FAST FACTS AND CONCEPTS #279
CANNABIS FOR SYMPTOM CONTROL

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Background The use of cannabis (marijuana) for medical purposes has become legalized in many US states and Canada. This *Fast Fact* reviews the use of plant-based cannabis preparations to treat symptoms associated with advanced illness. *Fast Fact* #93 reviewed the use of prescription single molecule cannabinoid medications.

Legal Issues A number of countries have implemented pharmacy stocking and dispensing systems for herbal cannabis and/or oral cannabis extracts, available to patients by prescription. Nabiximols (Sativex®), a specific cannabis extract made by combining liquid CO_2 extracts of two strains of herbal cannabis, has been approved for prescription use in multiple countries for a variety of symptom indications. Cannabis is an "Investigational New Drug" in the US and is not considered an FDA-approved treatment for any condition. It is classified as a Schedule I controlled substance in the US making federally legal prescribed use by patients extremely rare and only under investigational circumstances. In recent decades, however, an increasing number of US states have legalized cannabis for medical use. Since 2012, some states have legalized it for recreational/unrestricted personal use by adults. State medical cannabis programs allow authorized patients to obtain cannabis from dispensaries and others allow personal or collective cultivation for medicinal use. In most of these states, patients who qualify for medical cannabis must have specific chronic, debilitating, or terminal illness diagnoses. Providers must be familiar with their own state's laws and regulatory climate around authorizing cannabis use (1).

Pharmacology There are a large number of cannabis strains used medicinally; each may vary by morphology, odor, and chemotype; each may produce plant resin with varying ratios of the pharmacologically active cannabinoids tetrahydrocannabinol (THC) and cannabidiol (CBD) as well as other molecules. Although other receptors play a role, the majority of the effects of THC from cannabis are mediated through partial agonism of central and peripheral cannabinoid receptors (2). Cannabinoid receptors (CB1, CB2) are part of the endocannabinoid system, a pro-homeostatic modulatory system composed of several endogenous ligands (3). Physiologically, the ECS been shown to impact pain perception, movement, appetite, aversive memory extinction, hypothalamic-pituitary-adrenal (stress) axis modulation, immune function, mood, inflammation, and others (4). THC is excreted via both hepatic and renal mechanisms. No specific studies have been done with cannabis-based medicines in patients with significant hepatic or renal impairment, but it can be expected that effects would be more exaggerated or prolonged in these settings (5). Given that cannabinoids are highly protein bound in the plasma, it is unlikely they will be effectively removed by hemodialysis (6).

Dosing Exact dosages depend upon individual patient need and tolerance of side effects. Cannabis preparations include resin-containing herbal flowers, which can be heated and delivered to the lungs via inhalation of smoke or vapor, and cannabis-based extracts, which include oral, oromucosal, rectal, and topically delivered preparations in the form of concentrates, suppositories, edibles, and salves. Because cannabinoids are volatile, they will vaporize at a temperature below actual combustion, and can be inhaled without the generation of potentially harmful smoke (7). Cannabinoids are lipophilic and have nearly immediate onset of action when smoked or vaporized. Vaporization has the advantage of rapid onset of effect and easy dose titration, as the patient can slowly increase use to achieve desired therapeutic effect. Patients can be advised to pause briefly between inhalations to ascertain effectiveness of the medicine and to stop when maximum effect is achieved. Oral ingestion of cannabis products has a delayed onset of action compared to inhalation and titration is more difficult. Maximum cannabinoid blood levels are reached up six hours post oral ingestion, with a half-life of 20-30 hours (4).

Side Effects/Risks Cannabis use can cause xerostomia, palpitations, flushing, nausea, confusion, anxiety, dysphoria, and acute psychosis. Cannabis ingestion raises the risk of a motor vehicle accident (8). Epidemiological data from non-medical settings suggest an association between chronic cannabis use and schizophrenia, but the causal direction of this link has not been established (9-10).

Indications Over the last several decades cannabis and cannabinoid therapeutics have been studied in over a 100 controlled clinical trials of varying size and quality, investigating a wide range of conditions (11). As with the evidence base for most pharmacologic symptom interventions, there are a lack of

comparative data between cannabis and other commonly used treatments for, e.g., spasticity or neuropathic pain. Of relevance to palliative care settings (12-15), cannabis medicines, both orally administered and inhaled, have been shown to have efficacy in randomized, double-blind, placebo-controlled trials (RCT) for a number of symptoms.

- For *cancer pain*, a multicenter RCT, involving 360 patients, showed oral cannabis to have analgesic efficacy to treat breakthrough cancer pain in subjects who were started on a long-acting opioid. It was also well-tolerated (16).
- *Chemotherapy induced nausea and vomiting*: three RCTs, involving 43 subjects in total, demonstrated inhaled cannabis to be an efficacious anti-emetic (17-19).
- *Multiple sclerosis*: numerous symptoms – spasticity, spasm frequency, insomnia, pain, and impaired mobility – were shown to be improved in a 630-subject multicenter RCT (20).
- *AIDS Wasting Syndrome*: Three RCTs of inhaled cannabis involving 107 subjects in total congruently showed efficacy for appetite stimulation and weight gain (21-23),
- *Neuropathic Pain*: 2 RCTs of inhaled cannabis showed significant analgesic efficacy for HIV sensory neuropathy (24-25) with a combined number-needed-to-treat of 3.38, superior to all other medications similarly tested for this indication (26). Three additional RCTs, involving 100 subjects in total, of inhaled cannabis for chronic, intractable neuropathic pain due to multiple etiologies all congruently showed efficacy for smoked and vaporized cannabis (27-29).

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