Cannabis in History

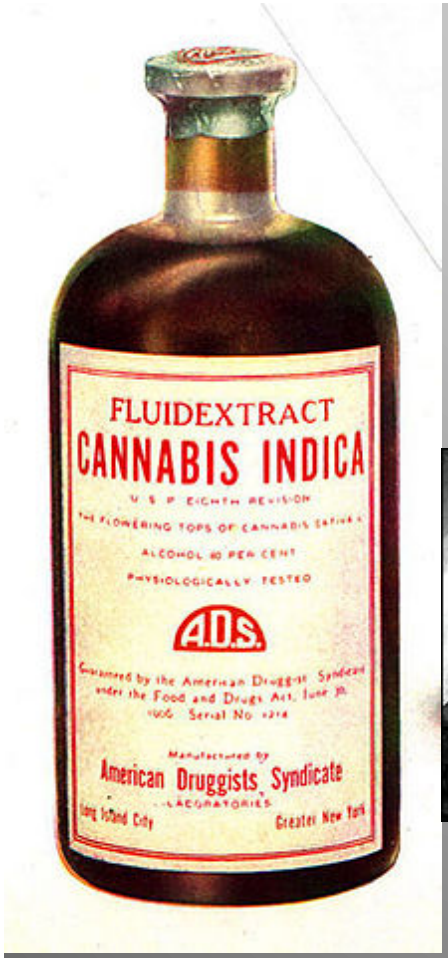
References to its psychoactive properties appear in the Atharva-Veda

The world's first pharmacy book, published in China, recommends hemp as a remedy for relief of cramps, rheumatic and menstrual pain.

Herodotus (500 BC) wrote of the Scyths warriors purifying themselves in steam baths filled with smoke from burning hemp seeds

The Greeks and the Romans cultivated hemp mainly for medicinal use, although there are a few references to its use as a social lubricant at banquets "to promote hilarity and enjoyment"

During middle-age hemp fibre was essentially used for ropes and sails.



Cannabis in History

Up until the 1930s and 1940s extracts of Indian hemp were used medically to treat a wide variety of diseases. In the USA it was a legal medicine until 1969 and in Britain it was legal until 1971.

Cannabis in History

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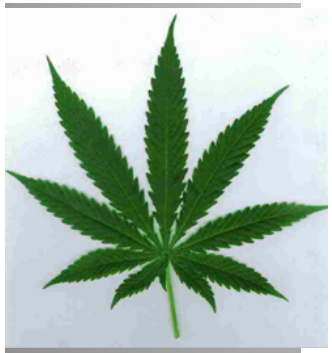
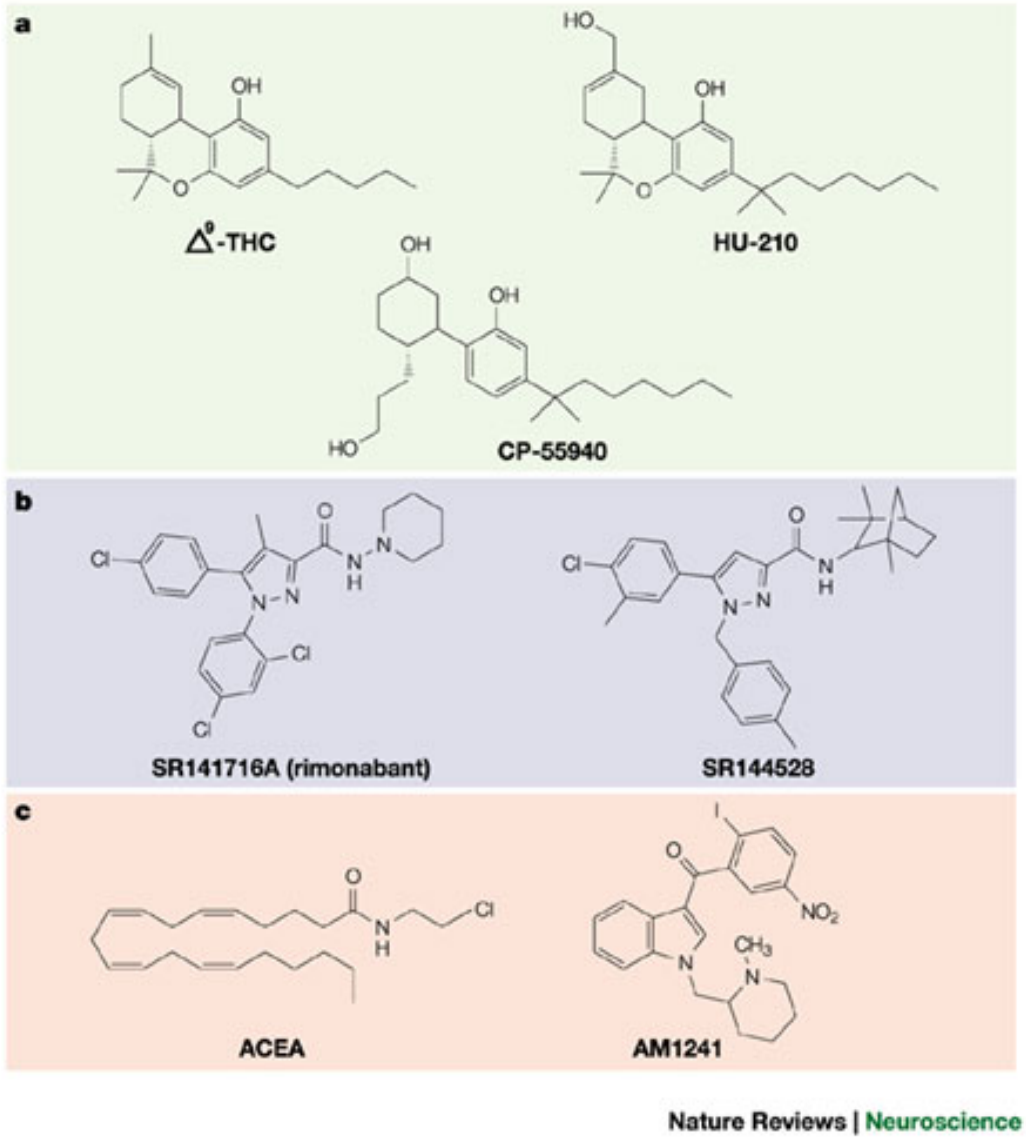
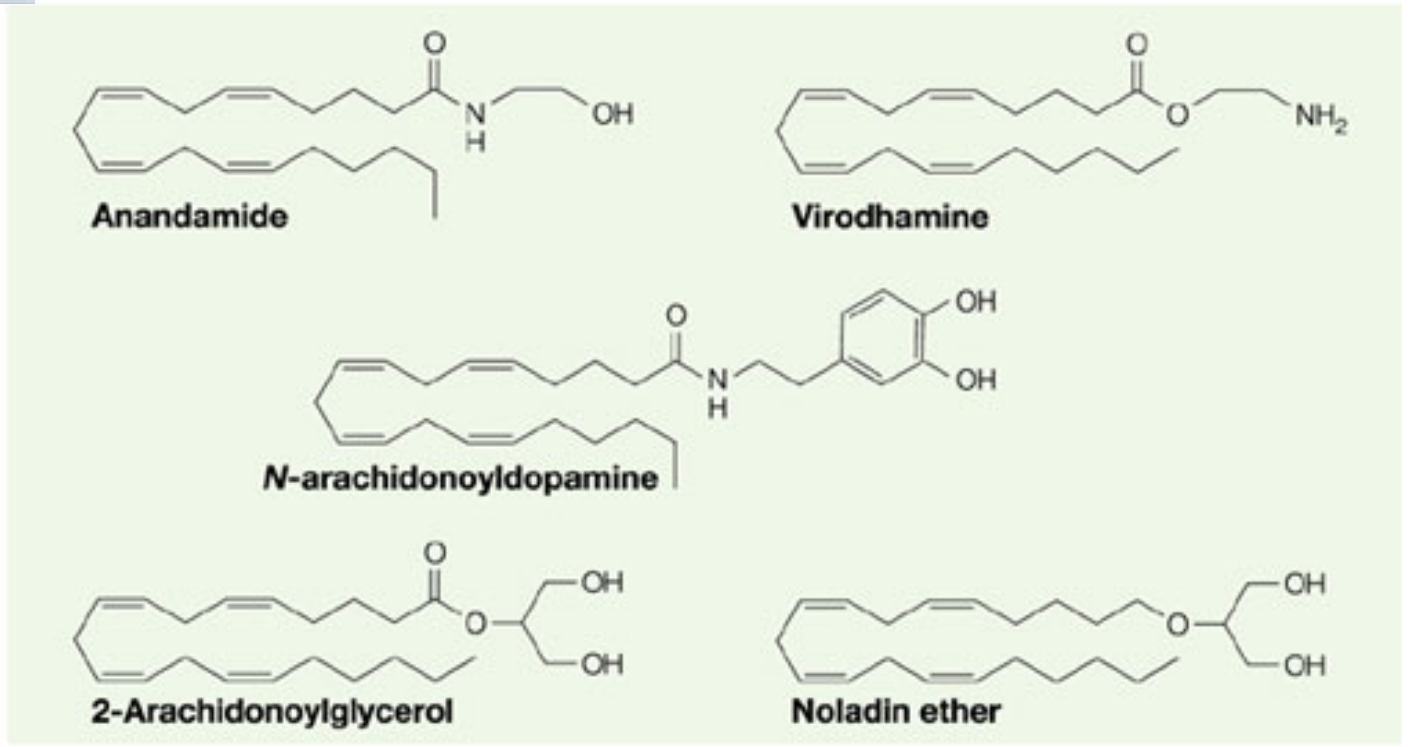




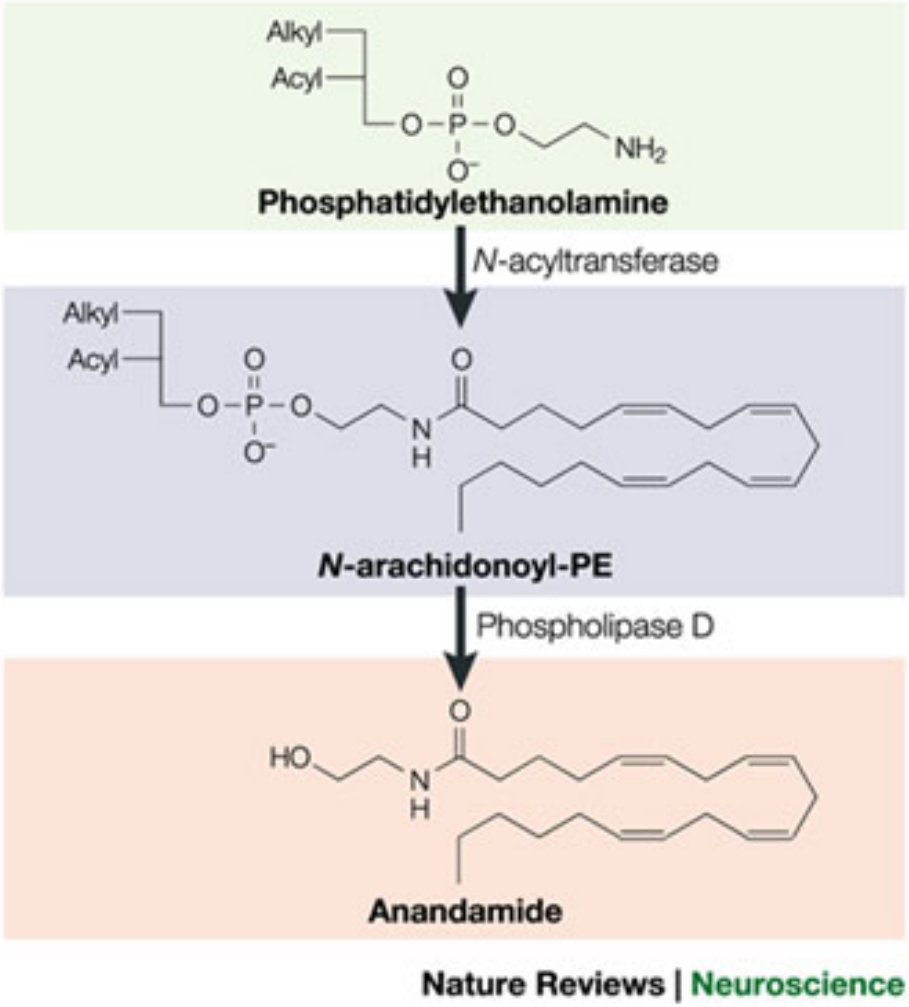
a | Cannabinoid receptor agonists, which activate both CB_1 and CB_2 receptors. THC, tetrahydrocannabinol

b | Selective CB_1 antagonist (SR141716A, rimonabant) and CB_2 antagonist (SR144528)

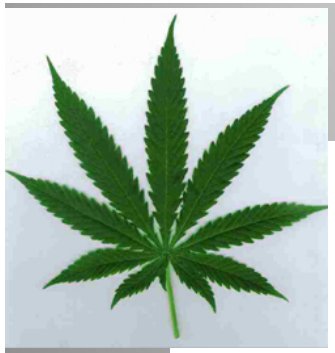
c | Selective CB_1 agonist (arachidonoyl-2'-chloroethanolamide, ACEA)[145] and CB_2 agonist (AM1241)

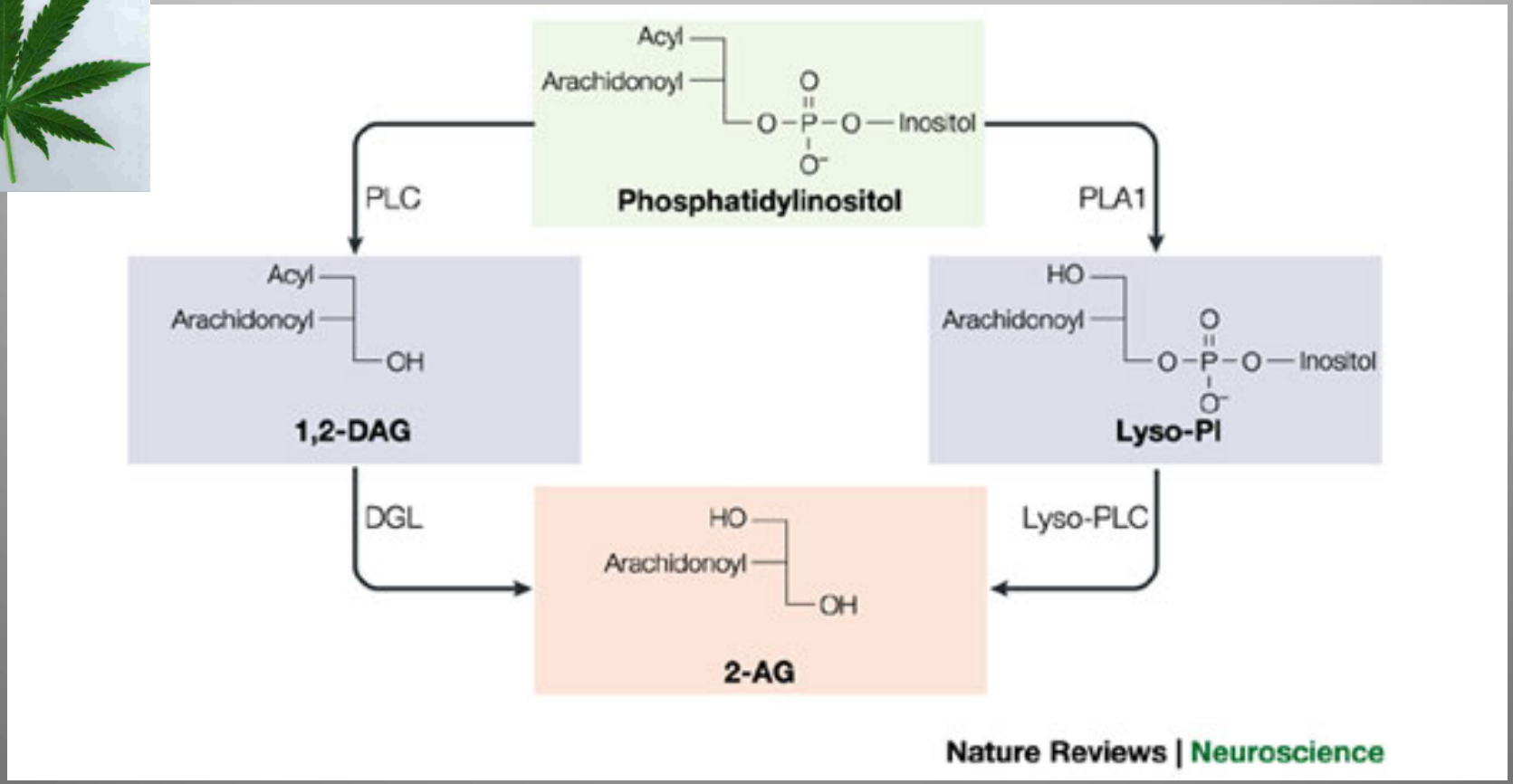


Nature Reviews | Neuroscience

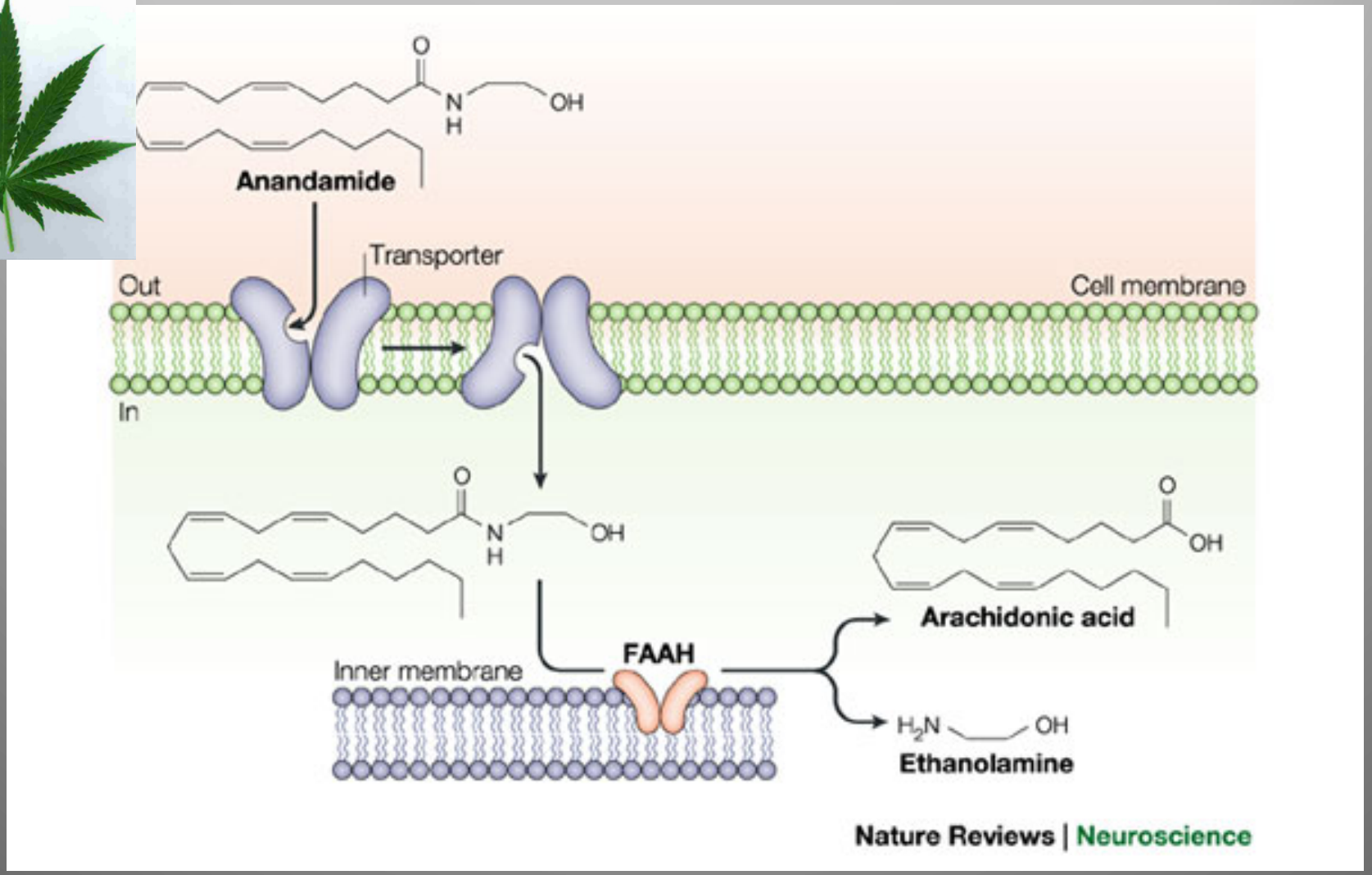


The sequence of reactions is thought to include: first, the synthesis of the anandamide precursor N-arachidonoyl-phosphatidylethanolamine (PE), catalysed by the enzyme N-acyltransferase; second, the cleavage of N-arachidonoyl-PE to yield anandamide, catalysed by phospholipase D.

