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REVIEW

Targeting the endocannabinoid system: a predictive, preventive, and personalized medicine-directed approach to the management of brain pathologies

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Abstract

Cannabis-inspired medical products are garnering increasing attention from the scientific community, general public, and health policy makers. A plethora of scientific literature demonstrates intricate engagement of the endocannabinoid system with human immunology, psychology, developmental processes, neuronal plasticity, signal transduction, and metabolic regulation. Despite the therapeutic potential, the adverse psychoactive effects and historical stigma, cannabinoids have limited widespread clinical application. Therefore, it is plausible to weigh carefully the beneficial effects of cannabinoids against the potential adverse impacts for every individual. This is where the concept of "personalized medicine" as a promising approach for disease prediction and prevention may take into the account. The goal of this review is to provide an outline of the endocannabinoid system, including endocannabinoid metabolizing pathways, and will progress to a more in-depth discussion of the therapeutic interventions by endocannabinoids in various neurological disorders.

Keywords Endocannabinoid system · Anandamide · 2-Arachidonyl glycerol · Cannabinoid receptor · Neurological disorder · Traumatic brain injury · Alzheimer's disease · Parkinson's disease · Amyloid lateral sclerosis · Cancer · Pain · Epilepsy · Multiple sclerosis · Huntington's disease · Schizophrenia · Stroke · Anxiety · Depression · Multi-professional expertise · Therapeutic strategies · Health policy · Disease management · Predictive preventive personalized medicine (PPPM)

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Introduction

Cannabis sativa is an herbaceous plant widely recognized for its psychotropic activity and recreational abuse. Undoubtedly, the most recognized cannabis-derived molecule is delta-9-tetrahydrocannabinol (Δ^9-THC), which acts on the endocannabinoid system (ECS) and mediates the psychotropic effects of marijuana. Regardless of this activity, marijuana is being used for recreational purpose for centuries. In addition, anecdotal reports of medicinal value coupled with enormous interest from the public in natural medical products have sparked a keen interest in understanding the potential clinical utility of cannabis and targeted modulation of ECS. Indeed, oral formulations of cannabinoids (i.e., nabilone, dronabinol) having Δ^9-THC may be useful for the treatment of nausea and vomiting in cancer patients undergoing chemotherapy [1, 2]. Despite potential prophylactic and/or therapeutic functions, the historical stigma of cannabinoids limited the performance of randomized controlled clinical trials to demonstrate the utility of cannabis in alleviating human diseases.

Incidences of neurological disorders increase manifold globally with the rise in life expectancy. According to a systematic analysis, neurological disorders were leading in disability-adjusted life years (DALYs) with 276 million incidences and was second most cause of death at 9 million in 2016, whereas stroke (42.2%), migraine (16.3%), and Alzheimer's disease (AD) and other dementia (10.4) were highest contributors for DALYs [3, 4]. The DALYs and death counts due to neurological diseases increased by 15% and 39% respectively in between 1990 and 2016 [3]. According to WHO report, global DALYs and death for all combined neurological disorders could reach up to 6.77% and 12.22% respectively [5], and therefore, a close attention and action are needed from medical and scientific world to emphasize on therapeutic intervention of these diseases.

While dysregulation of the ECS is associated with detrimental outcomes in neurological injuries, targeted modulation of ECS remains an understudied approach to improve outcomes [6–16]. Of note, preclinical studies by our group and others found that selective activation of the non-psychoactive cannabinoid receptor 2 (CB2R) reduced neuropathology after a variety of neuropsychiatric and neurodegenerative diseases, including cerebral ischemia [11, 17, 18], traumatic brain injury (TBI) [15, 19], neuropathic pain [20], stroke [11], neurodegenerative disease [21–23], depression [24], anxiety [25], schizophrenia-like behaviors [26], and drug addiction [27–29]. The goal of this review is to describe the functions of the ECS with respect to neurological function, including potential utility in neurological impairments. With this understanding, the medical community can use an evidence-based approach to inform public policy regarding the consumption of cannabis products as therapeutics to improve brain health.

ECS: understanding components and their functions in health

ECS is an endogenous regulatory system comprised of ligands (endocannabinoids), cannabinoid receptors (CBRs), and endocannabinoid synthesizing/degrading enzymes (Fig. 1). In the following sections, we discuss the different roles and physiological functions of ECS and how dysfunction within the ECS may result in neuropathology.

Endogenous cannabinoids: ligands, metabolism, and receptors

Endocannabinoids and their synthesis

Endocannabinoids are arachidonate-based lipids (eicosanoids), such as anandamide (*N*-arachidonoylethanolamide, AEA) and 2-arachidonoylglycerol (2-AG), which are endogenous ligands to the cannabinoid receptors (CB1R and CB2R) [30, 31]. Both ligands AEA and 2-AG act as neurotransmitters affecting behavior in a manner different to that of THC [32], which is an exogenously derived cannabinoid and often has multiple side effects [33]. Both endogenous ligands are originated from arachidonic acid, as needed, to meet the physiological requirements of the body on a situational basis [34]. AEA synthesis involves multiple paths involving different phospholipases. AEA synthesis generally begins with *N*-arachidonoyl phosphatidyl ethanol (NAPE) as its starting material. NAPE is hydrolyzed primarily by NAPE-phospholipase D (NAPE-PLD) into products which subsequently form AEA [35–37]. 2-AG synthesis generally involves sequential hydrolysis of an arachidonoyl-containing phosphatidylinositol 4,5-bisphosphate (PIP2) by a phospholipase C-beta (PLC-β) [38, 39] to form diacylglycerol, which is then hydrolyzed by diacylglycerol lipase (DAGL) to form 2-AG [40]. While both endocannabinoids, AEA and 2-AG, bind to CBRs, they exhibit different responses, efficacy, and specificities. In general AEA, which has a moderate affinity to both CBRs, is activated in response to CNS stress and act as a response to pain in peripheral nervous system (PNS) [33, 41–43]. In contrast, 2-AG which is formed as an intermediate in several lipid metabolism pathway, is more abundant than AEA and thus, has high efficacy at both CBRs [33, 42–47].

Endocannabinoid metabolism

The enzyme fatty acid amino hydrolase (FAAH) degrades all fatty acid amides, including AEA [48]. In addition, cyclooxygenase-2 (COX-2) enzymatically degrades AEA to generate prostamides [49–51]. 2-AG, the most abundant endocannabinoid within the CNS, is primarily metabolized by three hydrolytic enzymes: monoacylglycerol lipase (MAGL) and alpha/beta domain hydrolases 6 and 12 (ABHD6 and 12) [51, 52]. Beyond this, 2-AG may additionally be degraded by COX-2 and FAAH enzymes [53]. Degradation by COX-2 occurs in neural tissue and results in the production of prostaglandin E_2 (PGE_2), an excitatory oxidative metabolite also found to be involved with synaptic transmission and plasticity [32]. 2-AG can also serve as an intermediate for lipid synthesis by acting as a source of arachidonic acid during prostaglandin synthesis [54].

Cannabinoid receptors

There are two primary cannabinoid receptors—CB1R and CB2R—which bind with different endogenous or exogenous cannabinoids to mediate the downstream effects. Both receptors share 44% homology in amino acid sequence [55] and act as Gi/o-linked G protein-coupled receptors (GPCRs). Both receptors can inhibit adenylyl cyclase and can activate mitogen-activated protein kinase (MAPK) [56, 57]. However, CB1Rs may also inhibit N

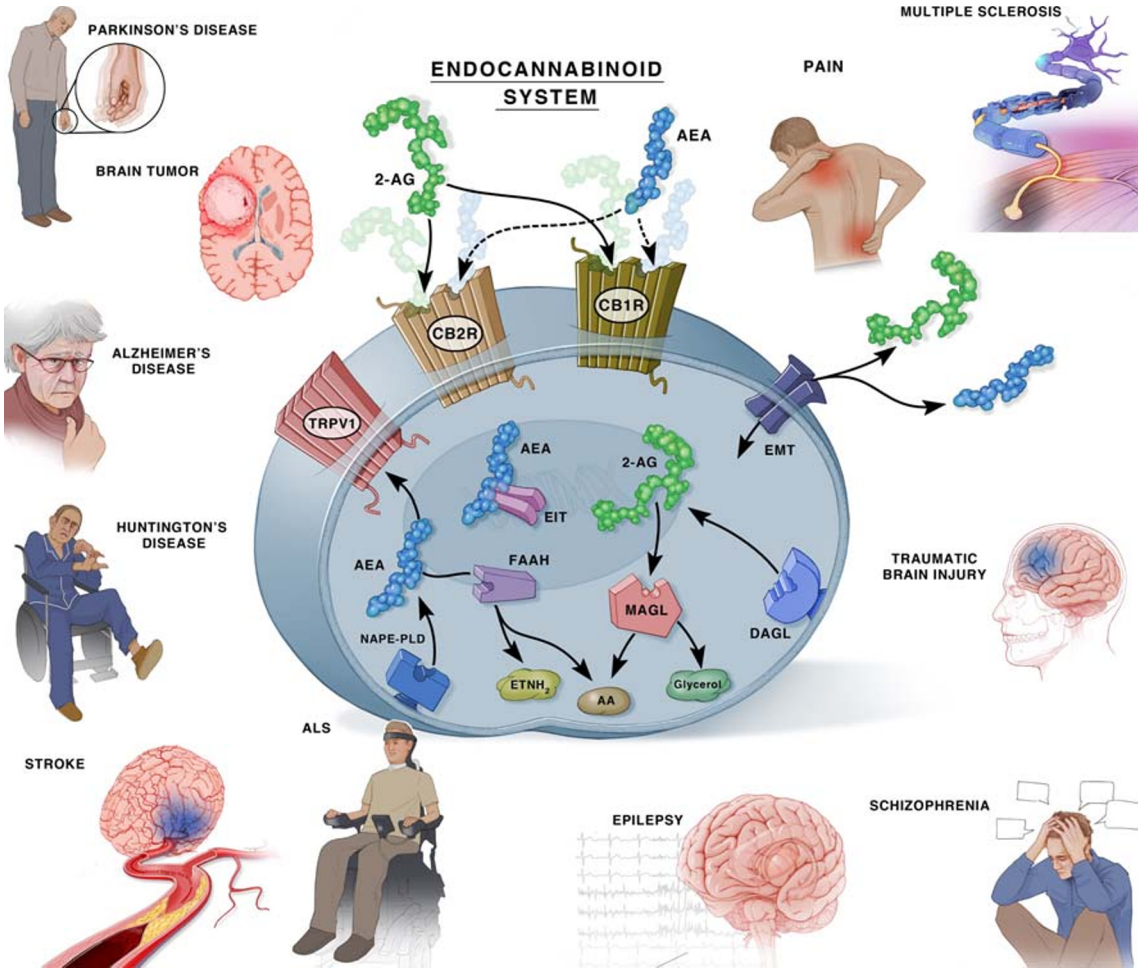

Fig. 1 The endocannabinoid system in normal cellular homeostasis and its dysregulation in different neuropathologies. Schematic diagram shows ECS and its different components in normal cellular physiology. The dysregulated ECS as result of injury or pathologies to brain, becomes inefficient to maintain cellular homeostasis, and exaggerates the progression of different neurological disorders

