Therapeutic Reviews

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Cannabinoids *AHFS 56:22:92*

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In the USA, only dronabinol and nabilone are available. For international educational and comparative purposes, this article also refers to formulations not available in the USA, e.g., nabiximols (Sativex®).

Indications

Chemotherapy-induced nausea and vomiting (dronabinol, nabilone); AIDS-related anorexia (dronabinol); refractory spasticity in multiple sclerosis (nabiximols); †pain unresponsive to standard treatments.

Contraindications: history (including family history) of psychosis.

Pharmacology

Endocannabinoids have important regulatory roles throughout the nervous system, immune system, and elsewhere, making them a potential therapeutic target for a wide range of disorders, including nausea, pain, inflammation, cancer, cardiovascular disease, spasticity, epilepsy and immunomodulation.[1–7]

Currently available cannabinoids all contain the psychoactive constituent of *Cannabis sativa*, Δ^9-tetrahydrocannabinol (Δ^9-THC) or a synthetic analogue. They are generally less effective or less well tolerated than alternative drugs and are relatively expensive. Their use as antiemetics has been limited, and was rapidly eclipsed by the advent of $5HT_3$ antagonists. Although dronabinol reduced AIDS-related anorexia and weight loss, there was a trend towards more rapid deterioration in performance status.[8] In cancer-related anorexia, they were shown to be inferior to megestrol and no more effective than placebo.[9,10] Their analgesic effect is modest, and despite interest in their respiratory effects,[11,12] benefit in breathlessness has *not* been confirmed by RCT.

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An improved understanding of the endocannabinoid system and *Cannabis sativa's* many non-psychoactive compounds[1,13] has led to several developments in an attempt to improve effectiveness and tolerability:

- CB_2-selective agonists[14,15]
- peripherally-acting cannabinoids[16]
- inhibitors of endocannabinoid breakdown[17,18]
- combining cannabinoids with different properties, e.g., Δ^9-THC with cannabidiol (CBD) (see below).[19]

Endocannabinoid System

The endocannabinoid system comprises:[20]

- two known receptors
  - ➢ CB_1, expressed mainly by central and peripheral neurons
  - ➢ CB_2, expressed mainly by immune cells
- endogenous cannabinoids (endocannabinoids), mainly fatty acids derived from arachidonic acid, produced *de novo* as required, and then rapidly removed by hydrolysis. Several have been identified, notably:
  - ➢ anandamide (arachidonylethanolamide)
  - ➢ 2-arachidonyl glycerin (2-AG)[21]
- enzymes and uptake systems involved in endocannabinoid metabolism, including COX-2 and fatty acid amide hydrolase-1.[17,18]

CB_1 (an inhibitory receptor) reduces neuronal excitability and neurotransmitter release by opening potassium channels and blocking N/P/Q-type calcium channels, respectively. It is part of a negative feedback loop which regulates neurotransmitter release and thereby the function of various CNS circuits (Fig. 1). This part explains some of the antispasticity, analgesic and other effects of cannabinoids.[20,22]

Central and peripheral CB_1 receptors also modulate appetite and energy metabolism, respectively. CNS receptors are expressed on hypothalamic and limbic neurons; those in the periphery exist on adipocytes,

