Cannabinoids: Overview [1-8,99]

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Clinical Pearls

- Routinely ask about cannabis use in primary care (just like tobacco/alcohol), & screen for cannabis use disorder (**1 in 5 may develop with ongoing daily use**).[76,77]
- Cannabinoids are not 1st or 2nd-line agents for any indication. Ensure adequate trial of evidence-based strategies (pharm & non-pharm), prior to trial.
- After non-response to trial of ≥3 other medications for neuropathic pain, a trial of prescription cannabinoids (rather than cannabis) may be reasonable.[2]
- When used, start cannabinoids at a low dose, and gradually titrate. Adverse effects are common; monitor & document; stop +/- taper if not tolerated.
- Inhaled cannabis (esp. smoked) is not a recommended route due to difficulty dosing, risk of respiratory damage, & multi-component composition.
- The potential harms of cannabinoids may be underappreciated by patients. Informed consent and patient education are recommended. See the **RxFiles** *Cannabis Patient Booklet* (available online: colour, or B/W, or print copy).

Definitions and Background Information

Cannabinoid receptors: CB1 receptors (primarily in the central and peripheral nervous systems) and CB2 receptors (primarily in the immune system) are part of the human endocannabinoid system.[1]

Cannabinoids: compounds that activate cannabinoid receptors. Endogenous cannabinoids in humans include AEA & 2-AG.

Phytocannabinoid: cannabinoid derived from cannabis (e.g. THC, CBD, & MANY others). Two studied phytocannabinoids, although still not well understood, are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).
THC: a partial CB1 & CB2 receptor agonist. CBD: uncertain mechanism of action.[88]

Cannabis (aka *marijuana)*: Contains 400+ compounds, including 140+ cannabinoids. Marketed based on concentration of THC & CBD, though it is uncertain if these are the only important compounds in cannabis (e.g. potential "entourage effect": see Misc. info below).

Non-Medical Prevalence (2024): 26% of Canadians ≥16yr used cannabis in last 12mo, 6% used daily, 69% consumed by smoking.[85]

Legal status in Canada: Rx cannabinoids are Schedule II in Controlled Drug & Substances Act. Dried cannabis, oils, topicals, drinks, & some edibles (<10mg THC) are legal from licensed producers with HCP authorization ("cannabis for medical purposes"). Since October 2018, cannabis may also be purchased from cannabis retail stores (including for non-medical purposes).

Are Cannabinoids Helpful (For Therapeutic Use)?

Cannabinoids may (limited, generally low-quality evidence, compared to placebo):

- ↓ **chemotherapy-induced nausea/vomiting** (CINV)
  NNT≈3 for control of CINV over ~1 day (mostly nabilone/dronabinol).[11]
- ↓ **spasticity of multiple sclerosis or spinal cord injury**
  NNT≈6 for ≥30% ↓ spasticity over ~6-14 wks (nabiximols).[21]
- ↓ **seizures in Lennox-Gastaut & Dravet syndrome** with CBD (**EPIDIOLEX**)
  NNT≈4-7 for ≥50% reduction in seizure frequency over ~14 wks.[2]
- ↓ cachexia in HIV/AIDS, cancer,[12] palliative care: weak evidence.
- ↓ **chronic neuropathic pain**: severity ↓ ~0.5/10 points on numerical rating scale with nabiximols (small effect with mod-large ↑ in dizziness, sedation, & nausea), non-significant for ≥30% reduction over 4-15 wks. Less benefit seen with other cannabinoids.[22]
  See below for more information about *Cannabinoids for Chronic Pain*.

Cannabinoids do not have evidence to support use (yet are commonly used[114]) for:

- anxiety disorders – literature mixed, many limitations, no demonstrated effectiveness & potential for harm (possibly associated with worsened anxiety).[68,91,92]
  See **RxFiles**: Cannabis in Anxiety Disorders: FAQs.
- sleep disorders / insomnia – literature mixed, many limitations, potential for harm (may contribute to next-day sedation, withdrawal after regular use can cause sleep disruptions).[93]

Are Cannabinoids Safe? (Potential Downsides)

Patients frequently underappreciate or are unaware of the potential adverse events (AE) related to cannabinoids.