or P/Q-type calcium channels and may activate inwardly correcting potassium channels [58, 59]. Although both these receptors possess similar binding pattern for cannabinoids [55], they acquire different functional roles (Table 1). CB1R is psychoactive whereas CB2R is thought to lose this effect.

CB1Rs are found predominantly in the CNS on presynaptic axon terminals and stomata [60]. In particular, CB1Rs are expressed heavily in cortical association areas and the direct nigrostriatal pathway but less in the primary somatosensory cortex. Subcortically, CB1Rs are localized in the amygdala [61, 62], basal ganglia [63], hippocampus [64, 65], and cerebellum [66]. CB2R has lower expression in CNS, but is more involved with peripheral immune cells [67], including lymphocytes, followed by natural killer (NK) cells, monocytes, neutrophils, and T helper cells [68]. Consistent with higher expression on immune cells, CB2R is predominant found on microglia within the CNS, with lesser expression noted in CNS vascular elements [69, 70]. High expression of CB2R mRNA was also observed in ventral tegmental area (VTA), specially on dopaminergic neurons [71], with reports showing most neuronal CB2R localization post-synaptically on the cell body [64, 71]. In contrast to the constitutive expression of CB1R, CB2Rs are strongly induced following trauma or pathology [15, 63], making this a potentially interesting target for disease/injury mitigation. This inducible activity has also be correlated with neuropathic pain [20], stroke [11], traumatic brain injury [19], neurodegenerative disease [21–23], depression [24], anxiety [25], schizophrenia-like behaviors [26], and drug addiction [27–29].

Besides classical CBRs, non-cannabinoid receptors also may be involved with the ECS. For instance, transient receptor potential (TRP) channels may also be influenced by cannabinoids in the context of peripheral pain and temperature sensation [72]. Of the TRP receptors, TRPV1 has garnished the most attraction given its inducibility and

Table 1 Comparison between cannabinoid receptors CB1R and CB2R. CB1R and CB2R are two main cannabinoid receptors that share similar ligand binding pattern and has 44% homology in amino acid sequence in whole protein and 68% homology in transmembrane domain [55, 57]. However, both receptors act as Gi/o-linked GPCRs [56, 57, 479, 480] and are functionally quite different as highlighted in the given table

Properties	Cannabinoid receptor 1 (CB1R)	Cannabinoid receptor 2 (CB2R)
History	a. First discovered from rat brain P2 membrane and synaptosomes in 1988 [55, 481] b. Cloned for the first time from rat cerebral cortex cDNA library [55, 56] c. Located on chromosome 6q14-15 [55, 482]	a. First discovered and cloned from human promyelocytic leukemia cell HL60 cDNA [55, 57] b. Located at chromosome 1p36 [55]
Localization	a. Mainly in the CNS, abundant in basal ganglia, cerebellum, cortex, and hippocampus [55, 483, 484] b. Also, present in the pituitary, thyroid, gonads, upper airways, adrenal, liver, and uterus [483, 484] c. Predominantly on presynaptic neurons [483, 484]	a. Mainly on immune cells and keratinocytes [483, 484] b. CB2R coexists with CB1R in the retina, heart, pancreas, stomach, bone, digestive tract, and CNS (microglia and astrocytes) in certain conditions [55, 483–487] c. Predominantly on glia cells and postsynaptic neurons [483–486]
Ligands	a. Shows a strict requirement for pentyl or longer alkyl tails in ligands [483, 484] b. AEA has high affinity for CB1R [Ki = 89 nM] with EC_{50} = 31 nM [338, 488–491] c. 2-AG is full agonist to CB1R, with lower affinity [Ki = 472 nM] than AEA and with EC_{50} = 519 nM [338, 492–496] d. Binds with THC [Ki = 41 nM] [338]	a. CB2R recognizes classical cannabinoids with shorter alkyl chains—dimethylpropyl or dimethylethyl [497, 498] b. AEA has comparatively lower affinity for CB2R than CB1R [Ki = 371 nM; EC_{50} = 27 nM] [338, 488–492, 494, 496, 499] c. 2-AG acts as a full agonist to CB2R [Ki=1400 nM] and has EC_{50}=618 nM) [42, 338, 492, 494, 496, 500, 501] d. Binds with THC [Ki = 36 nM] [338] and with mildly psychoactive component cannabinol (CBN) [483, 484]
Functions	a. Has psychoactive property [483, 484] b. Stimulates dopaminergic reward pathway [502] c. Motivates to eat, smoke or intake of drugs [502] d. Required for synaptic transmission [483, 484] e. CB1R signaling includes [58, 499, 503]: • Inhibition of forskolin-stimulated adenylyl cyclase • Inhibition of N-, P-, and Q-type calcium channels • Activation of inwardly rectifying potassium channels f. Plays an essential role in: • Fine-tuned motor control [504–506] • Central and peripheral regulation of food intake [504–506] • Fat accumulation [504–506] • Lipid and glucose metabolism [504–506]	a. Has immunological property [483, 484] • Regulates leukocytes adhesion and rolling on endothelium [70, 507–510] • Activation of CB2R improves microvascular circulation and protects BBB [70, 507–509, 511] • Regulates T cell differentiation [512, 513] • Inhibits melanoma cell transendothelial migration [514] b. CB2R may contribute to neuronal plasticity in mouse hippocampal CA3 and CA2 pyramidal neurons [64] c. CB2R signaling includes: • Phosphoinositide 3-kinase pathways [515] • Activation of de novo ceramide production or cyclooxygenase-2 (COX-2) induction [516]

affiliation with immune cells. Peroxisome proliferator-activated receptors (PPAR-α and PPAR-γ) also may be influenced by cannabinoid action to regulate gene transcription/regulation [73].

Physiological functions

ECS is a complex system that is intricately involved with human immunology, psychology, developmental process, neural plasticity, signal transduction, and metabolic regulation. With interplay into so many physiological components, understanding ECS and its implication in CNS homeostasis is critical to explore the therapeutic potential in various neurological diseases.

Neural transmission and synaptic regulation

Metabotropic suppression of inhibition/excitation (MSI/MSE) is also known as "synaptically evoked suppression of inhibition or excitation" or "endocannabinoid-mediated short-term depression" [32]. MSI/MSE is activated by the postsynaptic activation of Gq/11-linked GPCR which then activates PLC-beta to create diacylglycerol (DAG). This DAG gets deacetylated by diacylglycerol lipase (DAGL) to synthesize 2-AG which then diffuses presynaptically to CB1Rs and suppresses synaptic transmission [74]. This suppression is mediated by various GPCRs linked to Gq/11 including metabotropic glutamate receptor 1 (mGluR1) and 5 (mGluR5), M1 and M3 muscarinic receptor, orexin-A receptor, cholecystokinin A receptor, and $alpha_1$-adrenergic receptor [75].

Endocannabinoid-mediated long-term depression (eLTD) is the final mode of retrograde suppression and exhibits a long-lasting inhibition through multiple mechanisms primarily through endocannabinoid-induced homo-/heterosynaptic transmission. Homosynaptic eLTD is much more prominent at the glutamatergic synapse of ventral and dorsal striatum [76, 77]. In contrast, heterosynaptic eLTD affects adjacent synapses to the one being stimulated. Both types of eLTD work in various capacities throughout CNS including hippocampal inhibitory synapses via adenylyl cyclase inhibition as well as cortical circuit maturation [78–80]. There is research indicating that by removing inhibition of eLTD, inhibitory synapses could increase dendritic excitability, thus potentiating excitatory transmission over a narrow spatial domain [81]. Finally, an autonomous self-inhibition exists as 2-AG can directly suppress neuronal excitability especially during intense neuron stimulation, which activates somatic CB1Rs and somatic potassium conductance via an inward rectifying K channel [82–84].

The two cannabinoid receptors converge on some functions but are divergent in others due to a variety of ligand diversification. CB1R is localized on presynaptic neurons, modulates neurotransmission, and plays a role in neuronal excitability by suppressing exogenous or endogenous cannabinoid binding [60]. Its activation decreases presynaptic GABA release, eliminates GABAergic inhibitory control of postsynaptic neurons, and excites postsynaptic neurons through disinhibition [85, 86]. CB2R, on the other hand, is described as a "modulatory volume transmitter" which can gradually control the strength of nociception. In the CNS, CB2Rs have lower expression levels than CB1Rs which can explain their inability to respond to cannabinoids under physiologic conditions [69, 70]. CB2Rs, however, are expressed abundantly in neuronal post-synaptic somatodendritic region, suggesting an opposing effect from CB1Rs [66, 87]. Activation of these receptors reduces VTA-DA neuron firing and excitability which may aid in neuroprotection by hyperpolarizing membrane potential and inhibits postsynaptic neuronal function [32]. Thus, the ECS plays vital role in both short-term and long-term synaptic plasticity [88–93].