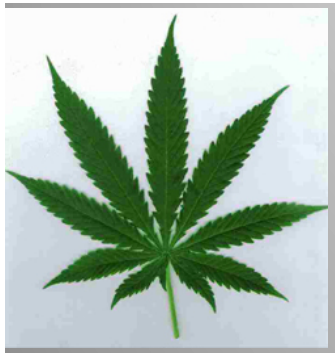


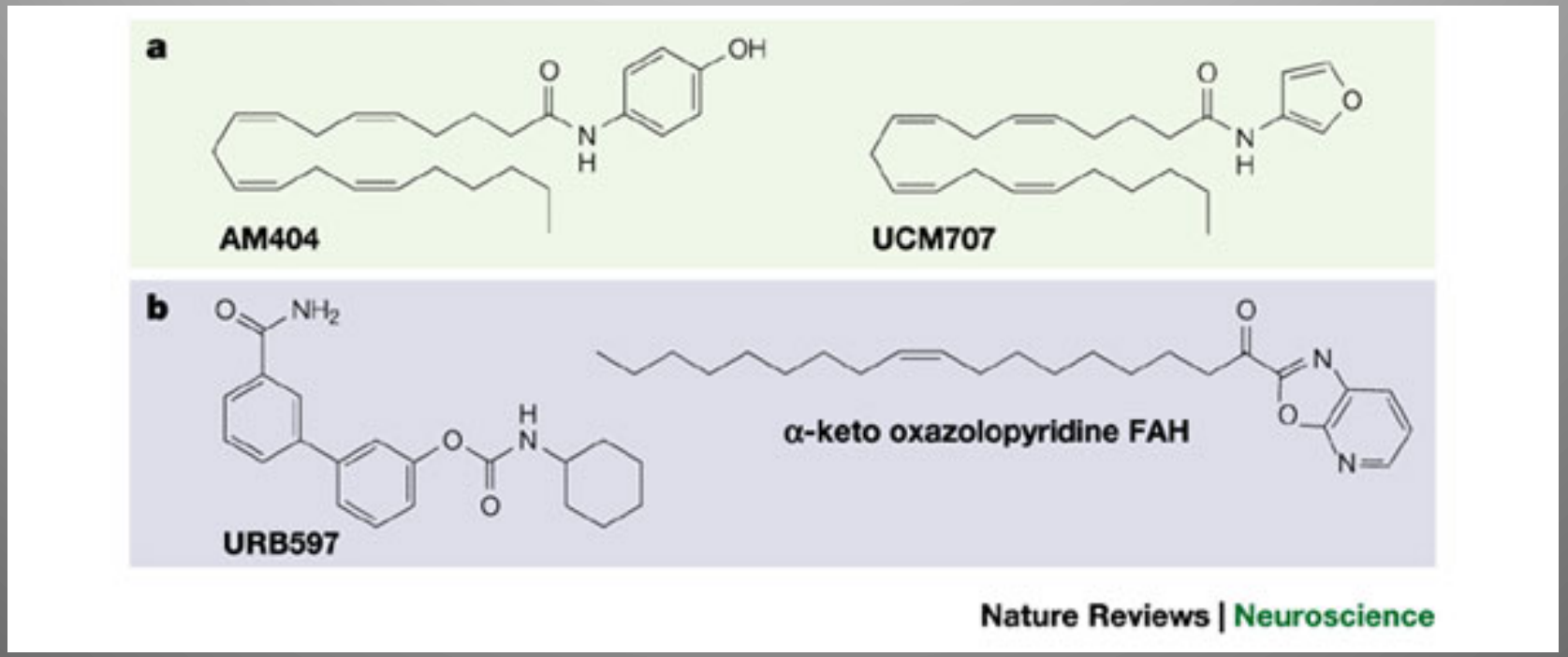


One possible sequence of reactions, shown on the left, includes the cleavage of phosphatidylinositol (PI) to yield 1,2-diacylglycerol (DAG), catalysed by a phospholipase such as phospholipase C (PLC), and the subsequent conversion of DAG to 2-AG, catalysed by diacylglycerol lipase (DGL). An alternative route, shown on the right, comprises the formation of a 2-arachidonoyl-lysophospholipid such as lyso-PI, catalysed by phospholipase A1 (PLA1), followed by the hydrolysis of the lysophospholipid to 2-AG, catalysed by lyso-PLC

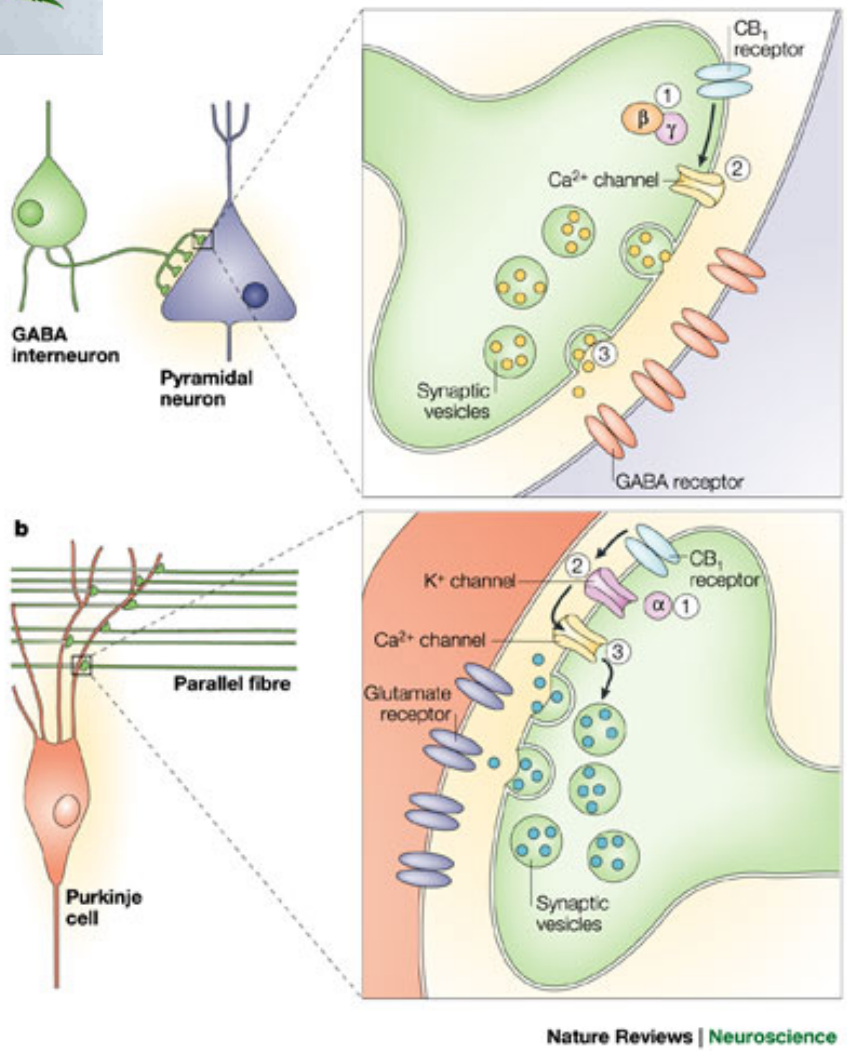


Anandamide and 2-arachidonoylglycerol (2-AG) can be internalized by neurons through a high-affinity transport mechanism, the 'endocannabinoid transporter'. Once inside cells, they can be hydrolysed by distinct serine hydrolases — anandamide by fatty acid amide hydrolase (FAAH) and 2-AG by monoglyceride lipase (MGL) (not shown) — to yield inactive breakdown products.



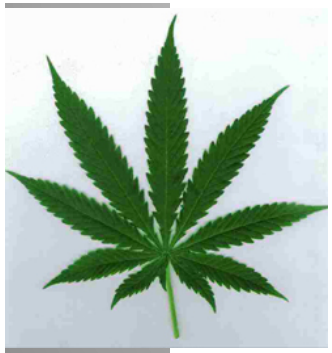


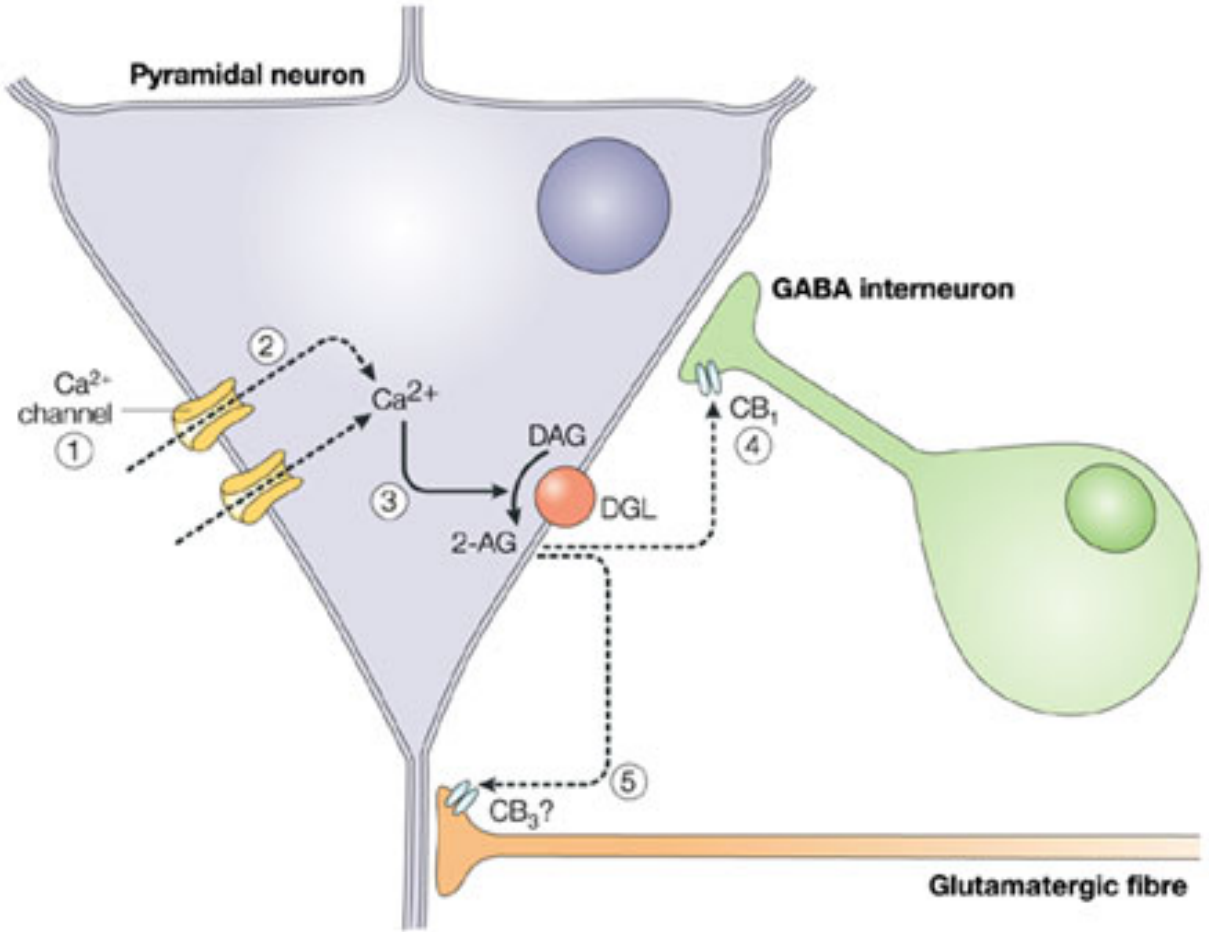
a | Endocannabinoid transport inhibitors: AM404 (Ref. 40) and UCM707 (Ref. 54). b | Fatty acid amide hydrolase (FAAH) inhibitors: substituted carbamates (URB597)[65] and substituted -keto oxazolopyridines



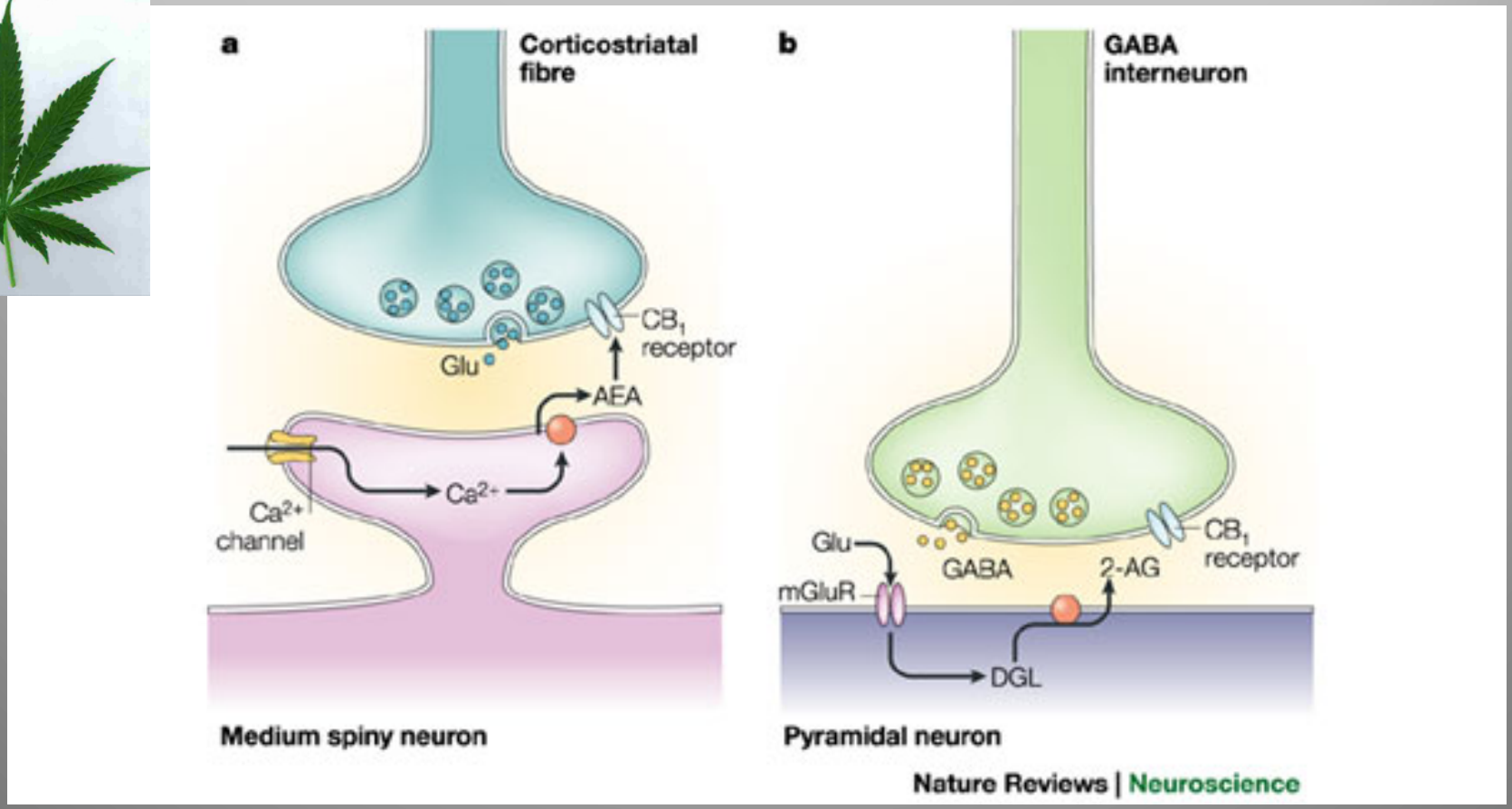
a | At synapses between GABA interneurons and pyramidal cells in the CA1 field of the hippocampus, activation of CB_1 receptors can initiate a series of intracellular events, which include (1) activation of G-protein –subunits, (2) closure of voltage-gated Ca^{2+} channels and (3) inhibition of GABA release.

b | At parallel fibre–Purkinje cell synapses in the cerebellum, CB_1 activation can (1) engage G-protein -subunits that (2) cause the opening of K^+ channels; the resulting membrane hyperpolarization can (3) reduce Ca^{2+} entry and inhibit glutamate release. Mechanisms similar to those illustrated above are thought to underlie cannabinoid-mediated inhibition of neurotransmitter release in other brain regions

