Advanced Clinical Cannabinoid Provider™

ACCP™

National Cannabis Certification Services

www.CPRTrainingFast.com
THE ENDOCANNABINOID SYSTEM

The endocannabinoid system (ECS) is a chemical system in the brain responsible for homeostasis, providing even balance in the body. Think of the ECS as a system of receptors and keys. Balance in the ECS helps the body maintain itself and function properly, including appetite, pain response, mood and memory. Manipulation of ECS through introduction of cannabinoids may also determine the body’s response disease. Cannabinoid deficiencies have been noted in patients with migraines, MS, Parkinson’s, IBS, anorexia, fibromyalgia, menstrual disorders and motion sickness.

The endocannabinoid system (ECS) is the key between the body and mind. It is a signaling system composed of:

- G-protein-coupled receptors known as “cannabinoid receptors” types-1 and -2 (CB₁ and CB₂)
- Endogenous agonists - endocannabinoids anandamide (N-arachidonoyl-ethanolamine) and 2-AG (2-arachidonoyl-glycerol)
- Endocannabinoid tissue level regulating enzymes and other proteins
- Enzymes and proteins which in conjunction with endocannabinoids regulate.

The body naturally produces cannabinoids such as anandamide and 2-Arachidonoylglycerol (2-AG). Cannabis plant THC and TBC fill gaps in the network of existing receptors.

Cannabinoid Receptors

<table>
<thead>
<tr>
<th>CB₁ located in:</th>
<th>CB₂ located in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Monocytes</td>
</tr>
<tr>
<td>Testes, uterus</td>
<td>Macrophages</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>B-cells</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>T-cells</td>
</tr>
<tr>
<td>Endocrine glands</td>
<td>Liver</td>
</tr>
<tr>
<td>Exocrine glands</td>
<td>Spleen</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>Spleen</td>
</tr>
<tr>
<td>Spleen</td>
<td>Tonsils</td>
</tr>
<tr>
<td>Heart</td>
<td>CNS</td>
</tr>
<tr>
<td>GI tract</td>
<td>Enteric nervous system</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
</tr>
</tbody>
</table>

Cannabinoid Keys

- Tetrahydrocannabinol (THC) – the key to CB₁ receptors, predominantly concentrated in the brain and central nervous system; stimulates brain cells to create “euphoria”
- Cannabidiol (CBD) – Indirect effects on CB₁ and CB₂ receptors; non-psychoactive and reduces the negative effects of THC
- Cannabinol (CBN)- the key to CB₂ receptors, predominantly located in peripheral organs and immune system cells; mildly psychoactive, more sedative than other cannabinoids, analgesic and anti-convulsant
The Human Endocannabinoid System

THC and CBN are known to "fit" like lock and key into network of existing receptors. The Endocannabinoid System exists to receive cannabinoids produced inside the body called "Anandamide" and 2-Arachidonyl-glycerol. Stimulating the ECS with plant-based cannabinoids restores balance and helps maintain symptoms.

CB1 receptors are concentrated in the brain and central nervous system but also sparsely populates other parts of the human body.

Receptors are found on cell surfaces

CBD does not directly "fit" CB1 or CB2 receptors but has powerful indirect effects still being studied.

CB2 receptors are mostly in the peripheral organs especially cells associated with the immune system.
(A) Structure of the most common cannabinoids found in Cannabis plants. All the compounds have been represented in their acidic, native form, and with a pentylic side chain; (B) the non-enzymatic decarboxylation of Δ⁹-tetrahydrocannabinolic acid (THCA) to THC.
Biosynthesis of Main Cannabinoids

\[
\begin{align*}
geranyl diphosphate \quad \text{(terpenic moiety)} & \quad \text{geranyl diphosphate} \\
\text{O-P}_{\text{1}}P_{\text{1}} & \quad \text{olivetolic acid} \quad \text{(phenolic moiety)} \\
\end{align*}
\]

\[
\begin{align*}
\text{GOT} & \\
\text{CBGA} & \\
\text{CBCA} \quad \text{synthase} & \quad \text{THCA} \quad \text{synthase} \\
\text{CBDA} \quad \text{synthase} & \\
\end{align*}
\]

\[
\begin{align*}
\text{CBCA} & \\
\text{CBDA} & \\
\text{THCA} & \\
\end{align*}
\]
CANNABINOID INDUCED CELLULAR SIGNALING IN NEUROLOGICAL DISEASE

- Parkinson's Disease:
  - Δ⁹-THC, CBD
  - Δ⁹-THCV
  - Anti-inflammatory activity (modulation of Nrf-2).
  - Decreases pro-inflammatory cytokines and NFκB activity.
  - Decreases pro-inflammatory cytokines (TNF-α, IL-1β) and ROS.
  - Increases trophic factors and anti-inflammatory cytokines (IL-10).

- Huntington's Disease:
  - Δ⁹-THC, CBD
  - CBG
  - CB1/CB2
  - Decreases reactive microglia and astrogliosis.
  - Decreases oxidative stress and edema.
  - Attenuates reactive microgliosis.
  - Counteracts upregulation of pro-inflammatory markers.
  - Reduces mutant Htt protein aggregation.

- Alzheimer's Disease:
  - Δ⁹-THC
  - WIN 55212-2
  - CB1/CB2
  - CB1
  - Decrease Aβ production.
  - Reduces amyloid plaque formation.
  - Decreases ROS production and lipid peroxidation.
  - Modulates NOS expression.
  - Decreases p38 MAP kinase, NFκB, and tumor necrosis factor-α.

- Multiple Sclerosis:
  - Δ⁹-THC
  - WIN 55212-2
  - CB1/CB2
  - CB1
  - CB2
  - CB1
  - Promotes oligodendrocyte survival, reducing demyelination and apoptosis.
  - Reduces inflammation, probably due to a decreasing of TNF-α and IL-1β release.
  - Promotes oligodendrocyte survival.
  - Reduces microglia activation, nitrotyrosine formation, T cell infiltration, production of TNF-α and promotes oligodendrocyte survival.

- Amyotrophic Lateral Sclerosis:
  - Δ⁹-THC
  - WIN 55212-2
  - CB1/CB2
  - CB1
  - CB2
  - Reduces excitotoxicity (glutamate levels), and oxidative cell damage (cytokines, NO and ROS).

- Hypoxia-Ishchemia:
  - CBD
  - GPR55, TRPV1, 5-HT1A, α1 and δ glycine receptor
  - Reduces Ca²⁺ via interaction with the mitochondrial sodium-calcium exchanger.
  - Modulates GABA release.

- Epilepsy:
  - Δ⁹-THCV
  - CB1
  - Modulates GABA release.
Abbreviations: D9-THC, D9-tetrahydrocannabinol; D8-THC, D8-tetrahydrocannabinol; CBN, cannabinol; CBD, cannabidiol; D9-THCV, D9-tetrahydrocannabivarin; CBC, cannabichromene; CBG, cannabigerol; D9-THCA, D9-tetrahydrocannabinolic acid; CBDA, cannabidiolic acid; TRPV1, transient receptor potential vanilloid type 1; PPARg, peroxisome proliferator-activated receptor g; ROS, reactive oxygen species; 5-HT1A, 5-hydroxytryptamine receptor subtype 1A; FAAH, fatty acid amide hydrolase. (+), direct or indirect activation; ,, increase; #, decrease
Cannabinoids: New Promising Agents in the Treatment of Neurological Diseases
Sabrina Giacoppo 1, Giuseppe Mandolino 2, Maria Galuppo 1, Placido Bramanti 1 and Emanuela Mazzon 1,*

1 IRCCS Centro Neurolesi “Bonino-Pulejo”, Via Provinciale Palermo, contrada Casazza, 98124 Messina, Italy
2 Consiglio per la Ricerca e la sperimentazione in Agricoltura, Centro di Ricerca per le Colture Industriali (CRA-CIN), Via di Corticella 133, 40128 Bologna, Italy

* Author to whom correspondence should be addressed; E-Mail: emazzon.irccs@gmail.com; Tel.: +39-090-6012-8708; Fax: +39-090-6012-8850.

External Editor: Derek J. McPhee
Received: 6 October 2014; in revised form: 7 November 2014 / Accepted: 7 November 2014 / Published: 17 November 2014

Abstract:
Nowadays, Cannabis sativa is considered the most extensively used narcotic. Nevertheless, this fame obscures its traditional employ in native medicine of South Africa, South America, Turkey, Egypt and in many regions of Asia as a therapeutic drug. In fact, the use of compounds containing Cannabis and their introduction in clinical practice is still controversial and strongly limited by unavoidable psychotropic effects. So, overcoming these adverse effects represents the main open question on the utilization of cannabinoids as new drugs for treatment of several pathologies. To date, therapeutic use of cannabinoid extracts is prescribed in patients with glaucoma, in the control of chemotherapy-related vomiting and nausea, for appetite stimulation in patients with anorexia-cachexia syndrome by HIV, and for the treatment of multiple sclerosis symptoms. Recently, researcher efforts are aimed to employ the therapeutic potentials of Cannabis sativa in the modulation of cannabinoid receptor activity within the central nervous system, particularly for the treatment of neurodegenerative diseases, as well as psychiatric and non-psychiatric disorders. This review evaluates the most recent available data on cannabinoids utilization in experimental and clinical studies, and highlights their beneficial effects in the prevention of the main neurological diseases and for the clinical treatment of symptoms with them correlated.

Keywords:
Cannabis sativa; cannabinoids; cannabinoid receptors; neurodegenerative diseases; epilepsy

1. Introduction
Cannabis is probably one of the most ancient non-food crops cultivated by mankind; it belongs to the botanical family of Cannabaceae, along with Humulus, the cultivated hop. It is an annual, dioecious
plant, though monoecious varieties have been bred, and its diploid chromosomal complement is 2n = 20, with 18 autosomes and a couple of sexual chromosomes (XY for male and XX for female and monoecious plants [1].

The Cannabis species originated from Central Asia, where it was probably domesticated over 6000 years ago, but it has since been cultivated at virtually all latitudes for a large number of end-products deriving from the seed (e.g., fatty acids and proteins), the fiber, the wooden core and from the inflorescences, where cannabinoids are produced and secreted [2]. There still is limited agreement on whether Cannabis sativa should be considered a single species or a poly-species genus; however, the species boundaries, if existing, are weak, as full intercrossing between the different Cannabis accessions can occur, and several molecular markers-based analyses confirmed that Cannabis is a highly heterozygous species, with the intra-accession variation as wide as the inter-accession one [3].

In recent years, the debate on Cannabis re-introduction in our agricultural landscapes went beyond the agronomical and productive virtues of the plant, and especially focused on the potential of the plant’s main metabolites, the cannabinoids, as medicines useful for a number of therapeutical applications [4].

In fact, medications based on Cannabis have been used for therapeutic purposes in many cultures for centuries [5], with descriptions of its effects including alterations in mood, cognitive functions, memory and perception of the user [6].

In Europe, they were used at the end of the 19th century to alleviate a wide variety of conditions, including pain, spasms, dysentery, depression, sleep disturbance and loss of appetite [7]. In the first half of the 20th century cannabinoid medications fell into almost complete disuse, partly because scientists were unable to establish the chemical structure of the ingredients of the Cannabis plant (Cannabis sativa L.).

It was only in 1964 that the psychoactive component of the Cannabis resin and flowers, Δ⁹-tetrahydrocannabinol (Δ⁹-THC) was isolated [8]. Following, numerous non-psychoactive cannabinoids have been identified, such as cannabidiol (CBD), cannabigerol (CBG), cannabichromene (CBC), Δ⁹-tetrahydrocannabivar (Δ⁹-THCV) and cannabidivar (CBDV). These compounds exert multiple actions through mechanisms that are only partially related to modulation of the endocannabinoid system.

In recent years, a growing interest has been dedicated to the study of cannabinoids for their antioxidant, anti-inflammatory and neuroprotective effects [9,10]. Specifically, Δ⁹-THC is the most widely studied phytocannabinoid, but also the predominant psychotropic component of Cannabis, strongly limiting its therapeutic use as an isolated agent. Therefore, recently research focused to include non-psychotropic compounds, some of which exhibit potential as therapeutic agents in preclinical models of central nervous system (CNS) disease.

The present review focused on the current state of evidence regarding the possible usefulness of cannabinoid agents (psychotropic and non-psychotropic) in prevention of the main neurological disorders and/or in the treatment of symptoms correlated to them, at least in association with existing conventional therapy.