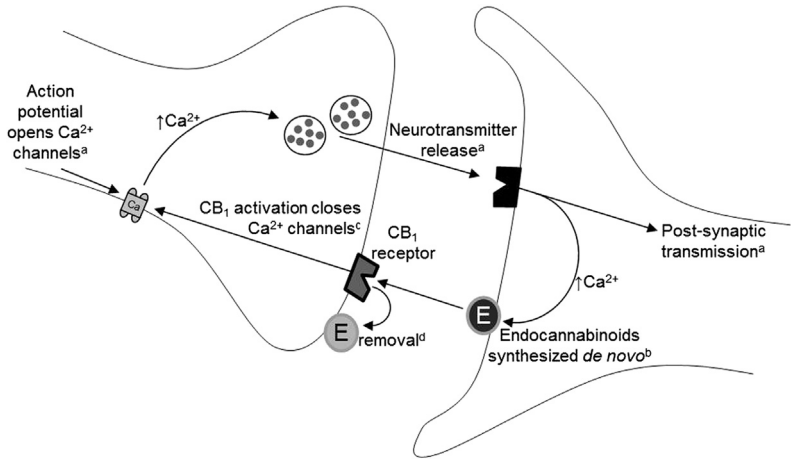

Fig. 1. Cannabinoids and neurotransmission. Endocannabinoids are retrograde neurotransmitters, traveling from the post- to the pre-synaptic neuron as part of a negative feedback loop that regulates neurotransmitter release. a. arriving action potential opens voltage-gated calcium channels; increasing *pre-synaptic* intracellular calcium triggers the release of stored neurotransmitter. Post-synaptic events depend on the neurotransmitter but include an increase in intracellular calcium. b. increasing *post-synaptic* intracellular calcium triggers the *de novo* synthesis of endocannabinoids from arachidonic acid. c. activation of CB_1 closes *pre-synaptic* calcium channels preventing further calcium influx, thereby terminating neurotransmitter release. These channels are also targeted by other drugs of analgesic relevance, e.g., gabapentin, pregabalin, ziconotide. d. endocannabinoids removed by hydrolysis, e.g., fatty acid amide hydrolase-1.

skeletal muscle cells and hepatocytes. Activation of peripheral CB_1 receptors promotes fat deposition and insulin resistance.[23]

Animal studies suggest that central and peripheral CB_1 receptors also impact on the cardiorespiratory system. In the brainstem, CB_1 stimulation elicits respiratory depression, bradycardia and hypertension.[24] In the lung, the effect is variable, with CB_1 stimulation able to attenuate capsaicin-induced bronchoconstriction but also induce bronchoconstriction in vagotomized animals.[25]

CB_2 is implicated in immune regulation. Located on antigen-presenting cells, it influences their cytokine profile and thus that of T-helper cells.[4] This may partly explain its anti-inflammatory and antihyperalgesic effects. Its expression on microglia is upregulated in the dorsal root ganglia and spinal cord following sciatic nerve injury. It also may be expressed on neurons.[26]

The antihyperalgesic effects of CB_1 and CB_2 activation are distinct and additive, and include:[27]

- peripheral immunomodulation (antigen-presenting cell CB_2; interactions between immune cells and neurons contributes to peripheral sensitization and neuropathic pain)[28]
- dorsal columns (microglial CB_2)
- disinhibition of antinociceptive neurons of a descending pain modulatory pathway (CB_1 on the pathway's GABAergic "brake"; cf. opioids).[14,15,29,30]

Further, unlike opioid receptors, CB_1 persists in the spinal cord after peripheral nerve injury.[31,32]

Endocannabinoids also act at other receptors, including the capsaicin receptor (TRPV1, involved in pain signaling), and perhaps also G protein-coupled receptors 55 and 119.[33]

Exogenous Cannabinoids

Δ^9-THC is a CB_1 and CB_2 partial agonist. Its effects include muscle relaxation, analgesia, antiemesis, but also psychosis, anxiety and sedation. Dronabinol is a synthetic preparation of its (-)-*trans* isomer, the best studied of several isomers present in *Cannabis sativa*; nabilone is a synthetic analogue.

The effects of Δ^9-THC are modified by other cannabinoids present in *Cannabis sativa*. For example, cannabidiol (CBD) reduces Δ^9-THC-induced anxiety in healthy volunteers, perhaps by inhibiting the metabolism of Δ^9-THC to a more psychoactive metabolite, 11-hydroxyTHC. CBD is also a CB_1/CB_2 antagonist; its apparently low affinity for both receptors suggesting non-competitive antagonism through a separate binding site. Although a less potent analgesic and antiemetic, CBD is anxiolytic, antipsychotic and non-sedating.[34,35]

In an attempt to improve the efficacy/tolerability profile of Δ^9-THC, a formulation which combines Δ^9-THC and CBD has been developed. Nabiximols, an extract of cannabis plants containing 2.7mg of Δ^9-THC and 2.5mg of CBD in each oral spray, is commercially available for spasticity or pain in several countries. Results of RCTs comparing the Δ^9-THC:CBD combination with Δ^9-THC alone in patients with pain have been mixed; two found modest improvements in tolerability and patient preference,[36,37] one found modest improvements in efficacy, but not tolerability,[38] and one found no difference.[39]

