Cannabinoids: Now and in the Future (FR431)
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Objectives
• Recognize the evidence for benefit of commercially available cannabinoids and their limitations.
• Recognize the diverse nature of cannabinoid pharmacology.
• Recognize why CB2r agonists are being rapidly developed and placed in clinical trials.

Cannabinoids target orphan receptors GPR-55 and GPR-18, ion channels, monoamine receptors, and mu receptors. Cannabinoids have labeled indications for chemotherapy-induced nausea and vomiting but are reported to improve appetite in patients with AIDS, central pain from multiple sclerosis, and neuropathic pain. The benefits of cannabinoids for cancer pain are mixed. Commercially available cannabinoids are subject to psychotomimetic and addiction (cannabinomimetic) adverse effects largely through activation of the cannabinoid 1 receptor (CB1r). The number needed to treat (NNT) to benefit a single individual with either THC or THC-CBD ranges between six and nine. In a systematic review of cannabis studies (vaporized cannabis, THC, THC-CBD), the standardized mean difference in pain intensity is -0.61 (95% CI, -0.84 to -0.37). However, the number needed to harm (NNH) was five for motor dysfunction, seven for altered perception, and eight for cognitive dysfunction. Although the present commercially available cannabinoids have modest benefits, they also have a narrow therapeutic index. Recently developed peripherally restricted cannabinoids; regionally administered cannabinoids; bifunctional cannabinoid ligands; cannabinoid enzyme inhibitors; endocannabinoids such as palmitoylethanolamine (PEA), which do not interact with classic cannabinoid receptors (CB1r and CB2r); cannabinoid receptor antagonists; and selective CB1r agonists hold promise as future analgesics. Regional and peripherally restricted cannabinoids reduce cannabinomimetic side effects. Spinal cannabinoids increase the therapeutic index by minimizing drug exposure to supraspinal sites. Bifunctional ligands amplify analgesia or block side effects. Combinations CB2r agonists with TRPV 1 antagonist improve the therapeutic index of the CB2r agonist. Limitations include development of analgesic tolerance with enzyme inhibitors and pronociceptive effects of prostamides and certain cannabinoids. Most clinically important developments over the next 5 years will be in selective CB2r agonists. These agents are being tested in various inflammatory, osteoarthritis, and neuropathic pain phenotypes.