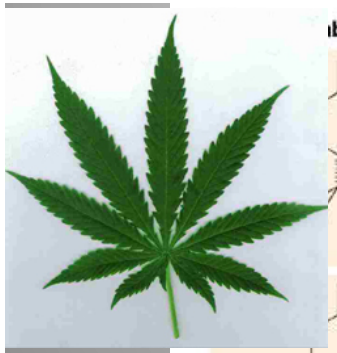


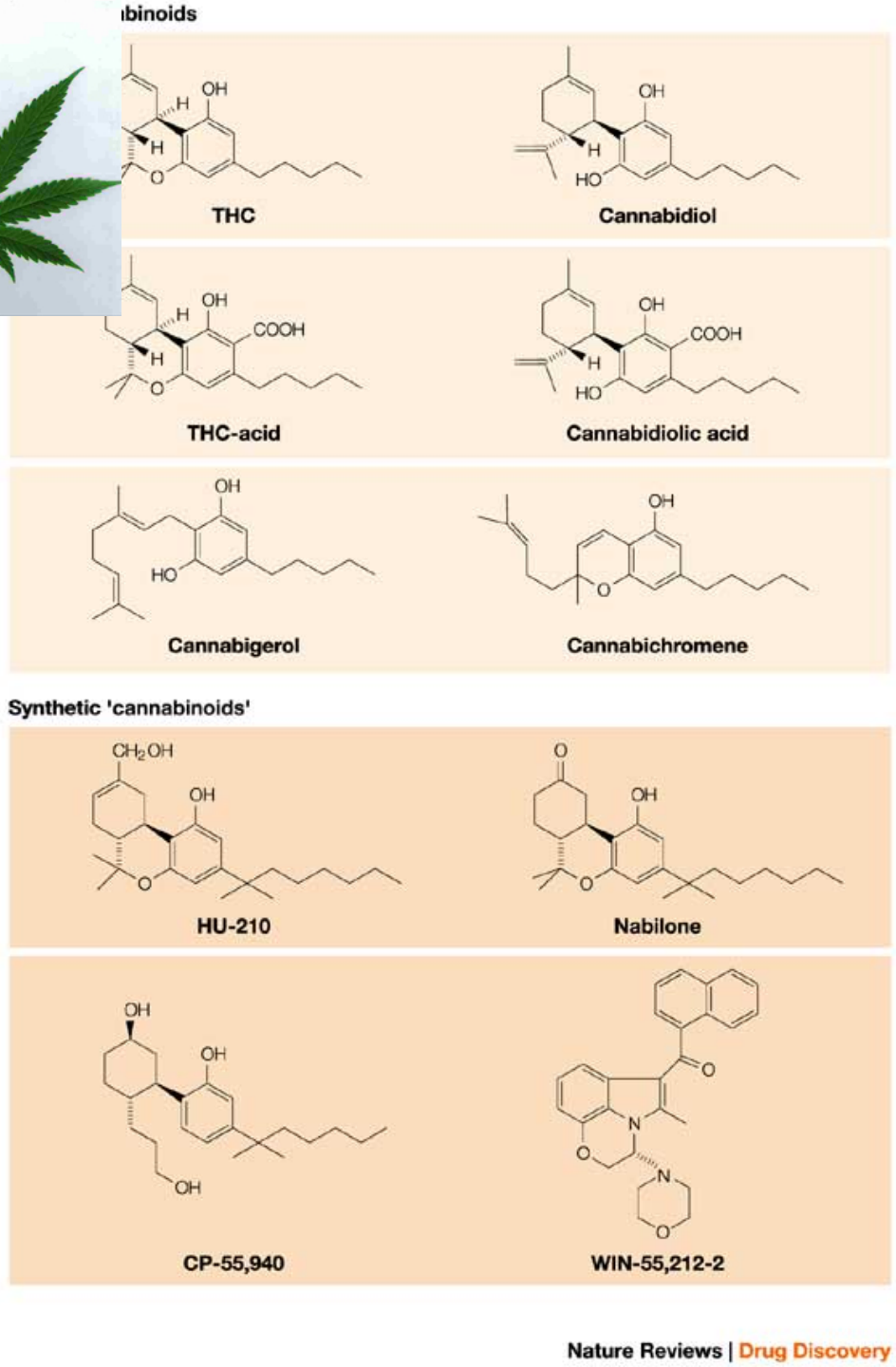


In the CA1 field of the hippocampus, membrane depolarization (1) opens voltage-activated Ca^{2+} channels in pyramidal neurons, producing (2) an elevation of intracellular Ca^{2+} concentrations. Ca^{2+} can (3) stimulate the synthesis of 2-arachidonoylglycerol (2-AG) through the diacylglycerol lipase (DGL) pathway or the synthesis of anandamide through the phospholipase D pathway (not shown). The newly formed endocannabinoids might travel across the synapse to interact with (4) CB_1 receptors on axon terminals of GABA (-aminobutyric acid) interneurons, leading to



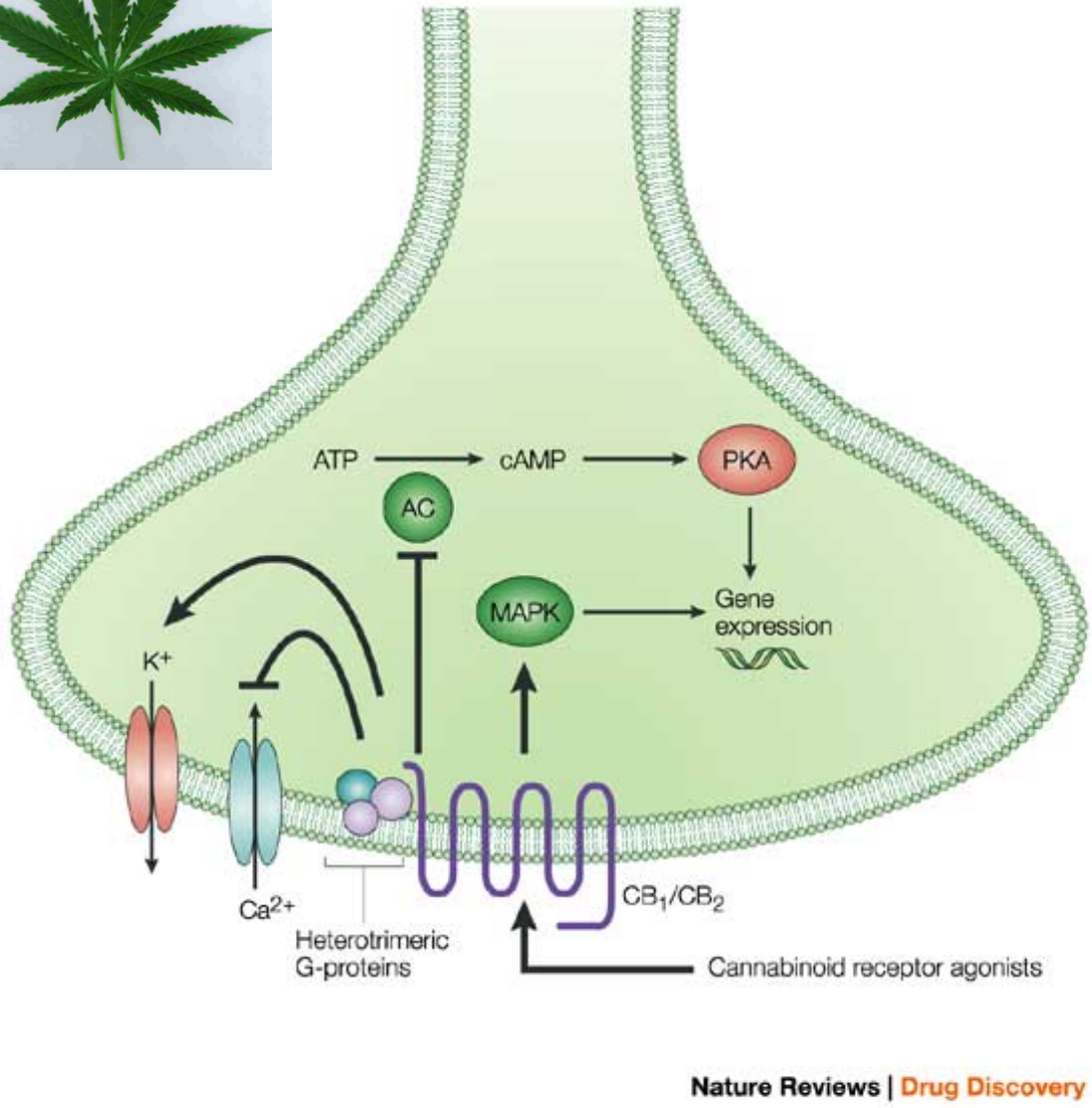
a | Repetitive activation of corticostriatal fibres causes a persistent reduction of glutamate release, called long-term depression (LTD), which might be mediated by anandamide. The elevated Ca^{2+} concentrations produced in postsynaptic spines of striatal medium spiny neurons after the stimulation could trigger anandamide (AEA) formation, which in turn might induce LTD by engaging CB_1 cannabinoid receptors on glutamatergic axon terminals. b | High-frequency stimulation of glutamatergic Schaffer collaterals in the hippocampus elicits a prolonged reduction of GABA (-aminobutyric acid) release that might be mediated by 2-arachidonoylglycerol (2-AG). This heterosynaptic form of plasticity, called inhibitory-LTD (I-LTD), is induced when glutamate activates metabotropic receptors (mGluR) on pyramidal neurons, eliciting 2-AG formation through the diacylglycerol lipase (DGL) pathway. 2-AG might then travel sideways to engage CB_1 receptors on contiguous terminals of GABA interneurons, producing I-LTD.





Of the plant CANNABINOIDS shown, only 9-tetrahydrocannabinol (THC)[4] binds to cannabinoid receptors with high affinity. Of the synthetic ones, none is selective for one type of cannabinoid receptor over the other[1]

Chemical structures of the two best-studied endocannabinoids, ANANDAMIDE and 2-arachidonoylglycerol[11, 12, 13]; of three recently proposed endogenous ligands of cannabinoid receptors[159, 160, 161]; and of more metabolically stable synthetic endocannabinoid analogues[162]. The rank of affinity of each compound for cannabinoid receptor subtypes 1 or 2 is shown.



Activation of both cannabinoid CB_1 and CB_2 receptors, and the subsequent stimulation of $G_{i/o}$ heterotrimeric proteins, is well known to be coupled to inhibition of denylate cyclase (AC) with corresponding inactivation of the rotein kinase A (PKA) hosphorylation pathway, or to timulation of mitogen-activated rotein kinase (MAPK). These ntracellular events lead to, among ther effects, the regulation of xpression of several genes. However, nore complex protein hosphorylation cascades — pecifically, those involving hosphoinositide-3-kinase and protein inase B — are also proposed to be riggered by CB_1 receptors[14, 15, 16, 17, 18]. urthermore, stimulation, rather than nhibition, of AC by CB_1, but not CB_2, receptors, via G_s proteins, has also been described occasionally. CB_1-, but not CB_2-, receptor stimulation of $G_{...}$

Hydrolytic enzymes are involved in both the biosynthesis of endocannabinoids (ECs) and in their inactivation (Box 1). The enzymes for 2-arachidonoylglycerol (2-AG) biosynthesis, the phospholipases C (PLC)[82, 83] and the sn-1-selective diacylglycerol lipases (DAGLs)[88] seem to be mostly localized on the plasma membrane. The DAGLs, in particular, are located on postsynaptic neurons in the adult nervous system[88], whereas the monoacylglycerol lipase (MAGL) for 2-AG inactivation is localized in presynaptic neurons[110], which supports a possible role as retrograde messenger at presynaptic CB_1 receptors for this compound[157]. The anandamide biosynthetic enzymes N-acyltransferase (NAT)[84] and N-acylphosphatidyl-ethanolamine-specific phospholipase D (NAPE-PLD)[85] and the inactivating enzyme fatty acid amide hydrolase (FAAH)[104] are all located on intracellular membranes. FAAH seems to be most abundant on neurons postsynaptic to CB_1 receptors[158], indicating that anandamide acts principally on these neurons. However

Inhibitors of both endocannabinoid cellular

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FAAH) that have been
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ossibly more selective
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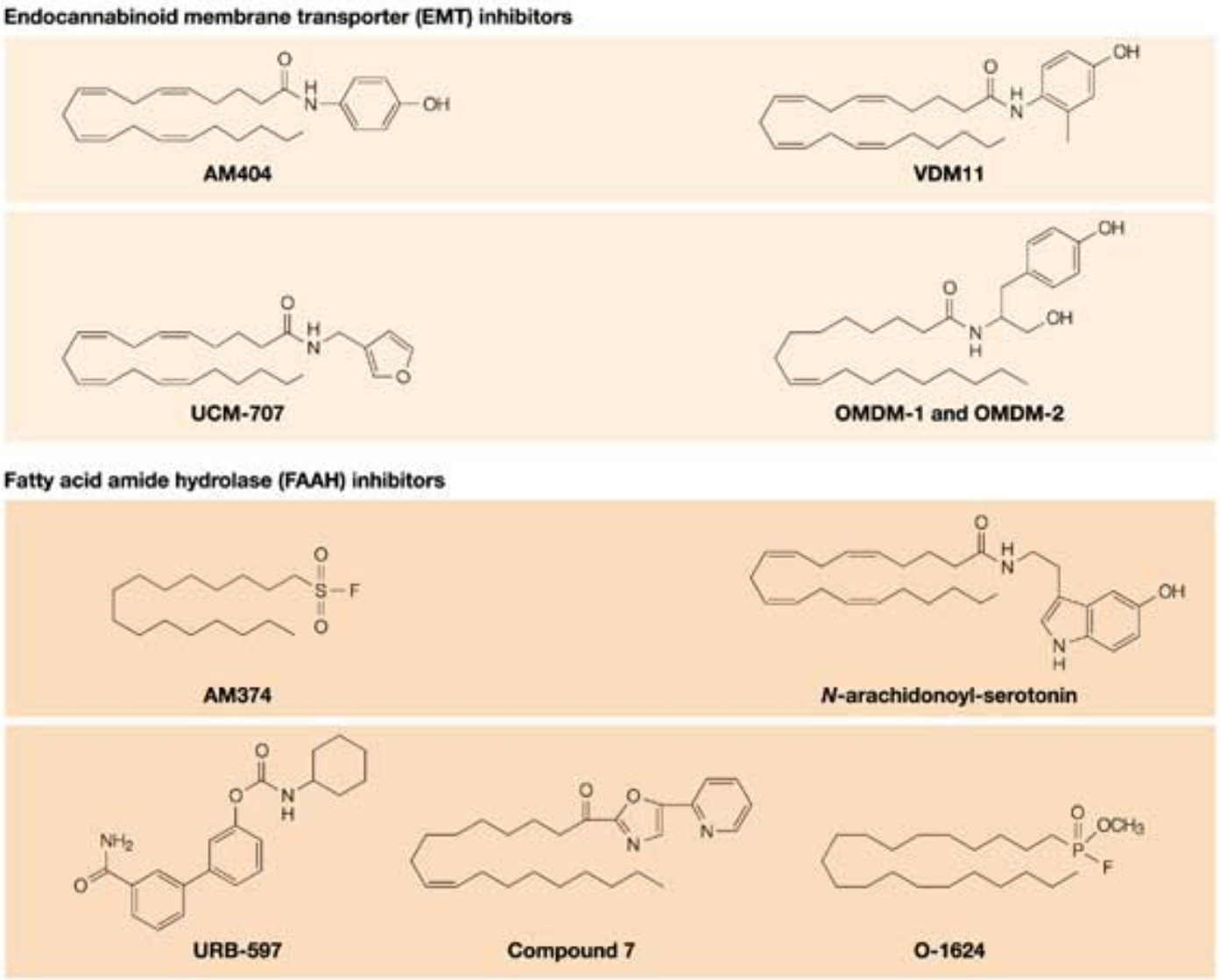
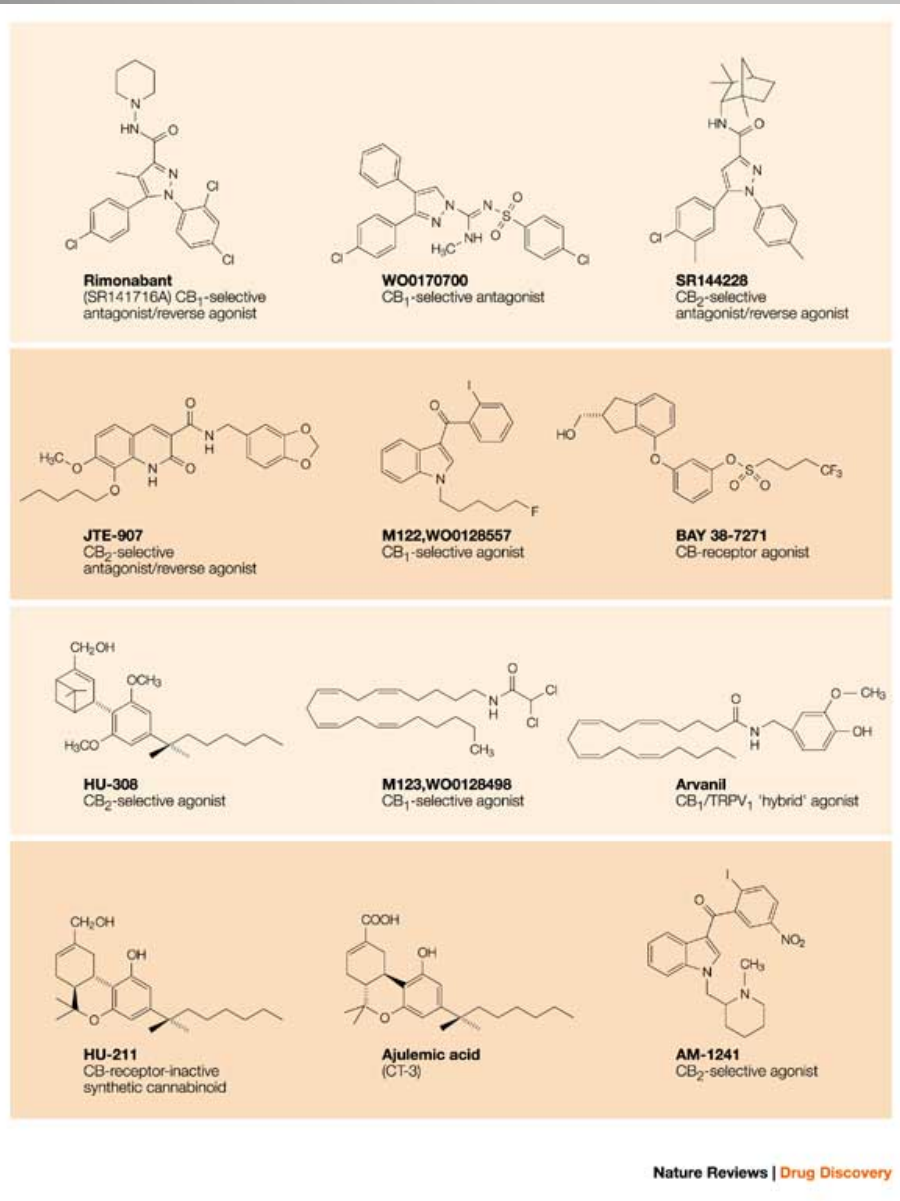


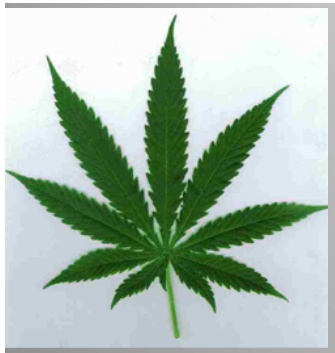


The most important feature of each compound is shown (collated from Refs [112–115,124,131,132,137–142]). Arvanil activates both CB_1 and vanilloid ($TRPV_1$) receptors, and for this reason is defined as 'hybrid'.

