Medical Marijuana: A Review of the Endocannabinoid System and Medical Cannabis

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1. Endocannabinoid System (ECS): a neuromodulary system that functions to maintain homeostasis in many physiological processes
   1. Cannabinoid Receptors
      1. CB-1 receptors are primarily found in the brain, and to a lesser extent in the periphery. CB-1 regulates psychoactive, CNS, and some anticonvulsant effects
      2. CB-2 receptors are located mostly in the periphery, specifically the immune system and GI tract.
   2. Cannabinoids: substances that bind to ECS receptors
      1. Endocannabinoids: naturally occurring cannabinoids
         1. Anandamide (AEA) is the principal ligand for CB-1 receptors, and is involved in short-term memory, pleasure associated with food, responses to stressors, sleep onset, and nociception.
         2. 2-Arachidonylglycerol (2-AG) primarily binds to CB-2 receptors and modulates neuropathic pain in the spinal cord as well as the inflammatory response in immune cells and intestinal tract.
      2. Phytocannabinoids: cannabinoids found in the marijuana plant. They act similar to endocannabinoids except their binding is not as specific. There are several phytocannabinoids present in the marijuana plant. The two most discussed are:
         1. Delta-9-tetrahydrocannabinol (THC) mimics the effects of AEA by binding to CB-1 receptors in the brain. It is psychoactive, anti-inflammatory, analgesic, neuroprotective, and decreases intraocular pressure, spasticity, and muscle tension.
         2. Cannabidiol (CBD) has greater affinity for the CB-2 receptors and acts similarly to 2-AG
      3. Synthetic Cannabinoids: pharmaceutical company have been able to develop synthetic THC analogues such as dronabinol (Marinol) and nabilone (Cesamet).
   3. Terpenes: fragrant, volatile compounds that give cannabis its unique properties. They exist in other plants, not just cannabis, and have several medicinal benefits. For example:
      1. Linalool: found in lavender; calming effect
      2. Pinene: found in pine trees; increases alertness
      3. Myrcene: found in bay, hops, and mangos; acts as a muscle relaxant, sedative, anti-inflammatory, and analgesic
   4. Dominance: primarily refers to the various plant shapes and structures, as well as therapeutic effects
      1. Sativa: The plants typically grow taller, thinner, and have narrower leaves. When consumed they produce stimulating, energizing, and more uplifting effects. They are typically best consumed during the daytime
      2. Indica: These plants are typically shorter, bushier, and their leaves are broader. When consumed, indica plants produce a more sedating, relaxing, and grounding effect. They are best consumed in the evening or before bedtime
      3. Hybrid: A cross-breed between an indica and sativa plant, or possibly multiple indicas or sativas over time. They carry the traits from their predecessors and may sway dominance to one side.
   5. Strains: Varieties are bred to incorporate specific characteristics of the plant and the breeders assign them specific names.
   6. The Entourage Effect: the synergistic or modulating effects that occur when several cannabinoids and terpenes are present at one time, as opposed to the effects when just one compound is present at the receptors.
2. Routes of Administration: highly dictated by patient preference, convenience, and disease state
   1. Oral: capsules and tinctures:
      1. Onset of action depends on the ADME process: onset is typically 30-45 minutes and duration is about 4-8 hours & may be longer in cannabis naïve patients.
      2. Excipients typically include cocoa butter for capsules and MCT or Coconut Oil for tinctures. Some tinctures are alcohol based.
   2. Sublingual: Tinctures have SL bioavailability when held under the tongue for at least 15 seconds and may produce a more immediate response, within 15 minutes. The remaining liquid is swallowed and then goes through the ADME process. Tinctures may also be combined with a more palatable liquid to assist in drug delivery.
   3. Patches: not as common, but should be applied with the same care as pharmaceutical patches. Cresco Yeltrah manufactures patches that follow a drug-in-matrix model and have a duration of action of 12 hours, as well as a lag time of about an hour. They also contain essential oils to provide a counterirritant effect topically.
   4. Lotions: The active drug only penetrates the first layer of skin, meaning it only has topical properties. Effects may begin immediately and last for 1-2 hours.
   5. Vaporization: uses conduction rather than combustion to heat the product with out burning it. The onset of action can be immediate, but may take up to 15 minutes and last for about 2 hours. It is possible for the duration of action to be longer in cannabis naïve patients.
      1. Oils in Cartridges: once the cannabis plant goes through the extraction process, the oil that is extracted can be loaded into a cartridge for vaporization.
      2. Concentrates: a highly concentrated form of the plant in which the extracted product is manipulate by heat and/or mixing to create the desired end-product. These include but are not limited to wax, shatter, budder, badder, sugar, and crystals. They’re consumed by heating in a concentrate-specific pen or dab rig (\*Dag rigs are not a DOH approved method of consumption).
      3. Flower: Currently the DOH only approves the consumption of flower in a dry herb vaporizor
3. Role of Cannabis as Adjunctive Therapy: Cannabis is rarely ever used as first-line treatment for any condition, but it serves as supportive therapy for treatment of specific symptoms or medical conditions. In some cases is may slow the progression of the disease.
4. Pennsylvania Qualifying Conditions:
   1. Amyotrophic lateral sclerosis
   2. Autism
   3. Cancer, including remission therapy
   4. Crohn’s disease
   5. Damage to the nervous tissue of the central nervous system (brain-spinal cord) with objective neurological indication of intractable spasticity, and other associated neuropathies
   6. Dyskinetic and spastic movement disorders
   7. Epilepsy
   8. Glaucoma
   9. HIV/AIDS
   10. Huntington’s disease
   11. Inflammatory bowel disease
   12. Neuropathies
   13. Opioid use disorder for which conventional therapeutic interventions are contraindicated or ineffective, or for which adjunctive therapy is indicated in combinations with primary therapeutic interventions
   14. Parkinson’s disease
   15. Post-traumatic stress disorder
   16. Severe chronic or intractable pain of neuropathic origin or severe chronic or intractable pain
   17. Sickle cell anemia
   18. Terminal illness
5. Opioid use disorder:
   1. Opioid use disorder is a problematic pattern of opioid use that causes significant impairment or distress. Manifestations include a strong desire to use opioids, increased tolerance to opioids, failure to meet obligations, trouble reducing use, and withdrawal syndrome with discontinuation. Withdrawal symptoms may include nausea, muscle aches, diarrhea, trouble sleeping, low mood.
   2. Proposed Mechanism of Action: The endocannabinoid system regulates the body’s response to reward and stress, which is a major factor in drug abuse and addiction. Cannabinoids may impact one or more phases of addictive behaviors: the positive rewards and rituals of the intoxication phase, the physical and psychological aspects of the withdrawal phase and the cravings and risk of drug-seeking behaviors in the relapse phase. It also plays a key role in brain plasticity which enables the brain to rewire itself and recover (Cannabis Pharmacy).
   3. Symptoms Treated: suppresses addictive behaviors
   4. Clinical Pearls of Wisdom: CBD use is preferred due to lack of abuse or dependency potential.
   5. Recommended Route of Administration: any
   6. Helpful Terpenes: Caryophyllene. \*\*Avoid myrcene.