AE are very common with cannabinoids. Approximately 8-9 out of 10 patients will develop an adverse event with cannabinoid therapy and ~1 out of 10 patients will stop therapy because of an adverse event.[2]

- Notable AEs include **feeling "high" NNH≈4**; **dizziness NNH≈5**; **sedation NNH≈5**; **speech disorders NNH≈5**; and **ataxia / muscle twitching NNH≈6**.[2] Additional concerns include driving impairment, addiction risk, euphoria, and psychosis.
- Caution needed if using in older adults: ↓ metabolism, ↑exposure due to higher fat stores, more vulnerable to CNS effects.[75]
- **Cannabis use disorder** (CUD) is associated with self-harm & overdose death in youth.[74]
- Some cannabinoids may have fewer AE than others, yet this is not well studied (including specific THC/CBD ratios) & few head-to-head trials have been conducted.
- Likelihood of AE tends to ↑with dose & duration (e.g. >24wk).[90]

Challenges with the evidence[11,17,90]

Quality evidence (without mod-high bias risk) is lacking & difficult to obtain for many outcomes. Results in low confidence assessing benefits & harms. Noted due to:

- difficulty blinding patients due to psychoactive components (~90% can guess their allocation, may bias toward benefit),
- variability in product potency, forms, route of administration, & standardization of dose.
- enrolled patients tend to have prior cannabis exposure (contributing to selection bias),
- frequent exclusion of important populations (e.g. older adults) & patients with common comorbidities (e.g. mental health dx), and
- often small sample size, with short duration.
  - Trials with *longer duration* tend to show less benefit,[11] suggesting that if a beneficial effect exists, it may wear off over time.

Cannabinoids for Chronic Pain[2,15,22,100,102-105]

Chronic pain is the most common reason patients seek cannabis for therapeutic reasons.[63]

- **Chronic pain guideline recommendations**: Conflicting. ❖NICE'21 & IASP'21 advise against use.[103,104] ❖PEER:'22 harm > benefits for OA & LBP (not recommended); might consider for neuropathic pain (unclear benefit) after other agents with stronger evidence considered.[102] ❖One guideline:BMJ'21 may trial **non-inhaled** medical cannabinoids (for any chronic pain) if standard care insufficient,[100] & another'24 suggests potential benefits > non-serious harms[105] { e.g. chronic pain esp neuropathic, HIV/MS related muscular/neuropathic pain; strongest evidence for oils, capsules; THC >CBD for benefit but also ↑AE}[105].
- **Effectiveness**: A SR updated annually, notes no high-quality evidence; most studies evaluate neuropathic pain (very few for OA/LBP – no benefit) for short duration (1-6mo) vs placebo in white, mature adults (mean age 50's, not studied in adolescents). Nabiximols (mean 8 sprays/day for up to 15wk) have mod QE suggesting small improvement in pain intensity (↓0.54/10pt NRS), but no improvement in overall function & with mod-large ↑ in dizziness, sedation, & nausea. THC-only products (e.g. nabilone 0.25-2mg BID) have low QE suggesting small improvement in pain intensity, no ↑function, with dizziness, sedation, & nausea + moderate ↑ withdrawals for AE. CBD-only products appear to have no effect on pain severity or function (Fibromyalgia – no benefit in 1 RCT[119]). Insufficient evidence for: 1) whole-plant cannabis & topical CBD, 2) comparisons between cannabis-related products or with active treatments, & 3) impact on opioid use (i.e. not established whether cannabis is opioid-sparing).[22]
- **If considering a trial**: weigh potential benefits vs downsides (AE). Risk-benefit balance will differ from patient to patient. See Online Extras: *Prescribing/Authorizing Cannabinoids Safely*.
- **Product selection**: Nabiximols have the most evidence, yet costly (vs nabilone ↓cost, yet ↓supporting evidence). Starting with trial of whole-plant cannabis, especially inhaled route, not recommended. If patient prefers to trial a non-prescribed product (may be due to cost), encourage preference for oral doses (can be measured, titrated), "start low, go slow" approach,[87] generally start with higher CBD / lower THC for tolerability despite the limited evidence for benefit, & close monitoring/follow-up for achievement of therapeutic goals / AE. Also caution about potential inaccuracy for product labelling, even from regulated sources.[111]
- **Bottom line**: Balance of evidence for possible small ↓ in pain, however some ↑harms → requires shared decision-making[78,79,100] Formulations with most benefit (e.g. nabiximols) come with AE & cost barriers; long-term benefits & AE unknown.