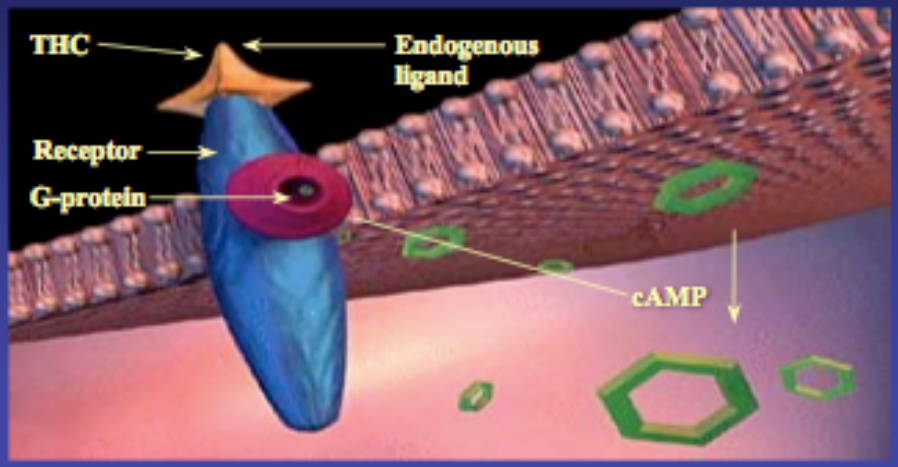
Table 2 | **Therapeutic strategies from the endocannabinoid system***

Strategy	Available	Routes of administration tested	Advantages	Disadvantages	Clinical trials complete?	Indications tested clinically or preclinically
CB_1 agonists	Yes	Oral, suppository	Wide range of applications	Psychotropic effects, tolerance	Yes	Nausea, Tourette's, Parkinson's disease, pain‡, cachexia, MS, glaucoma, cancer, diarrhoea, stroke
CB_2 agonists	Yes	Oral	No psychotropic effect	Limited range of applications	No	Pain, gliomas, lymphomas, inflammation
Partial agonists	Yes	None	Unlikely development of tolerance	Limited efficacy	No	Pain
'Soft' agonists and agonists unable to cross the BBB	No	None tested	No psychotropic effect	Applications limited to 'peripheral disorders'§	N/A	N/A
CB_1 antagonists	Yes	Oral	No psychotropic effect, very few side effects	Limited range of applications	Yes	Obesity, nicotine and alcohol dependence, ileus
Inhibitors of biosynthesis	No	None tested	No psychotropic effect, very few side effects	Limited range of applications	N/A	N/A
Inhibitors of inactivation	Yes	None	Higher selectivity, wide range of applications	Residual side effects	No	Pain, anxiety, diarrhoea, Parkinson's disease
Multi-target preparations and 'hybrid' agonists	Yes	Oral, mixed	Higher efficacy, low tolerance	Limited range of applications	Yes	Pain, spasticity in MS
Cannabinoid receptor-inactive cannabinoids	Yes	Oral	No psychotropic effect; very few side effects	Unknown mechanism of action	Yes	Pain, head injury, rheumatoid arthritis
Cannabis extracts	Yes	Sublingual spray	Toxicology well investigated	Initial side effects	Yes	Pain, spasticity in MS

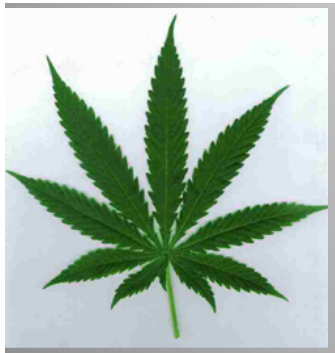
*See text for details and references. ‡'Pain' denotes chronic, neuropathic, inflammatory, MS-related and post-oprative pain. §'Peripheral disorders' denote those disorders that occur in peripheral organs or tissues as opposed to those developing in the central nervous system. BBB, blood–brain barrier; MS, multiple sclerosis and its animal model (allergic experimental encephalomyelitis); N/A, not applicable.



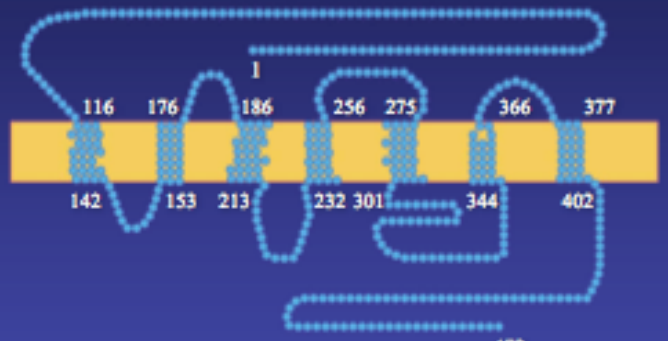
Endogenous Cannabinoid System



Adapted from Joy JE, et al, eds. *Marijuana and Medicine*. 1999.
Artwork adapted from NCADI publication #AVD145.

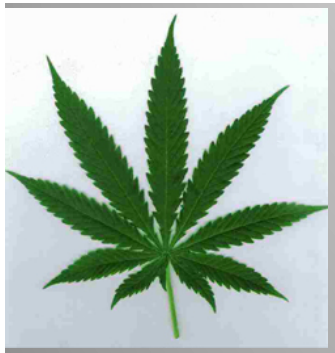


CB_1 Receptor



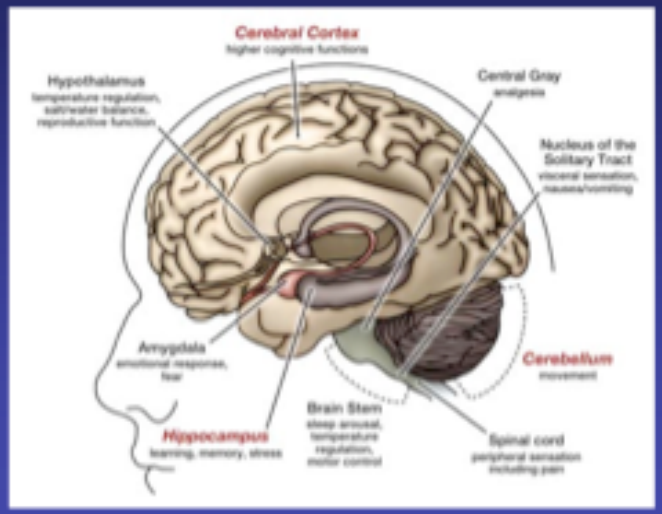
Adrenal gland
Bile duct
Bone marrow
Brain
Colon
Heart
Kidney
Liver
Lung
Muscle
Ovaries
Pancreas
Pituitary gland
Placenta
Prostate
Small intestine
Spleen
Stomach
Superior cervical ganglion
Testes
Thymus
Tonsils
Urinary bladder
Uterus
Vas deferens

Adapted from Joy JE, et al, eds. *Marijuana and Medicine*. 1999.



Some Brain Regions Containing CB_1 Receptors

Red = abundant CB_1 receptors Black = moderately abundant CB_1 receptors



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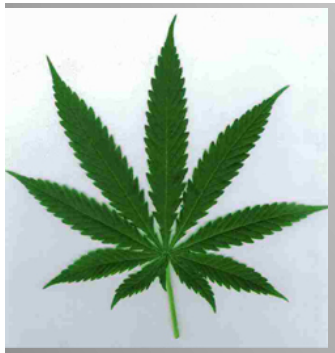
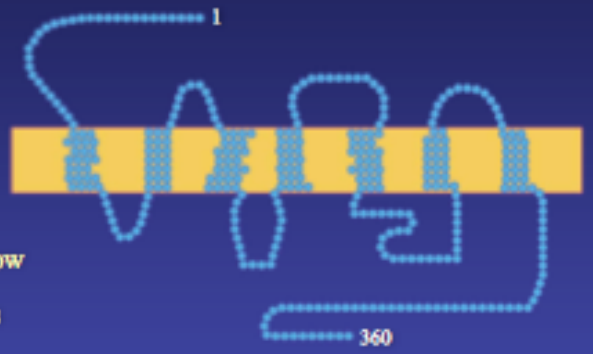


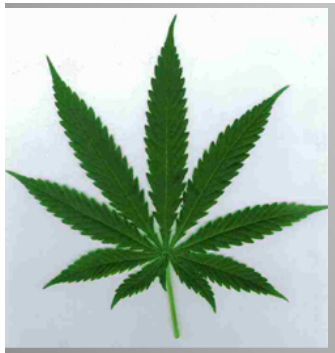
CB_2 Receptor

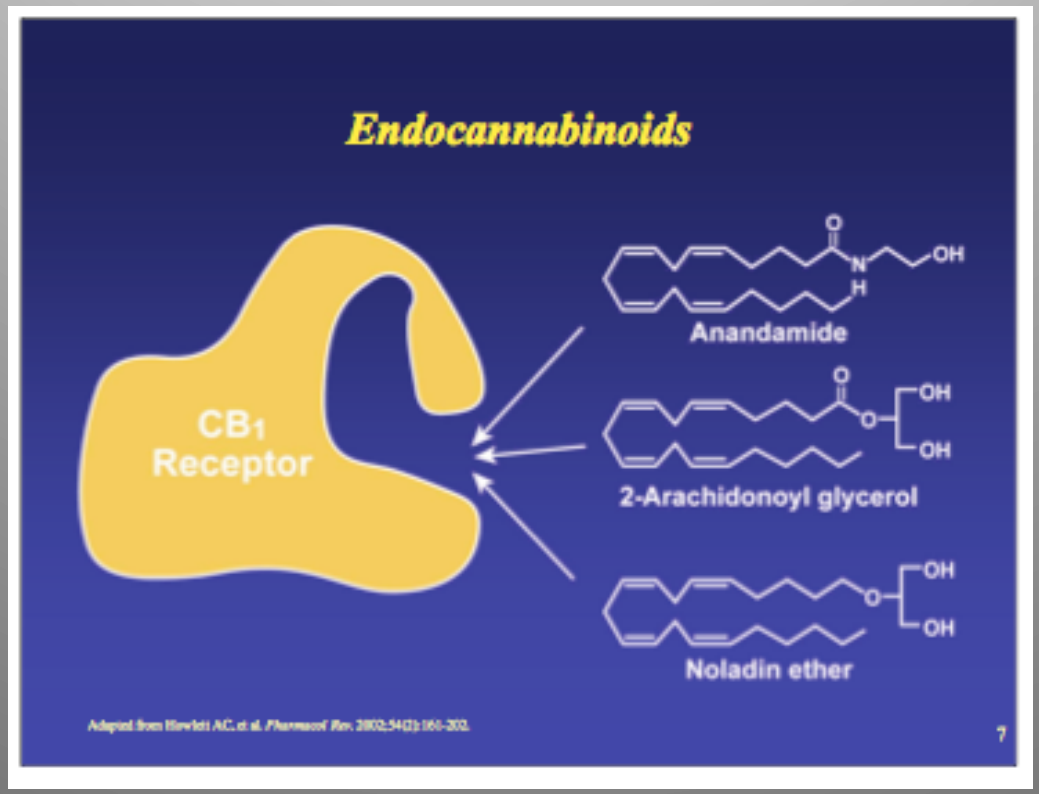


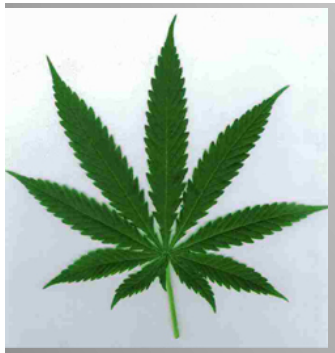
Adrenals
Bone marrow
Heart
Leukocytes
Lung
Monocytes
Natural killer cells
Ovaries
Pancreas
Peritoneal mast cells
Polymorphonuclear neutrophils

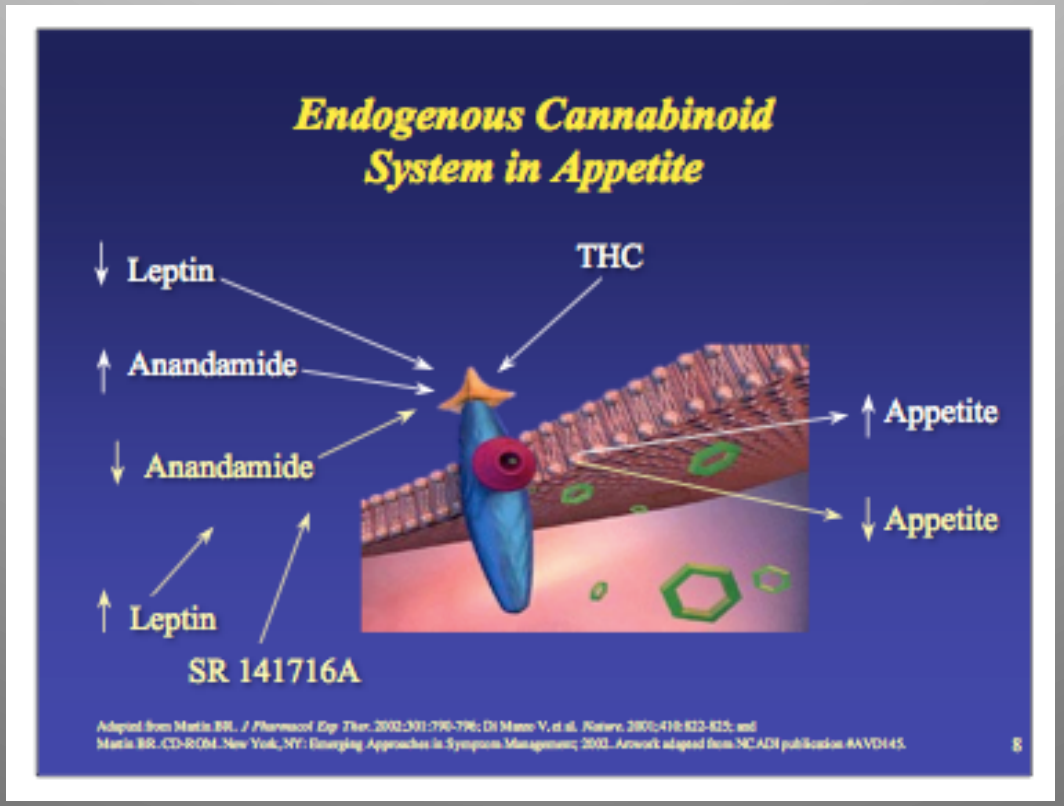
Prostate
Spleen
Testes
Thymus
Tonsils
Uterus

Adapted from Joy JE, et al, eds. *Marijuana and Medicine*. 1999.




Endocannabinoids
CB1 Receptor
Anandamide
2-Arachidonoyl glycerol
Noladin ether
OH
N
H
O
7




Endogenous Cannabinoid System in Appetite
Leptin
THC
Anandamide
Anandamide
Appetite
Appetite
Leptin
SR 141716A
Adapted from Matin BR. J Pharmacol Exp Ther. 2002;301:790-796; Di Marzo V, et al. Nature. 2001;410:822-825; and Matin BR. CD-ROM. New York, NY: Emerging Approaches in Symptom Management; 2002. Artwork adapted from NCADI publication #AVD145.
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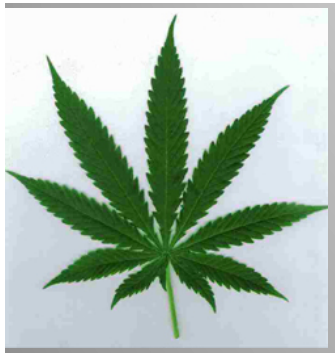

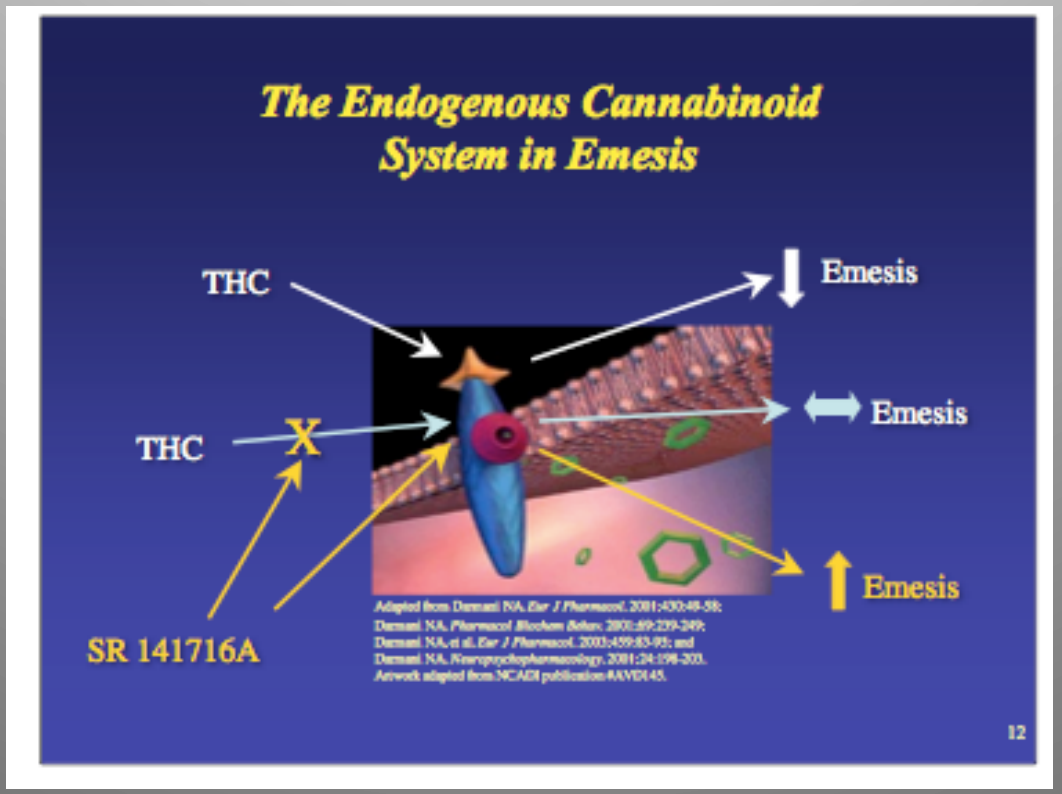
The Endogenous Cannabinoid System in Emesis
THC
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Adapted from: Darmani NA. Eur J Pharmacol. 2001;430:49-58;
Darmani NA. Pharmacol Biochem Behav. 2001;69:239-249;
Darmani NA, et al. Eur J Pharmacol. 2003;459:83-93; and
Darmani NA. Neuropsychopharmacology. 2001;24:198-203.
Artwork adapted from NCADI publication #AVD145.
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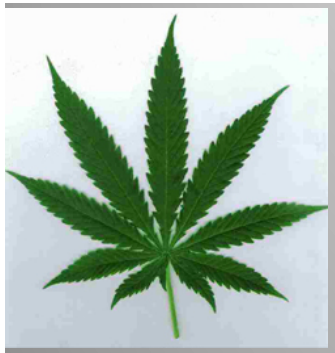
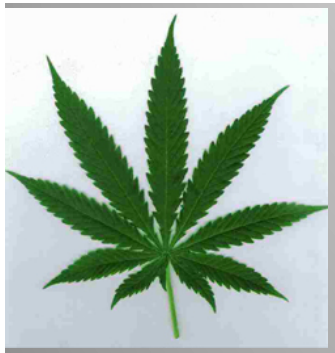


Multiple Clinical Challenges: The Role of MARINOL®

With its unique pathway, MARINOL® is the only agent indicated for both:

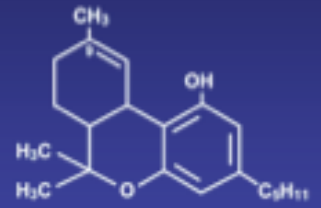
- Treatment of anorexia associated with weight loss in AIDS patients
- Treatment of nausea/vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetics



What is MARINOL® (dronabinol)?