2. Current Cannabinoid-Based Drugs
Despite the illegality of Cannabis in most nations, a renewed interest in its medicinal properties has led to development of a number of cannabinoid-based medicines. Currently three drugs are used in clinical practice.

Dronabinol (Marinol®, Solvay Pharmaceuticals, Brussels, Belgium) capsules, a synthetic formulation of Δ9-THC, was approved by the U.S. Food and Drug Administration in 1986, for the management of nausea and vomiting associated with cancer chemotherapy in patients who have not responded to conventional antiemetic treatments [11]. Dronabinol is also used for the treatment of anorexia with weight loss in patients with HIV/AIDS [12].

Nabilone (Cesamet®, Valeant Pharmaceuticals International Inc, Mississauga, ON, Canada) capsules, is another synthetic derivative of Δ9-THC that is similar to dronabinol, but appears to be more potent. It was first approved in Canada in 1982 and is now also available in the United States and United Kingdom, still for the treatment of emesis [13].

Unlike Dronabinol and Nabilone, Sativex® (GW Pharma, Ltd, Salisbury, Wiltshire, UK) is administered in an oral spray, consisting of a mixture of two extracts in approximately a 1:1 ratio (2.7 mg of Δ9-THC and 2.5 mg of CBD) in an alcoholic solution (50% ethanol). In Spain, Germany, Denmark as well as in Canada, United Kingdom and Italy, Sativex® is used as treatment to alleviate spasticity in adult multiple sclerosis (MS) patients which did not show an appropriate response to other drugs during an initial trial period of therapy [14, 15]. Compared to the oral route, its advantage is a faster plateau of plasma concentration. Also, it has been established that coadministration of CBD and Δ9-THC can reduce unwanted effects of Δ9-THC.

3. Synthesis and Production of Phytocannabinoids

Although Cannabis plant can be defined as a true “chemical factory” extremely rich in secondary compounds, therapeutic applications essentially rely on the cannabinoids. According to a recent review [16], there are almost 500 different chemical compounds synthesized by the Cannabis plant, and about 70 among these are cannabinoids. Cannabinoids are secondary compounds unique to the genus Cannabis, and therefore of taxonomic significance; they are terpenophenols, produced by the enzymatic condensation of a terpenic moiety (geranyl diphosphate) with a phenolic one (mainly olivetolic or divarinic acid).

There are two chemical characteristics of the cannabinoid molecule that are particularly relevant (Figure 1). The first is the carboxylic group on the phenolic ring of the cannabinoid; this group is readily lost upon drying or mild heating, leaving the decarboxylated form of the different cannabinoids. It is this decarboxylation that converts the native Δ9-tetrahydrocannabinolic acid (THCA) into Δ9-THC, the cannabinoid well known for its intoxicating and psychotropic effects. All cannabinoids in Cannabis plants are synthesized and accumulated in their acidic form [17].
Figure 1. (A) Structure of the most common cannabinoids found in Cannabis plants. All the compounds have been represented in their acidic, native form, and with a pentylic side chain; (B) the non-enzymatic decarboxylation of Δ⁹-tetrahydrocannabinolic acid (THCA) to THC.

The second relevant characteristic of the cannabinoid molecule is the polyketide chain present in meta position to the hydroxylic group of phenolic portion (Figure 1). The most abundant cannabinoids in Cannabis have in this position a pentyl chain, but also propyl and even methyl side chain groups have been described [18, 19].

Cannabis sativa accessions and varieties have been divided into chemotypes, according to the main cannabinoid they produce at maturity and to their content ratio. Five chemotypes can be recognized as most commonly occurring: chemotype I has a very low cannabidiolic acid (CBDA)/THCA content ratio, and is mainly the chemotype found in drug strains. Chemotype III, on the contrary, is characterized by a very high CBDA/THCA ratio, and is typical of all cultivated fiber varieties. Chemotype II is a mixed chemotype, containing roughly equal amounts of CBDA and THCA, as can be found in hashish strains, but also in some old fiber varieties. Chemotype IV accumulates cannabigerolic acid (CBGA) as the main cannabinoid. Finally, plants showing no cannabinoids upon gas-chromatographic analysis of mature inflorescences have been described, and for these plants the chemotype V has been proposed.
Clearly, plants belonging to the different chemotypes have different potentials as sources for the active principles they synthesize, and the breeding of *Cannabis* for pharmaceutical purposes had as its first target the exploration and exploitation of the variability available in *Cannabis* germplasm for cannabinoid synthesis.

The sites of biosynthesis and accumulation of cannabinoids are the glandular trichomes (Figure 2A,B). Glandular trichomes are particularly dense in inflorescences, especially on the bracts, but also the leaves and, to a minor extent, the stems of *Cannabis* plants carry trichomes. Roots and seeds are devoid of any trichome, and, accordingly, these organs contain no cannabinoids. Glandular trichomes can be capitate-stalked, capitate-sessile, or bulbous, and these different morphologies are associated with a different quantity of cannabinoids accumulated [21].

![Figure 2](image.png)

**Figure 2.** Capitate-sessile (A) and bulbous (B) glandular trichomes. In (A), also some non-glandular trichomes (not secreting) are visible. (C), schematic representation of the current model of secretion of cannabinoids from the trichomes.

The glandular trichomes density is a trait especially important when breeding *Cannabis* for pharmaceutical purposes. In nature, the meaning for the plant’s fitness of the accumulation of cannabinoids in trichomes is still debated; it has been proposed that the conjugate bonds system characterizing THCA might have helped to protect plant functions from UV, a hypothesis partially supported by the origin of high-THCA *Cannabis* strains in regions with a high UV irradiance.

The first committed step in the biosynthesis of cannabinoids is the prenylation of terpene geranyl diphosphate with olivetolic acid (or, less frequently, divarinic acid), to yield the cannabinoid considered today to be the precursor of all other cannabinoids, the CBGA (Figure 3). This enzymatic step is
catalyzed by the enzyme geranylpymophosphate: olivetolate geranyltransferase (GOT). The length of the side chain (determined by the preferential use of olivetolic or divarinic acid as the phenolic component of the cannabinoid) is a genetically determined trait, though specific genes involved have not yet been identified [22]. From the pharmaceutical point of view, this “variations on the theme” due to the different length of the alkyl side chain has a great potential, as it is likely that each member of the alkyl-homologs series for each cannabinoid could be endowed with different and specific therapeutical properties [23].

Figure 3. The biosynthesis of the main cannabinoids.

CBGA is the precursor of the most abundant cannabinoids deriving from enzymatic transformation, i.e., THCA, CBDA and cannabichromenic acid (CBCA). These three cannabinoids are synthesized through the oxidocyclization of CBGA mediated by three specific enzymes, THCA-synthase (THCAs), CBDA-synthase (CBDAs) and CBCA-synthase (CBCAs) (Figure 3). These enzymes have been isolated from inflorescences of different Cannabis strains or growth stages, and biochemically characterized in detail [24].

The hypothesis that the THCAs and CBDAs genes were alleles at the same locus, and that therefore the two proteins were isoenzymes, found confirmation by in-depth genetic analysis. The cross of pure-THCA breeding lines with pure-CBDA ones systematically yields F1 progenies producing equal amounts of both cannabinoids; besides, upon selfing or intercrossing of F1 plants, the F2 offspring obtained showed a perfect 1:2:1 segregation of pure-THC: mixed THC+CBD: pure CBD chemotypes [19], as expected for a single locus (termed B) with two codominant alleles, B_T and B_D, respectively, coding for THCAS and CBDAS. These data confirmed that, despite the several environmental factors able to modulate the total amount of cannabinoids, the chemotype (i.e., the THCA/CBDA content ratio)
has a simple Mendelian inheritance, while the amount of cannabinoids produced by the plant is a typically quantitative trait. The two aspects of inheritance of cannabinoids had a great impact on breeding of *Cannabis*, mainly for pharmaceutical purposes.

Nowadays, the increased availability of sequence data for several *Cannabis sativa* strains related to genes encoding for the biosynthesis of secondary compounds of therapeutic interest has led to the development of advanced tools for breeding and selection of therapeutic *Cannabis* varieties. For their use in modern pharmaceutical industry, these varieties are highly uniform, and devoted to the production of a specific single cannabinoid, or of a specific blend of different cannabinoids; even the zero-cannabinoid varieties have been used in clinical tests as *placebo*. The completion of the sequencing of the *Cannabis* genome and the extensive characterization of the alleles encoding for different cannabinoid synthase variants, promises to further widen the portfolio of phytocannabinoids available for therapeutic applications; besides, the recent definition of the tertiary structure of THCAS by X-ray crystallography at the 2.75 Å resolution, with the identification of specific aminoacids crucial for enzyme function, pave the way for several biotechnological applications for synthesis of the cannabinoids *ex planta* [25].

4. Cannabinoid Receptors

In the human body there are specific binding sites for cannabinoids, distributed on the surface of many different cells. To date, two types of receptors have been identified to have different tissue distribution and mechanisms of signaling.

CB1 receptors, of which CB1α and CB1β represent two subtypes [26,27], are localized in the CNS [28]. Particularly, in the brain CB1 receptors are mainly expressed in areas involved in motor coordination and movement (cerebellum, basal ganglia and *substantia nigra*), attention and complex cognitive functions (cerebral cortex), learning, memory and emotions (amygdala and hippocampus) [29,30]. In addition, CB1 receptors are present to a lesser extent in some organs and peripheral tissues, including endocrine glands, leukocytes, spleen, heart and part of the reproductive, urinary and gastrointestinal systems [31].

CB1 receptors reduce neuronal cell activity and interfere with the release of some neurotransmitters, such as serotonin, gamma-aminobutyric acid (GABA), acetylcholine, dopamine, histamine, glutamate and noradrenaline, preserving the CNS from overstimulation or over-inhibition that may be caused by other neurotransmitters.

CB2 receptors are expressed predominantly in cells of the immune system [31] and hematopoietic, but more recently their presence has been detected in the brain, in particular microglial cells, though at low concentrations [32]. It is well known that in response to damaging events, such as neuro-inflammation and cerebral hypoxia-ischemia, microglial cells may upregulate CB2 receptors expression in brain. Indeed, CB2 receptors exhibit potent anti-inflammatory effects modulating the release of cytokines [33,34].

Both CB1 and CB2 receptors belong to the family of G-protein coupled receptors (GPCRs) that, after cannabinoid agonist binding and signaling, exert an inhibitory effect on adenylate cyclase activity [35,36]. This inhibits the conversion to cyclic adenosine triphosphate (ATP) to cAMP, an important
cellular secondary messenger involved in the mechanisms of signal transduction, which activates kinase protein A (PKA).

CB1 and CB2 receptors signaling leads to the downstream activation of all mitogen-activated protein kinase (MAPK), p44/42, p38 and c-JUN amino terminal kinase, which can regulate nuclear transcription factors. Also, their activation is strictly linked to ion channel regulation by inhibition of calcium channels and activation of potassium channels [37].

There is increasing evidence supporting the existence of additional cannabinoid receptors (no-CB1 and no-CB2) in both central and peripheral system, identified in CB1 and CB2- knockout mice [38,39]. Indeed, some actions of certain cannabinoid ligands seems that are mediated by other receptors like transient receptor potential vanilloid type 1 (TRPV1), G protein-coupled receptor 55 (GPR55), G protein-coupled receptor 18 (GPR18), G protein-coupled receptor 119 (GPR119) and 5-hydroxytryptamine receptor subtype 1A (5-HT1A).

TRPV1 is a non-selective cation channel for calcium, magnesium and sodium ions. It exhibits various activation and modulatory mechanisms, involving in the stimulation by GPCRs, noxious heat, low pH, and various endogenous cannabinoids such as anandamide (AEA), 12-hydroperoxy-eicosatetraenoic acid (12-HPETE) and N-arachidonoyl dopamine (NADA) [40]. Also, TRPV1 receptors play a role in transmission and modulation of nociception, as well as the integration of diverse painful stimuli [41]. They are found mainly in the nociceptive neurons of the peripheral nervous system, but they have also been described in CNS, specifically, in the hippocampus, cortex, and substantia nigra [42,43].

