medicalized/semi-legalized environment. Few nurses receive formal training on the endocannabinoid system of the body or the effect of exogenous cannabinoids, both for good and for ill. Dispensary "budtenders" know more than most clinicians about cannabis.

The intention of this two-part article series is not to discuss cannabis as a drug of abuse, but rather to help nurses understand the endocannabinoid system, the exogenous cannabinoids 9Δ-Tetrahydrocannabinol (THC) and cannabidiol (CBD), the existing evidence for cannabinoid use in psychiatry, the gaps in existing studies, and how to best guide patients who are already using cannabinoids or are interested in adding them to their psychopharmaceutic regimens. This article reviews the endocannabinoid system of the body and the basic botany of the cannabis plant. The next

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article will discuss the mechanism of exogenous cannabinoid CBD, its risks, and the evidence for its use in psychiatric practice.

IMPORTANT CAVEAT

Research into the benefits of cannabinoids has historically been thin, in part because of the challenges of studying the benefits of a Schedule I drug (as opposed to studying harm, which has been funded through the National Institute of Drug Abuse). At the same time, there is a rising cannabis industry, intent on selling a product, that makes intimations of health claims for cannabis that are not subject to the same scrutiny or legislation as that of U.S. Food and Drug Administration (FDA)–approved medications. To the cannabis industry, anecdotal evidence is sufficient, and many patients have had confirmatory experiences of these claims of benefit from cannabis. As such, the experiences of patients often far surpass the accreted knowledge of the scientific literature, leaving clinicians struggling to know how to advise patients. Many clinicians have taken an absolute stance: that cannabis cannot be helpful. With this, I disagree. Although certain components of cannabis, in certain populations (e.g., THC in patients susceptible to psychosis), can be harmful, there are also many candidate indications for cannabinoids that have yet to be rigorously studied by controlled studies. Until such studies are performed, it is impossible to know if the claims are true or panacea. However, I would encourage that we as clinicians remain open minded and view these anecdotes as seeds of hypotheses for further investigation. The cannabis industry is unlikely to take these studies on themselves. Therefore, it is incumbent on the scientific community to take inquiry into the benefits of cannabinoids. I encourage clinicians to take patients' interest in cannabinoids seriously by engaging them in conversations of the benefits and risks of cannabinoids, being honest about what we do and do not know, as the best way to reduce harm.

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ENDOCANNABINOID SYSTEM

Before discussion of exogenous cannabinoids, it must be understood that the mammalian central nervous system expresses endocannabinoid receptors. The endocannabinoid system is critical in fine-tuning multiple neurotransmitter systems. Like other, more well-known systems such as serotonin, the endocannabinoid system comprises neurotransmitters (ligands), synthesizing enzymes for these neurotransmitters, receptors, and degrading enzymes. Interestingly, unlike the serotonergic or dopaminergic systems, which largely propagate a signal downstream, the endocannabinoid system is a retrograde signaling mechanism used to regulate neurotransmission (Ohno-Shosaku, Tanimura, Hashimotodani, & Kano, 2012).

The receptors, CB1 and CB2, were only discovered in 1990 and 1993, respectively (Matsuda, Lolait, Brownstein, Young, & Bonner, 1990; Munro, Thomas, & Abu-Shaar, 1993), and are the most widely distributed G-protein coupled receptors in the central nervous system. As is often the case in the history of receptor pharmacology, the discovery of the cannabinoid receptor launched efforts to discover the endogenous ligand for this receptor. The two primary endocannabinoid neurotransmitters are anandamide (Sanskrit for "bliss," AEA) and 2-Arachidonoylglycerol (2-AG). AEA and 2-AG are synthesized in response to increased intracellular calcium at the postsynaptic terminal. AEA is synthesized by N-arachidonoyl phosphatidylethanolamine (NAPE) and 2-AG is synthesized by diacylglycerol (DAG) (Marco et al., 2011). It is important to understand that these neurotransmitters are not stored in vesicles like monoamines but are made on demand and released across the synaptic cleft toward the CB1 receptors, which are expressed on the presynaptic membrane. CB2 receptors are mostly located on immune cells (Turcotte, Blanchet, Laviolette, & Flamand, 2016) and may modulate inflammation, which is beyond the scope of this review.

At the CB1 receptor, AEA works as a partial agonist and 2-AG as a full agonist (Ohno-Shosaku et al., 2012). Activation of the CB1 receptor leads to a cascade of intracellular secondary messenger activity via G-protein coupled receptor changes (Zhornitsky & Potvin, 2012). These endocannabinoid messengers are deactivated and metabolized by degrading enzymes. The degrading enzyme for AEA is fatty acid amide hydrolase (FAAH), and for 2-AG, it is monoacylglycerol lipase (MGL) (Acton, 2012). Much in the same way that the more familiar monoamines serotonin and dopamine are degraded by monoaminoxidase (MAO) and these enzymes provided a target for the early antidepressants,

MAO inhibitors, FAAH and MGL represent potential targets for inhibition if a disease state were to benefit from increased endocannabinoid signaling. As will be reviewed in the subsequent article, inhibition of these enzymes and an increase in AEA signaling are two mechanisms of action of CBD.