- The only FDA-approved synthetic cannabinoid
- Synthetic delta-9-THC[1]
- Delta-9-THC:
  - One of >400 chemicals in the *Cannabis sativa* plant[2]

MARINOL® Chemical Structure



$C_{21}H_{30}O_2$ (molecular weight = 314.47)

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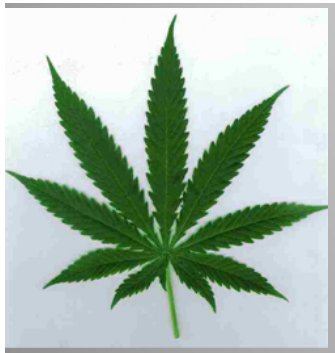
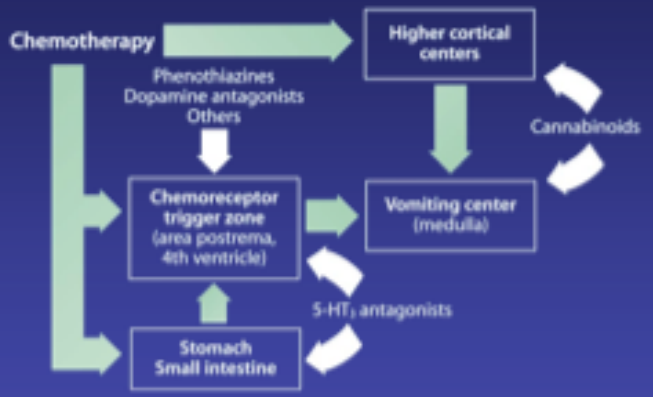
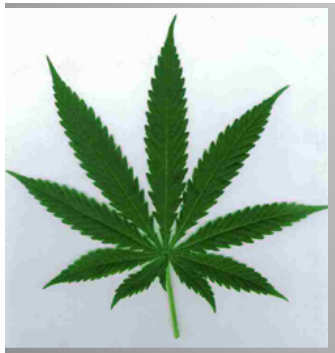
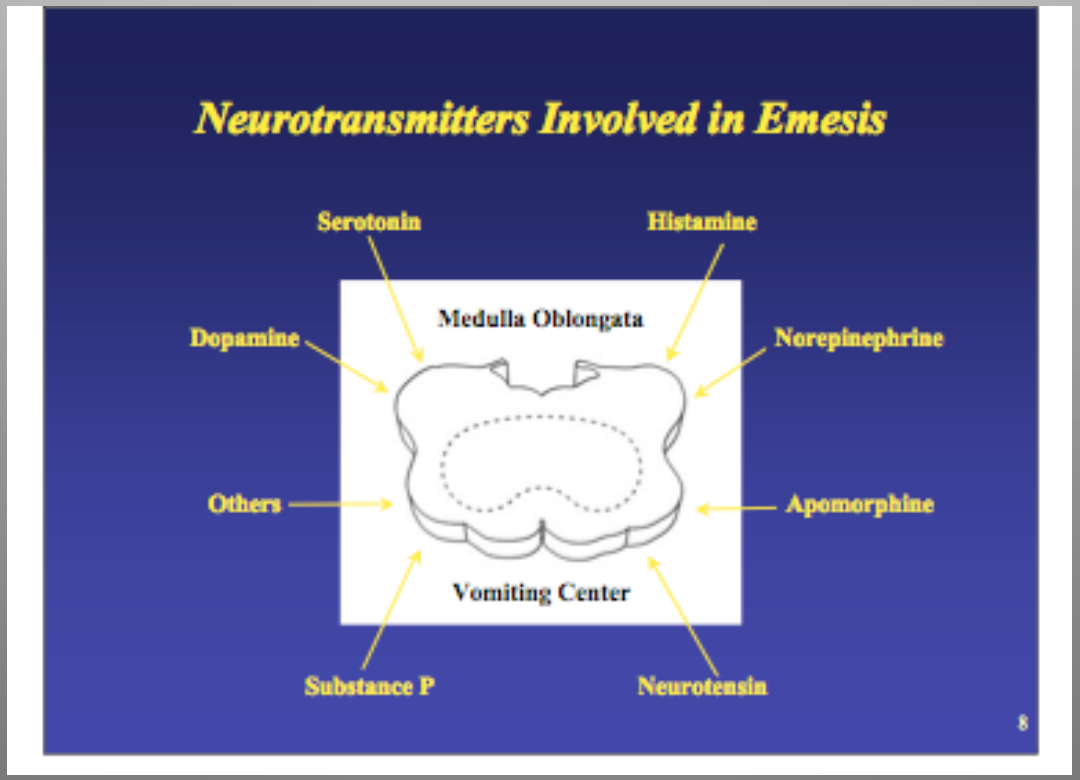


CINV Involves Multiple Pathways

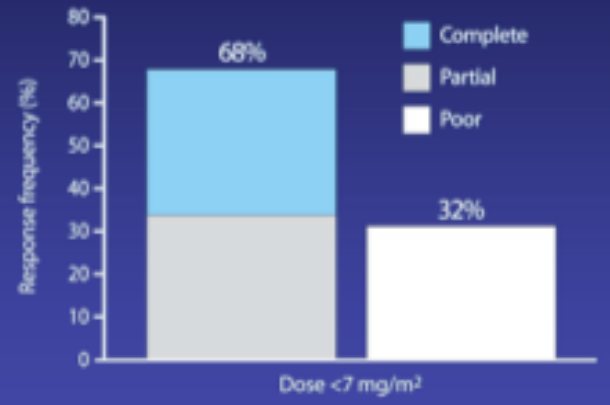


Combinations of antiemetics often needed for effective therapy.




Neurotransmitters Involved in Emesis
Serotonin
Histamine
Medulla Oblongata
Dopamine
Norepinephrine
Others
Apomorphine
Vomiting Center
Substance P
Neurotensin
8

MARINOL® Reduced Emesis in >2/3 of Treatment Courses in NCI Studies*



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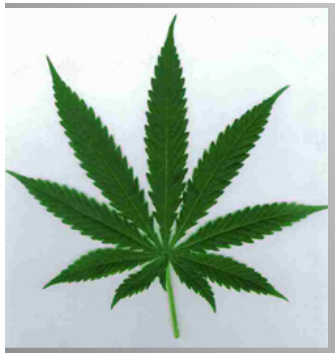
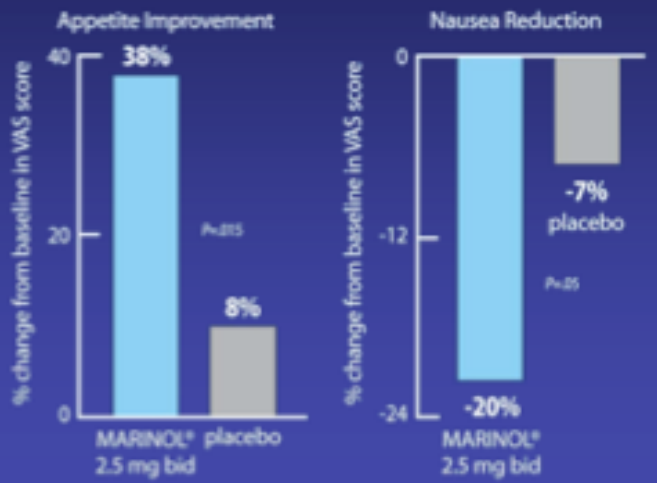
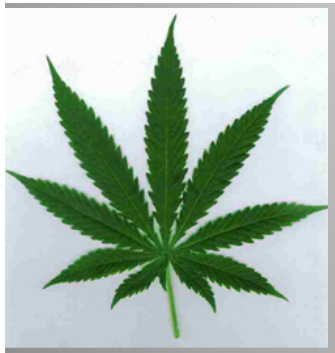


MARINOL® Appetite Stimulation: 6-week Study in AIDS Patients

139 AIDS patients with anorexia associated with weight loss



Beal JE, et al. *J Pain Symptom Manage.* 1995;10(2):89-97.



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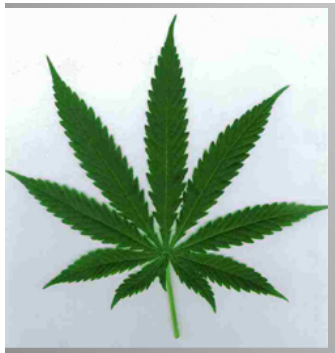
- Warn patients not to drive or engage in hazardous activity until tolerance established

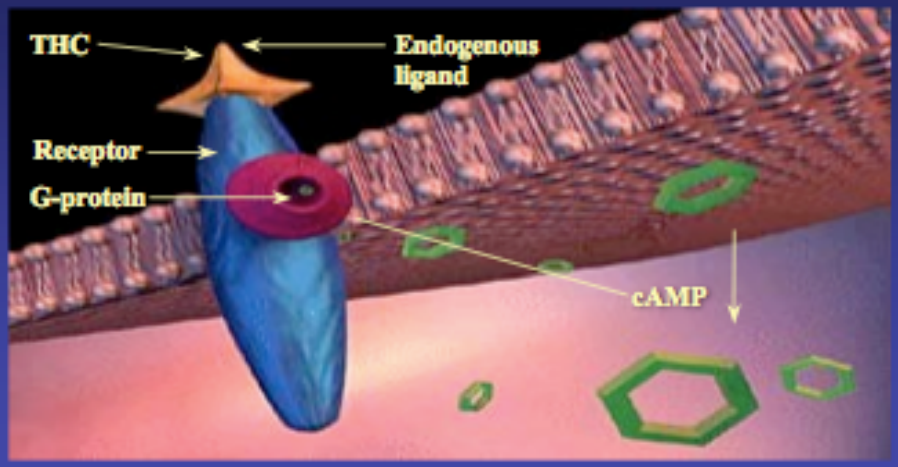
Use with caution in patients:

- With cardiac disorders
- With a history of substance abuse
- With mania, depression, or schizophrenia (along with careful psychiatric monitoring)
- Taking sedatives, hypnotics, or other psychoactive drugs
- Who are pregnant or nursing
- Who are children

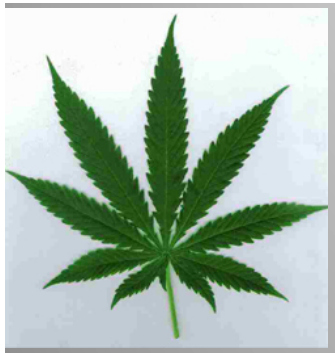
MARINOL® (dronabinol) CII Capsules package insert. October 2002.



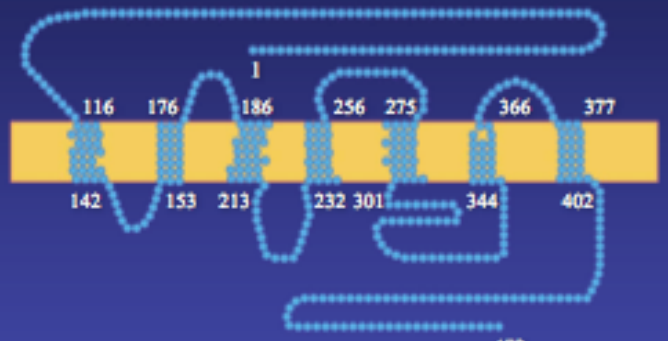
Endogenous Cannabinoid System



Adapted from Joy JE, et al, eds. *Marijuana and Medicine*. 1999.
Artwork adapted from NCADI publication #AVD145.



CB_1 Receptor



Adrenal gland
Bile duct
Bone marrow
Brain
Colon
Heart
Kidney
Liver
Lung
Muscle
Ovaries
Pancreas
Pituitary gland
Placenta
Prostate
Small intestine
Spleen
Stomach
Superior cervical ganglion
Testes
Thymus
Tonsils
Urinary bladder
Uterus
Vas deferens

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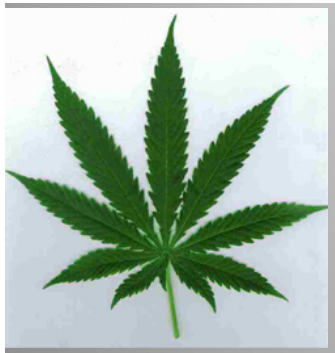
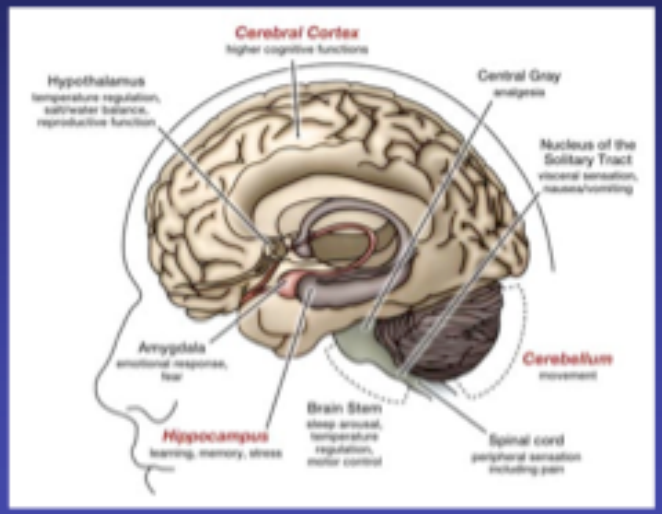


Some Brain Regions Containing CB_1 Receptors

Red = abundant CB_1 receptors Black = moderately abundant CB_1 receptors



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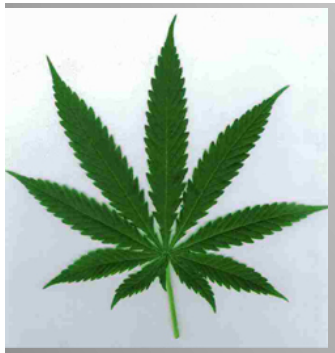
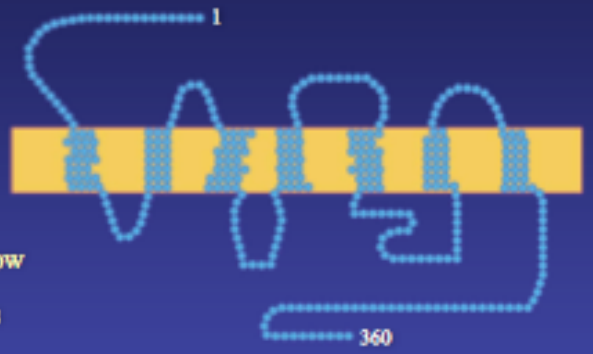


CB_2 Receptor



Adrenals
Bone marrow
Heart
Leukocytes
Lung
Monocytes
Natural killer cells
Ovaries
Pancreas
Peritoneal mast cells
Polymorphonuclear neutrophils