Orphan GPCRs, most notably GPR55, GPR18 and GPR119 have been proposed as potential novel cannabinoid receptors [44]. GPR55 is widely expressed in the brain, especially in the cerebellum. GPR55 can be characterized as a cannabinoid receptor, on the basis of sequence homology at the binding site, in fact the encoded integral membrane protein is a likely CB1 and CB2 cannabinoid receptors [45]. Also, it was demonstrated that GPR55 responds to a variety of both endogenous and exogenous cannabinoid ligands, such as Δ9-THC, CP55940 (CB1 and CB2 agonist), AEA and virodhamine [46] as do the cannabinoid receptors. These features led to suggest GPR55 as a putative third cannabinoid receptor [46,47]. GPR55 may be involved in several physiological and pathological processes by activating a variety of signal transduction pathways [48]. Combining with an extracellular signal and transmitting the signal across the membrane by activating an associated G-protein, promotes the exchange of GDP for GTP on the alpha subunit of a heterotrimeric G-protein complex. Also its activation promotes activation of the small G proteins rhoA, cdc42 and rac1 and a transduction mediated by the ERK1 and ERK2 cascade [49,50].

Recently a fourth potential receptor GPR18 activated by N-arachidonoylglycine (NAGly), a metabolite of AEA, has also been described [51]. GPR18 is expressed in gastrointestinal, immune and testicular tissues, as well as the striatum, cerebellum and brain stem [52]. Also, GPR18 is found on microglial cells in the brain where it regulates the migration of these cells following CNS damage or inflammation [51].

GPR119 is another orphan receptor originally identified in genome-sequencing efforts and expressed predominantly in the pancreas and gastrointestinal tract [53]. The identification of GPR119 as a putative cannabinoid receptor comes from reports of activation of GPR119 by oleylethanolamide, a
monounsaturated analogue and functional antagonist of AEA [54], although controversy remains on its physiological role.

5-HT1A receptor is a subtype of serotonin receptor expressed both as a presynaptic autoreceptor on raphè neurons, and as a major postsynaptic receptor in several brain regions including cerebral cortex, amygdala and hippocampus involved in mood, memory, emotion and stress response [55]. Activation of both pre- and postsynaptic 5-HT1a receptors decreases neuronal excitability [56,57]. Also, 5-HT1A is a GPCR that inhibits adenylate cyclase and activate receptor operated potassium channel, whereas inhibits voltage gated calcium channel [58].

Particularly, it was demonstrated that CBD exerts many of its effects by binding 5-HT1A receptor. Activation of this receptor in key brain areas related to defensive responses, including the dorsal paeriaqueductal grey, bed nucleus of the stria terminalis and medial prefrontal cortex, leads to anxiolytic, antidepressant and antipsychotic effects showed by CBD [59].

Δ⁹-THC, of which are well-known psychotropic effects, is believed to perform the majority of its actions in the CNS binding CB1 and CB2 receptors [60]. Non-psychotropic phytocannabinoids (CBD, CBG, CBC, Δ⁹-THCV and CBDV), exert multiple pharmacological effects via CB1/CB2 receptors as well as no-CB1 and no-CB2 receptors [50] involving intracellular pathways that play a key role in neuronal physiology. These compounds, especially CBD, are able to suppress the production of a wide range of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β [61,62]. They show also a potent action in inhibiting oxidative and nitrosative stress, modulating the expression of inducible nitric oxide synthase (iNOS) and reducing the production of reactive oxygen species (ROS) [63]. Moreover, non-psychotrophic phytocannabinoids attenuate high-glucose-induced mitochondrial superoxide generation and NF-κB activation, along with the expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule (VCAM-1) [64]. Together, these activities suggest that these compounds can exert neuroprotective, antioxidant and anti-inflammatory effects.

Figure 4 summarizes the mechanisms of action and cannabinoid-induced cellular signaling in the neurological diseases investigated.
5. Cannabinoids in the Treatment of Neurodegenerative Diseases

Neurodegenerative diseases are chronic and progressive disorders characterized by the gradual loss of neurons in discrete areas of the CNS. Parkinson’s disease (PD), Huntington’s disease (HD), Alzheimer’s disease (AD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS) and cerebral ischemia are considered the disorders with the highest incidence in the population worldwide.

While the etiopathogenesis of these diseases is different, a number of common mechanisms underlying their progressive nature have been elucidated, such as neuro-inflammation, oxidative stress, excitotoxicity, protein misfolding and mitochondrial dysfunction.

Nowadays, for these diseases there is no cure, current therapies have focused on treatment of symptoms and try to delay their progression. It has been demonstrated that endocannabinoid signaling is altered in many neurodegenerative diseases [65]. Therefore, it is believed that modulation of the endocannabinoid system could be a useful alternative in neurodegeneration treatment. Furthermore, preclinical research from animal models of neurodegeneration and clinical trials have suggested a potential role of cannabinoids in the attenuation of inflammation and the protection of neurons at risk.
of damage. Below we reported the most significant data regarding the current status of therapeutic
effects of cannabinoids in neurodegenerative disease management.

5.1. Cannabinoids in Parkinson’s Disease

PD is a chronic, progressive neurodegenerative disorder, characterized by the progressive
degeneration of dopaminergic neurons in the substantia nigra pars compacta and consequent reduction
in dopamine (DA) content in striatum [66]. The enzyme tyrosine hydroxylase (TH) present in all
dopaminergic cells, catalyzes the formation of L-DOPA, the rate-limiting step in the biosynthesis of
DA, thereby directly linking PD with TH [67]. Thus, a TH deficiency in the striatum is a hallmark of
PD [68].

The death of nigral dopaminergic neurons leads to the typical motor symptoms observed in PD,
bradykinesia, tremor, and rigidity.

Several experimental and clinical studies have demonstrated that endocannabinoid system undergo
evident neurochemical and neurophysiological alterations after dopamine depletion [69,70,71,72]. In
fact, as consequence of reduction in dopaminergic signaling, endocannabinoids levels as well as CB1
receptor expression result to be up-regulated in basal ganglia [73,74], sugging that cannabinoids
could have a therapeutic role in the treatment of movement disorders associated with PD.

To better understand what is the cannabinoid mechanism of action in PD and their antiglutamatergic
effects, it is vital to explain the network of synapses involved in the genesis and in the control of voluntary and involuntary movements. For this purpose, it will be beneficial to summarize and comment on mechanism prospects outlined by many authors [75,76,77].

At level of basal ganglia, when the prefrontal sensorial cortex receives a stimulus to perform a
movement, sensitive cortical neurons send glutamatergic excitatory signals to striatum nucleus
(putamen) that, via GABAergic neurons, inhibits the activity of internal globus pallidus. This is known
as the direct pathway of movement control. So doing, the GABAergic inhibitory signal of globus pallidus,
that normally controls the activity of thalamic nucleus, is lost and thalamus can send an
excitatory glutamatergic signal to motor cortex that perform the movement.

There is also an indirect pathway triggered from putamen: GABAergic neurons project to external
globus pallidus that is inhibited to send, in turn, its GABAergic inhibitory signal to subthalamic nucleus.
Subthalamic nucleus can now activate three pathway trough glutamatergic excitatory signals direct to:
(1) substantia nigra pars reticulate; (2) internal segment of globus pallidus; (3) substantia nigra pars compacta. Among them, substantia nigra pars compacta is crucial to release dopamine neurotransmitter activating striatum that stimulates the triggering of direct pathway via D1 receptors and, parallel, the
inhibition of indirect pathway via D2 receptors. In PD, a depletion of dopamine in the striatum causes
a cascade that lead to invert the normal balanced functioning of the basal ganglia circuitry. All this
cascade of events lead to the blocking of the direct pathway and to the activation of the indirect pathway,
so that we have bradykinesia as well as distorted muscle movements characteristic of PD patients.

Overall, the results is a disinhibition of the striatal neurons and therefore a relative glutamatergic
overactivity, that antiglutamatergic therapies with cannabinoids counteract, mostly via CB1 receptor
sited at level of presynaptic region of glutamatergic terminal [78].

www.CPRTrainingFast.com
More in detail, since the glutamatergic excitation is mediated by N-methyl-D-aspartate (NMDA) receptors of the neurons sited in the striatum and subthalamic nucleus, antagonists of NMDA receptors could reduce activity through the indirect pathway [77]. The result of cannabinoids action is translated in a reduction of glutamate release, decreasing calcium influx, as well as of local inflammatory events.

Current therapeutic strategies aim to increase dopaminergic transmission in basal ganglia by administration of dopamine precursors, such as L-DOPA [79], however, in a proportion of patients the efficacy of the treatment declines through time.

The majority of PD patients undergoing levodopa therapy develop disabling motor complications (dyskinesias) within 10 years of treatment. Recent studies in animal models and in the clinic propose that CB1 receptor antagonists could prove useful in the treatment of both Parkinsonian symptoms and levodopa-induced dyskinesia, whereas CB1 receptor agonists could have a role in reducing levodopa-induced dyskinesia (LID) [69].

In reserpine rat model of PD, the dopamine D2 receptor agonist quinpirole led to a significant reduction of akinesia [80]. This effect was substantially reduced by coinjection with the cannabinoid CB1/CB2 receptor agonist WIN 55,212-2. The concomitant administration of the CB1 antagonist rimonabant (SR141716A) with quinpirole and WIN 55,212-2 blocked the effect of WIN 55,212-2 on quinpirole-induced reduction of akinesia [80]. This suggests that cannabinoid antagonists might be therapeutically advantageous together with dopamine agonists in reversing the endocannabinoid effects upon inhibitory motor function observed in PD.

In Lastres-Becker et al. [81] study, PD was induced in rats injected stereotaxically with a 6-hydroxydopamine (6-OHDA), and then administered for two weeks with Δ9-THC and CBD. The authors found that both compounds were equally effective in protecting nigrostriatal dopaminergic neurons from the neurotoxin 6-OHDA. Also, it was shown that CBD can attenuate dopamine depletion and TH deficits, which are indicative of the degree of neurodegeneration of nigrostriatal dopaminergic projections [81]. These cannabinoids may function as neuroprotective agents in PD due to their capability to reduce oxidative stress. Δ9-THC and CBD might restore the balance between the excessive production of ROS and a relative deficiency in antioxidant properties by acting as ROS scavengers as well as improving antioxidant enzymes through the activation of signaling triggered by nuclear factor-erythroid 2 (Nfr-2) [82].

Also, CBD showed anti-inflammatory properties, reducing the generation of pro-inflammatory cytokines, such as TNF-α and IL-1β, as well as ROS and anti-inflammatory cytokines like IL-10 [83].

Moreover, Δ9-THCV has been shown to have neuroprotective effects, both in rats subjected to injection of 6-OHDA [84] as well as in mice injected with lipopolysaccharide (LPS) [84], possibly mediated through its antioxidant effects as well as through upregulation of CB2 receptors, and can therefore affect microglia activation. Also, in both models of PD, it was demonstrated that administration of Δ9-THCV delayed disease progression, reducing motor inhibition, presumably through changes in glutamatergic transmission [84].

However, despite the encouraging data achieved on the potential therapeutic utility of cannabinoids in PD rodent models, studies with non human 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned primates have also produced conflicting results.
It was been demonstrated that the therapy with plant-derived cannabinoid agonists for attenuating hypokinetic signs was useless and did not alleviate motor deficits [85,86]. In MTPT-treated common marmosets, the blockade of CB1 receptors with SR141716A (rimonabant), a cannabinoid CB1 receptor antagonist, reduced LID without affecting the anti-Parkinsonism efficacy of L-DOPA [87]. Similarly, Meschler et al. [88] using cynomolgus monkeys (Macaca fascicularis), confirmed that SR141716A did not improve motor disability. Also in the same study it was demonstrated that cannabinoid agonist levonantradol produced a decrease in locomotor activity and an increase in bradykinesia in primates. Also, cannabinoid agonists did not induce catalepsy in primates, a property that differs from their effects in rodents [88].

Furthermore, as for the animal studies, drug trials in PD patients have produced conflicting results. In a randomized, double-blind, placebo-controlled study the cannabinoid receptor agonist significantly reduced LID in PD [89]. On the contrary, in a double-blind, cross-over study, Cannabis extracts, while well tolerated, did not show effects on LID [90].