The non-psychoactive constituents of *Cannabis sativa* are poorly understood but they may interact with non-CB_1/CB_2 cannabinoid receptors and/or the metabolism of endocannabinoids.[13] However, an RCT examining an inhibitor of endocannabinoid breakdown found no benefit for osteoarthritic pain.[18]

Table 1
Pharmacokinetic Profiles of Selected Cannabinoids[19,40]

	Oral Biovailability (%)	Time to Peak Plasma Concentration (h)	Half-life (h)	Metabolism
Cannabidiol	Not known	1–4	5–9	Multiple pathways[a,b]
Nabilone	85	1–4	2 5–10[a]	Multiple pathways[a,b]
Tetrahydrocannabinol	≥50	1–4	2–5	CYP2C9[c]

[a]Has active metabolite(s).
[b]Eliminated by both biliary and renal pathways.
[c]Affected by combined use: cannabidiol reduces Δ^9-THC-induced anxiety in healthy volunteers, perhaps by inhibiting the metabolism of Δ^9-THC to a more psychoactive metabolite, 11-hydroxyTHC.

The therapeutic potential of cannabinoid antagonists and inverse agonists also has been investigated. Rimonabant, a CB_1 inverse agonist (i.e., results in a reduction in basal activity of the receptor), was approved for appetite suppression in obesity. However, it also caused depression, anxiety and aggression, and has been withdrawn.

The pharmacokinetic profiles of selected cannabinoids are summarized in Table 1. Food increases the absorption of Δ^9-THC and CBD oral spray, suggesting a proportion of the dose is swallowed before absorption.

Cautions

For full list, see manufacturers' Prescribing Information.

Psychiatric history (mood, cognitive and behavioral changes can occur); severe ischemic heart disease, heart failure or arrhythmias (risk of postural hypotension or reflex tachycardia); renal or hepatic impairment (no data, but active hepatic metabolites undergo biliary and renal clearance); epilepsy (cannabinoids can either lower or raise seizure threshold).

Drug Interactions

For full list, see manufacturers' Prescribing Information.

Additive CNS depressant effects with other psychotropics.

Cannabinoids inhibit numerous CYP450 enzymes, although generally not at typical therapeutic concentrations. Caution is advised when substrates for CYP2C19, 2D6 (e.g., amitriptyline) and 3A4 (e.g., alfentanil, dofetilide, fentanyl, sufentanil) are used concurrently with nabiximols.

The metabolism of nabiximols is marginally inhibited by CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole, ritonavir) and may be induced by CYP3A4 inducers, (e.g., carbamazepine, rifampin).

Undesirable Effects (Box A)

These vary between cannabinoids; for full list, see manufacturers' Prescribing Information.

Box A. Undesirable Effects of Cannabinoids

Psychological[a]

Common (<10%, >1%): depression, euphoria, disorientation, dissociation

Uncommon (<1%, >0.1%): hallucinations, paranoia, delusions, suicidal ideation

Neurological[b]

Very common (>10%): dizziness (nabiximols, particularly during titration)

Common: ataxia, amnesia, drowsiness, blurred vision

Gastrointestinal[c]

Common: appetite (↑ or ↓), nausea

Uncommon: abdominal pain

Cardiovascular

Uncommon: palpitations, tachycardia, syncope, hyper/hypotension

Buccal irritation[d] (nabiximols only)

Common: ulceration, pain

Uncommon: discoloration

[a] Illicit use is a risk factor for schizophrenia.[41]

[b] Tolerance to CNS depressant effects generally develops after a few days.

[c] Delayed onset nausea and vomiting ("cannabinoid hyperemesis") are described with illicit use of *Cannabis sativa*. Symptoms are generally worst in the morning (70%), associated with abdominal colic (86%), and resolve when the cannabinoid is discontinued. Although most patients have used cannabis weekly for at least 2 years before symptom onset, a third have symptoms within one year.[42]

[d] Nabiximols contains 50% v/v ethanol and propylene glycol. Two reports of suspected leukoplakia occurred in RCTs.

Use of Cannabinoids in Palliative Care

Chemotherapy-induced Nausea and Vomiting (Dronabinol, Nabilone)

Although cannabinoids have some antiemetic efficacy in *moderately* emetogenic chemotherapy regimens (see Prescribing Information for details), $5HT_3$ antagonists, which are more effective and better tolerated, are generally used instead.[43] The manufacturer advises against the use of nabilone for non-chemotherapy related nausea.