Prostate
Spleen
Testes
Thymus
Tonsils
Uterus

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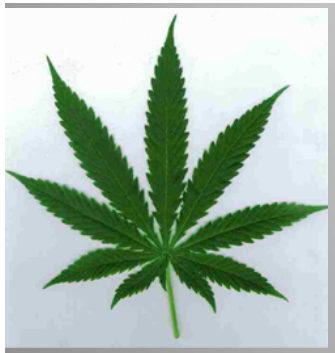
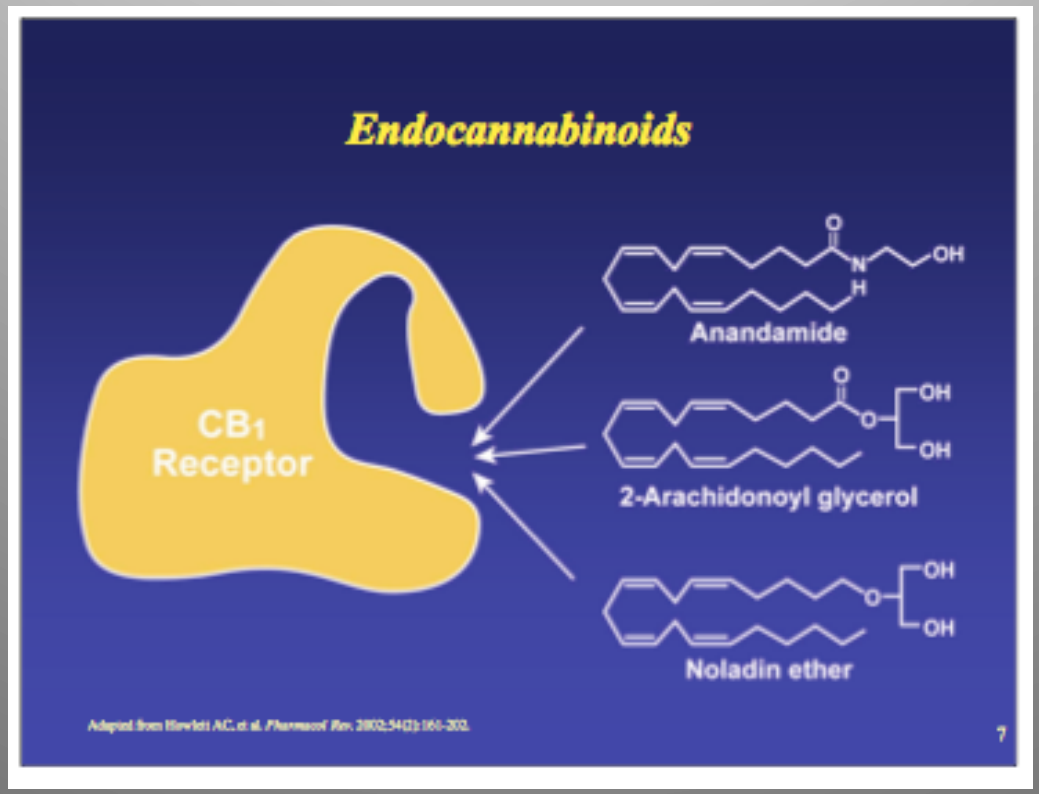
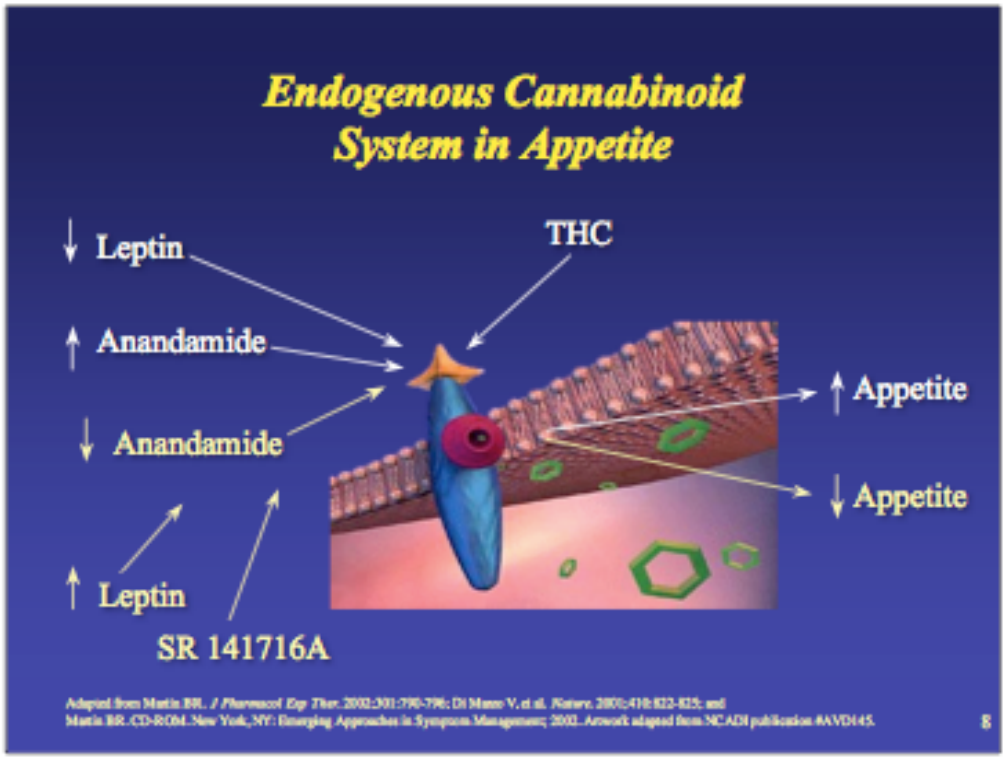
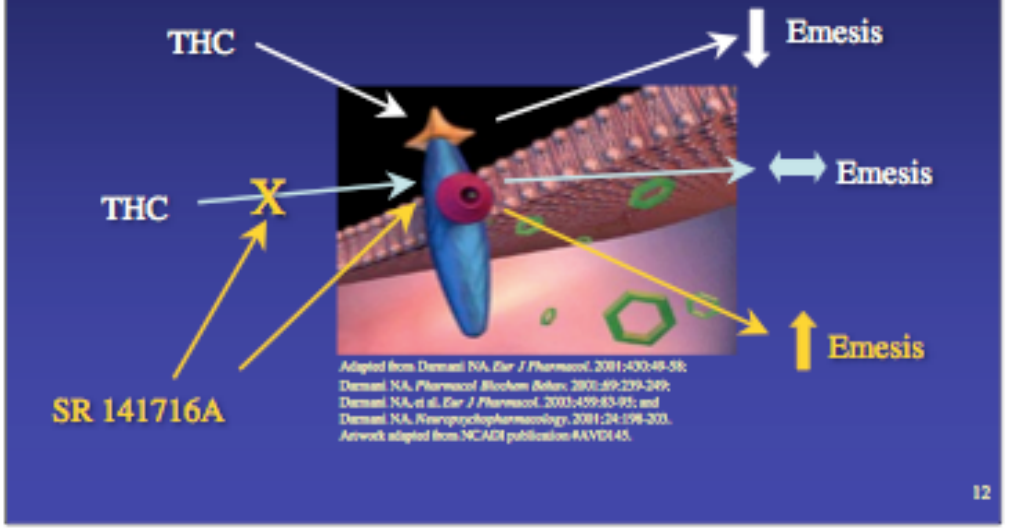



Endocannabinoids
CB1 Receptor
Anandamide
2-Arachidonoyl glycerol
Noladin ether
OH
N
H
O
7


Endogenous Cannabinoid System in Appetite
Leptin
THC
Anandamide
Anandamide
Appetite
Appetite
Leptin
SR 141716A
Adapted from Matin BR. J Pharmacol Exp Ther. 2002;301:790-796; Di Marzo V, et al. Nature. 2001;410:822-825; and Matin BR. CD-ROM. New York, NY: Emerging Approaches in Symptom Management; 2002. Artwork adapted from NCADI publication #AVD145.
8

The Endogenous Cannabinoid System in Emesis



Adapted from: Darmani NA. *Eur J Pharmacol*. 2001;430:49-58; Darmani NA. *Pharmacol Biochem Behav*. 2001;69:239-249; Darmani NA, et al. *Eur J Pharmacol*. 2003;459:83-93; and Darmani NA. *Neuropsychopharmacology*. 2001;24:198-203. Artwork adapted from NCADI publication #AVD145.

Multiple Clinical Challenges: The Role of MARINOL®

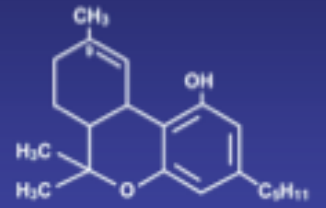
With its unique pathway, MARINOL® is the only agent indicated for both:

- Treatment of anorexia associated with weight loss in AIDS patients
- Treatment of nausea/vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetics

What is MARINOL® (dronabinol)?

- The only FDA-approved synthetic cannabinoid
- Synthetic delta-9-THC[1]
- Delta-9-THC:
  - One of >400 chemicals in the *Cannabis sativa* plant[2]

MARINOL® Chemical Structure



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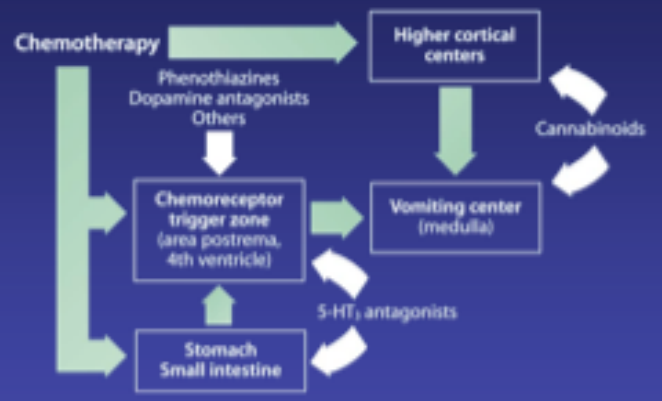

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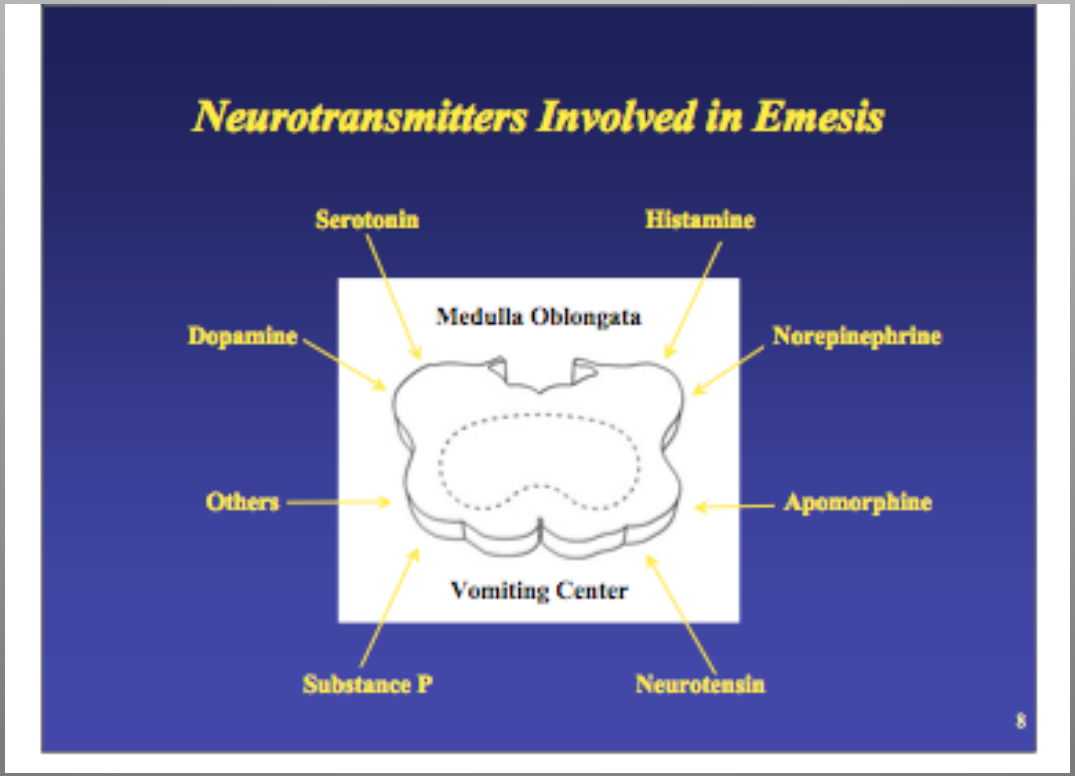
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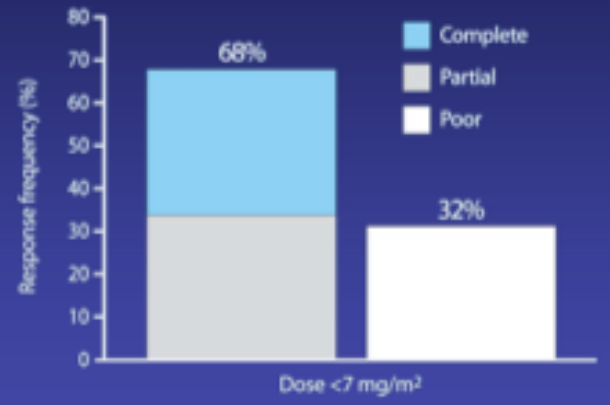

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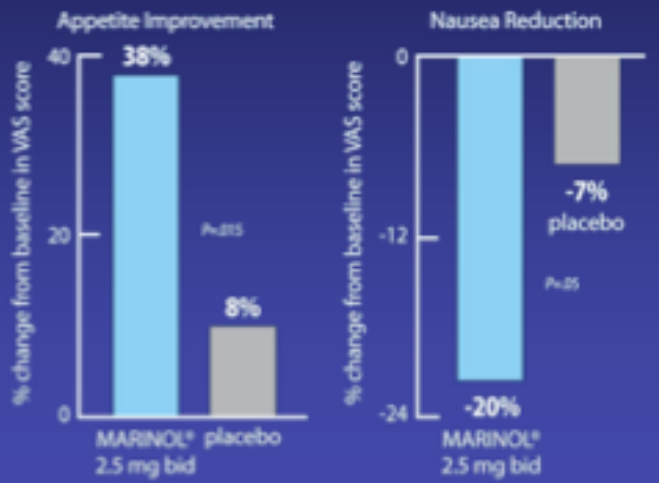

Beal JE, et al. *J Pain Symptom Manage.* 1995;10(2):89-97.

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- Who are pregnant or nursing
- Who are children

MARINOL® (dronabinol) CII Capsules package insert. October 2002.

What is Sativex?

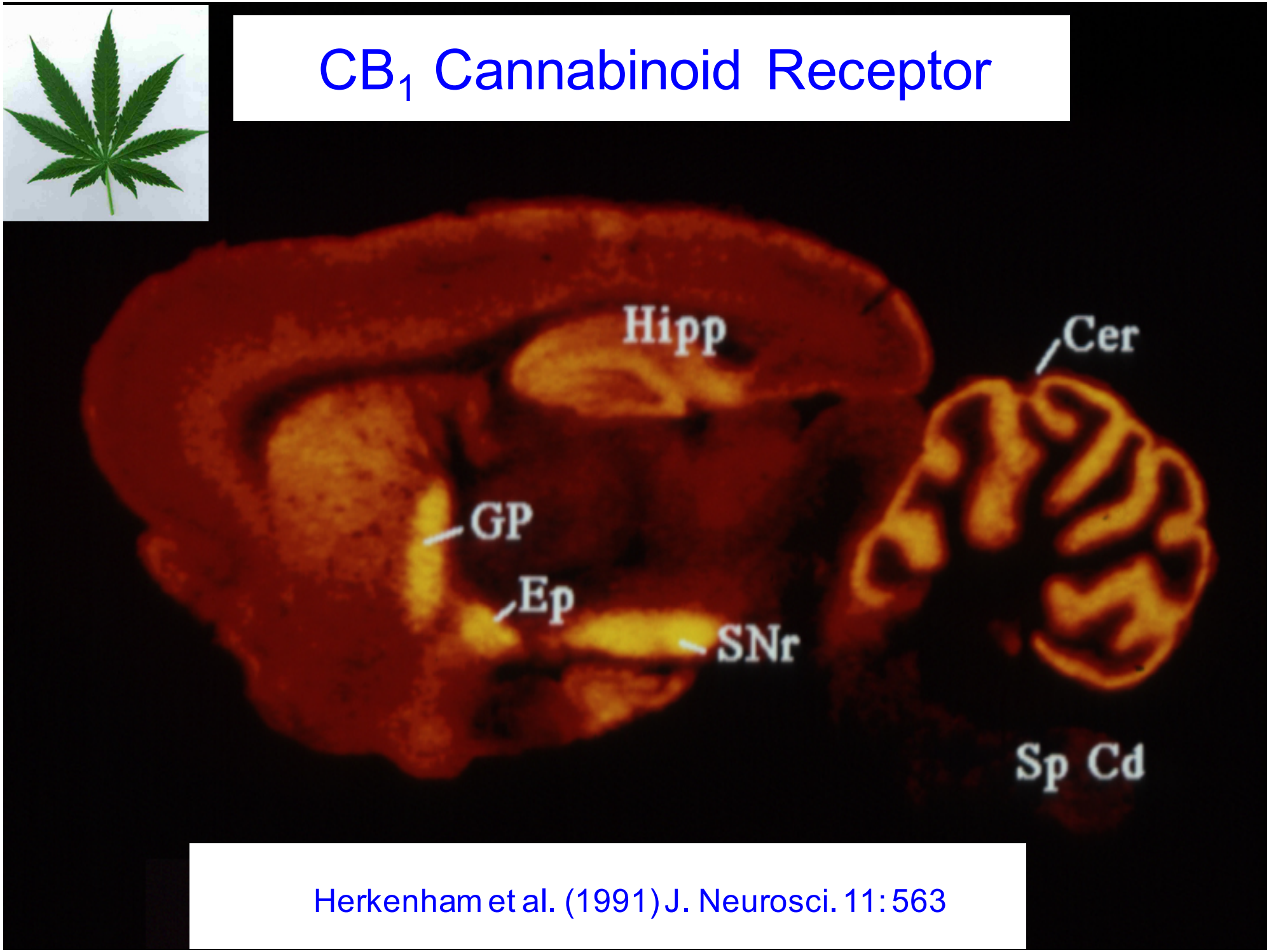
Sativex is a natural marijuana extract develope
Pharmaceuticals. It is a li quid that is sprayed into tl
Made from marijuana plants bred for specific levels
active components, called cannabinoids, Sativex is
marijuana-based extracts and tinctures that wer
available in the United States until 1937.

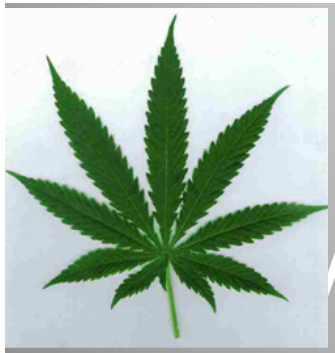
What conditions has Sativex been tested for?

Most testing thus far has been done on patients suffe
multiple sclerosis and various types of chronic pain,
cancer pain. These studies have shown Sativex to ha
benefits and mild side effects, and patients do not
tolerance to it.

Is Sativex licensed for prescription sale anywher

The Canadian government approved the prescriptio
sale of Sativex on April 19, 2005. An application is als
pending in Great Britain, which could be granted by th
end of 2005.