5.2. Cannabinoids in Huntington’s Disease

Huntington’s disease (HD) is an autosomal-dominant inherited disorder characterized by striatal neurodegeneration. Literature reports that the cause of the disease is a mutation in the huntingtin (HTT) gene consisting of a CAG triplet repeat expansion translated into an abnormal polyglutamine (polyQ) tract in the amino-terminal portion of huntingtin (Htt) protein [91]. Htt aggregation and its accumulation are extremely toxic for striatal and cortical neuronal subpopulations [92,93,94]. The loss of motor inhibition that follows results in an evident abnormal and involuntary writhing, commonly defined as “choreiform” movements [95], associated with dementia [96] and cognitive impairment [97].

The brain region to which is ascribed the pathology is the corpus striatum that has the functional role to control both posture and gait via GABA neurons that project to globus pallidus and zona reticulata of the substantia nigra, controlling in turn subthalamic nucleus. So doing, it inhibits or gates inappropriate or uncontrolled movements [98,99].

About neuroprotective effects of cannabinoid compounds in experimental HD, three mechanism of neuroprotection have been hypothesized: CB1-dependent, CB2-dependent and CB1-/CB2-independent [96]. The first hypothesis is corroborated by the fact that CB1 receptor is early down-regulated in ongoing disease, even in asymptomatic phases, so that CB1 receptor loss could have a role in HD pathogenesis [96]. The second hypothesis born from the evidence given by CB2 receptor localization. It was observed that it is poorly expressed in striatal parenchima under healthy condition while it is progressively over-expressed during degenerative events leading to HD. In this circumstance, CB2-activation preserve striatal neurons from inflammatory insults produced by reactive microglial cells, maybe through the release of neurotrophins, anti-inflammatory cytokines and metabolic substrates [100,101].

Finally, the CB1-/CB2-independent pathway, involved in the neuroprotection during experimental models of HD seems related to some cannabinoids with antioxidant properties, such as Δ9-THC and CBD, since their particular phenolic structures could exert a scavenger action against ROS. Parallel, there is also the assumption of an intracellular signal regulation via the expression control of antioxidant
enzymes of phase II (i.e., Nrf-2/ARE signaling) [96]. On this framework, there are conflicting data and the literature about it is very wide.

From a research on MEDLINE about “Huntington’s disease and cannabinoids” we got 61 results, extended to 103 when the search was related to “Huntington’s disease and cannabinoid receptor”.

Among them, noteworthy was a recent preclinical study published on PNAS on January 2014 performed on R6/2 mouse [102]. It is the most commonly used model of HD. R6/2 mouse expresses exon 1 of the human huntingtin gene with around 150 CAG repeats. It also exhibits a progressive neurological phenotype that mimics many of the features of HD, including choreiform-like movements, involuntary stereotypic movements, tremor, and epileptic seizures [103].

The paper reported that a restricted population of CB1 receptors, and more precisely those located on glutamatergic terminals, play a crucial role in the neuroprotective activity of Δ⁹-THC and, more in general, of (endo)cannabinoids, so that the authors look at these receptors as a promising target for neuroprotective strategies of therapy during HD [102].

Also, Valdeolivas et al., last September published in Neurotherapeutics, the neuroprotective effects of CBG treatment in two in vivo models of HD, such as R6/2 mutant mouse and 3-nitropropionate (3-NP) acid-lesioned mice [104].

Authors ascribe CBG effects both to cannabinoid receptor-dependent and/or independent mechanisms. So, in the toxic model of HD authors show the neuroprotective CBG capability to attenuate the reactive microgliosis and to counteract the upregulation of pro-inflammatory markers, while in genetic model of HD they describe a recovery in the deteriorated rotarod performance typical of R6/2 mice, an expression partially normalized by CBG treatment of genes linked to HD, as well as an up-regulation of BDNF, IGF-1 and PPARγ genes. Finally, CBG-treated animals showed a reduction in the aggregation of mutant Htt protein in striatal parenchyma.

Moreover, a MEDLINE research performed on “Huntington’s disease and preclinical study and cannabinoids” gave just two results: “Neuroprotective effects of phytocannabinoid-based medicines in experimental models of Huntington’s disease” published in Journal of Neuroscience Research in September 2011 [105] and the other one entitled “Sativex-like combination of phytocannabinoids is neuroprotective in malonate-lesioned rats, an inflammatory model of Huntington’s disease: role of CB1 and CB2 receptors” published on ACS Chemical Neuroscience in May 2012 [106].

The first study tests a 1:1 botanical combination of extracts enriched in either Δ⁹-THC or CBD (the main constituents of the cannabis-based drug Sativex®) on rats stereotaxically subjected to unilateral injection into left striatum of the complex II inhibitor malonate, inducing HD through: (1) increasing the volume of edema; (2) reducing the number of Nissl-stained cells and enhancing the number of degenerating cells (3) causing reactive microglia and astrogliosis (4) increasing oxidative stress. According to these authors, the reversion of these effects would be mediated by a CB1 and CB2 receptor-independent mechanism provided by both cannabinoids [106].

Differently by other studies, but in accordance with evidences also reported by Fernández-Ruiz et al. [107], the above-reported study ascribes a balanced role to CB1/CB2 receptors with a likely involvement in drug treatment showing an up-regulation of CB2 followed by a down-regulation of CB1
receptors, suggesting that CB2 receptors could play a particularly important role in the protective effect of Sativex®.

Furthermore, about synthetic cannabinoids HU210 and WIN 55,212-2, they seem to work in transgenic R6/1 mice, expressing exon 1 of the human HD gene carrying a 115 CAG repeat, through a mechanism mediated by G-protein alpha subtype i/o (G(i/o))-linked and ERK-dependent signal transduction [108]. This promotes the coupling of CB1 receptors to Gi/o and attenuate toxicity associated with Htt aggregation [108].

Despite the encouraging results obtained by the experimental investigations about the potential therapeutic use of cannabinoids in HD symptoms management, clinical trials have not confirmed these results. Particularly, studies performed using cannabinoids have not shown expected improvement in the hyperkinetic symptoms of HD. Consroe et al. [109] published one of the first clinical trials in which CBD was evaluated for symptomatic efficacy and safety in 15 neuroleptic-free patients with HD. Authors demonstrated that CBD, was neither symptomatically effective nor toxic in these patients. Also, in literature, are reported two uncontrolled, single patient studies evaluating efficacy of nabilone, but these studies yielded conflicting results for reducing chorea severity [110,111]. Thus, although nabilone induced signs of improvement in one of these studies, in the other study [110] it made symptoms worse [111]. Nabilone was also used in a double-blind, placebo controlled, cross-over study in which it induced improvements in motor and cognitive indices [112].

The data obtained recently in animal models led to suggest that the combination of different cannabinoids, such as Sativex® may be an interesting tool for developing novel therapies in HD although to date there have been no results.

5.3. Cannabinoids in Alzheimer’s Disease

AD is the most frequently form of dementia, with an incidence of about 34 million people worldwide [113]. AD is characterized by lesions in CNS due to the formation of beta-amyloid (Aβ) plaques, neurofibrillary tangles and cortical atrophy [114,115].

It has been demonstrated that in microglia of AD patients, CB1 and CB2 receptor expression is significantly increased, while in basal ganglia and hippocampus neuronal CB1 receptor expression is decreased [116]. Therefore, endocannabinoid system might play an important role in AD pathogenesis.

To date, the majority of drugs in use for AD treatment are acetylcholine esterase (AChE) inhibitors. According to Eubanks and colleagues [117], Δ⁹-THC competitively inhibits enzyme AChE and prevents Aβ peptide aggregation in the brains of Alzheimer patients.

In rat pheochromocytoma PC12 cells and in vivo models, it was shown that CBD also inhibits β-amyloid plaques formation, reducing ROS production and lipid peroxidation [118].

Also, using mice inoculated with human Aβ (1–42) peptide into the right dorsal hippocampus, Esposito et al. [119] have demonstrated anti-inflammatory and antioxidant actions of CBD. Indeed, CBD is able to attenuate α-amyloid plaques formation modulating iNOS expression and also decreasing p38MAP kinase and NF-κB levels. Thus, limiting propagation of neuro-inflammation and oxidative stress.
In addition, Martin-Moreno and colleagues [120] have showed that in Aβ-mice, CBD and synthetic cannabinoid WIN 55,212-2 are able to modulate microglial cell function and cytokine expression, improving learning behavior.

Also, CBD appears able to exert a beneficial effect in the amyloidogenic pathway, through a specific molecular mechanism involving peroxisome proliferator-activated receptor-γ (PPARγ) [121]. Scuderi et al. [121] investigated CBD as a possible modulating compound of amyloid precursor protein (APP) in transfected human neuroblastoma SHSY5Y APP+ cells. Achieved results indicated the CBD capacity to induce the ubiquitination of APP protein, which led to a substantial decrease in APP full length protein levels in SHSY5Y APP+ with the consequent decrease in Aβ production. As consequence, CBD has promoted an increased survival of SHSY5Y APP+ cells reducing their apoptotic rate and increasing their survival in long-term period of cell culture. All CBD effects showed were dependent on the selective activation of PPARγ [121].

In a recent paper, Aso and co-workers [122] tested the therapeutic properties of combination of Δ9-THC + CBD (0.75 mg/kg each) in a AβPP/PS1 transgenic mice, an experimental model of AD, which replicates the most relevant features of disease, including cognitive impairment and several pathological alterations, such as Aβ deposition, dystrophic neurites, synaptic failure, mitochondrial dysfunction, and oxidative stress damage. Authors demonstrated that mixture of the two compounds preserved memory and reduced learning impairment in AβPP/PS1 transgenic mice when chronically administered during the early symptomatic stage [122].

A significant decrease in soluble Aβ (1-42) peptide levels and a change in plaques composition were also observed in Δ9-THC + CBD-treated AβPP/PS1 transgenic mice, due to a reduced microgliosis and expression of several cytokines and related molecules of neuro-inflammation [122]. In this study authors suggest that combination of Δ9-THC + CBD exhibits a better beneficial effect than each Cannabis component alone and support the consideration of a Cannabis-based medicine as potential therapy in AD [122].

Currently, there are only limited data displaying clinical effects of phytocannabinoids on human AD. A single, open-label, non-placebo controlled study [123] performed with AD patients reported that Dronabinol derived from Δ9-THC has a beneficial role in reducing anorexia and improving behavior, like nocturnal motor activity and agitation.

Despite these encouraging results, the usefulness of cannabinoid based medicines for the treatment of AD awaits the results of severe clinical trials. Also, to date there are no significant data reported in the literature on the use of phytocannabinoids in the treatment of vascular dementia.

5.4. Cannabinoids in Multiple Sclerosis

MS is an autoimmune inflammatory neurodegenerative disease characterized by nerves demyelination in CNS [124]. However its etiology is still unknown. Therefore, in order to better understand the etiopathogenesis of MS and to find new therapeutic strategies, researchers use some experimental models. The most used is the experimental autoimmune encephalomyelitis (EAE), which mimics the main features of human MS.

Numerous studies have been performed to evaluate the role of cannabinoids on treatment of EAE-associated spasticity as well as on modulation of the neurodegenerative process.
According to a study performed using CB1-knockout mice, it was demonstrated that the mechanism of improvement spasticity was dependent on CB1 receptors, not CB2 [125]. Also, Δ⁹-THC was reported to delay or prevent signs of spasticity in EAE mice, as well as increasing survival rates and reducing neuro-inflammation via a CB1-dependent mechanism [126].

Using synthetic cannabinoid agonists of CB1 and CB2 receptors, such as dexamabinol (HU210, (−)-1,1-dimethylheptyl analog of 11-hydroxy-Δ⁹-THC) and WIN 55,212-2 in EAE mice, it was demonstrated that they promote oligodendrocytes survival via CB1 and CB2 receptor-mediated effects, potentially reducing demyelination and apoptosis [127,128]. Also, these cannabinoids were able to reduce inflammation, probably by suppression of TNF-α and IL-1β and enhances the release of anti-inflammatory cytokines such as IL-10 in brain and peripheral blood [129]. Same results were confirmed by Arevalo-Martin et al. [130], using Theiler’s murine encephalomyelitis virus-induced demielinating disease (TMEV-IDD) model of chronic-progressive MS. Indeed, it was demonstrated that systemic treatment with synthetic cannabinoid CB1/CB2 receptor agonist WIN 55,212-2 in TMEV-IDD mice can limit axonal loss and neuro-inflammation in animal models of MS, by modulating microglia and lymphocyte infiltration in spinal cord [130].