AIDS-related Anorexia (Dronabinol)

In cancer-related anorexia, cannabinoids are inferior to megestrol and no more effective than placebo.[9,10]

- 2.5mg PO b.i.d., generally before lunch and dinner
- if undesirable effects occur which do not resolve within 3 days of continued use, reduce dose to 2.5mg before dinner (or at bedtime)
- if tolerated but ineffective, consider gradually increasing the dose to a maximum of 20mg/24h.

Refractory Spasticity in Multiple Sclerosis (Nabiximols)

- start with 1 spray at bedtime
- increase over 2 weeks to a maximum of 12 sprays/24h given in divided doses, e.g., 1−2 sprays b.i.d.−3 sprays q.i.d.
- because food can increase drug absorption, consistent timing of administration with regard to mealtimes might be an important consideration in some patients.

Direct spray beneath the tongue or inside the cheeks (not towards the pharynx). Vary the site and inspect buccal mucosa regularly for signs of irritation caused by the excipients, ethanol (50%v/v) and propylene glycol.

Refractory Pain (Nabiximols, Nabilone)

Generally, such use is off-label. In Canada, nabiximols is approved under the Notice of Compliance with Conditions for neuropathic pain in multiple sclerosis and for cancer pain unresponsive to the optimal use of strong opioids. Nabiximols also is approved in the U.K. and Israel.

A systematic review found moderate benefit for a variety of non-cancer pains (NNT 3.5−9 for 30% pain reduction). Oromucosal cannabis extracts, nabilone, smoked cannabis and dronabinol were effective for neuropathic pain, fibromyalgia, and painful spasticity. Undesirable effects were generally mild.[44−46] Most trials were short (<6 weeks) but open-label extension studies found that analgesia was maintained without dose escalation for up to 1.5 years.[47−49]

Two RCTs have examined nabiximols for intractable cancer pain with mixed results. In one, it was more effective than placebo or Δ^9-THC alone (NNT 4.5 for 30% pain reduction) but withdrawal due to undesirable effects was three-times higher with nabiximols than placebo (17% vs. 5%).[38] The other study found no difference between nabiximols and placebo in the primary endpoint of the proportion of patients reporting ≥30% reduction in pain. However, this was a graded dose study, which did not include titration to an optimal effect.[50]

Nabiximols (adapted from the Canadian Product Monograph)

- start with 1 spray up to q4h (maximum 4 sprays in the first 24h)
- titrate up on a daily basis (but more slowly if dizziness occurs)
- most patients require ≤12 sprays/24h (median dose = 5−8 sprays/24h).

For general use of nabiximols, see above.

Nabilone

- start with 0.25mg to 0.5mg b.i.d.
- titrate in 0.5mg increments on a weekly basis
- maximum dose 1mg b.i.d.[51]

Note. Only a 1mg capsule is available in the U.S.; lower strength capsules, e.g., 0.25mg, 0.5mg, are available in other countries, including Canada.

Supply
Dronabinol
A schedule III controlled substance.

Dronabinol (generic)
Capsules (all contain sesame oil) 2.5mg, 5mg, 10mg, 30 days @ 2.5mg b.i.d. = $207.

Marinol® (Roxane)
Capsules (all contain sesame oil) 2.5mg, 5mg, 10mg, 30 days @ 2.5mg b.i.d. = $549.

Nabilone
A schedule II controlled substance.
Cesamet® (Valeant Pharmaceuticals)
Capsules 1mg, 30 days @ 1mg b.i.d. = $1,680.

Abbreviations

†	Off-label use
$5HT_3$	5-hydroxytryptamine type 3 (receptor)
AIDS	Aquired immune deficiency syndrome
b.i.d.	Bis in die, twice daily
$CB_{1,\ 2}$	Cannabinoid type 1, 2 (receptor)
CBD	Cannabidiol
CNS	Central nervous system
COX	Cyclo-oxygenase
CYP450	Cytochrome P450
GABA	Gamma-aminobutyric acid
NNT	Number needed to treat
q3h, etc.	Every 3 hours, etc.
RCT	Randomized controlled trial
THC	Tetrahydrocannabinol
t.i.d.	Ter in die, three times daily
TRPV1	Transient receptor potential channel (subfamily V member 1)
v/v	Volume/volume

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