Immune regulation

The release of endocannabinoids within the injured CNS enhances endogenous neuroprotection via undefined mechanisms [70, 94–96]. We reported upregulated CB2R expression on myeloid cells with unaltered cerebral CB1R mRNA expression within days of experimental TBI [15]. Functionally, we and others showed that selective activation of CB2R reduced inflammation, attenuated edema, limited disruption of the BBB, improved cerebral perfusion, and enhanced behavioral outcomes post-TBI [15, 70]. Moreover, CB2R activation is associated with anti-inflammatory effects in preclinical models for atherosclerosis [97], multiple sclerosis [98], Alzheimer's disease [99], and arthritis [100]. Interestingly, early treatment with CB2R agonist AM1241 suppressed microglial activation in stroke rats, while the same agonist did not show any significant effect when administered in delayed manner [11].

Administration of the selective CB2R agonist, JWH133, shifted macrophages from a pro-inflammatory (M1) state into an anti-inflammatory (M2) state after acute liver failure, via a mechanism postulated to involve negative regulation of TLR4 [101]. Inhibition of TLR4 mitigates hypoperfusion-induced cognitive dysfunction and protects the BBB and white matter by reducing autophagy and inflammation [102–106]. Interestingly, pharmacological inhibition of MAGL, a principal 2-AG metabolizing enzyme, reduced macrophage infiltration during liver fibrosis [107]. Further, expression of macrophage MAGL inhibits tumor progression by promoting $CD8^+$ T cell-mediated inflammation, while MAGL deficiency promoted CB2R/TLR4-dependent macrophage activation and suppression of inflammation [108]. CNS accumulation of infiltrating macrophages and T_H cells were associated with parenchymal inflammation and neurodegeneration after experimental TBI or in resected brain tissue from TBI patients [109, 110]. Whereas the T_H1/T_H2 ratio remained unchanged in pediatric TBI patients [111], T_H17 cells were increased after comorbid post-traumatic stress disorder with mild TBI in rats [112–114], suggesting a role for T_H polarization in chronic neurological injury. CB2R agonist, GP1a, significantly reduced macrophage infiltration in the acute period after insult and protected CBF by polarizing macrophages into M2 (anti-inflammatory) phenotypes [15]. Further, CB2R agonists, β-caryophyllene, and COR167 were able to inhibit demyelination through modulating T cells [115, 116]. Although CB2R is highly recognized as anti-inflammatory receptor on immune cells, the role of other components in immune regulation cannot be ignored, and therefore, studies specifically focused on different components of ECS should be encouraged.

ECS and neurological diseases

The association of the ECS in different physiological processes, such as synaptic plasticity and neuronal transmission, advances the probability of its role in neurological recovery [11–16, 117]. Indeed, promising results have demonstrated that modulation of the ECS attenuates key features of neurological injury, including neurodegeneration, excitotoxicity, and immunomodulation [118]. Along these lines, activation of CB1R decreased neuronal excitotoxicity, whereas CB2R activation limited post-ischemic [17] and post-traumatic inflammation [15]. Thus, cannabis has the potential to influence injury progression involved in neurodegeneration and neurological recovery. In the following subsections, we discuss the

evidence supporting a potential role for cannabinoids in a variety neurological disorders.

Traumatic brain injury: modulation of ECS improves recovery post TBI

Traumatic brain injury (TBI) is described as occurring in a series of two separate events [118]. The first insult consists of a purely mechanical trauma, resulting in cell death and axonal injury through vascular damage and edematous pressure. The secondary injury follows the mechanical damage and activates apoptotic pathways within surrounding neural tissues through the release of glutamate-mediated excitotoxicity and Ca^{2+} influx [119, 120]. Such secondary damage also involves cerebrovascular derangements and immunologic activation. This twofold positive cycle consisting of both mechanical and self-regulated cellular components complicates the clinical management of TBI [121].

Reduced CB1R expression negatively correlated with edema formation and behavioral impairments while increased, post-traumatic expression of CB2R was associated with higher neurological deficits after experimental TBI in rodents [19]. In line with these data, an increased ratio of CB2R density was observed in a porcine pediatric fluid percussion injury model of TBI [122]. Functionally, mice exposed to CB2R agonists, or CB1R antagonists, or inhibitors of cannabinoid degradation demonstrated a reduction in neurodegeneration [123]. In addition, CB2R agonists reduced lymphocyte rolling and adhesion, which can ameliorate lesion size and improve motor function [124]. Interestingly, repeated stress-induced loss of CB2R deprived improvement post TBI in females, while high basal level of CBR expressions in young naive females protected against TBI [125], suggesting a possible role for the ECS in modifying TBI outcomes.

Endocannabinoids 2-AG and AEA seem to play a major role in the neuromodulation after TBI. A transient increase in 2-AG at the injured site was observed and was thought to serve as a protective factor, while inhibition of this protective effect by SR-141716A, a CB1R antagonist, showed increasingly detrimental outcomes post TBI [126]. Further, exogenous 2-AG administration reduced edema, inhibited transactivation of the nuclear factor NF-kB, protected BBB, and reduced pro-inflammatory cytokine mRNA (Il-1β, TNFα, and IL-6) [127–129]. However, deletion of CB1R eliminated these effects, suggesting that CB1R receptors mediated the protective effects of exogenous 2-AG [128]. While direct effects of AEA or 2-AG on traumatic brain are not entirely explored, inhibition of specific metabolizing enzymes (e.g., FAAH, MAGL, and ABHD6) have shown promise in modulating cellular and molecular hallmarks of TBI pathology, such as cell death, excitotoxicity, inflammation, cerebrovascular breakdown, and cell death [12, 130–135], and improved functional outcomes [118]. JZL184, an inhibition of MAGL, a primary metabolizing enzyme for 2-AG, showed improved neurological recovery and reduced astrocytosis, synaptic hyperexcitability, and glutamate dyshomeostasis up to 2 weeks after mild TBI in rats [130]. The protein aggregates such as amyloid-β plaques [136], p-tau [137], and TDP-43 [138], found to be accumulated in traumatic brain within hour after axonal damage [136], were reduced by treating with MAGL inhibitors [12]. Further, inhibition of MAGL after repetitive mild closed TBI reduced inflammation, Aβ plaque formation, and tau phosphorylation, while improving synaptic transmission, recovering spatial memory, and preventing chronic traumatic encephalopathy (CTE) [12, 135]. Thus, inhibition of MAGL protected against TBI-induced microglial activation [12, 133], whereas inhibition of ABHD6 promoted microglia/macrophage shift from a pro-inflammatory M1 to an anti-inflammatory M2 phenotype possibly via upregulation of CBRs and inhibition of iNOS and COX-2 [131]. In addition, inhibition of FAAH restored the level of AEA [132], prevented microglial activation and BBB disintegration [133], activated CB2R receptors [139], and minimized COX-2 and iNOS activities [134]. Inhibition of FAAH further increased synaptophysin [134], a synaptic vesicle protein whose elimination impairs object recognition and spatial learning in mice [140], and prevented amyloid precursor protein and phosphorylation of tau protein [132]. While the mechanism of protection of BBB by ECS is not known completely, AEA decreased BBB permeability via TRPV1 in ischemic stroke [141]. Given that activation of TRPV1 receptors disrupts BBB integrity [142], it is possible that AEA, as a partial agonist at TRPV1 channels [143], maybe be acting as a functional antagonist against a high efficacy endogenous ligand.

Interestingly, cannabinoids are also shown to improve effect of exogenous drugs against traumatic injury. For example, modulation of CB2R by SMM-189 or raloxifene, a FDA-approved estrogen receptor-targeting drug reduced blast-induced visual impairment and retinal pathology post TBI [144, 145]. Similarly, leptin, a hormone that regulates energy balance, showed its neuroprotective effect against TBI via modulation of CB2R which was attenuated in presence of CB2R antagonist AM630 [146]. In addition, protective effect of minocycline after TBI was abolished by treatment with CB1R or CB2R antagonists (AM251 or AM630, respectively) [147]. Estradiol decreased the number of TBI-induced immunoreactive astrocytes, which was inhibited by CB1R/CB2R antagonists, while also increasing cerebral cortex mRNA levels of CB2Rs [148]. Thus, it can be claimed that eCB receptors in response to TBI may exert effect via endocrine as well as paracrine signaling mechanisms.

Use of marijuana either alone or with other drugs is common among TBI (single or multiple impact) patients that may affect the existing mental health and may lead to higher mortality [149, 150]. An observational study in Colorado revealed

three common reasons of cannabis use—recreational (72%), to reduce stress/anxiety (62%), and to improve sleep (55%) among TBI victims [151]. One of the very interesting results published by Nguyen et al. investigated the relation between THC consumption and mortality after TBI [152]. Out of 446 patients included in study, 82 patients (18.4%) were found THC(+) and showed decreased mortality (2.4%; 2 deaths) in comparison to 42 deaths (11.5%) in THC(−) screened group [152].

A recent study with 307 acute concussion patients with average age 33.7 years did not observe significant impact on recovery by continuous use of cannabis, cigarette, and alcohol within 4 weeks of injury. However, use of cannabis was found to be associated with lower severity than the other two [153]. Most of the time patients are indulged in cannabis use post-injury, unaware of its proven benefits or multiple effects [151, 154]. Moreover, cannabis abuse may cause neurological stress and enhance risk of psychosis in adolescent patients and may outweigh its potential therapeutic benefits [155]. However, there is paucity of extensive data on efficacy and efficiency of natural cannabinoids in TBI, and therefore, more extensive studies on cannabis use in TBI and a strict guideline for use of cannabis and patient management must be incorporated clinically to avoid unwanted effects of cannabis abuse.