Strategies for Safer Use[3]

To ↓ health harms from cannabis use:

- Ideally delay to after late adolescence (i.e. >25yr) due to ongoing brain & social development (+ younger use associated with CUD[107])
- Preferred route: edible / oral ingestion > vaping > smoking
- Avoid driving after cannabis use (inhalation: 6-8hr, edible: 8-12hr)
- Choose lower potency products; ↓ THC / ↑ CBD
- Avoid daily use (for non-medical use)
- Avoid during pregnancy / lactation
- Avoid if personal / family history of psychosis

Misc. info: **Entourage effect**: an unproven hypothesis that efficacy of phytocannabinoids is increased (or AE ↓) when used in combination and/or in particular ratios and/or with flavonoids, terpenoids. **Topical cannabis** e.g. creams: a dosage form promoted as a local analgesic without systemic effect, but without trials to support (See RxFiles Q&A: Topical Cannabis). **Travelling with cannabis outside of Canada**: not recommended. **Perioperative Resource**: ASRA Pain Medicine Consensus Guidelines for the perioperative patient who uses cannabinoids.[86] **Resource for counselling adolescents:** Counselling Adolescents & Parents About Cannabis Infographic (CPS).
Synthetic unregulated cannabinoids: e.g. K2, Spice – highly potent CB1/CB2 receptor agonists; case reports of severe acute toxicity (avoid).[52] **Concentrated Cannabis** e.g. hash, shatter, budder, wax, dabs: contains THC as high as 90%, often inhaled quickly. **Note of CAUTION - very high potency** cannabis products are sometimes available which may pack THC several hundred times stronger than the federal standard, increasing harms! Newslink

Cannabinoids: Comparison Chart

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Prescription Cannabinoids (pharmaceutical grade)

Nabilone CESAMET, g

synthetic THC analogue

0.5, 1mg cap ☎ ▼

0.25mg cap ✗ ▼

Indications & Comments:

Preferred over cannabis.[CFP'18]

- ✓ severe nausea/vomiting from cancer chemotherapy

off-label: AIDS-related anorexia ☎

palliative pain

neuropathic pain (see 2018 guideline: https://www.cfp.ca/content/cfp/64/2/111.full.pdf)

- Not detected in SK urine drug screen

DOSING:

Initial: 0.25-0.5mg po HS

Usual:

1-2mg po daily-BID for CINV

1mg po BID for neuropathic pain

Usual max: 6mg/day

{Onset 60-90min; duration 8-12hr}

$/30d:

$62-72 g

$130-470 g

$252 g

$690 g [$1450]

Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitor M

AE: Some notes on adverse events:

- percentages below are often "worst case scenarios" from systematic reviews, yet due to trial-design issues could also be underestimates.
- adverse events **dose-related** (↑dose =↑AE), & more common with THC products
- it is difficult to compare AE rates between agents, due to few head-to-head trials.
- **THC** appears the main psychoactive component responsible for causing a "high".[44] **CBD** appears safer than THC, yet some of its psychotropic effects are underappreciated (e.g. vs placebo in pediatric trials: aggression/anger 3-5% vs <1%; irritability/agitation 5-9% vs 2%; somnolence 25% vs 8%).[31]

Nabiximols SATIVEX ✗ ⊗

extracted THC/CBD

2.7mg THC & 2.5mg CBD per spray (from whole plant)

(peppermint flavour; poor taste; (contains alcohol)

❄ refrigerate prior to dispensing

Not available in USA.

Indications & Comments:

Preferred over cannabis.[CFP'18]

- ✓ advanced cancer pain (adjunctive)
- ✓ multiple sclerosis neuropathic pain or spasticity (adjunctive)
- Spasticity may require lower doses than pain (e.g. 4-5 sprays vs >8 sprays per day).
- Detected in SK urine drug screen

DOSING:

- Spray under the tongue or into side cheek (may alternate sides).
- Shake vial gently. Device requires priming (3 sprays).

Initial: 1 spray sublingually HS

Usual: 1 spray sublingually q4h

Usual max: 12 sprays per day

{Onset 15-40min; duration 2-4hr}

$/30d:

3 vial pack = $673

($2.50/spray) (90 spray/vial)

$75

$468

$917

AE noted across cannabinoids (specific cannabinoid not reported, tend to be more common with THC products[90,107]): • **drowsiness or sedation** up to 50%.[2]

- **psychiatric disturbances** e.g. depression, anxiety, bipolar, paranoia, hallucination, panic, suicidality, hyperactive delirium, up to 17%.[2,89]
- **acute psychosis or dissociation** up to 5%.[2] **1st episode psychosis** daily cannabis ↑3x & THC ≥10% ↑5x vs never users.[Forti'19] **Schizophrenia unmasking:** cannabis may hasten first psychotic episode by 2-6yr.[8] Mental health risk ↑with onset of use <16 yr.[113]
- **dry mouth, nausea** • **speech disorders** up to 32%, & **ataxia** up to 30% (falls risk).[2]
- **impaired memory** up to 11%.[2] Also **impaired cognitive performance** (up to 28d after use).
- **cannabis hyperemesis syndrome** severe abdominal pain/vomiting;[32,110] tx requires drug D/C; relieved by hot bath/shower; capsaicin to abdomen useful; ?IV haloperidol
- **cannabis use disorder** risk ↑ with duration & daily use[97] (see more info on next page 💻).
- **withdrawal** with abrupt discontinuation (see withdrawal symptoms on next page 💻).
- **CV:**[98, 117-18] ↑HR,[1] postural ↓BP,[1] ↑MACE, ?↑MI esp 1hr after smoking[39] & use >4x/mo,[81] arrhythmia[101]
- **rare or uncertain:** ?sexual problems, ?cancer testicular, ?↓BMD, ?pancreatitis.