Also, it was demonstrated that CB52, a newly developed cannabinoid compound (AEA and Δ⁹-THC hybrid), is more effective than other commonly used cannabinoids and its protection on oligodendrocytes is mediated by the activation of the CB2 receptor [131].

Using EAE mice, Ribeiro et al. [131], proved that CB52 reduced microglia activation, nitrotyrosine formation, T cell infiltration, production of TNF-α, oligodendrocyte toxicity, myelin loss and axonal damage in the mouse spinal cord white matter and alleviates the clinical scores when given either before or after disease onset.

Moreover, significant alterations of the endocannabinoid system have been found in the brain of EAE and Chronic Relapsing Experimental Allergic Encephalomyelitis (CREAE) mice. Particularly, increased levels of AEA and 2-arachidonoyl glycerol (2-AG), were detected in areas associated with nerve damage in CREAE [4] and in EAE [132], when compared to non-spastic mice.

Also, reduced CB1 expression was showed during acute phases of CREAE [133] and CB2 transcription may be increased in EAE [33]. Administration of SR141716A and SR144528, CB1 and CB2 antagonists, has been shown to worsen tremor and spasticity in CREAE mice, whilst WIN 55,212-2, methanandamide and JWH-133 CB2 agonists reduced both tremor and spasticity in diseased mice [134,135]. In addition, spasticity could also be ameliorated by the inhibition of AEA reuptake and enzymatic hydrolysis, causing a subsequent increase in AEA concentration in the CNS [4].

As well-known endocannabinoids are to be released in response to a wide range of neuronal insults [136], and levels are increased in the CSF and peripheral lymphocytes of patients with MS [137]. Centonze et al. [137] indeed reported a relevant increase in AEA, but not 2-AG levels, in the CSF of relapsing-remitting MS patients experiencing current relapse with a strong correlation between AEA levels and the number of inflammatory lesions visible on imaging. AEA concentrations were also higher in peripheral lymphocytes of these patients; an effect associated with increased synthesis and reduced degradation of this endocannabinoid [137]. Another study also showed elevated AEA levels in MS
patients when compared with healthy controls, across the clinical spectrum, this time in the plasma, again suggesting that the peripheral endocannabinoid system may reflect those occurring centrally [138].

Benefits from cannabinoids use seen in animal studies have also been shown in the treatment of MS patients suffering spasticity, with a significant associated disability and quality of life impairment. It is clear that spasticity results from alterations in the balance, possibly secondary to selective neuronal loss, between excitatory and inhibitory neural circuits. Under physiological conditions, inhibitory signals are sent via the corticospinal tract to the spinal cord, but following injury, damage to the corticospinal tract, causes disinhibition of the stretch reflex, leading to reduction in the triggering threshold. This leads to loss of control of neurotransmission between muscles and CNS, resulting in uncontrolled spastic movement [139].

Current therapies for spasticity include GABA receptor agonist, baclofen, tizanidine, benzodiazepine and anxiolytics [140]. Also, local administration of botulinum toxin have also shown efficacy in clinical trials [140]. The use of phytocannabinoids may be useful in MS patients, which show resistance to these conventional therapies, as shown in clinical studies reported in literature.

The Cannabinoids in MS (CAMS) study [141], a double-blind, randomized, placebo-controlled trial, was the first large-scale study designed to test the hypothesis that cannabinoids may have a beneficial effect on spasticity associated with MS. This study involved 630 MS patients treated with dronabinol (a synthetic Δ⁹-THC), cannador (2.5 mg of Δ⁹-THC, 1.25 mg of CBD, and 5% of elements other than cannabinoids per capsule) and placebo. It did not show any significant improvement in spasticity at 15 weeks [141], but this was evinced with both Cannabis compounds after one year of treatment [142]. Also, MS patients perceived a significant improvement in pain and sleep disorders [142]. Other studies performed with smaller numbers of patients and crossover studies [14] have confirmed the same results previously obtained.

Following CAMS study, comes the Cannabinoids Use in Progressive Inflammatory brain Disease (CUPID) study [143], another double-blind, randomized, placebo-controlled trial (duration of three years) in United Kingdom involving 493 patients with progressive MS. The full results from this study are pending, but initial data shows that dronabinol has no overall effect on MS progression, measured with the Expanded Disability Status Scale (EDSS) scale.

Analysis of a subgroup of patients in this study suggested a possible benefit from dronabinol in those who began the trial with milder disability, but not in those who began the trial with more severe disability [143].

A recent randomized, double-blind, placebo-controlled study involving 15 relapsing-remitting MS patients with MS-induced neuropathic pain was conducted to evaluate Nabilone combined with gabapentin. Results suggest that Nabilone as an adjunctive to gabapentin is an effective, well-tolerated combination for MS-induced neuropathic pain and thus can be used as a novel therapeutic combination in MS treatment [144].

In addition, use of Sativex® has been extensively investigated in the management of patients with MS [14,15]. Currently, this spray preparation is used as treatment to alleviate symptoms of spasticity and neuropathic pain in adult MS patients that did not show an appropriate response to other drugs during an initial trial period of therapy. It has also been reported that Sativex® shows efficacy in the treatment
of bladder dysfunction, frequent in MS patients, showing a decrease of incontinence episodes and an increase in bladder retention volume. According to another study [145], MS patients treated with Cannabis extract; Δ9-THC, showed an important reduction in events of urge incontinence compared to placebo. Thus, suggesting that phytocannabinoids might compensate for the bladder neural circuitry disregulation that often accompanies disease progression in MS.

Spasticity, neuropathic pain and uncontrollable bladder and bowel are symptoms observed also in patients affected by spinal cord injury (SCI).

Therefore, use of cannabinoids and mixture of extracts could be useful in treatment of this pathology. Unfortunately, in the literature there are only a few studies that do not report interesting data.

5.5. Cannabinoids in Amyotrophic Lateral Sclerosis

ALS is the most prevalent form of motoneuron disease, characterized by degeneration and death of motor neuron populations in the cerebral cortex, brainstem and spinal cord [146]. Several mechanisms have been involved in ALS pathogenesis, such as neuro-inflammation, mostly mediated by excitotoxicity and oxidative damage on motor neurons [147, 148].

There is rapidly emerging evidence that the cannabinoid receptor system has the potential to reduce both excitotoxic and oxidative cell damage.

Numerous studies reported in literature, have been conducted using ALS hSOD(G93A) transgenic mice, the strain predominantly used. Indeed, the disease in these animals closely mimics human ALS.

It was shown that mice treated with Δ9-THC exhibited an improvement of motor impairment by administration of the molecule, either before or after signs onset, a prolonged survival by 5% [149]. According to Bilsland et al. [150], a significant delay was found in disease progression when CB1/CB2 receptor agonist WIN 55,212-2 was administered to ALS hSOD(G93A) mice beginning after onset of motor impairment and tremor (at 90 days old), however, survival was not extended.

Furthermore, using the same experimental model of ALS, it was demonstrated that CB1 deletion, had no effects on disease onset, but extend lifespan by 15 days, a 13% increase in survival [150].

Also, it is important determining CB2 receptor role, since microglia from ALS hSOD(G93A) mice seems to possess increased cytotoxic potential [151]. Indeed, CB2 activation blocks β-amyloid induced microglia activation [152]. On the contrary, with other stimuli, CB2 activation showed increasing microglial migration and proliferation.

Using selective CB2 agonist, AM1241, it was reported that ALS hSOD(G93A) mice showed slowing of disease progression if administered after disease onset [153]. Administration at the onset of tremors delayed motor impairment in treated mice when compared with vehicle controls. Also, in these mice an increase of 56% in survival interval was shown [153].

In a recent study, Moreno-Martet et al. [154] evaluated neuroprotective effects of Sativex® in SOD(G93A) transgenic mice. Sativex® has proven to be effective in delaying ALS progression in the early stages of disease and in animal survival, although the efficacy was decreased during progression of disease. Also, it has been demonstrated that changes occur in endocannabinoid signaling, particularly a marked up-regulation of CB2 receptors in SOD(G93A) transgenic mice. Thus, Sativex® may be used as an adjunctive therapy with only one medicine already approved, Rilutek®, which shows modest efficacy on disease progression.
To date, there have been few studies on human ALS. According to Yiangou et al. [155], in human ALS patients, spinal cord demonstrates motor neurons damages marked by CB2-positive microglia/macrophages. Moreover, a recent study analyzing activated microglia from spinal cord in human ALS patients demonstrated a CB2 increase. So all these data show how editing CB2-mediated processes could change ALS progression and how much the endocannabinoid system is potentially involved in reducing neuro-inflammation, excitotoxic, and oxidative cell damage [156].

Finally, in literature it has been reported in a single case study of patients with ALS, the 10% who admitted consuming Cannabis, have reported moderate relief of several symptoms, including appetite loss, depression, spasticity and drooling [157].

### 5.6. Cannabinoids in Cerebral Ischemia and Hypoxia

Ischemia is the result of a transient or permanent reduction in cerebral blood flow caused by occlusion of a cerebral artery via an embolus or local thrombosis, sufficient to alter cerebral functions. This causes a complex sequence of events, including mechanisms of excitotoxicity, release of neurotransmitters, breakdown of blood-brain barrier, inflammation, cytokines production, adhesion molecules upregulation, oxidative and nitrosative stress and programmed neuronal cell death [158,159,160].

Recently, cannabinoids have emerged as promising neuroprotective agents in several experimental model of brain damage. It seems that the endocannabinoid signaling system has various features for which appears to be involved in ischemic damage. Among these, endocannabinoids and related lipids accumulate in ischemic tissues and play a role in maintaining metabolic homeostasis and responsiveness of the brain to stress [161].

It was demonstrated that CBD can invert brain damage following cerebral ischemia in mice, decreasing brain edema and seizures associated with temporary occlusion of carotid arteries [162]. CBD was able to reduce cerebral hemodynamic impairment and ameliorate brain metabolic activity post-injury [162]. Also, it seems that CBD exerts a neuroprotective effect toward brain ischemia, causing an increase in cerebral blood flow mediated by 5-HT1A receptor and/or be secondary to its cannabinoid receptor-independent anti-inflammatory activity [163].

To date, few studies were carried out in patients with cerebral ischemia, because the limiting factor seems to be that only some compounds results are useful, and only if taken shortly before or within a few hours after cerebral damage. Clinical trials using dexabinol a synthetic Δ^9-THC, showed no efficacy in cerebral ischemia treatment [164].

Similarly, the same mechanisms involved in cerebral ischemia, were found in hypoxic-ischemic brain injury events. Frequently, this devastating condition is one of the most important causes of neonatal brain injury and also results in adverse developmental outcomes [165].

To date, there are few reports on the possible neuroprotective effect of cannabinoids in newborns and existing publications consider their beneficial effects against excitotoxicity. CBD demonstrated neuroprotective effects in the brain of newborn Wistar rats following hypoxia-ischemia, associated with the modulation of excitotoxicity, oxidative stress and inflammation [166]. Indeed, CBD modulates glutamate and cytokines release, as well as the induction of iNOS and type 2 cyclooxygenase (COX2) [167]. Also, using a hypoxic-ischemic brain injury model in newborn pigs, Pazos et al. [168] confirmed that CBD modulates these mechanisms acting on CB2 and 5HT1A receptors.
Moreover, CBD activity was tested in newborn piglets, subjected to temporary occlusion of both carotid arteries plus hypoxia [162]. CBD administration reduced short-term brain damage, in a manner that can be attributed to a CBD-induced reduction of cerebral hemodynamic impairment, improvement of brain metabolic activity post-insult, reduction of brain edema, and reduction of seizures. These neuroprotective effects were not only free from side effects but also associated with some cardiac, hemodynamic, and ventilatory benefits [162].

Therefore, CBD may be considered an important candidate for future clinical trials with hypoxic newborns.

6. Other Therapeutic Applications of Cannabinoids

The use of Cannabis has been shown in the treatment of many diseases through time. Among these, treatment of epilepsy seems to be one of the most ancient.

Epilepsy is a chronic neurological disease that affects 50 million people worldwide, characterized by recurrent seizures and often accompanied by cognitive deficits and mood disorders [169]. The targeting of neuronal ion channels and both GABA and glutamate receptors has been the primary approach to eliminate convulsions. Despite the availability of a wide range of antiepileptic drugs, about one-third of individuals with epilepsy still experience seizures that do not respond to medications [170].