Stroke: cannabinoids reduce infarct volume

Stroke is one of the debilitating pathologies and has 13–35% of first month case-fatality rate [156]. The percentage of young population receiving stroke is alarmingly increasing and involves many factors such as genetic predisposition, alcohol consumption, sedentary lifestyle, and hypertension. Polivka et al. identified two less explored factors—primary vascular dysregulation and Flammer syndrome (FS)-associated symptoms in the disposition of young age stroke [156]. Therefore, innovative screening programs, targeted risk-mitigating measures, and exploration of new treatment options emerge as new therapeutic strategies for treatment of stroke.

Ischemic stroke has been reported to alter ECS in both clinical and preclinical conditions, indicating an important role of this system in normal blood circulation [17]. A recent meta-analysis by England and colleagues revealed that all subclasses of cannabinoids, cannabis-derived, synthetic and specific CB1R, and CB2R agonists significantly reduced infarct volume in transient/permanent ischemia and improve both early and late functional outcomes in experimental stroke [157]. Further, a selective and potent CB1R/CB2R agonist TAK-937 reduced infarct volume and improved functional outcomes in middle cerebral artery occluded (MCAO) rats, while minimizing infarct volume and S100β release in CSF following middle cerebral artery occlusion in non-human primates [158]. Similarly, administration of CB1R agonist HU-210 significantly reduced motor disability and infarct volume via hypothermia in a dose-dependent manner and was useful 4 h after stroke onset [159]. CB2R agonist JWH133 promoted neuroblast migration into lesioned tissue to encourage neurogenesis [160]. Interestingly, early treatment with CB2R agonist AM1241 suppressed microglial activation in stroke rats, while delayed treatment did not show any significant effect [11]. Further, exogenous AEA and 2-AG in combination reduced infarct size in focal ischemic rats, but could not facilitate effects alone [161]. AEA has been reported to protect BBB permeability in ischemic stroke, possibly through TRPV1 [141]. Given that activation of TRPV1 receptors disrupts BBB integrity [142], it is possible that AEA, being partial agonist to TRPV1 channels [143], may be acting as a functional antagonist in presence of stroke-induced endogenous agonist.

Phytocannabinoid CBD reduced the ischemia-induced gliosis, neuronal loss, and excitotoxicity to protect behavioral functions in neonatal MCAO rats [162]. Moreover, CBD reduced brain edema and BBB permeability associated with ischemic condition [163] and was also effective in diabetes-related atherosclerosis [164]. In mouse and piglet models of stroke, CBD improved cerebral blood flow [165, 166]. CBD protected cerebral hemodynamic and produced beneficial cardiac effects in stressful conditions, but not in normal condition [167, 168]. CBD showed trends to infarct reduction with administration of less than 6 h after stroke onset [157] and showed functional improvements even at the later time point [169]. Multiple targets have been reported to mediate the neuroprotective effects of CBD such as a combination of a potent antioxidant, immunosuppression, and anti-inflammatory actions [170]. However, CBD has negligible activity on CBRs, but may interfere with the ECS via non-cannabinoid receptors such as 5-hydroxytryptamine 1A receptors, adenosine receptors, TRPV1, and nuclear receptors of the peroxisome proliferator-activated receptor family [170]. Another component of cannabis, THC also showed trends to infarct reduction with administration of less than 4 h [157]. However, THC inhibits voltage-dependent calcium channels via CB1R and, thus, reduces excessive glutamate release, hypothermia, and loss of CBF [171, 172]. Further, THC, when acting on the CB2R on immune cells, was found to decrease the severity of stroke. Low oral doses of THC modulated myeloid and lymphoid cells to improve ischemia in atherosclerosis model [173].

Although numerous studies have evaluated cannabinoids and ECS in experimental stroke, reports are somewhat conflicting and thus start a debate on role of cannabinoids in stroke. A meta-study on 98 stroke patients having mean age 32.7 ± 12 years were identified as chronic cannabis users and thus indicated a correlation between cannabis consumption and incidence of stroke [174]. Additionally, pre-ischemic administration of 2-AG enlarged infarct volume and reduced CBF via platelet aggregation [175–177]. A possible

explanation of this event occurred through an increase in downstream product arachidonic acid stimulated by increase in 2-AG [176, 177], as inhibition of COXs prevented platelet aggregation in the presence of 2-AG [175]. Further, platelet-dependent disease progression were not mediated via CB1R or CB2R, but through MAGL [176, 177]. On contrary, a recent systematic review reported neuroprotective effects of cannabis from a variety of methodologies to use of cannabinoids [157]. Since cannabinoids have shown excellent tolerability and beneficial effects in ischemic stroke, they may be capable candidates for therapeutic intervention in future. However, a cautious approach and model are needed as there is scarcity of clinical trials related to cannabinoids and stroke. The model of centralized stroke care as successfully run by the Czech Republic [178] may be a preferable model to adopt in this case. This model system meets the criteria for predictive, preventive, and personalized medicine (PPPM) and will ensure ideal prevention, diagnosis, and treatment of possible complications and prediction of outcomes with cannabinoid therapy [178].

Huntington's disease: phytocannabinoids attenuate the symptoms of HD

Huntington disease (HD) is an autosomal dominant disorder, characterized by debilitating changes of mood, cognition, and movement control. It stems from an expansion of the CAG trinucleotide repeat found in chromosome 4, which leads to a decrease in GABA and acetylcholine-producing neurons of the basal ganglia [179]. Subsequent atrophy of the caudate nucleus and increase in dopamine production results in the characteristic findings described above. As there currently exists no cure for this disease, current investigations are attempting to more fully understand the disease process and invent potential therapeutic targets.

Recent studies have found that both CB1R and CB2R play vital roles in the progression of this disease [180–188]. Interestingly, the loss of CB1R from the GABAergic neurons is found to be an early sign of HD as well as a significant degeneration of receptors in globus pallidus externa. In contrast, CB2Rs are actually upregulated in postmortem HD basal ganglia [189]. Endocannabinoid levels of AEA and 2-AG were decreased in the striatum of patients with HD and correlate with disease burden, measured via trinucleotide repeats [190]. A study by Sapp et al. reported loss of CB1R early in the disease with an increase in CB2R that might be a protective mechanism in order to reduce pro-inflammatory cascade. However, this protective mechanism is not substantial enough to prevent progression of neuronal death [191]. Previously, Sativex, which is a combination of botanical extracts enriched with THC and CBD, attenuated oxidative stress and inflammation, and protected striatal neurons in a model of striatal injury indicative of HD [192]. Cannabigerol (CBG), a non-psychoactive phytocannabinoid, improved motor deficits and protected striatal neurons in both 3-nitropropionate (3-NP) intoxicated and R6/2 transgenic mice which replicate many features of HD [193]. Particularly, expressions of HD-associated genes, such as Huntington-associated protein 1, Sin3a, Rcor1, symplekin, and GABA-A, were normalized by CBG treatment, while CBG improved the gene expressions of BDNF, IGF-1, and $PPAR_Y$ in R6/2 mice [193]. Another CBG derivative, VCE-003.2, enhanced neuronal progenitor cell survival, improved motor deficits, and inhibited inflammation probably through $PPAR_Y$ in a mouse model of HD [194]. In addition, a recent study with cannabinoids in HD patients showed improvement in motor symptoms, mainly dystonia with less irritability, apathy, and hypersalivation in some cases [195]. Overall, the emerging scenario of cannabinoid-based therapies in HD and other neurodegenerative disorders suggests their pharmacological efficacy in attenuating disease progression and related symptoms and warrants for more experimental and clinical efforts.

Amyotrophic lateral sclerosis: cannabinoids delay the progression of disease

Amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease) is a fatal motor neuron disease, disabling common activities, e.g., chew, speak, and walk. ALS causes the loss of voluntary muscle movement and thus causes gradual weakening, twitching, and wasting away. Other clinical symptoms are weakness, spasticity, cachexia, dysarthria, drooling, and pain secondary to immobility [54, 196–198]. ALS can be categorized into two types—sporadic (90%) and familiar (10%). Genetically, ALS is associated with mutations in the superoxide dismutase-1 gene (*SOD-1*), TAR-DNA binding protein-43 (TDP-43), fused in sarcoma (FUS) [199], and in non-coding hexanucleotide repeat sequence (GGGGCC) in the chromosome 9 open reading frame 72 (*C9orf72)* genes [54, 200].

ALS most of the time is difficult to diagnose as it presents similar symptoms to those of Parkinson's disease, multiple sclerosis, and Huntington's disease. Timely treatments of ALS may slow the progression of disease and reduce complications and discomfort. The US FDA has approved four medications for ALS—Rilutek (riluzole tablet), Tiglutik (riluzole oral suspension), Nuedexta (a combo of dextromethorphan and quinidine), and Radicava (edaravone). Riluzole, a glutamate antagonist, was able to block voltage-gated sodium channels to inhibit the presynaptic release of glutamate and can only prolong survival by 3–5 months [197, 198, 201]. Its tablet form (Rilutik) was approved in 1995, while much later in September 2018, a liquid form of riluzole (Tiglutik) was approved to avoid difficulty of swallowing tablets in ALS patients. Rilutek has also been approved for treatment for ALS in Canada, Australia, and across Europe. Radicava, the

first intravenous treatment specifically for ALS was approved by the FDA in May 2017. Nuedexta was approved to treat pseudobulbar affect (inappropriate laughing or crying) in 2011. The quinidine in Nuedexta inhibits the metabolism of principal compound dextromethorphan in liver and thus increases its availability in circulation [54, 197, 198, 201]. However, with established treatment options, patients get partial benefits, and therefore, medical and research communities are trying to find more efficacious treatment options.