CB1 Cannabinoid Receptor
Hipp
Cer
GP
Ep
SNr
Sp Cd
Herkenham et al. (1991) J. Neurosci. 11: 563

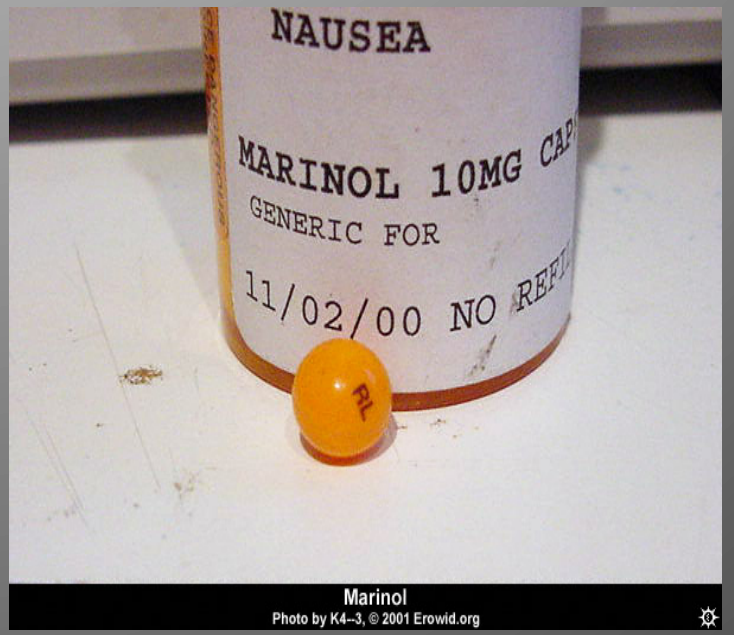


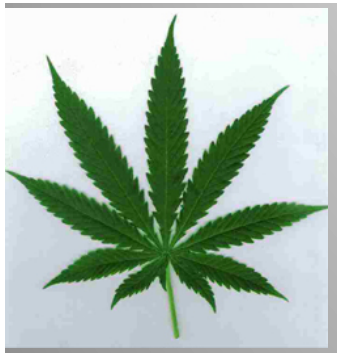
ynthetic THC: Oral Cannabinoids

- Narcotics prescription
- Nausea, vomiting with chemotherapy, anorexia associated with HIV/AIDS

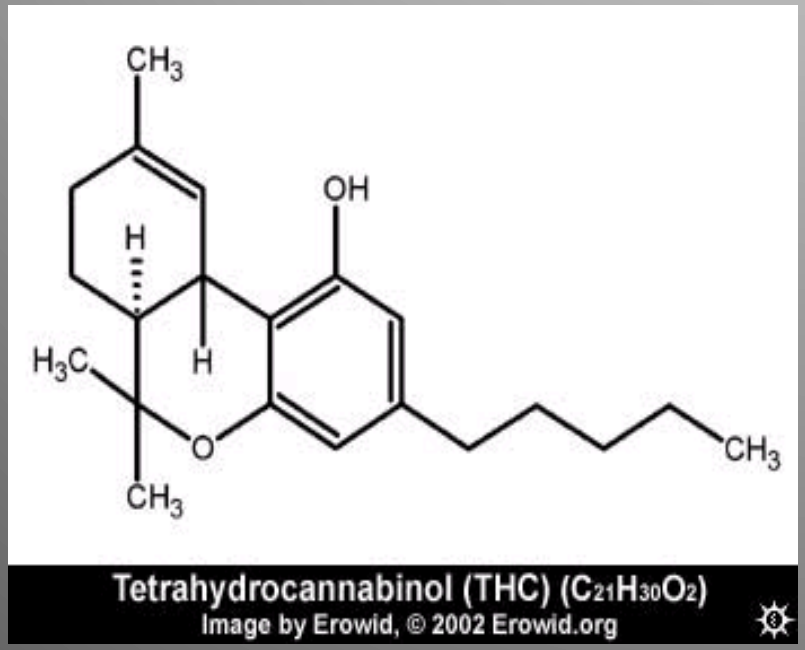
- Cesamet (Nabilone) (0.5, 1 mg)
  - purified synthetic cannabinoid
  - nitrogen analogue to THC
  - $T_{1/2}$ 8-12 hrs

- Marinol (dronabinol) (2.5, 5 mg)
  - Delta-9-THC
  - $T_{1/2}$ 4-6 hrs
  - metabolites long $T_{1/2}$

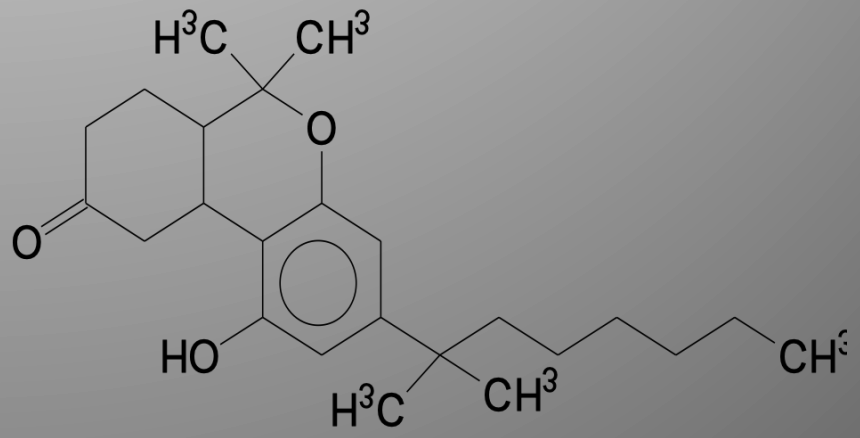




Molecular Structure
Δ9-THC vs Nabilone



Tetrahydrocannabinol (THC) ($C_{21}H_{30}O_2$)
Image by Erowid, © 2002 Erowid.org



Nabilone (THC analogue) $C_{24}H_{36}O_3$
Product monograph. ICN Canada Ltd. 2002

Cannabinoid Profile Summary

Product	Sativex Bayer/GW	Marinol Solvay	Cesamet Valeant	Medical Marijuana Health Canada
Composition	THC and CBD extracts terpenes falvanoids	Synthetic THC (dronabinol)	Synthetic THC analog (nabilone)	~60 cannabinoids terpenes flavanoids
Delivery	Buccal spray – 27mg/ml THC, 25mg/ml CBD Self-titration	Oral – 2.5mg, 5mg, 10mg BID	Oral – 0.5mg, 1mg BID	Smoked or ingested – 12.5% THC No dosing guidelines
Indications	Adjunctive treatment for symptomatic relief of multiple sclerosis neuropathic pain	Antiemetic in cancer chemothearpy Appetite stimulant in AIDS-related anorexia	Antiemetic in cancer chemothearpy	Anticonvulsant Severe pain in arthiritis Specific symptoms in multiple sclerosis, spinal cord injury/disease, cancer and AIDS
Schedule	Narcotic	Narcotic	Narcotic	Schedule II
Evicence	RCT: Pain, spasticity in MS	RCT: Pain and spasticity in MS	No RCT in MS	No RCT in MS
Adverse Events	Dizziness Dry mouth Euphoric mood Fatigue Nausea	Dizziness Drowsiness Nausea Psychological high	Depression Drowsiness Dry mouth Psychological high Vertigo	Risk of lung disease Drowsiness Psychological high

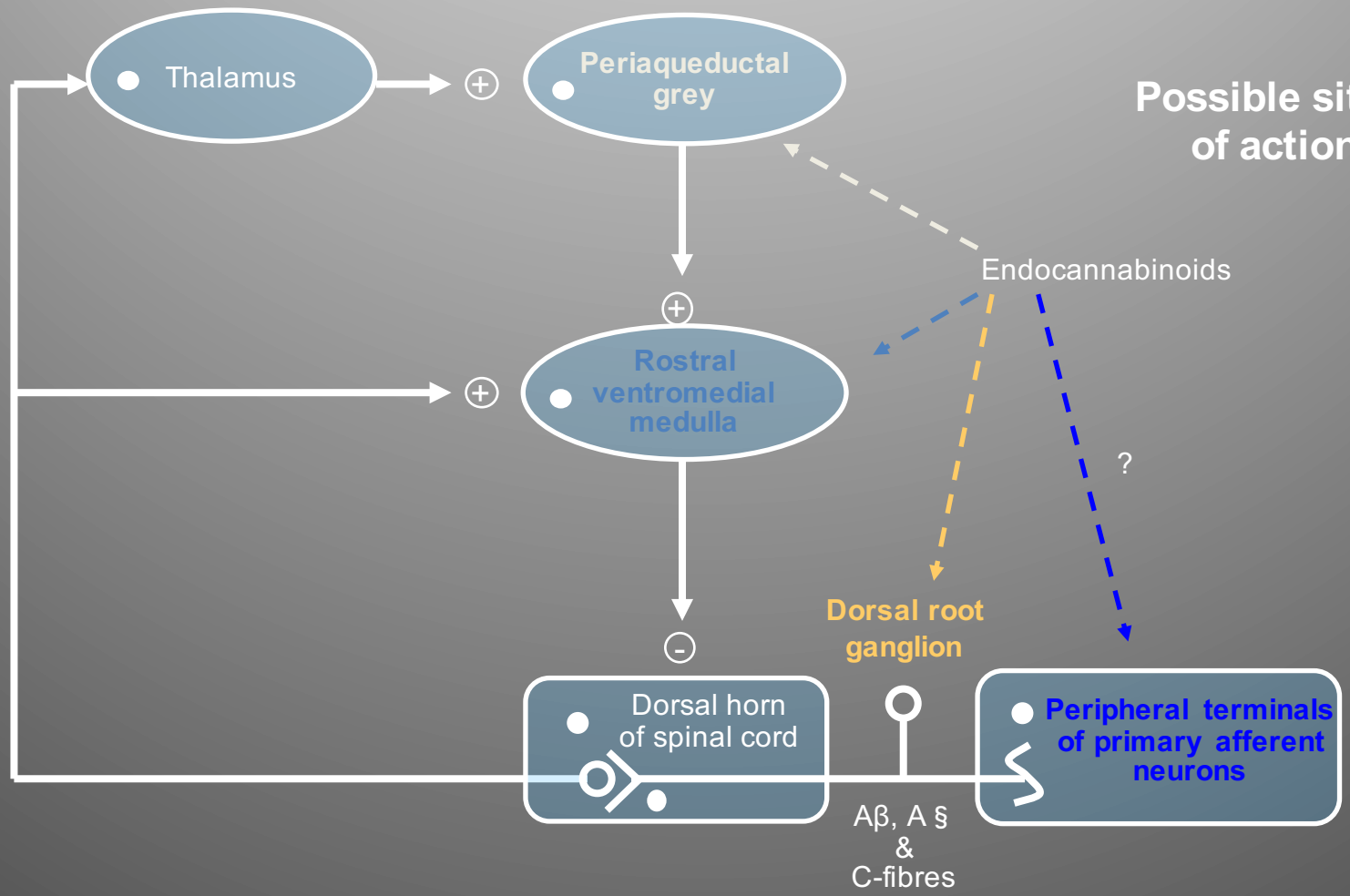
Recent RCT results: MS

Study drug	*Primary outcome*	*Effect*	*Reference*
Oral extract	Objective spasticity	No change	Zajicek 2003, 2005
Oral THC	Subjective central pain	Improved	Svendsen 2004
Oral THC and CBD	Spasm frequency	Improved	Vaney 2004
Sublingual extract	Subjective spasticity	Improved	Wade 2004, 2006

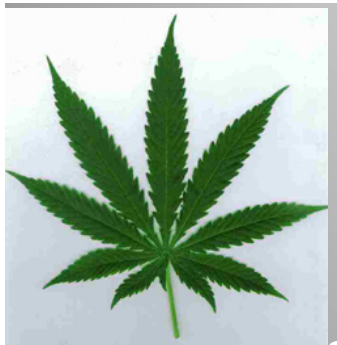
Cannabinoids in MS

	Treatment	Results
Petro et al (1981)	oral THC, placebo	reduced spasticity
Clifford (1983)	oral THC, placebo	improved coordination
Ungerleidere et al (1987)	oral THC, placebo	reduced spasticity
Meinck et al (1989)	cigarette smoke marijuana	reduced spasticity and ataxia
Greenberg et al (1994)	cigarette smoke THC, placebo	impaired balance, posture
Martyn et al (1995)	oral nabilone, placebo	improved well-being, spasms, nocturia
Schon et al (1999)	oral THC, cigarette smoke	reduced nystagmus amplitude
Hamann et al (1999)	oral nabilone	complete pain relief
Killestein et al (2002)	oral THC, plant extract, placebo	worse or no improvement
Zajicek et al (2003)	oral THC, cannador, placebo	no effect on spasticity
Svendsen et al (2004)	oral THC, placebo	decrease pain intensity
Vaney et al (2004)	oral cannador, placebo	no improvement in spasticity

Cannabinoids and Pain Pathways

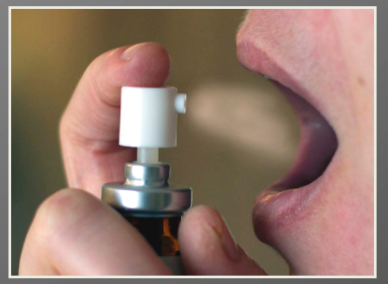


Adapted from Di Marzo 2001



THC:CBD 1:1

- Extracts of 2 *Cannabis sativa L* strains
  - Equal amounts of
    - Tetranabinex®: high-THC strain
      - 27 mg/mL Δ-9 THC
    - Nabidiolex®: high-CBD strain
      - 25 mg/mL CBD
- Buccal spray
  - Ethanol/propylene glycol vehicle
  - 2.7 mg THC and 2.5 mg CBD per spray
- Therapeutic dose
  - High inter-patient variability
  - Administered on self-titration regimen



Pharmacokinetics: Cannabis

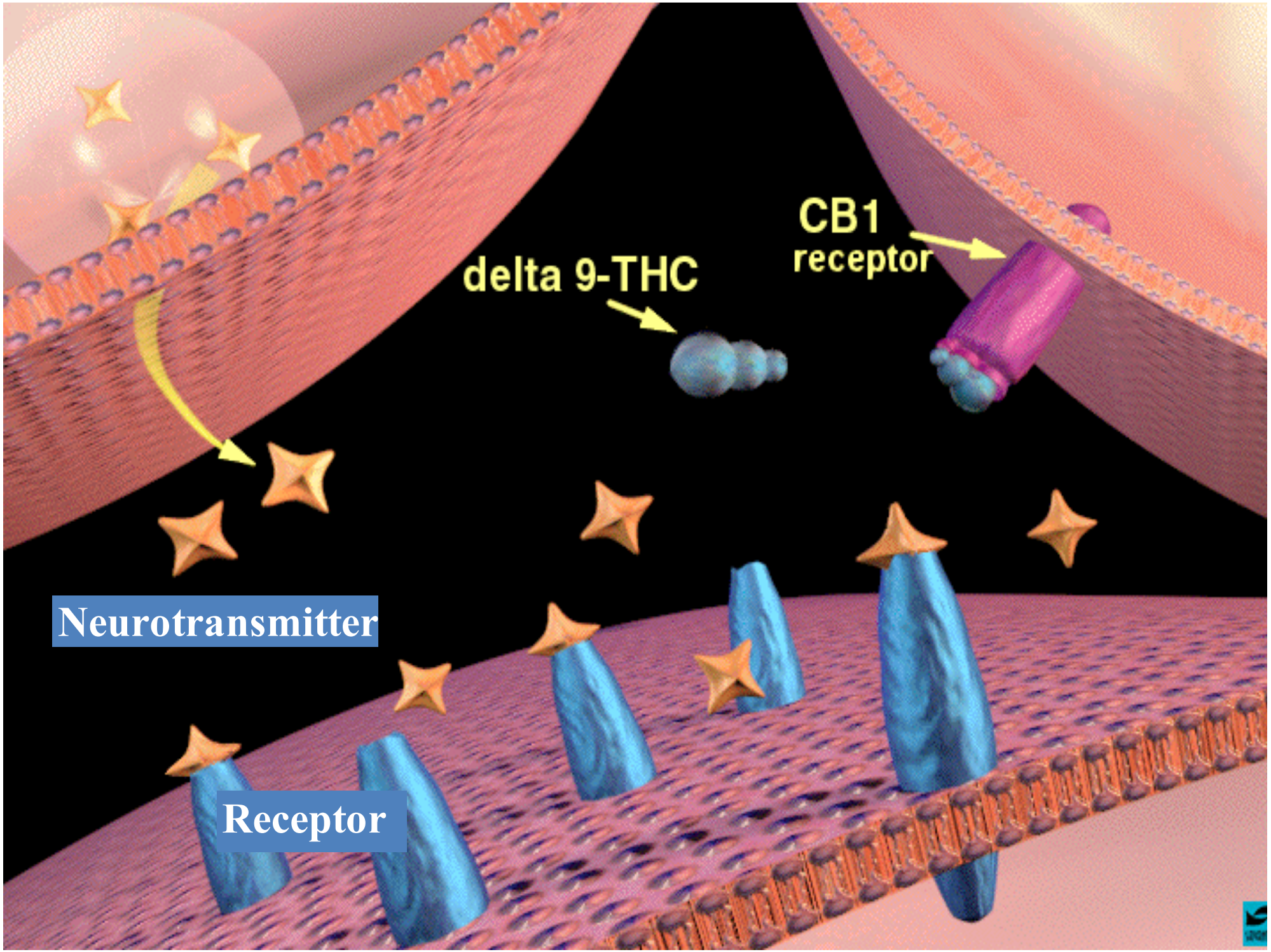
Cannabis clinical effects by route of administration compared with THC:CBD 1:1

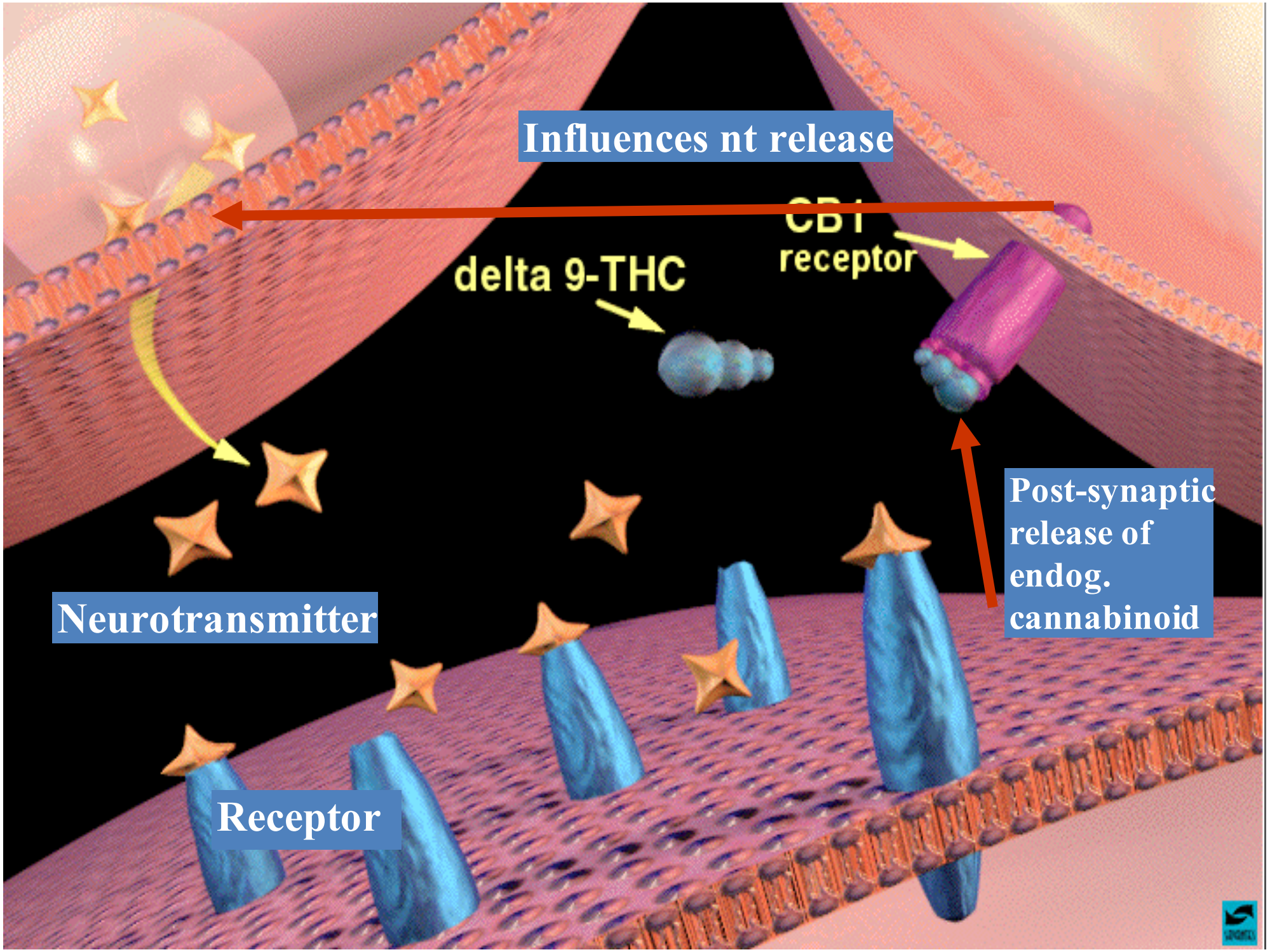
Cannabis form	Onset	Peak	Duration
Smoked	Seconds to minutes	15–30 minutes	2–3 hours
Oral	30–90 minutes	2–3 hours	4–12 hours
THC:CBD 1:1	30–150 minutes	1.5–4 hours	6-8 hours