The biological reason to believe that cannabinoids could suppress epileptic seizures is the abundance of CB1 receptors in some areas of the brain (hippocampus and amygdala) where partial seizures originate [171].

Various cannabinoids have been show in several clinical studies to have significant anticonvulsive properties, especially CBD and more recently CBDV and Δ⁹-THCV [172,173,174].

The antiepileptic mechanisms of CBD are not well known, since CBD has low affinity for CB1 and CB2 receptors [23], it seems that CBD may exert its effects through different mechanisms, including effects on the equilibrative nucleoside transporter, GPR55, TPRV-1, 5-HT1A, and the α3 and α1 glycine receptors. Also, antiepileptic mechanism of action of CBD might involve a reduction of Ca²⁺, via interaction with the mitochondrial Na⁺/Ca²⁺ exchanger [175].

Likewise CBDV and, to a far smaller extent, Δ⁹-THCV produces anticonvulsant effects in animal models of epilepsy. Scutt and Williamson [176] reported that CBDV acts via CB2 cannabinoid receptor-dependent mechanisms but direct CB2 receptor effects were not shown. Recently, it was also demonstrated by other studies that CBDV acts via non-CB1/CB2 mechanisms. These compounds in fact interact with TRPV1, TRPV2, TRPA1, and TRPM8 channels, but their molecular pharmacology and mechanisms of action are less well known [177].

Additionally, CBDV has been shown to inhibit the primary synthetic enzyme of the endocannabinoid, 2-arachidonoylglycerol, diacylglycerol lipase α in vitro[178]. While the pharmacological significance of these effects remains unconfirmed in vivo and the targets identified have not yet been linked to epilepsy, they support the emergent role of multiple non-CB receptor targets [179].

Moreover, Δ⁹-THCV has demonstrated interesting potential use in treatment of convulsions. Δ⁹-THCV increases, in a GABA antagonist sensitive manner, inhibitory neurotransmission in mouse cerebellum and also exhibits anticonvulsant activity in a rat piriform cortical (PC) model of epilepsy.
Possible mechanisms underlying cannabinoid actions in the CNS include CB1 receptor antagonism or inverse agonism at constitutively active CB1 receptors [180].

Also, Hill et al. [173] have shown that Δ⁹-THCV reduced Purkinje cell firing via an increase in inhibitory neurotransmission at interneuron-Purkinje cell synapses in mouse acute parasagittal cerebellar brain slices, most likely by reducing CB1 receptor-mediated, endocannabinoid-induced inhibition of GABA release. Interestingly, Δ⁹-THCV was shown to modulate GABA release onto Purkinje cells at a network level, as it did not affect Purkinje cell spike firing following GABA-receptor blockade [181].

It is well known that CBD has therapeutic potential over a wide range of non-psychiatric and psychiatric diseases, such as anxiety, depression, bipolar disorder, psychosis and sleep disorders.

Although pharmacological effects of CBD in several biological systems have been widely investigated, mechanisms responsible for its therapeutic potential are still not clear. From studies on different animal models, it seems that CBD exerts anxiolytic-like effects by activating post-synaptic 5-HT1A receptors in key brain areas related to defensive responses, including the dorsal periaqueductal grey, bed nucleus of the stria terminalis and medial prefrontal cortex [59,182].

Other effects, such as anti-compulsive, blockade of the anxiogenic consequences of chronic unpredictable stress, increased extinction and impaired reconsolidation of aversive memories, and facilitation of adult hippocampal neurogenesis may depend on potentiation of anandamide-mediated neurotransmission. Activation of TRPV1 channels may be invoked to explain the antipsychotic effect and the bell-shaped dose-response curves commonly observed with CBD [59].

In addition to these mechanisms, CBD can interfere in different other important biological processes (inhibition of adenosine uptake, inverse agonism at CB2, CB1 antagonism, GPR55 antagonist, intracellular Ca²⁺ increase). Therefore, further studies are needed to investigate their possible involvement on CBD behavioral effects.

Russo et al. [183], reviewed the effects of Cannabis, and highlighted the benefits that can accrue in this regard, particularly with respect to symptom reduction permitting better sleep, as opposed to a mere hypnotic effect. In several clinical studies, it has been found that low doses of Cannabis improve mood, in particular, Δ⁹-THC increase serotonin levels in the brain, interacting with CB1 receptors.

Therefore, non-psychotropic compounds require further studies to propose these as a potentially useful drug in the treatment of a variety of intractable conditions, at least in association with current conventional therapy.

Finally, cannabinoids have been shown to be potent analgesics in animal models of hyperalgesia and thus might be useful in the treatment of inflammatory pain as well as neuropathic pain [184].

Neuropathic pain is a debilitating form of chronic pain resulting from peripheral nerve injury, toxic insults, and disease states, such as diabetes, cancer, human immunodeficiency virus, MS, and herpes zoster infection [185,186,187]. Neuropathic pain remains a significant clinical problem because it responds poorly to available therapies, needing validation of novel analgesic drugs. More recently, CBD was shown to be effective in well-established experimental models of neuropathic pain. It is believed that the analgesic effect of CBD is mediated, at least in part, by TRPV1 [188]. There is also evidence to suggest that cannabinoids can induce antinociception via supraspinal mechanisms and peripheral CB2
receptors [189]. Also, the analgesic effects may be mediated in part at the level of spinal cord via CB1 receptors activation [190].

7. Conclusions

In this review, we showed how the Cannabis plant, an ancient industrial crop, is drawing increasing attention as a pharmaceutical plant, and is today considered a true “bioreactor” source of botanical raw material from which high amounts of potentially valuable cannabinoids can be extracted. In the future, these molecules will be increasingly used in clinical trials necessary to assess the potential of each phytocannabinoid for the treatment of several diseases, among which CNS disorders.

Whereas, current treatments for CNS diseases are partially effective and have risks of side effects that are not easily tolerated by patients, the development of new synthetic cannabinoids or cannabinoid-derived drugs may represent an alternative strategy to pursue.

The observations from experimental models of neurological diseases, and now increasingly from clinical trials, underline the therapeutic usefulness of cannabinoids-based medicines for treatment of symptoms associated to these. In addition, there is growing evidence from experimental studies that Δ9-THC and other cannabinoids, notably CBD, have neuroprotective effects as a result of their antioxidant, anti-inflammatory and anticytotoxic properties which may prove disease modifying in CNS disorders.

Despite emerging evidence regarding putative therapeutic activities of cannabinoids, their effective introduction in the clinical use is still controversial and strongly limited by unavoidable psychotropic effects, exhibited by many of them.

The possibility of overcoming these side effects and developing novel approaches represents the main open question about the use of cannabinoids as new therapeutic drugs for the treatment of neurological disorders.

Acknowledgments

The authors would like to thank the Giuseppe Galletta and Massimo Messina belonging to the secretary office of IRCCS Centro Neurolesi “Bonino-Pulejo”-Messina, for their excellent technical assistance.

Author Contributions

Sabrina Giacoppo performed bibliographic research and drafted and reviewed the manuscript. Giuseppe Mandolino contributed to the manuscript drafting. Galuppo Maria performed bibliographic research and supported manuscript correction. Emanuela Mazzon and Placido Bramanti designed the paper and supervised manuscript drafting.

Conflicts of Interest

The authors declare no conflict of interest.

References


19. De Meijer, E.P.; Bagatta, M.; Carboni, A.; Crucitti, P.; Moliterni, V.M.; Ranalli, P.; Mandolino, G. The inheritance of chemical phenotype in *Cannabis sativa* L. *Genetics* 2003, 163, 335–346. [Google Scholar] [CrossRef] [PubMed]


www.CPRTrainingFast.com


and in experimental autoimmune encephalomyelitis. *Brain* 2007, 130, 2543–2553. [Google Scholar] [CrossRef] [PubMed]


www.CPRTrainingFast.com


www.CPRTrainingFast.com


Since the beginning or recorded history, cannabis has been used by various cultures for its medicinal properties. In modern times, European and US researchers have continued to explore the potential clinical applications, despite various social and legal norms. Additionally, the discovery of the endocannabinoid regulatory system has increased our understanding of how and why cannabis is an acceptable treatment option for a number of conditions. The understanding of its seemingly limitless applications is growing rapidly as research continues. Overwhelming scientific conclusions continue to develop and substantiate the clinical value of cannabis.
**DIAGNOSIS:** ALZHEIMER’S

### Delta-9-tetrahydrocannabinol for night-time agitation in severe dementia

<table>
<thead>
<tr>
<th>Title</th>
<th>Delta-9-tetrahydrocannabinol for night-time agitation in severe dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Walther S, Mahlberg R, Eichmann U, Kunz D</td>
</tr>
<tr>
<td>Major outcome(s)</td>
<td>Reduction in night-time agitation in actigraphy and in the neuropsychiatric inventory NPI</td>
</tr>
</tbody>
</table>

| Indication | Alzheimer’s disease |
| Medication | Delta-9-THC |
| Route(s) | Oral |
| Dose(s) | 1 x 2.5 mg |
| Duration (days) | 14 days |
| Participants | 6 patients with severe dementia and agitation/circadian disturbance |
| Design | Open study |
| Type of publication | Medical journal |
| Address of author(s) | Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin, Campus Charité Mitte (FUK), Berlin, Germany, sebastian.walther@gei.be.ch |

**RATIONALE:** Nighttime agitation occurs frequently in patients with dementia and represents the number one burden on caregivers today. Current treatment options are few and limited due to substantial side effects. OBJECTIVES: The aim of the study was to measure the effect of the cannabinoid dronabinol on nocturnal motor activity. METHODS: In an open-label pilot study, six consecutive patients in the late stages of dementia and suffering from circadian and behavioral disturbances—five patients with Alzheimer’s disease and one patient with vascular dementia—were treated with 2.5 mg dronabinol daily for 2 weeks. Motor activity was measured objectively using actigraphy. RESULTS: Compared to baseline, dronabinol led to a reduction in nocturnal motor activity (P=0.028). These findings were corroborated by improvements in Neuropsychiatric Inventory total score (P=0.027) as well as in subscores for agitation, aberrant motor, and nighttime behaviors (P<0.05). No side effects were observed. CONCLUSIONS: The study suggests that dronabinol was able to reduce nocturnal motor activity and agitation in severely demented patients. Thus, it appears that dronabinol may be a safe new treatment option for behavioral and circadian disturbances in dementia.
Animal and human studies indicate that cannabidiol (CBD), a major constituent of cannabis, has anxiolytic properties. However, no study to date has investigated the effects of this compound on human pathological anxiety and its underlying brain mechanisms. The aim of the present study was to investigate this in patients with generalized social anxiety disorder (SAD) using functional neuroimaging. Regional cerebral blood flow (rCBF) at rest was measured twice using (99m)Tc-ECD SPECT in 10 treatment-naive patients with SAD. In the first session, subjects were given an oral dose of CBD (400 mg) or placebo, in a double-blind procedure. In the second session, the same procedure was performed using the drug that had not been administered in the previous session. Within-subject between-condition rCBF comparisons were performed using statistical parametric mapping. Relative to placebo, CBD was associated with significantly decreased subjective anxiety (p<0.001), reduced ECD uptake in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus (p<0.001, uncorrected), and increased ECD uptake in the right posterior cingulate gyrus (p<0.001, uncorrected). These results suggest that CBD reduces anxiety in SAD and that this is related to its effects on activity in limbic and paralimbic brain areas.
**DIAGNOSIS: **

**ASTHMA**

<table>
<thead>
<tr>
<th>Title</th>
<th>Acute and subacute bronchial effects of oral cannabinoids.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Gong H Jr, Tashkin DP, Simmons MS, Calvarasa B, Shapiro BJ</td>
</tr>
<tr>
<td>Major outcome(s)</td>
<td>acute bronchodilator activity of delta 9-THC, no effect of cannabidiol, daily use of delta 9-THC not associated with tolerance</td>
</tr>
</tbody>
</table>

| Indication | Asthma |
| Medication | Delta-9-THC |
| Route(s) | Oral |
| Dose(s) | 20 mg THC daily, 1200 mg cannabidiol daily |
| Duration (days) | 20 days |
| Participants | experienced marijuana smokers |
| Design | Open study |
| Type of publication | |
| Address of author(s) | |

The bronchodilating activity of oral cannabinoids was evaluated in three double-blind experiments that involved the study of dose-response and interactive relationships and the potential development of tolerance. Data indicated that delta 9-tetrahydrocannabinol (delta 9-THC), cannabidiol (CBN), and cannabidiol (CBD) in maximal doses of 75 mg, 1200 mg, and 1200 mg, respectively, did not induce significant dose-related physiologic effects in experienced marijuana smokers. Delta 9-THC (75 mg) was, however, associated with bronchodilation, tachycardia, and peak highs less than that after delta 9-tetrahydrocannabinol (delta 9-THC). The combinations of CBN and CBD with low-dose delta 9-THC (5 mg) did not induce significant bronchodilation but did exert interactive effects on heart rate and “high.” A 20-day study of daily delta 9-THC (20 mg), CBN (600 mg), and CBD (1200 mg) did not indicate tolerance or reverse tolerance to any drug. We conclude that delta 9-THC and, to a lesser extent, delta 9-THC, have acute bronchodilator activity but that CBN, CBD, and their combinations do not provide effective bronchodilation. The daily use of delta 9-THC was not associated with clinical tolerance.
### DIAGNOSIS: BIPOLAR DISORDER

**Title**: Opposite relationships between cannabis use and neurocognitive functioning in bipolar disorder and schizophrenia.