Recent in vivo studies suggest beneficial effect of cannabinoids in ALS. In transgenic hSOD(G93A) mice, which develop symptoms similar to human ALS, Δ9-THC administration either before or after symptoms emerged, improved motor impairment and increased survival [202]. It was argued that THC exerted anti-ALS effect by its anti-glutaminergic and antioxidant properties as THC attenuated oxidative stress in ALS hSOD(G93A) mouse spinal cord primary cultures exposed to the oxidant *tert*-butyl hydroperoxide (TBH) as assessed by lactate dehydrogenase (LDH) and SOD-1 release. However, this antioxidant effect of THC was independent of CB1R, as CB1R-antagonist SR141716A did not inhibit the antioxidant effect of THC [202]. But, anti-excitotoxic effect of THC was CB1R dependent as protective effect of THC against kainic acid-induced excitotoxicity in ALS hSOD(G93A) mouse spinal cord primary neuronal cultures was blocked with antagonist SR141716A [202]. Moreover, cannabinol (CBN), a non-psychotropic cannabinoid which has residual affinity to CB1R, was able to delay disease onset in ALS hSOD(G93A) mice. Further, commercially available Sativex® (2.7 mg of $^{\Delta 9}$-THC and 2.5 mg of CBD) treatment delayed ALS progression in the early stages of disease in ALS hSOD(G93A) transgenic mice [203]. However, the molecular mechanisms remain undefined [204].

CB1R/CB2R agonist WIN 55,212-2 delayed the disease progression, while deletion of FAAH abolished disease symptoms in 90 days old ALS hSOD(G93A) mice after onset of motor impairment and tremor, but had no effect on survival [205]. On the contrary, CB1R deletion did not affect onset of disease, but increased survival by 13% and extended lifespan by 15 days in ALS hSOD(G93A) mice [205]. CB2R and NAPE-PLD both were also found to be upregulated in the spinal cords of ALS hSOD(G93A) mice paralleling disease progression [203, 206, 207], and CB2R agonist AM-1241 increased survival by 56% and delayed motor deficits in ALS hSOD(G93A) mice after disease onset [207]. Therefore, it may be presumed that the beneficial effects of cannabinoids may be mediated by non-CB1R, such as CB2Rs, and were ascribed to regulation of microglial/macrophage activation, glutamate excitotoxicity, and oxidative stress [205–208].

Cannabinoids were also investigated clinically in ALS. In a single observational study with cannabinoids, only the 10% of ALS patients showed moderate improvement in appetite, pain, depression and salivation [209, 210]. In addition, *Cannabis* has been reported to subjectively improve spasticity [209]. A randomized, double-blind, and single-center study with 30 participants (Clinicaltrial.gov NCT03690791) on the safety, tolerability and efficacy of cannabis-based medicine extract (Centrist CBD Oil) in slowing the disease progression in ALS or motor neuron disease patients is currently under phase 3 trial. Participants are given 25 mg of CBD delayed-release (DR) capsules containing < 2 mg of THC or placebo. Difference in mean ALS Functional Rating Scale-Revised (ALSFRS-R) total score between groups at end of treatment (Total score: min 0–max 48) will be analyzed as primary outcome measure. Higher score represents better outcome [211]. However, paucity of clinical studies related to efficiency of cannabinoids in ALS remains a major challenge for future research.

Parkinson's disease: cannabinoids protect dopaminergic system

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease, characterized by the loss of dopaminergic neurons from substantia nigra pars compacta of basal ganglia. The etiology of PD is not fully defined, but may be caused by gene mutations, protein inclusions, oxidative stress, and sustained inflammation [212]. The symptoms of PD are multi-factorial and classically defined by the triad of cogwheel: muscle rigidity, resting tremor, and bradykinesia in addition to behavioral and psychiatric manifestations, including sleep disturbances, cognitive deficits, anxiety, depression, and psychotic symptoms, occurring in the early stages of disease progression [213–217]. Currently, levodopa (L-DOPA) is the most widely used drug for treatment of PD, but prolonged L-DOPA administration may increase dyskinesia [212]. Thus, safe and efficacious therapies are needed to combat the negative symptoms associated with PD.

Components of the ECS are abundantly expressed in the basal ganglia and interact with glutamatergic, γ-aminobutyric acid-ergic (GABAergic), and dopaminergic neurotransmitter systems, suggesting therapeutic potential in PD [185, 218–228]. Endocannabinoid receptors are particularly vital in PD because both CB1R and D1/D2-like receptors are colocalized in striatal neurons [229]. In PD patients, a fourfold increased expression of CB2R was observed when compared to control samples [230], although gene expression profiling revealed a decrease in CB2R gene expression in the cerebellum and hippocampus of PD patients, as compared with healthy control patients [231]. Similarly, CB2R expression was decreased in putamen, while CB1R remained unchanged [230]. Sierra et al. found both CB1R and CB2R mRNA was localized within pallidothalamic-projecting neurons in both uninjured and MPTP-treated non-human primates, with reduced expression levels noted in dyskinetic subjects [232];

however, other reports showed elevated CB2R expression in striatal microglial cells in experimental models [22, 233] and in astrocytes within the substantia nigra of PD patients [230], suggesting the potential for model-, species-, and/or cell type-specific regulation of CBRs in PD.

Increased AEA levels within the cerebrospinal fluid of PD patients were normalized by L-DOPA treatment [219, 223, 234, 235], suggesting a compensatory protective role for AEA in PD. In line with these findings, increased striatal levels of AEA were observed in 6-hydroxydopamine (6-OHDA)-infused rodents (a preclinical model of PD), correlating with reduced activity of AMT and FAAH, although it is important to note that neither 2-AG levels nor AEA binding to CBRs were altered [228]. Functionally, chronic FAAH inhibition reduced AEA metabolism and prevented both MPTP-induced dopaminergic cell loss and motor impairment [236, 237]. Further studies showed that the increased levels of AEA, secondary to FAAH inhibition, increased dopamine levels in the nucleus accumbens shell and attenuated dyskinesia via CB1R activation in lesioned rats [238, 239]. In a similar manner, chronic inhibition of MAGL increased 2-AG levels, prevented motor impairments, and preserved the nigrostriatal pathway in MPTP-infused mice [240]. Together, these findings point to a possible beneficial role for targeted modulation of the ECS in the context of PD.

A number of preclinical and clinical PD studies demonstrated that CB1R modulates motor symptoms and components of cognitive processing [185, 213, 219, 227, 228, 241–244]. A [18F]MK-9470 PET study in PD patients found significant regional alterations in CB1R that are unrelated to levodopa-induced dyskinesia severity [245]. Low CB1R in mid-superior frontal gyrus and in midcingulate cortex was observed to be associated with poor mind, poor executive functioning, and poor episodic memory, while PD patients with severe visuospatial dysfunction had reduced CB1R in the precuneus, midcingulate, supplementary motor cortex, inferior orbitofrontal gyrus, and thalamus [213]. MPTP-lesioned marmosets displayed increased CB1R in the striatum, an effect normalized by L-DOPA treatment [246]. Pharmacological inhibition of CB1R promoted antiparkinsonian effects in rats with severe, but not lesser, nigral lesions [242], while low-dose rimonabant (0.1 mg/kg), a CB1R antagonist, attenuated dopaminergic neuronal cell death, blocked neuroinflammation, and partially reduced hypokinesia in 6-OHDA lesioned animals, independent of striatal dopaminergic, GABAergic, and glutamatergic neurotransmission [244, 247]. Moreover, the synthetic, non-selective CBR agonists, HU-210 and WIN55,212-2, protected nigrostriatal neurons in MPTP-lesioned rodents via a proposed antioxidant mechanism secondary to CB2R, but not CB1R, activation [248, 249]. Of note, HU-210 maximally reduced 6-OHDA-induced cell death in mouse cerebellar granule neurons when cocultured with glial cells, suggesting astrocytes may mediate the protective effect of cannabinoid in PD [246]. Together, these results indicate that nigrostriatal lesions are associated with changes in the ECS within the basal ganglia [250]. Although the mechanisms whereby CB1R modulating drugs affect PD progression remain only partially resolved, it is interesting to note that SR141716 almost fully protected SH-SY5Y neurons against MPP+ toxicity (an in vitro model of PD), even in the presence of the CB1R selective agonist, ACEA [251].

A number of research studies have investigated the role of natural cannabinoids in the treatment of PD symptoms. THC protected MPP^+-treated neuronal cells in vitro and attenuated the loss of dopaminergic neurons in a 6-OHDA-induced neurodegeneration model [246, 252]. Interestingly, the beneficial effects of THC were mimicked by ACEA-induced CB1R activation, but not by the CB2R agonist, HU-308 [253]. Garcia and colleagues showed Δ9-tetrahydrocannabivarin (Δ9-THCV), a phytocannabinoid with antioxidant properties [254] decreased 6-OHDA-evoked motor deficit and diminished the dopaminergic neuron loss in the SNpc in hemiparkinsonian rodents [255]. Similarly, the phytocannabinoid β-caryophyllene attenuated gliosis, oxidative stress, and loss of nigrostriatal dopaminergic neurons in a rotenone-induced PD [256], while VCE-003.2, an aminoquinone derivative of the non-psychotropic phytocannabinoid cannabigerol (CBG), attenuated inflammatory neuronal injury, and improved behavioral outcomes after preclinical PD [257, 258]. CBD, the most widely utilized phytocannabinoid, protected neuronal cells against MPP^+ toxicity, restored axonal and synaptic proteins, and attenuated microglial activation [259–261]. Administration of CBD (5 mg/kg) for 5 weeks did not reduce dopaminergic neuronal loss or improve motor deficits in MPTP-infused mice, although daily administration of a lower dose (3 mg/kg), initiated at the time of 6-OHDA injection, preserved striatal dopamine and tyrosine hydroxylase in rats, whereas delayed CBD treatment was ineffective [236, 246]. In line with reports showing a correlation between the antinociceptive effect of exercise and increased CB1R/CB2R expression within the anterior cingulate cortex and periaqueductal gray matter and in a rat model of PD [262], CBD-produced an antinociceptive effect in preclinical PD model while an inverse agonist of CB1R and CB2R prevented this effect [263]. Although the mechanisms underlying the beneficial effects remain undefined, CBD may decrease FAAH activity to facilitate AEA-mediated effects [264].