AE with specific mention of THC (most associated with AE causing withdrawal from therapy):

- **dizziness** up to 32%.[2] • **euphoria** up to 15%, and **feeling "high"** up to 35%.[2]
- **driving impairment** risk of fatal car crash approximately doubles with THC.[28,55]
- **acute panic attack & anxiety disorder** • **red eyes** reported with non-medical use.
- **appetite changes** - increased appetite in up to 38% of patients on dronabinol.[18]

AE with specific mention of CBD (caution, non-prescription products may contain unlabeled THC):

- **GI issues** diarrhea up to 20%, vomiting up to 15%.[19,31] **SATIVEX**: mouth irritation.
- **irritability / agitation** up to 9%, & **anger / aggression** up to 5%.[31] • **pneumonia** up to 8%.[31]
- **drowsiness, somnolence** (which may impair driving ability, contribute to falls).
- **appetite changes** decreased appetite in up to 22% of patients on CBD.[31]
- **↑ transaminases** up to 16%;[31,116] ?related to concomitant valproate/clobazam in peds.

Harms specific to smoked cannabis:

- **respiratory:** cough 7%, ↑phlegm, dyspnea, development of COPD, pulmonary aspergillosis, ?lung cancer, vocal fold changes.[35]
- **other harms**: ↑**psychiatric disturbances** (up to 27% COMPASS), ?steatosis with hep C, ?gynecomastia, ?thrombophlebitis, ?contaminants in unregulated cannabis (e.g. lead, fentanyl, pesticides), ↑self-harm/suicidality, if at risk.

CI:pregnancy ↓birth wt & ↑preterm,[83] ?stillbirth, ?negative neurodevelopment; **breastfeeding**; <21-**25**yr (CBD exception: tx-resistant seizure); psychosis/schizophrenia hx.[6] **Caution**: in older adults (↑AE),[82] **SUD history**, **driving** (sometimes contraindicated) <4-5hr after inhalation/<6hr after ingestion / <8hr after euphoria (studies focused on THC component); hx of seizures, psychiatric disorders (e.g. bipolar, anxiety), CVD, or respiratory dx.[9] Caution: ped toxicity → edible ingestion (THC ≥1.7mg/kg[112]).

Allergy: Type 1 & 4 reactions possible (e.g. sneezing/runny nose, itchy eyes, wheezing →rare anaphylaxis).[106]

DI: A note on drug interactions: Interactions not fully understood; many are theoretical / in vitro. Cannabis has many compounds besides THC & CBD; these may have unknown drug interactions. Watch closely for **pharmacodynamic** (additive) interactions.

All cannabinoids: additive CNS effects (e.g. sedation, confusion) with EtOH, BZD, opioids, anticholinergics, anti-epileptics, & others. Avoid ≥ 3 CNS drugs.[BEERS'23]

Also consider additive effects: sympathomimetic, CNS depressant, & anticholinergic.

THC-containing products 2C9 & 3A4 substrate: e.g. ↓ levels by CBZ, SJW, phenytoin; ↑ levels by clarithromycin, fluoxetine, fluvoxamine, gemfibrozil.

CBD-containing products 2C19 & 3A4 substrate: e.g. ↓ levels by CBZ, SJW, phenytoin; ↑ levels by clarithromycin, fluconazole, fluoxetine, fluvoxamine, gemfibrozil.

2C19 inhibitor: e.g. ↑ levels of citalopram/escitalopram, **clobazam**, warfarin, DOAC; ↓ levels of clopidogrel; ?additive hepatotoxicity risk with valproic acid or clobazam.[19,20]

Smoking cannabis: may cause 1A2 induction e.g. ↓ levels of antipsychotics, TCA, warfarin

Nabilone: while a THC-mimic, does not have THC drug interactions.