The endocannabinoid system, in addition to helping fine-tune other neurotransmitters through the aforementioned retrograde signaling pathways, appears to be essential in regulating appetite and feeding behaviors (hence the hyperphagic side effect of THC), influencing sleep and relaxation, modulating pain, and affecting memory and forgetfulness (Di Marzo, 1998; McPartland, Guy, & Di Marzo, 2014). These domains of the endocannabinoid system are leveraged by patients who often use exogenous cannabinoids to address pain, insomnia, and appetite. Although the cognitive and amnesiac side effects of cannabis use are often problematic for users, this observation about the endocannabinoid system raises interesting questions about the evolutionary value of forgetting. Undoubtedly, when attempting to learn something, forgetting what was just learned is an obstacle to acquiring new knowledge. However, forgetting is also an essential task for clearing mental space by discarding unessential pieces of information. It is likely that the endocannabinoid system plays a role in this process of forgetting. However, when cannabis is used by young people who are in school, this side effect can become significantly problematic.

CANNABIS BOTANY

Cannabis is the genus of a plant that has been cultivated by humans for centuries. References to cannabis can be found in 5,000-year-old Chinese pharmacopeia (Booth, 2003). Historically, the plant has three primary species: *sativa*, *indica*, and *ruderallis* (Pollan, 2001; Pollio, 2016). These three cultivars have been selectively bred for different portfolios of not only cannabinoids, but also terpenes, phenolic compounds (e.g., flavonoids), steroids, and enzymes. It is important to understand that the interplay between these different exogenous compounds, known as "the entourage effect," (Ben-Shabat et al., 1998, p. 23) is what makes the subjective and likely medicinal properties of a single cannabinoid different than when it is ingested in whole-plant cannabis (Russo, 2011).

This selective breeding has led to a wide range of different chemovars available in the commercial market (Russo, 2011). Cannabis plants are sexed, and in a cannabis plantation, male plants are eliminated to prevent fertilization and seed production. Typically, cannabis plants are cloned by growing from cuttings, and not from seeds. As such, only the female plants produce the cannabinoid resin–heavy flower buds in the absence of fertilization. Cannabis is grown indoors and outdoors; however, indoor horticulture techniques allow for more precise manipulation of exposure to light, humidity, and temperature, leading to a more consistent product.

After the plant flowers, it is harvested and processed. Heating cannabis flowers decarboxylates the acidic compounds (i.e., THCA and CBDA) into their more potent THC and CBD forms (Aizpurua-Olaizola et al., 2016; Wang et al., 2016). Increasingly, cannabinoids are extracted and separated using polar solvents such as alcohol (to make tinctures) or carbon dioxide (to extract oils). By separating out these cannabinoids, they can be packaged in various ratios and strengths in commercial products intended for oral, inhaled, or topical ingestion.

The cannabis plant has also, confusingly, been called hemp. Hemp is typically a strain of *Cannabis sativa* that is grown as a fiber crop. In the years before the prohibition of cannabis, hemp farmers grew cannabis to be made into rope and paper. In addition, hemp is a phytoremediator, as it takes up heavy metals, such as lead and cadmium, from contaminated soil (Girdhar, Sharma, Rehman, Kumar, & Mohan, 2014). However, this same property of the plant risks exposing people who ingest cannabinoid products from industrial hemp to these toxins, depending on where it is grown. Legally, the definition of *industrial hemp* has been a plant with less than 0.3% THC by weight. This definition was recently re-introduced in the 2018 Federal Farm Bill, in which hemp could be grown, with state oversight, if it contains negligible amounts of intoxicating THC (Hudak, 2018). It is from this source (i.e., hemp) that products purporting to contain CBD have proliferated. Of concern is the absence of clear regulation from the FDA about health claims made by vendors of these products. In addition, the purity of these products grown from industrial hemp does not appear to be regulated.

CONCLUSION

Humans have had a relationship with cannabis for millennia. As cannabis becomes increasingly acceptable, it is incumbent upon psychiatric clinicians to understand the complexity of not only the plant and its constituent compounds, but also the endocannabinoid system upon which it works. By developing a more sophisticated understanding of this relationship between the body, disease state, and plant, nurses will be better positioned to help patients under their care.

The second article of this series will discuss the psychopharmacology of THC and CBD and their action on the endocannabinoid system, as well as examine the evidence for their risks and benefits in clinical psychiatric practice.

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