An open-label pilot study showed that CBD in combination with standard of care minimized psychotic symptoms without affecting cognitive or motor alterations in PD patients [265]. In another randomized double-blind clinical trial with 21 PD patients, CBD (75 and 300 mg daily) improved most quality of life outcomes for 6 weeks with CBD treatment, although motor function was not affected [266]. Similarly, a pilot study with 4 PD patients with REM sleep behavior disorder reported

a reduction in incidences of agitation, beating, kicking, and nightmares after treatment with 99.9% purified CBD (75 or 300 mg orally per day) [267]. An open-label observational study in 22 PD patients showed significant improvements in resting tremor, rigidity, and bradykinesia and the non-motor aspects sleep and pain after smoking cannabis (500 mg, unspecified composition) [268]. Further, in a Web-based self-reported assessment ($n = 595$), 454 identified PD patients, who have consumed cannabis daily and for longer than 12 months, reported lower disability and fatigue, while 47.8% patients reported decline in intake of prescribed medicines since beginning of cannabis consumption [269]. These exciting early-stage clinical results showing a potential benefit of cannabinoids after PD will be further explored in the upcoming phase II, randomized, placebo-controlled, and double-blind enriched enrollment withdrawal study (The NMS-Nab Study) [270]. In this study, 4-week outcomes will be assessed in 38 PD patients following administration of a synthetic cannabinoid, nabilone [270]. Given the safety and early-stage efficacy, continued exploration of cannabis-inspired medicines, including studies aimed to identify and standardize the optimal substance(s), route of administration, doses, time point of analysis, and endpoints, is warranted in PD patients.

Multiple sclerosis: cannabis formulation modulates spasticity

Multiple sclerosis (MS) is an autoimmune chronic inflammatory disease that promotes the loss of myelin and damage axons in the central nervous system (CNS). The etiology of MS is poorly understood. However, it is known that inflammation present in MS promotes myelin loss and neuro-axonal degeneration. These events are responsible for impairing the signal conduction through the neurons resulting in disability [271–273]. The symptoms of MS can include, but are not restricted to, spasticity, ataxia, fatigue, pain, difficulty in speaking, constipation, loss of bladder control, depression, or anxiety [271, 274–276]. Interestingly, MS patients show well-described signs and symptoms which are also associated with Flammer syndrome (FS). These symptoms may work as a directive markers for therapeutic benefits and functional outcomes [277, 278]. MS patients most often show nine FS signs and symptoms, such as cold hands/feet, reduced thirst, dizziness, drug side effects, headaches from tension or medication overuse, weight loss, feeling cold, long sleep-onset time, and skin blotches [277, 279]. Scientific studies suggest a potential role of the ECS in controlling either the symptoms or the evolution of MS [280, 281]. The cannabinoids seem to have the potential to slow down the disease progression by exerting a neuroprotective effect [282]. However, patients with MS can present an impaired ECS with reduced levels of anandamide (AEA), palmitoylethanolamide (PEA), 2-AG, and oleoyl ethanolamide (OEA) in the CSF [283].

The fact that both natural and synthetic cannabinoids can act on the human by exerting immunosuppressive role and acting through the components of the ECS make them great allies in the search for an effective treatment for MS. Indeed, patients with MS reported relief after smoking cannabis or using cannabinoids [284–286]. The Δ9-THC was the first cannabinoid to be studied as a means of relieving spasticity, tremor, and pain in MS [284, 287]. This cannabinoid shows effective results in experimental autoimmune encephalomyelitis (EAE) models of MS [288] and in humans [287]. However, the use of Δ9-THC could be limited by its psychotropic effects which may induce acute psychosis, and impact executive function [289–291]. On the other hand, CBD was seen as a potential safe alternative for alleviating neuroinflammation and neurodegeneration in MS, also with lower toxicity and better psychological outcome (i.e., anxiolytic) in patients compared to Δ9-THC [290, 291]. However, CBD has no significant effect on spasticity, which seems more related to CB1R [281, 288, 292, 293].

Current pharmacological studies on MS have largely focused on a combination of Δ9-THC and CBD extracted from cannabis like Sativex® (nabiximols), a cannabinoid preparation with 1:1 ratio of Δ9-THC and CBD. While Δ9-THC promotes modulation of spasticity and has an anti-inflammatory property, CBD seems to reduce the psychoactive effects of Δ9-THC [294]. According to Zamil Al-Ghezi et al., Sativex® can change the expression of miRNA, down-regulating some and upregulating others, inducing cell cycle arrest and apoptosis in activated T cells. This process would be responsible for promoting a neuroprotective and anti-inflammatory role as well as a switch of cytokines from pro-inflammatory to anti-inflammatory [295]. Also, the post-marketing studies revealed no evidence of addiction, but mild-to-moderate dizziness as the most common adverse effect [296]. In addition to Sativex, there are two more licensed cannabinoid preparations to be used in MS treatment in some countries, Marinol® and Cesamet®. The Marinol® has an active ingredient, dronabinol, a synthetic form of Δ9-THC [297]. This synthetic cannabinoid reduced the intensity of central and radiating pain after taking dose of 10 mg/day for 15 weeks [298]. In addition to the pain relief, patients that used dronabinol also reported improvement on sleep but no treatment effect on spasticity was reported [299, 300]. Similar to Marinol®, Cesamet® is a brand name for a synthetic Δ9-THC cannabinoid, called nabilone. Like dronabinol, nabilone has shown significant improvement in pain relief, but no change in spasticity [301]. Besides the side effects reported by patients during the use of cannabinoids in MS treatment, the use of phyto- or synthetic cannabinoids seems to be very helpful in neuroprotection and improvement of life quality [299, 300]. However, long-term benefits and risks of MS therapy is still not completely understood.

The treatment approach for MS has taken a shift from relapse prevention to a more personalized establishment with the choice of the suitable drugs and their sequential application over the time-course of the disease, considering patient preference, clinical findings, and related symptoms such as fatigue, depression, and cognitive impairment. Thus, future trials specially with cannabinoids must assign higher relevance to patient outcomes and should implement predictive markers for individual response to new treatment strategies. Thus in this way, benefit to individual patients may be maximized, and adverse events and risk to study participants may be mitigated in clinical trials [302].

Alzheimer's disease: cannabinoids improve cognition

Changes within the ECS are strongly linked with the progression of Alzheimer's disease (AD) [187, 303–312]. Analysis of postmortem AD patient brains revealed increased expression of CB2R, primarily in CNS resident immune cells surrounding β-amyloid plaque deposition, within the hippocampus and entorhinal cortex [313, 314]; however, positron emission tomography (PET) scans using [^{11}C]NE40, a radioligand with low selectivity for CB2R over CB1R, suggested lower CB2R availability in AD patients, with no relationship to amyloid beta (Aβ) plaques [315]. CB2R expression paralleled the development of chronic neuroinflammation during the advanced stages of AD, whereas an initial rise in hippocampal and cortical CB1R expression was followed by reduced expression in the later stages of AD [316–318]. Similarly, PET studies demonstrated lower binding ratios of CB1R, with a more pronounced effect in males, in the parieto-temporal cortex and hippocampus of APP/PS1–21 mice, as compared with age-matched wild-type mice [319]. While no significant correlation was observed between CB1R expression and β-amyloid deposition in AD patients, as compared to age-matched controls [320], amyloid precursor protein (APP), which given rise to β-amyloid, interacts with and inhibits the biological activity of CB1R during presymptomatic stage in transgenic mice predisposed to develop AD [321]. Together, these data support a potential relationship between the expression of CBRs and AD progression.

The endocannabinoids, AEA and 2-AG, are released in response to Aβ-amyloid deposition, although transgenic mice predisposed to develop AD exhibit reduced AEA levels [322]. Although an explanation for these seemingly disparate results is lacking, endogenous levels of AEA are regulated by fatty acid amide hydrolase (FAAH), an enzyme expressed by astrocytes that degrades AEA into arachidonic acid. Indeed, arachidonic acid accumulates around pathogenic plaques, leading to pro-inflammatory responses to perpetuate the pathophysiology of AD [305]. A decrease in FAAH activity was observed in the frontal cortex of AD patients. Similarly, reduced FAAH activity was observed in cerebrocortical synaptosomes from aged rat brain, while elevated activity was noted in cerebrocortical membranes [323]. Of interest, CB2R selective agonist-JWH-133 slightly increased AEA hydrolysis in human controls, but suppressed AEA metabolism in cerebrocortical synaptosomes and membranes isolated from adult or aged rat. In comparison, WIN55,212-2, a mixed CB1/CB2-R agonist, increased AEA hydrolysis in AD patients, but decreased activity in human controls and in aged rat brain preparations [323]. Though FAAH activity is similarly regulated in aged rats synaptic endings and human AD brains, activity may be differentially modulated by CB1/CB2-R agonists [323]. In contrast, inhibition of the 2-AG metabolizing enzyme, monoacylglycerol (MAGL), reduces inflammatory activation and attenuates neuropathology, independently from CB2R, in AD-prone mice [304, 324].