M: HR, BP, CNS adverse event, psych symptoms, tx agreement, CUD, LFTs (with EPIDIOLEX)

Cannabidiol EPIDIOLEX ☎ ✆

extracted CBD

100mg/mL solution [FDA'18, CDN'24]

(contains alcohol, sesame oil; strawberry flavour)

Indications & Comments:

- ✓ Seizures: Lennox-Gastaut syndrome or Dravet syndrome & Tuberous sclerosis complex [≥2yr]
- Not detected in SK urine drug screen

DOSING:

Seizures (Lennox-Gastaut or Dravet):

≥2yr: 2.5-10mg/kg/dose po BID usually give before a meal

- Food (fat/caloric): ↑ absorption.

$/30d:

$1475/100mL

Dronabinol MARINOL

synthetic THC ❄

USA only: 2.5, 5, 10mg cap (in sesame oil); 5mg/mL solution SYNDROS (contains alcohol)

Indications & Comments:

- ✓ severe nausea/vomiting from cancer chemotherapy
- ✓ AIDS-related anorexia

(↓ nausea in up to 20% of pt with dronabinol.[18])

DOSING:

Initial: 2.5mg po HS

Usual: 2.5-5mg po TID-QID for chemo nausea/vomiting (~5mg/m²)

2.5mg po BID ac lunch and supper for anorexia [AIDS 3]

Max: 20mg/day

$/30d:

D/C from Canadian market

Cannabis from Whole-Plant (e.g. dried, oils)

Oral Cannabis Oils ✗ ⊗

THC/CBD in various ratios, e.g.:

25mg THC / 0mg CBD per mL

1mg THC / 20mg CBD per mL

3mg THC / 3mg CBD capsule

many other formulations (e.g lozenges, gummies) & potencies available.

Veteran's Affairs: coverage available for some patients

Indications & Comments:

No official indication. May be medically authorized in Canada to any patient for any indication (i.e. "off-label use").

- THC detected in urine drug screen up to 4 weeks after last dose (especially with chronic/heavy use)
- **Oral vs inhaled**: Oral has lower bioavailability (~10% vs ~25%),[1] slower onset (30-60min vs 5-10min),[4] longer duration (4-8hr vs 2-4hr),[1] & does not have respiratory risk.
- **Smoked vs vaped**: smoking speculated to have more respiratory risk (but data limited), yet vaping has risk too (2,602 reports of vaping lung injury in US).[70,73] Vaping ~2x more potent (smoking destroys some drug via combustion).
- **Vaping devices**: Consider a Health Canada approved vaporizer.

"Cannabis Math"

note: estimate only – some uncertainty!

What is the estimated THC dose if **1 joint**, containing 0.5 grams of 10% THC dried cannabis, is smoked?

Answer: 500mg cannabis x 10% THC x 50% loss to combustion ≈ **25mg THC**

Caution: Less well regulated products may have THC contamination, even if labelled as CBD only.

DOSING:

Initial: CBD 2.5-5mg po daily-BID +/- THC 1-2.5mg po daily-BID (for pain

Usual: Uncertain due to lack of randomized trials. Titrate slowly, e.g. CBD q2-3d, THC q2-7d.[87]

(Consider titrating CBD to 40mg/day first, then adding THC if needed, with THC then titrated to max 40mg/day)

- Food increases absorption.
- Consider 1st dose at 7 p.m. to leave time for assessing effect.
- Consider weekend trial start (or when impairment lower impact).

$/30d:

$7

e.g. 30mL bottle of oil containing ~700mg CBD ≈ $60

Use a calibrated dropper

Dried Cannabis ✗ ⊗

THC/CBD in various ratios, often to smoke/vape, e.g.:

12.5% THC

4% THC / 10% CBD

1% THC / 13% CBD

many other potencies available.

❄ refrigerate for max stability

Veteran's Affairs: coverage available for some patients

Trend: toward ↑ potency products.[54] (e.g. 4% THC in 1995 → 12% in 2014; some may now be in the ~20% range)

Average joint: ~0.3g dried cannabis.[69]

Medical use in USA: 38 States & D.C.

Non-medical use USA: 24 States & D.C.

Guidelines recommend **avoiding** smoked cannabis.[2,7,100]

Initial: 1-2 puffs inhaled HS

(1 puff of joint ≈ 1-10mg THC. Variation due to inhalation depth, puff size, THC potency, smoked vs vaped, joint size, etc.)

Usual: Uncertain due to poor quality evidence. Titrate slowly. Based on market data for 2017 in Canada, patients taking cannabis for medical purposes titrated themselves to an average dose of **750mg** dried cannabis per day.[16]

One Canadian report noted the average retail price was $8/g, compared to ~$6/g in the unregulated market.[72] Licensed Producer price ~$10-15/g.

$12-24 for 1-2 puff HS

$270 for 750mg/day

$1080 for 3g/day