**Author(s)**: Ringen PA, Vaskinn A, Sundet K, Engh JA, Jónsdóttir H, Simonsen C, Fríis S, Opjordsmoen S, Melle I, Andressen OA.


**Major outcome(s)**: In bipolar disorder subjects, cannabis use was associated with better neurocognitive function, but the opposite was the case for the schizophrenia subjects.

### Indication

- **Bipolar disorders**

### Medication

- **Cannabis**

### Route(s)

- **Inhalation**

### Dose(s)

### Duration (days)

### Participants

- 133 patients with bipolar disorder and 140 patients with sch

### Design

- **Survey**

### Type of publication

- **Medical journal**

### Address of author(s)

- Institute of Psychiatry, University of Oslo, N-0318 Oslo, Norway.

**BACKGROUND**: Cannabis use is associated with altered neurocognitive functioning in severe mental disorders, but data are still inconclusive and there are no studies of bipolar disorder. The aim of this study was to investigate the association between cannabis use and neurocognition in bipolar disorder compared with schizophrenia in a naturalistic setting. Methods: Total of 133 patients with bipolar disorder and 140 patients with schizophrenia underwent neuropsychological assessments and clinical characterization including measures of substance use. Relationships between cannabis users and neurocognitive function were explored in the two diagnostic groups. Possible interactions between diagnosis and cannabis use were investigated, and findings were controlled for possible confounders. Results: In bipolar disorder subjects, cannabis use was associated with better neurocognitive function, but the opposite was the case for the schizophrenia subjects. There was a statistically significant interaction effect of diagnosis and cannabis use on focused attention (p=0.019), executive functioning (verbal fluency - set shifting) (p=0.003), logical memory-learning (p=0.007) and on logical memory-recall (p=0.004). These differences in neurocognitive function could not be explained by putative confounders. Conclusions: The findings suggest that cannabis use may be related to improved neurocognition in bipolar disorder and compromised cognition in schizophrenia. The results need to be replicated in independent samples, and may suggest different underlying disease mechanisms in the two disorders.
DIAGNOSIS: APPETITE/WEIGHT LOSS CANCER

<table>
<thead>
<tr>
<th>Title</th>
<th>Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Brisbois TD, de Kock IH, Watanabe SM, Mirhosseini M, Lamoureux DC, Chazen M, Macdonald N, Baracos VE, Wismer WV.</td>
</tr>
<tr>
<td>Journal, Volume, Issue</td>
<td>Ann Oncol. 2011 Sep;22(9):2086-93</td>
</tr>
<tr>
<td>Major outcome(s)</td>
<td>THC improved taste and appetite</td>
</tr>
</tbody>
</table>

**Indication**: Appetite loss/weight loss, Cancer

**Medication**: Delta-9-THC

**Route(s)**: Oral

**Dose(s)**: 2x2.5 mg

**Duration (days)**: 18

**Participants**: 48 advanced cancer patients

**Design**: Controlled study

**Type of publication**: Medical journal

**Address of author(s)**: Department of Agricultural, Food & Nutritional Science, University of Alberta, Canada

BACKGROUND: A pilot study (NCT00316563) to determine if delta-9-tetrahydrocannabinol (THC) can improve taste and smell (chemosensory) perception as well as appetite, caloric intake, and quality of life (QOL) for cancer patients with chemosensory alterations. PATIENTS AND METHODS: Adult advanced cancer patients, with poor appetite and chemosensory alterations, were recruited from two sites and randomized in a double-blinded manner to receive either THC (2.5 mg; Marinol®; Solvay Pharma Inc., n = 24) or placebo oral capsules (n = 22) twice daily for 18 days. Twenty-one patients completed the trial. At baseline and posttreatment, patients completed a panel of patient-reported outcomes: Taste and Smell Survey, 3-day food record, appetite and macronutrient preference assessments, QOL questionnaire, and an interview. RESULTS: THC and placebo groups were comparable at baseline. Compared with placebo, THC-treated patients reported improved (P = 0.028) and enhanced (P < 0.001) chemosensory perception and food ‘tasted better’ (P = 0.04). Premal taste (P = 0.05) and proportion of calories consumed as protein increased compared with placebo (P = 0.008). THC-treated patients reported increased quality of sleep (P = 0.025) and relaxation (P = 0.045); QOL scores and total caloric intake were improved in both THC and placebo groups. CONCLUSIONS: THC may be useful in the palliation of chemosensory alterations and to improve food enjoyment for cancer patients.
### DIAGNOSIS: NAUSEA/VOMITING CANCER

An efficient new cannabinoid antiemetic in pediatric oncology.

<table>
<thead>
<tr>
<th>Title</th>
<th>An efficient new cannabinoid antiemetic in pediatric oncology.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Abrahamov A, Abrahamov A, Mechoulam R</td>
</tr>
<tr>
<td>Major outcome(s)</td>
<td>complete prevention of emesis</td>
</tr>
</tbody>
</table>

- **Indication**: Cancer chemotherapy; Nausea/Vomiting
- **Medication**: Delta-9-THC
- **Route(s)**: Oral
- **Dose(s)**: 4 x 18 mg/m2 every 6 hours
- **Duration (days)**: several days
- **Participants**: 8 children with cancer
- **Design**: Open study
- **Type of publication**: Department of Pediatrics, Shaare Zedek Hospital, Jerusalem, Israel

Delta-9-tetrahydrocannabinol (delta-9-THC), a cannabinoid with lower psychotropic potency than the main Cannabis constituent, delta-9-tetrahydrocannabinol (delta-9-THC), was administered (18 mg/m2 in edible oil, p.o.) to eight children, aged 3-13 years with various hematologic cancers, treated with different antineoplastic drugs for up to 8 months. The total number of treatments with delta-9-THC so far is 480. The THC treatment started two hours before each antineoplastic treatment and was continued every 6 hrs for 24 hours. Vomiting was completely prevented. The side effects observed were negligible.
DIAGNOSIS:  PAIN/CANCER

<table>
<thead>
<tr>
<th>Title</th>
<th>Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC/CBD Extract and THC Extract in Patients With Intractable Cancer-Related Pain.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Johnson JR., Borel-Auger II, Lassignol D, Banay-Meizeri D, Ports R, Fulton MT.</td>
</tr>
<tr>
<td>Major outcome(s)</td>
<td>A cannabis extract containing THC and CBD was superior in reducing pain than placebo</td>
</tr>
</tbody>
</table>

**Indication:** Cancer, Pain

**Medication:** Cannabis, Delta-9-THC

**Route(s):** Sublingual

**Dose(s):**

**Duration (days):** 14

**Participants:** 177 cancer patients with pain

**Design:** Controlled study

**Type of publication:** Medical journal

**Address of author(s):** Severn Hospice (J. R. J.), Shrewsbury, Shropshire, and St. Luke's Hospice (M. B.-N.), Tunchapel, Plymouth, United Kingdom, Association Hospitale De Brussels (D. L.), Centre des Tumeurs de FULB, Brussels, Belgium, Emergency Department (E.D.G.-M.), Hospital

**OBJECTIVES:** This study compared the efficacy of a tetrahydrocannabinol/cannabidiol (THC/CBD) extract, a nonopiod analgesic endocannabinoid system modulator, and a THC extract, with placebo, in relieving pain in patients with advanced cancer. **METHODS:** In total, 177 patients with cancer pain, who experienced inadequate analgesia despite chronic opioid dosage, entered a 2-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial. Patients were randomized to THC/CBD extract (n = 60), THC extract (n = 59), or placebo (n = 58). **RESULTS:** The primary analysis of change from baseline in mean pain Numerical Rating Scale (NRS) score was statistically significantly in favor of THC/CBD compared with placebo (improvement of -1.17 vs. -0.69), whereas the THC group showed a nonsignificant change (-1.01 vs. -0.69). Twice as many patients taking THC/CBD showed a reduction of more than 30% from baseline pain NRS score when compared with placebo (33 [43%] vs. 12 [21%]). The associated odds ratio was statistically significant, whereas the number of THC group responders was similar to placebo (12 [23%] vs. 12 [21%]) and did not reach statistical significance. There was no change from baseline in median dose of opioid background medication or mean number of doses of breakthrough medication across treatment groups. No significant group differences were found in the NRS sleep quality, nausea scores, or the pain control assessment. However, the results from the EUROpean Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire showed a worsening in nausea and vomiting with THC/CBD compared with placebo (P = 0.02), whereas THC had no difference (P = 1.0). Most drug-related adverse events were mild/moderate in severity. **CONCLUSION:** This study shows that THC/CBD extract is efficacious for relief of pain in patients with advanced cancer pain not fully relieved by strong opioids.
DIAGNOSIS: EPILEPSY

<table>
<thead>
<tr>
<th>Title</th>
<th>Marijuana: an effective antiepileptic treatment in partial epilepsy? A case report and review of the literature.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Mortari K, Dworetzky B, Devinsky O.</td>
</tr>
<tr>
<td>Major outcome(s)</td>
<td>Significant improvement of epilepsy with the use of cannabis</td>
</tr>
</tbody>
</table>

| Indication | Epilepsy |
| Medication | Cannabis |
| Route(s) | Inhalation |
| Dose(s) | |
| Duration (days) | |
| Participants | 1 patient with cerebral palsy and epilepsy |
| Design | Uncontrolled case report |
| Type of publication | Medical journal |
| Address of author(s) | Departments of Neurology, New York University School of Medicine, New York, NY. |

Although more data are needed, animal studies and clinical experience suggest that marijuana or its active constituents may have a place in the treatment of partial epilepsy. Here we present the case of a 46-year-old man with cerebral palsy and epilepsy who showed marked improvement with the use of marijuana. This case supports other anecdotal data suggesting that marijuana use may be a beneficial adjunctive treatment in some patients with epilepsy. Although challenging because of current federal regulations, further studies are needed to examine the role of marijuana in the treatment of this disorder.
DIAGNOSIS: GLAUCOMA

<table>
<thead>
<tr>
<th>Title</th>
<th>Dronabinol and retinal hemodynamics in humans.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Plange N, Arend KO, Kaup M, Doehmen B, Adams H, Hendricks S, Cordes A, Huth J, Sponsel WE, Remky A.</td>
</tr>
<tr>
<td>Major outcome(s)</td>
<td>THC reduced intraocular pressure and improved blood circulation in the retina.</td>
</tr>
</tbody>
</table>

**Indication**  Glaucoma

**Medication**  Delta-9-THC

**Route(s)**  Oral

**Dose(s)**  7.5 mg

**Duration (days)**  1

**Participants**  8 healthy subjects

**Design**  Open study

**Type of publication**  Medical journal

**Address of author(s)**  RWTH Aachen University, Department of Ophthalmology, Aachen, Germany.

PURPOSE: To investigate the effects of oral cannabinoids on retinal hemodynamics assessed by video fluorescein angiography in healthy subjects. DESIGN: Interventional study. METHODS: In a self-experiment, the cannabinoid dronabinol (delta-9-tetrahydrocannabinol [THC]) was administered orally to eight healthy medical doctors (7.5 mg Marinol; Unimed Pharmaceuticals, Chicago, Illinois, USA). At baseline and two hours after dronabinol intake, intrarocular pressure (ICP) was measured and retinal hemodynamics were assessed by fluorescein angiography. The retinal arteriovenous passage time was determined on the basis of dye dilution curves by means of digital image analysis in a masked fashion. RESULTS: Dronabinol resulted in a significant ICP reduction from 13.2 +/- 1.9 mm Hg to 11.9 +/- 2.0 mm Hg (P = .038). The retinal arteriovenous passage time decreased from 1.77 +/- 0.35 seconds to 1.67 +/- 0.31 seconds (P = .028). Systemic blood pressure and heart rate were not statistically significantly altered. CONCLUSIONS: Cannabinoids, already known for their ability to reduce ICP, may result in increased retinal hemodynamics. This may be beneficial in ocular circulatory disorders, including glaucoma.
**DIAGNOSIS:** MULTIPLE SCLEROSIS