The release of endocannabinoids activates neuronal CB1R, which is abundantly expressed within the hippocampus, basal ganglia and cerebellum—brain regions critical for memory function and cognition, to inhibit glutamate release, reduce intracellular Ca^{2+} concentrations, and enhance neurotrophin expression and neurogenesis [303, 314]. Endocannabinoids also interact with CB2R expressed on immune cells, including CNS resident macrophages/microglia, to attenuate the production of pro-inflammatory molecules implicated in the progression of AD [303, 314, 325]. Activation of CB2R reduced AD-like pathology, attenuated inflammation, and improved cognition [313, 326], while the non-psychoactive phytocannabinoid, CBD, reduced amyloid-β production, inhibited gliosis, suppressed oxidative stress and inflammation, decreased tau hyperphosphorylation, and chronically reduced both social and cognitive deficits in experimental AD models [260, 308, 327–329]. In contrast, CB2R$^{-/-}$ mice displayed AD-like tau hyperphosphorylation and hippocampus-dependent memory impairment while CB2R activation by JWH133 reduced tau phosphorylation in HEK293 cells [330]. Similarly, transgenic mice predisposed to develop AD that also lack CB2Rs (APP/PS1*CB2$^{-/-}$) exhibited elevated cortical Aβ deposition and increased the levels of soluble Aβ40, as compared to AD mice with CB2R; however, mortality, tau hyperphosphorylation associated with Aβ plaques, and the beneficial effects of cannabis-based medicines were unaffected in mice lacking CB2R [331]. An independent study reported reduced neuronal loss, decreased plaque levels, increased expression of Aβ-degrading enzymes, less inflammation, and improved behavioral outcomes in APP/PS1*CB2$^{-/-}$ mice [332]. Thus, CB2R may provide endogenous protective mechanism that elicits detrimental outcomes if continuously engaged.

THC, a psychoactive component of cannabis, reversibly disrupts short-term memory and dose-dependently impairs attention and cognition [333–338]; however, when chronically administered at low doses, THC improves neurological function in aged animals and promotes hippocampal neurogenesis while reducing neurodegeneration in animal models of AD [99,

339–343]. A recent open-label pilot study showed THC oil (7.5 mg twice daily) was well tolerated and reduced AD-associated delusions, agitation/aggression, irritability, apathy, and sleep disturbances in 11 AD patients [344]. A separate randomized, double-blinded, and placebo-controlled study with non-psychoactive doses of THC (1.5 mg thrice daily for 3 weeks) did not reduce dementia-related neuropsychiatric symptoms in mild to severely demented patients [345]. While anecdotal evidence and early-stage clinical trials suggest a possible benefit of cannabinoids on AD-associated symptoms and pathology in humans, small sample sizes, short trial duration, and lack of placebo control limit the interpretation of these results. Thus, high-quality clinical studies that assess both safety and efficacy are needed to more definitively determine the translational value of cannabinoids in AD [345–348]. Toward this end, the results from a randomized placebo-controlled study (Clinicaltrial.gov NCT02351882) of daily nabilone (2 mg) administered for 6 weeks was recently completed in 40 AD patients is expected within the next year [349, 350]. A second 3-week, placebo-controlled pilot study (Clinicatrial.gov NCT02792257) investigating the effect of 5–10 mg dronabinol (Marinol®) in 160 AD patients is ongoing and will be completed in late 2020. These important clinical trials will provide critical insight regarding the future of cannabinoids in AD.

Schizophrenia: cannabinoids show anti-psychotic effect

The pathogenesis of schizophrenia, which is defined as hallucinations, delusions, and altered speech for greater than 6 months, is linked with alterations in the ECS [351–359]. Genetic studies showed CB1R [353, 360–364] and CB2R [365] polymorphisms are associated with schizophrenia. In addition, people with low CB2R function exhibited an increased risk for schizophrenia [365]. A particular mechanism of how schizophrenia functions is through increased CB1R density [366–373] and increased anandamide levels in CSF [366, 374, 375], and plasma [358, 376] in schizophrenic patients. Further, CB1R agonists led to schizophrenia-like behaviors [377–381], while CB1R antagonists proved to have antipsychotic properties [382, 383] in animal models. The antipsychotic effects of AEA have been also reported [377]. Additional evidence has reinforced the antipsychotic properties of CBD in both clinical and preclinical models of schizophrenia [377, 384–388]. It should be noted that recreational marijuana usage in adolescents is clinically linked to the development of schizophrenia. Possible reasons for this could be explored further. Personalized medicine in specific settings of psychological disorders is being established as a model of individualized care [389]. An integration of molecular science with cannabinoid therapy in clinical settings will certainly lead to novel therapies and certainly promises to a better predictive, preventive, and personalized medicine (PPPM) in psychiatry. With substantial progress in the methodology, omics analyses and data integration, the future for PPPM in psychiatry is encouraging.

Epilepsy: cannabinoids limit the epileptic seizures

Intensive and continual neuronal activity as well as a healthy balance of excitatory and inhibitory neurotransmission is essential to proper brain function. However, when this balance is disrupted, epileptic seizure occurs. Epileptic seizures and their excessive neuronal activity lead to excitotoxicity causing damage to the CNS.

Throughout multiple animal models and clinical studies, cannabinoids have been shown to exert both anti- and pro-convulsive activities with little current evidence for a mechanism [390]. Although not confirmed by large clinical human studies, CB1R agonists are beneficial in epilepsy. Most studies showing improvement in seizure control were associated with low THC/high CBD products rather than endocannabinoids, but also do not disclose sufficient data about subject randomization, group comparisons, anti-epileptic drug doses, and study design [391]. Although treatment options may be far from conclusive, there is strong evidence that cannabinoid receptors, more specifically CB1R, has a role in the intrinsic protection of neural tissue via suppression of pathologic neuronal excitability. There are literature discrepancies with the exact role of the CB1Rs, however, in some studies, it is suggested that downregulation of CB1Rs, particularly on glutamatergic axon terminals, diminish the neuroprotective properties of the endocannabinoid system leading to excessive neuronal excitability and damage in epileptic patients [392]. Other reported seizure-associated increases in CB1R possibly to protect against hyperexcitability or seizure propagation [393].

Other reports suggested the anti-epileptic effect of inhibitors of endocannabinoid metabolism. For example, inhibition of MAGL by JZL184 reduced seizure in kindling model of temporal lobe epilepsy possibly through CB1R-dependent mechanism [394]. Similarly, MAGL inhibition by potent and selective inhibitor CPD-4645 alleviated the inflammation and neuronal loss in status epilepticus and its effect was similar to effect observed in CB1R-deficient mice [395]. In addition, inhibition of FAAH through URB597 exhibited anti-epileptic effect via increase in AEA and possibly through stimulation of CB1R. The restoration of AEA by inhibiting FAAH or AEA transport led to inactivation of TRPV1 channel and reduced Ca^{2+} entry into the hippocampal cells and thus showed anti-epileptic effect [396]. URB597 further prevented seizure-induced alterations in both STP and LTP and was devoid of any deleterious effects as CB1R agonist, WIN55,212-2, showed in naïve animal [397]. These evidences advocate that boosting the eCB tone rather than CB1 activation might represent a potential strategy for the

development of anti-epileptic drugs for treatment of both seizures and comorbid memory impairments associated with epilepsy. However, with a lack of widespread preclinical and clinical studies, it is apparent that the endocannabinoid system's involvement in epilepsy is an area of need for future research.

Pain: cannabis extract relieves disease-associated pain

Pain is a complicated and multifaceted concept in medicine, which makes it especially difficult to understand and target therapeutically. Pain is thought to be a combination of a subjective experience in psychophysics, an objective sensory neurophysiology, as well as an emotional reaction to distressing stimuli [398]. Just as there are various modalities of pain modulation, the endocannabinoid system has shown a particular link to a variety of pain pathways [399–403].

It has been found that CB2R agonists are analgesic in chronic pain models [404] and help with peripheral inflammation [405]. One possible mechanism by which this is possible is that CB2R agonists allow beta-endorphin release from keratinocytes [406]. Furthermore, PEA, an analgesic in inflammatory pain, is targeted by the endocannabinoid system allowing for a functional improvement in pain modulation [407]. Cannabinoids allow pain modulation through spinal, supraspinal, and peripheral mechanisms [408–410].

In addition to somatic pain, neuropathic pain also demonstrates interplay with CB2Rs. Neuropathic pain can be due to traumatic injury as well as metabolic changes and chemotherapy. CB2R agonists were found to suppress neuropathic nociception using a nerve ligation model of L5 and L6 spinal nerves in rats [406]. Chemotherapy-induced neuropathic pain was also shown to be significantly suppressed via CB2Rs, even in the absence of peripheral nerve degeneration [411]. Finally, two CB2R-selective agonists, L768242 (GW405833) and AM1241, have shown to suppress capsaicin-evoked release of calcitonin gene-related peptide in murine models, suggesting a neuronal mechanism of analgesia [412].

Among the increasing incidences of opioid abuse, natural cannabinoids have emerged as strong candidate for pain management [413]. Clinical studies with oral cannabis extract (OCE) on MS patients were found effective in spasticity and related pain [414, 415]. Nabiximols mouth spray (Sativex®), which is a mixture of CBD and THC, is currently approved for treating MS-associated spasticity and neuropathic pain in the UK, Canada, and several European countries [416–418]. However, it was suggested that cannabis extract, when having low THC content (< 4%), was safe and produced greater therapeutic benefits [415, 419]. Therefore, a complete understanding of action of cannabis and its components is desired as they are able to alter the brain normal functioning even consumed in small quantities [420].

Brain tumor: cannabinoids reduce tumor growth and promote chemotherapy response

Brain tumor is one of the deadliest type of cancer with incidence of 10.85% per 100,000 people annually worldwide [421]. There are over several clinical subtypes of brain cancers based on the originating cells, but glioblastoma multiforme (GBM) has the most aggressive and constitutes 60% of all brain tumors of adults [422]. The lethality of glioblastoma can be gauged from the fact that more than two third of patients with glioblastoma die within 2 years [423]. The brain cancer affects all ages and is diagnosed in all anatomical regions of CNS. Most common pathologies, especially in children, include astrocytoma, medulloblastoma, germ-cell tumors, brainstem-gliomas, and epyndemomas [424]. Therefore, developing new natural and synthetic anti-glioma drugs has become main focus for FDA and global research [425].