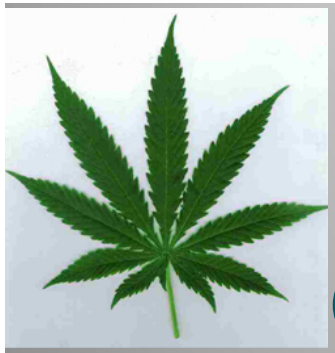
Grotenhermen F (2003), Sativex® Product Monograph (2005)

Clinical Review: Rog et al, 2005

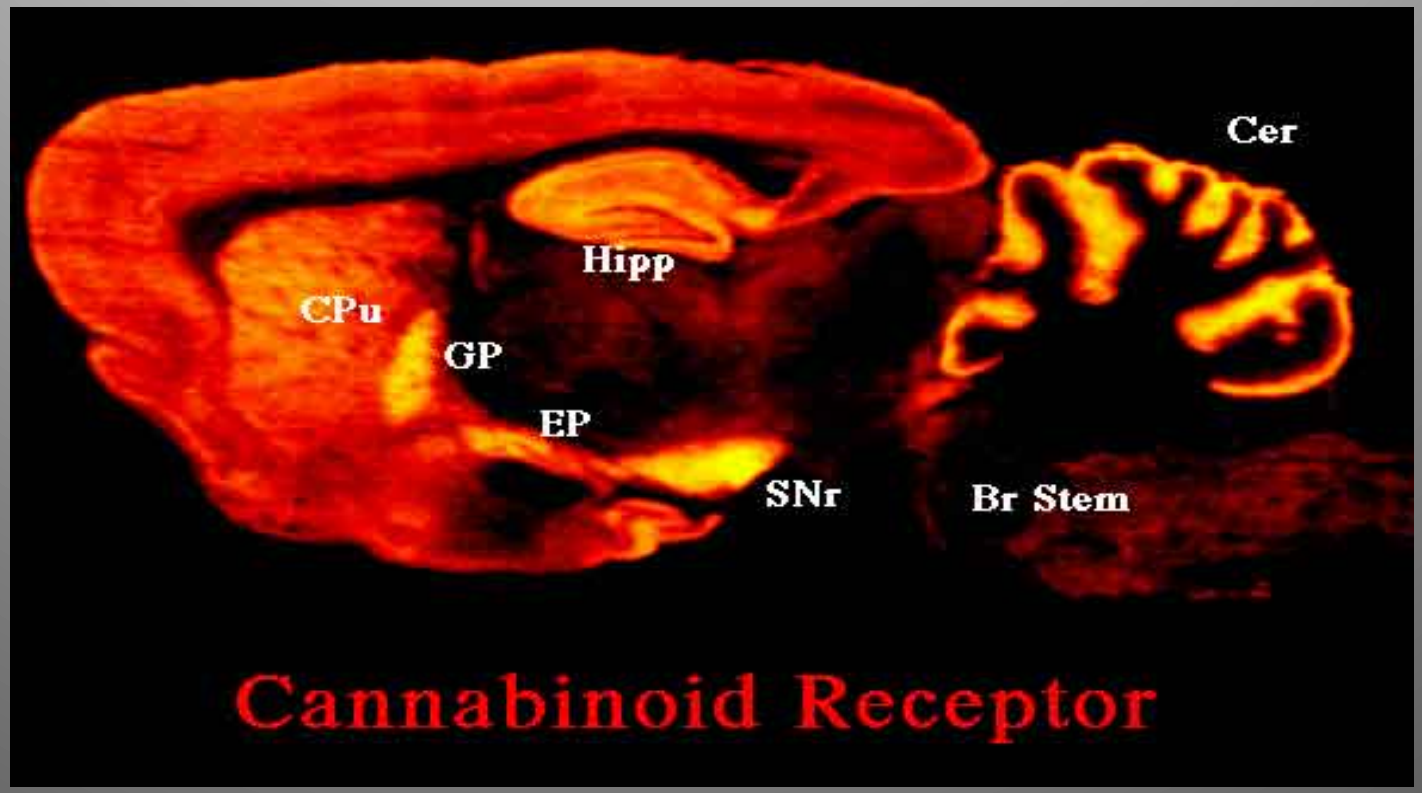
- Objective
  - Compare efficacy and tolerability of THC:CBD 1:1 with placebo
  - Adjunctive therapy in central neuropathic pain
- Patient population
  - Adult MS patients with central pain
    - Dysesthesia, painful spasm
  - 85 screened
  - 66 randomized
    - THC:CBD 1:1 (n=34) and placebo (n=32)


CB1
receptor
delta 9-THC
Neurotransmitter
Receptor

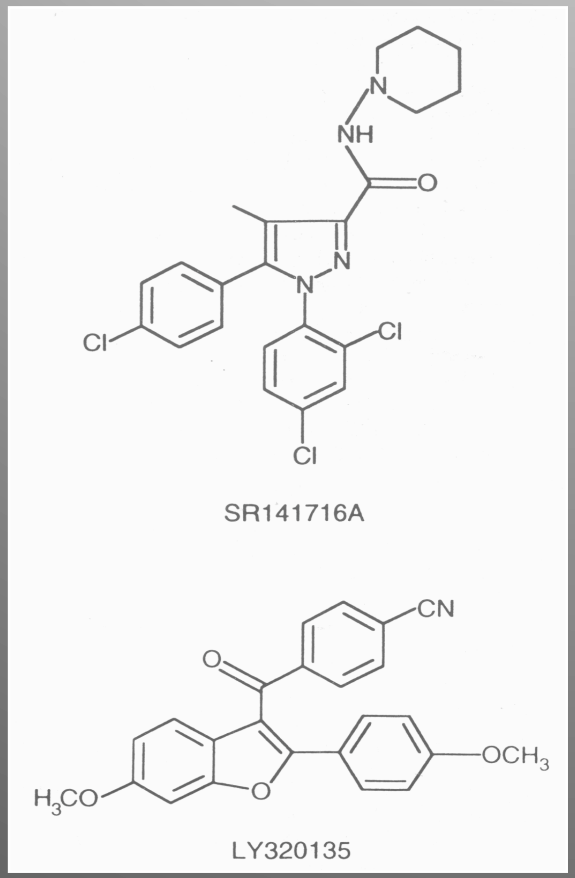

Influences nt release
CB1
receptor
delta 9-THC
Post-synaptic
release of
endog.
cannabinoid
Neurotransmitter
Receptor



Central mediation of some of the effects of cannabinoids



Cannabinoid receptor antagonists



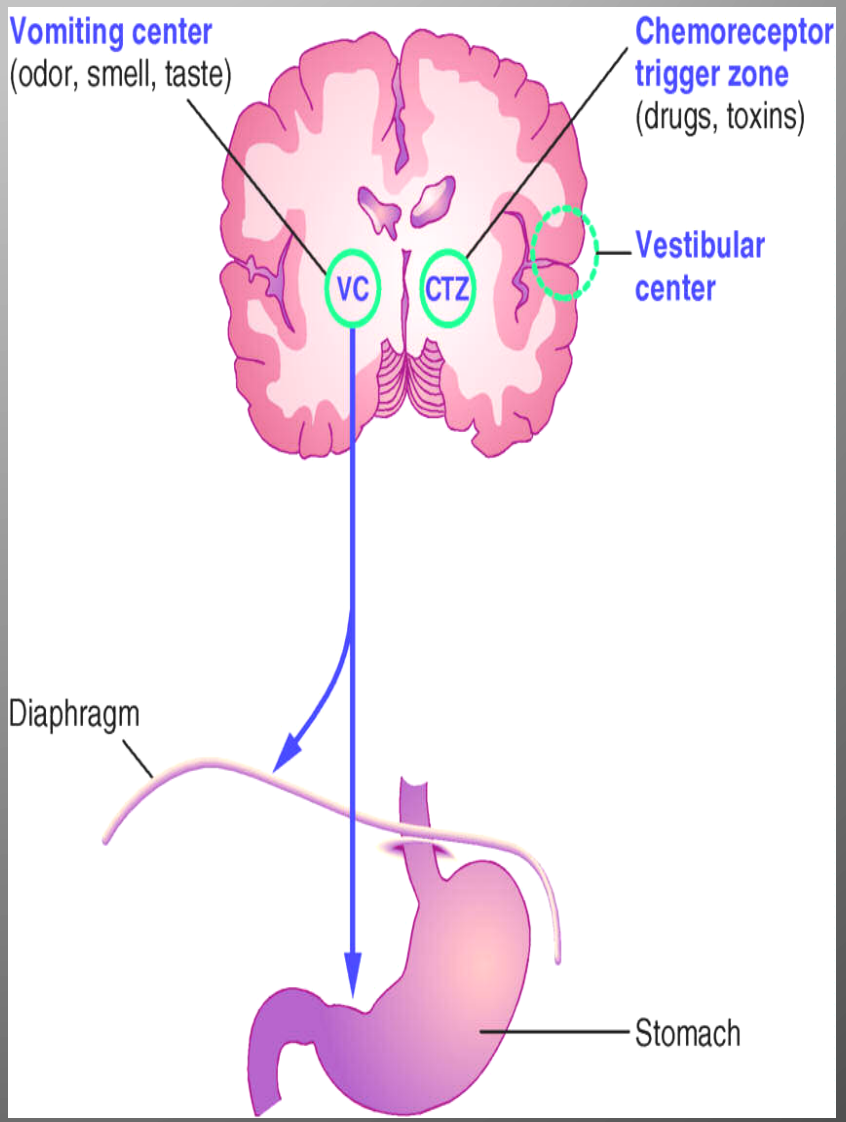
- SR 141716 (Rimonabant), LY320135 and AM281
- All have marked selectivity for CB_1 receptors over CB_2.

GI Agents
Vomiting - Antiemetics

- Vomiting = the expulsion of gastric contents Before treating, the cause of the vomiting needs to be identified
- Causes are many: motion sickness, viral & bacterial infection, food intolerance, surgery, PG, pain, shock, effects of some drugs, radiation, & disturbances of the middle ear affection equilibrium.
- Antiemetics can mask the cause & should not be used until cause is determined, unless vomiting is severe enough to cause dehydration & electrolyte imbalance

GI Agents
Vomiting - Antiemetics

- Two major cerebral centers are the chemoreceptor trigger zone (CTZ), which lies near the medulla, & the vomiting center, in the medulla - both cause vomiting when stimulated
- The CTZ receives most of the impulses from drugs, toxins, and the vestibular center. The neurotransmitter dopamine stimulates the CTZ, which stimulates the vomiting center, when triggered, motor neuron responds → contraction of diaphragm, anterior abdominal muscles, & the stomach. the glottis closes, the abdominal wall moves, upward & vomiting occurs.



GI Agents
Antiemetics

- Nonpharm Rx= weak tea, flattened carbonated drinks, Gatorade & pedialyte (children), crackers dried toast
- Nonprescription antiemetics = used to prevent motion sickness - minimal effect on severe vomiting from anticancer agents, radiation, and toxins.

  - take 30 min. before traveling
- **Dimenhydrinate (dramamine), meclizine HCL (Antivert), diphenhydramine HCL (Benadryl)**

  - SE = drowsiness, dryness of mouth, constipation

GI Agents-Antiemetics

- **bismuth subsalicylate (Pepto-Bismol)** - act directly on gastric mucosa to suppress vomiting - liquid & chewable – taken for gastric discomfort & diarrhea
- Phosphorated carbohydrate (Emetrol) Hyperosmolar carbohydrate →decreases N&V by changing the gastric pH

- Antiemetics were used in the 1st trimester of PG , but no more → due to poss. harm to fetus. Non – pharm methods should be used & OTC antiemetics avoided → unless N & V become life threatening to mom & baby. Then use Tigan given.

GI Agents
Antiemetics

- **Prescription Antiemetics** - eight categories:

1 & 2. Antihistamines & Anticholinergics - **Hydroxyzine (Vistaril, Atarax), Promethazine (Phenergan), Scopolamine (Transderm Scop) -** Act primarily on the vomiting center, dec. stimulation of CTZ

- SE = drowsiness, dry mouth, blurred vision (pupil dilation), tachycardia (anticholinergics), constipation

- Do not use in clients w/ glaucoma d/t dilation of pupils

GI Agents - Antiemetics

3. **Dopamine antagonists** - blocks dopamine-2 receptors in the CTZ. SE = Extrapyramidal symptoms (tremors, mask face, rigidity, shuffling gait)

- **Phenothiazine** - largest group of drugs used for N & V

  Chlorpromazine (Thorazine), prochlorperazine edisylate (Compazine) - most frequently prescribed, **perphenazine (Trilafon)** - frequently used w/ anticancer therapy

  - Action - inhibits dopamine in the CTZ thus dec. CTZ stimulation of the vomiting center
  - Use - severe N & V from sugery, anesthetics, chemo & radiation sickness
  - SE = dry mouth, drowsiness, EPS, dizziness, hypotension

GI Agents - Antiemetics

Perphenazine (Trilafon) used with anti cancer therapy, inhibits dopamine in the CTZ → decreasing CTZ stimulation vomiting center, also an antipsychotic

Onset 2 – 6 h, duration 6-12 h

Interactions: Taken with ETOH, antihypertensive agents, and nitrates, hypotension can result

CNS depression when taken with ETOH, narcotics, sedative- hypnotics and general anesthetics

SE: moderate sedation hypotension, EPS (parkinsonism) CNS effects (restlessness, weakness, dystonic reactions, agitation), and mild anticholinergic s/s (dose lower as antiemetic than antipsychotic, so SE not as severe.

GI Agents
Antiemetics

- **Butyrophenones** - **Haloperidol (Haldol), droperidol (Inapsine)** - block dopamine-2 receptors in the CTZ
  - Use - Rx of post-op N & V & emesis associated w/ toxins, chemo & radiation therapy
  - SE - EPS if used over extended time, hypotension
- **Metoclopramide** - **metoclopramide (Reglan)** - blocks dopamine & serotonin receptors in the CTZ
  - Use = post-op emesis, chemo & radiation therapy
  - SE = sedation & diarrhea w/ high doses

GI Agents
Antiemetics

4. Benzodiazepines - **Lorazepam (Ativan)** - for N & V d/t chemo - May be given w/ an antiemetic such as metoclopramide (Reglan)

5. Serotonin Antagonists - **ondansetron (Zofran), granisetron (Kytril)** -

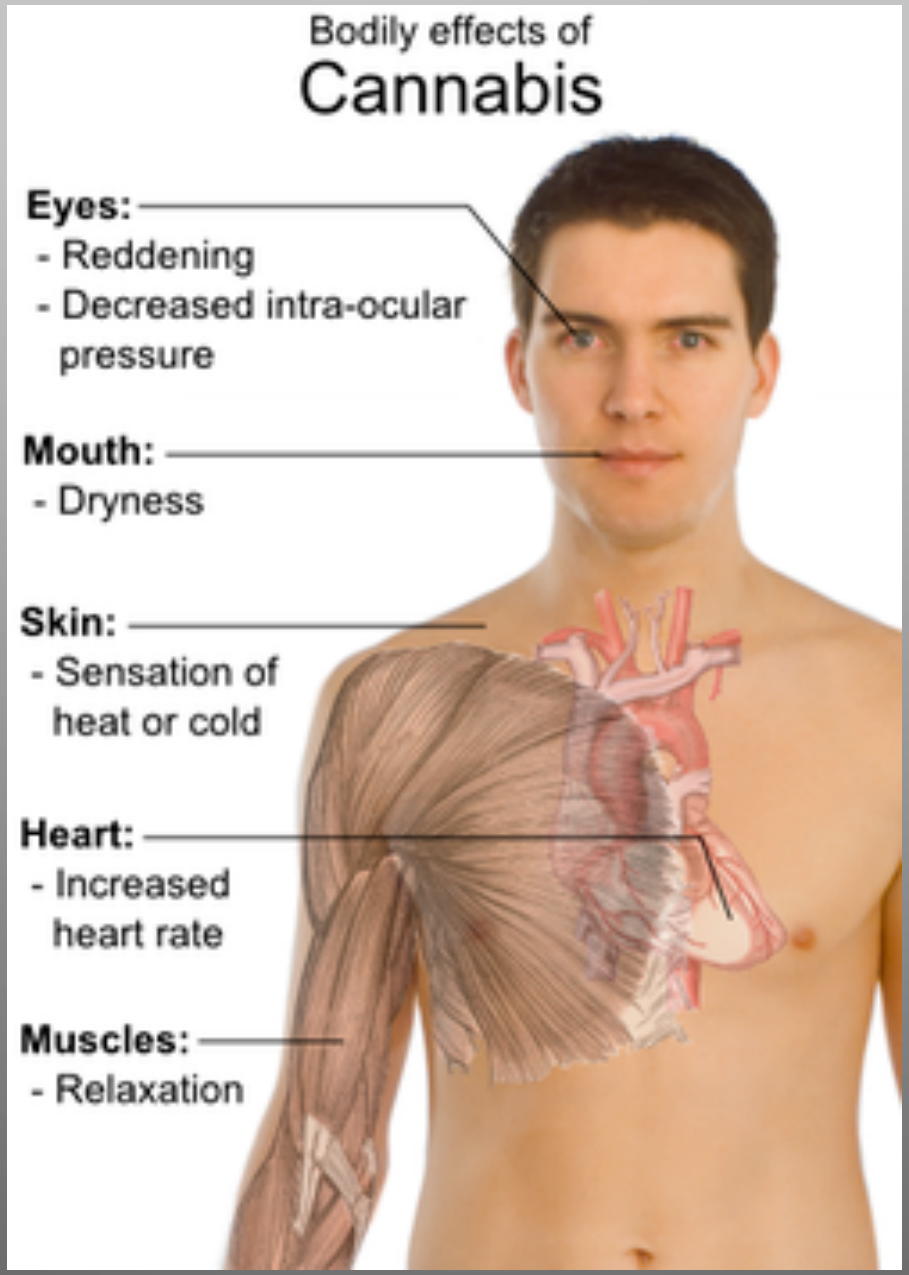
- Action - suppress N & V by blocking the serotonin receptors in the CTZ & afferent vagal nerve terminals in upper GI tract - Do not cause EPS symptoms
- Use - chemo induce emesis - PO & IV
- SE - headache, diarrhea, dizziness, fatigue

GI Agents - Antiemetics

6. **Glucocorticoids** - **Dexamethasone (Decadron), methylprednisolone (Solu-Medrol) -** effective w/ chemo treatment in suppressing emesis - given IV
7. **Cannabinoids** - active ingredient in marijuana - approved for clinical use since 1985 to alleviate N & V from cancer treatments - **dronabinol (Marinol), nabilone (Cesamet)**

   - for clients unable to use or respond to other antiemetics

   - SE = mood changes, euphoria, drowsiness, nightmares, dry mouth, confusion, HA, depersonalization, nightmares, incoordination, memory lapse, orthostasis, hypertension & tachycardia


Bodily effects of
Cannabis
Eyes:
- Reddening
- Decreased intra-ocular pressure
Mouth:
- Dryness
Skin:
- Sensation of heat or cold
Heart:
- Increased heart rate
Muscles:
- Relaxation