<table>
<thead>
<tr>
<th>Title</th>
<th>Delta-9-THC in the treatment of spasticity associated with multiple sclerosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Ungerleider JT, Andyrsik T, Fairbanks L, Ellison GW, Myers LW</td>
</tr>
<tr>
<td>Major outcome(s)</td>
<td>significant subjective improvement in spasticity at doses of 7.5 mg and above; no objective improvement</td>
</tr>
</tbody>
</table>

| Indication | Multiple sclerosis; Spasticity |
| Medication | Delta-9-THC |
| Route(s) | Oral |
| Dose(s) | 2.5-15 mg once or twice daily |
| Duration (days) | 5 |
| Participants | 13 patients with multiple sclerosis |
| Design | Controlled study |
| Type of publication | |
| Address of author(s) | Department of Psychiatry, U.C. L.A. School of Medicine 90024, USA |

Marijuana is reported to decrease spasticity in patients with multiple sclerosis. This is a double blind, placebo controlled, crossover clinical trial of delta-9-THC in 13 subjects with clinical multiple sclerosis and spasticity. Subjects received escalating doses of THC in the range of 2.5-15 mg, five days of THC and five days of placebo in randomized order, divided by a two-day washout period. Subjective ratings of spasticity and side effects were completed and semi-quantitative neurological examinations were performed. At doses greater than 7.5 mg there was significant improvement in patient ratings of spasticity compared to placebo. These positive findings in a treatment failure population suggest a role for THC in the treatment of spasticity in multiple sclerosis.
DIAGNOSIS: PAIN

**Table:** Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic PAIN

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Frank B. Serpell MG, Hughes J. Matthews JD, Kapur D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major outcome(s)</td>
<td>Nabilone as effective as hydrocodeine in treating neuropathic PAIN</td>
</tr>
</tbody>
</table>

**Indication:** Pain

**Medication:** Nabilone

**Route(s):** Oral

**Dose(s):** 2 mg

**Duration (days):** 48

**Participants:** 96 patients with chronic neuropathic pain

**Design:** Controlled study

**Type of publication:** Medical Journal

**Address of author(s):** Pain Management Unit, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP. bernhard.frank@ncl.ac.uk

**EXECUTIVE:** To compare the analgesic efficacy and side effects of the synthetic cannabinoid nabilone with those of the weak opioid dihydrocodeine for chronic neuropathic PAIN. DESIGN: Randomised, double blind, crossover trial of 14 weeks' duration comparing dihydrocodeine and nabilone. SETTING: Outpatient units of three hospitals in the United Kingdom. PARTICIPANTS: 96 patients with chronic neuropathic PAIN, aged 23-84 years. MAIN OUTCOME MEASURES: The primary outcome was difference between nabilone and dihydrocodeine in PAIN, as measured by the mean visual analogue score computed over the last 2 weeks of each treatment period. Secondary outcomes were changes in mood, quality of life, sleep, and psychometric function. Side effects were measured by a questionnaire. INTERVENTION: Patients received a maximum daily dose of 240 mg dihydrocodeine or 2 mg nabilone at the end of each escalating treatment period of 6 weeks. Treatment periods were separated by a 2 week washout period. Results Mean baseline visual analogue score was 68.6 mm (range 28.4-95.2) on a 0-100 mm scale. 73 patients were included in the available case analysis and 64 patients in the per protocol analysis. The mean score was 6.0 mm lower for nabilone than for dihydrocodeine (95% confidence interval 1.4 to 10.5) in the available case analysis and 5.6 mm (10.3 to 0.8) in the per protocol analysis. Side effects were more frequent with nabilone. CONCLUSION: Dihydrocodeine provided better PAIN relief than the synthetic cannabinoid nabilone and had slightly fewer side effects, although no major adverse events occurred for either drug.
DOSAGE GUIDELINES

Despite its potent psychoactive effects, THC has low toxicity with likely LD50 value of 1 to 20,000 or 1 to 40,000. This would mean 20,000 to 40,000 fold of one cannabis cigarette dosage would have to be inhaled in a very short period of time to overdose – approximately 628kg of cannabis smoked in a 15 minute time period would produce a lethal dose.

Dosage should take into consideration a number of variables including delivery method, sensitivity of the patient and type of cannabis. Dosages are extremely individualized given these variables and should be self-titrated.

The following information is based on research, publications and expert opinion. Safety and effectiveness may not be thoroughly tested and proven. This information does not apply to all products. All labels should be read and dosages should be thoroughly researched in relation to specific patient and conditions prior to any healthcare provider beginning therapy. Prior to prescribing, current guidelines for dosage should be researched prior to beginning therapy as this information is rapidly developing.

Ages 18+

Amyotrophic Lateral Sclerosis: 10 milligrams THC orally daily for two weeks

Nausea/Vomiting/Chemotherapy: 5 milligrams of meter squared of Marinol by mouth 1-3 hours before chemotherapy, followed every 2-4 hours after chemotherapy for a total of 4-6 doses daily; Nabilone 2 milligram dose taken by mouth the night prior to chemotherapy, 1-3 hours before and after chemotherapy. 10 milligrams per meter squared of THC by mouth 2 hours before and 4, 8, 16 and 24 hours after. Cannabinoids injected into muscle over the course of 24 hours in the form of 0.5-1 milligrams of Levonatradol 3 times daily

Atopic Dermatitis: hemp seed oil taken by mouth for 20 weeks

Weight Loss/Appetite/Cancer: 2.5 milligrams of THC taken by mouth with or without one milligram of CBD for 6 weeks

Chronic Pain: Cannabinoids by mouth as THC, CBD, Nabilone, Dronabinol at doses of 2.5-20 milligrams for 25 days. Cannabis smoked at doses of 1-9.4% used for 6 hours to 14 days.

www.CPRTrainingFast.com
**Pain/Cancer:** 5-10 milligrams of THC by mouth daily; 2-8 milligrams Nabilone by mouth daily; 0.25-1 milligram by mouth daily for 4 weeks; Sativex sprayed in mouth up to 48 sprays daily for 1-2 weeks followed by 10-15 sprays daily; 8 being the maximum one-time dose or within a 3 hour period.

**Dementia:** 2.5 milligrams Dronabinol taken by mouth twice daily for 6 weeks

**Epilepsy:** 200-300 milligrams of CBD taken by mouth daily for up to 4.5 months

**Sleep Disorders:** 40-160 milligrams of CBD by mouth

**Multiple Sclerosis:** 2.5 milligrams of dronabinol by mouth daily, increasing to a maximum of 10 milligrams daily for three weeks. A dose of 15-30 milligrams of cannabis extract capsules has been taken by mouth in five-milligram increments, based on tolerance, for 14 days. Cannabis extracts, including Cannador®, have been taken by mouth for 2-4 weeks. Cannabis plant extracts containing 2.5-120 milligrams of a THC-CBD combination have been taken by mouth daily for 2-15 weeks. A mouth spray (Sativex®, containing 2.7 milligrams of THC and 2.5 milligrams of CBD) has been used at a dose of 2.5-120 milligrams in divided doses for up to eight weeks. Eight sprays within any three hours, up to 48 sprays in a 24-hour period, have been used. Sativex® has been sprayed into the mouth for 6-14 weeks.

**Rheumatoid Arthritis:** up to 6 sprays of Sativex® have been used once daily 30 minutes before bed for five weeks.

**Glaucoma:** single dose of five milligrams of THC has been placed under the tongue. A dose of 20-40 milligrams of CBD has been placed under the tongue as a single dose

**Interactions with Drugs**

Marijuana may increase the risk of bleeding when taken with drugs that increase the risk of bleeding. Some examples include aspirin, anti-coagulants (blood thinners) such as warfarin (Coumadin®) or heparin, anti-platelet drugs such as clopidogrel (Plavix®), and nonsteroidal anti-inflammatory drugs such as ibuprofen (Motrin®, Advil®) or naproxen (Naprosyn®, Aleve®).

Marijuana may affect blood sugar levels. Caution is advised when using medications that may also affect blood sugar. People taking drugs for diabetes by mouth or insulin should be monitored closely by a qualified healthcare professional, including a pharmacist. Medication adjustments may be necessary.

Marijuana may cause low blood pressure. Caution is advised in people taking drugs that lower blood pressure.

Marijuana may interfere with the way the body processes certain drugs using the liver's cytochrome P450 enzyme system. As a result, the levels of these drugs may be increased in the blood and may cause increased effects or potentially serious adverse reactions. People using any medications should check the package insert and speak with a qualified healthcare professional, including a pharmacist, about possible interactions.

www.CPRTrainingFast.com
Marijuana may increase the amount of drowsiness caused by some drugs. Examples include benzodiazepines such as lorazepam (Ativan®) or diazepam (Valium®), barbiturates such as phenobarbital, narcotics such as codeine, some antidepressants, and alcohol. Caution is advised while driving or operating machinery.

Marijuana may also interact with agents that may affect blood vessel width, agents that may affect the immune system, agents that may be toxic to the liver, agents that may improve breathing or treat lung disorders, agents that may increase appetite, agents that may treat heart disorders, agents that may treat nausea or vomiting, agents that may treat nervous system disorders, agents that may treat psychiatric disorders, agents that may treat retrovirus infections (HIV), agents that may treat skin disorders, agents that may treat stomach disorders, anabolic steroids, anticancer agents, antipyrine, antiseizure agents, bromo-dragonFLY, cannabinoid CB1 receptor antagonists, central nervous system depressants, cocaine, corticosteroids, dopamine antagonists, ecstasy, estrogens, fertility agents, hormonal agents, nicotine, nonsteroidal anti-inflammatory agents, opioid receptor antagonists, pain relievers, p-glycoprotein-regulated agents, prochlorperazine, sedatives, and synthetic cannabinoids.

**Interactions with Herbs and Dietary Supplements**

Marijuana may increase the risk of bleeding when taken with herbs and supplements that are believed to increase the risk of bleeding. Multiple cases of bleeding have been reported with the use of Ginkgo biloba, and fewer cases with garlic and saw palmetto. Numerous other agents may theoretically increase the risk of bleeding, although this has not been proven in most cases.

Marijuana may affect blood sugar levels. Caution is advised when using herbs or supplements that may also affect blood sugar. Blood sugar levels may require monitoring, and doses may need adjustment.

Marijuana may cause low blood pressure. Caution is advised in people taking herbs or supplements that lower blood pressure.

Marijuana may interfere with the way the body processes certain herbs or supplements using the liver's cytochrome P450 enzyme system. As a result, the levels of other herbs or supplements may become too high in the blood. It may also alter the effects that other herbs or supplements possibly have on the P450 system.

Marijuana may increase the amount of drowsiness caused by some herbs or supplements.

Marijuana may also interact with anabolic steroids, anticancer herbs and supplements, antioxidants, antiseizure herbs and supplements, barbiturates, benzodiazepines, central nervous system depressants, corticosteroids, dopamine antagonists, fertility herbs and supplements, herbs and supplements that may affect blood vessel width, herbs and supplements that may affect the immune system, herbs and supplements that may be toxic to the liver, herbs and supplements that may improve breathing or treat lung disorders, herbs and supplements that may increase appetite, herbs and supplements that may treat heart disorders, herbs and supplements that may treat nausea and vomiting, herbs and supplements that may treat nervous system disorders, herbs and supplements that may treat
psychiatric disorders, herbs and supplements that may treat retrovirus infections (HIV), herbs and supplements that may treat skin disorders, herbs and supplements that may treat stomach disorders, hormonal herbs and supplements, nicotine, nonsteroidal anti-inflammatories, opioid receptor antagonists, pain relievers, p-glycoprotein-regulated herbs and supplements, phytoestrogens, and synthetic cannabinoids.