The therapeutic use of cannabinoids in neurological disorders like multiple sclerosis and epilepsy has generated interest in its efficacy for treating diseases such as brain tumor, since the elucidation of psychotropic constituent of *Cannabis sativa* opened way to identification of sites of action of THC, CB1R, and CB2R and subsequently endogenous agonists to these receptors [426–428]. Although, the anti-neoplastic activity of THC and its analogs was first reported in the early 1970 [429], recent studies reflect the possibility that ECB system could be targeted to retard or block cancer growth [426]. The endocannabinoids AEA and 2-AG are ubiquitous among both vertebrate and invertebrate tissues and have modulatory role in cell proliferation, differentiation, and apoptosis, suggesting their roles in control of cell survival, transformation, and death [426, 430]. Further, the endocannabinoid signaling pathway that involves CB1R and CB2R is implicated in brain development and function physiologically. CB2R stimulation via sustained synthesis of ceramide and activation of ERK triggers nuclear events that lead to programmed glioma cells death [426]. Non-psychoactive CBD administration to the human glioma cell lines resulted in dramatic drop of glioma cell viability in a concentration-dependent manner evident within 24 h after administration. The reduction of viability was correlated to induction of apoptosis which was not reverted by cannabinoid antagonists. The CBD administered to nude mice at 0.5 mg/mouse inhibited the growth of subcutaneously implanted human glioma cells significantly, suggesting possible application of CBD as anti-neoplastic agent [431]. Also, administration of CBD in glioma stem cells displayed an increase in ROS and thus inhibition of cell survival and a significant increase in survival of glioma stem cells (GSC)-bearing mice [432].

The endocannabinoid system functions as tumor suppressive through variety of cytostatic, apoptotic, anti-angiogenic, and anti-metastatic mechanism [433]. The generation of malignant cells involve imbalance of endogenous ligands and

receptors of cannabinoid system. THC has shown to downregulate the expression of E2F1 and cyclin A which leads to G1 arrest in GBM cells [434]. THC has also shown to induce apoptosis by releasing cathepsins leading to organelle permeabilization and apoptosis [435]. One of the first studies that showed the therapeutic benefits of cannabinoids in brain tumor demonstrated its efficacy by reduction in size of tumors in rats [436]. Additionally, oral administration of Sativex-mimic extract (THC/CBD in 1:1 ratio) in conjunction with temozolomide exhibited strong antitumor effect in subcutaneous and intracranial glioma cell-derived tumor xenograft [437].

The expression of CB2R have been shown to be upregulated in glioblastoma patients [438]. The grade of tumor varies from G1 (well-differentiated, least aggressive, low grade) to G4 (undifferentiated, most aggressive, high grade). The expression of CB2R was found to be twofold higher in tumor of high grade compared to low grade [439]. A highly selective CB2R-agonist COR167 restricted the growth of glioblastoma and anaplastic astrocytoma via reduction of TGF-β1 and TGF-β2 [440]. CB2R expression analysis can assist in the efforts to identify biomarkers that can identify patients that can respond to therapies. Tumor angiogenesis is an important component for growth and expansion of malignant cells as it provides new blood vessels for supply of oxygen and nutrition. Cannabinoids have shown to disrupt tumor angiogenesis by suppressing pro-angiogenic factors like VEGF and Ang2 and inhibition of endothelial cell migration and proliferation [441].

The clinical management of brain tumors is difficult as these tumors have low response rates to chemotherapeutic agents. A growing number of data from in vivo and in vitro studies with cannabinoids elucidated the beneficial role of cannabinoids as tumor-suppressing agent. The cannabinoids increase the chemo-sensitivity of GBM cells by acting as agonist for cationic receptor TRPV2 [442]. The transient loss of TRPV2 expression using siRNA showed downregulation of Fas and procaspase-8 and increased proliferation in human glioma cell lines [443]. Synthetic THC-mimics (dronabinol and nabilone), CBD, and a refined cannabis extract, nabiximols (THC/CBD = 1.08:1.00) have demonstrated calming effects against cancer-associated nausea, vomiting, pain, anxiety, anorexia, weight loss, or sleep disturbance [444]. Recently, a prominent increase in use of cannabinoids in conjunction with immunotherapy have been observed [445, 446]. In an observational study in patients treated with nivolumab, cannabis use during immunotherapy treatment decreased response rate [445]. In another case study, daily dose of CBD (400 mg/ day) alongside tumor resection followed by radio-chemotherapy increased the survival of patients with a mean survival time of 22.3 months [446].

In an interesting phase 1 interventional study with three patients with epilepsy with associated tumors enrolled in The University of Alabama at Birmingham CBD Program (Clinicaltrial.gov: NCT02700412 and NCT02695537), CBD (Epidiolex; Greenwich Biosciences) reduced tumor-associated seizure frequency and severity [447]. The phase II clinical trial of THC and CBD underway for its benefit in glioblastoma patients (ClinicalTrials.gov: NCT03529448). The preliminary results have showed better 1-year survival (83%) of treatment group compared to placebo control (53%) [448]. Cannabinoids executed their therapeutic effects by reducing tumor growth, by reducing angiogenesis, and by promoting tumor cell death. Moreover, cannabinoids inhibited the stem cell-like properties and invasiveness of GBM tumors [449]. Taken together, the importance of pharmacological effectiveness and the molecular mechanisms of the cannabinoid system in tumor pathophysiology cannot be ignored. In last two decades, there has been rapid development in field of personalized medicine due to development of technologies like next-generation sequencing (NGS) which can assist in rapid screening of clinically responsive patients [450]. Along with recent advances in multi-omics genomics, transcriptomics and proteomics screening of cancer patients which can be responsive to patient stratification and accurate, quick, and personalized treatments [451], the endocannabinoid system could be a potential pharmacologically target for novel anti-cancer drugs.

Therapeutic strategies and translational approaches

The ECS has emerged as a new therapeutic target in a variety of neurological and neuroinflammatory disorders [452]. The cannabinoids possess broad-spectrum activity at multiple cellular and molecular mechanisms that involve not only the ECS itself but also the immune system [309]. Cannabinoids can prevent excitotoxicity, oxidative stress, and neuroinflammation and can augment neuronal metabolism through either specific cannabinoid receptor-mediated signaling pathways or via direct interactions with transcription factors.

Current treatments involve the use of CB1R/CB2R activators or agonists. The current clinical CB1R/CB2R activators available are Cesamet (nabilone), Marinol (dronabinol; Δ9-tetrahydrocannabinol [Δ9-THC]), and Sativex (Δ9-THC with cannabidiol) [63]. The only selective agonist clinically approved by the FDA is a CB1R-selective agonist Resunab™; however, this drug is only designated for a fast-track development program in a phase II human clinical trial for scleroderma and is not openly clinically available [63]. Most of the agonists are synthetic exocannabinoids, typically derived some way from THC. A study showed lower post-TBI mortality in the THC(+) patients (2.4%) as compared with the THC(−) group and thus suggested an association of positive THC screen with decreased mortality in adult patients sustaining TBI [152]. THC, in itself has gained much media attention with few understanding its actual role in treatment or physiological effect. Similar to the endocannabinoid AEA, THC is a

low effector agonist [42, 43, 453, 454]. THC or THC synthetics are also not equivalent to natural endocannabinoids. THC has multiple effects at once in a very imprecise and irregularly responsive manner compared to natural endocannabinoids that function with "right place, right time" manner that is precise in effect location and tightly controlled. Furthermore, endocannabinoids do not have the psychoactive effects of exocannabinoids or synthetics targeting CB1Rs and CB2Rs. Adding to the complications of THC use, the exocannabinoid was shown at times of low endocannabinoid receptor density or limiting postreceptor effectors to antagonize CB1Rs usually controlled by 2-AG showing potential adverse receptor response and imprecision in receptor targeting [455–458]. These adverse effects become a primary challenge to overcome in the future of endocannabinoid system involved treatments. The lack of specificity could also become dangerous as synthetic highly efficacious street cannabinoid agonists such as Spice can cause much greater psychoactive side effects [459]. However, some studies have shown promising results in limiting withdrawal symptom effects. High doses of a CB1R antagonist rimonabant attenuated "high" with no withdrawal effects in humans taking a supervised moderate dose of THC [460]. However, in rodent models, long-term high doses of THC elicited withdrawal symptoms, thus showing that the mechanism is much more complicated than just THC "highjacking" CB1Rs for physiological effect [461]. Current research has sought to target CB2Rs more heavily than CB1Rs due to their lower risk of adverse psychoactive effects. However, many complications regarding the use and study of CBR2s make the future challenging. There are currently a lack of highly selective CB2R antibodies [462] to study as well as no availability of CB2R floxed or Cre mouse to use. Under some conditions, CB1Rs and CB2Rs actually create a heteromer making it difficult to isolate each receptor's function from one another in testing [463]. Furthering the isolation challenges, there has been trouble inducing only CB2Rs without CB1R effect as well as trouble selecting only for CNS CB2Rs without affecting PNS CB2Rs where they are most prevalent [32].

Phytocannabinoids: a viable treatment option?

The potential medicinal properties of marijuana have been the subject of intense scientific debate for decades. The approvals of nabiximols and purified CBD extract for the treatment of spasticity and pediatric epilepsy have drawn global medical attention to cannabinoids [464]. Thirty-two states and Washington, DC in the USA allow the use of marijuana to treat certain medical conditions. However, medical marijuana laws differ widely from state to state [465]. Cannabinoids may differ in composition and biological effects, depending on marijuana preparations. Medical cannabinoids, particularly non-psychotropic CBD, have demonstrated considerable promise in ameliorating chronic pain and various diseases ranging from neurological and movement disorders to cancer [466–468].

Clinical studies on patients with MS revealed efficacy of oral cannabis extract (OCE) in spasticity and related pain [414, 415]. In addition, nabiximols, a cannabis extract preparation, reduced bladder void in urinary infection [414]. Further, the studies reinforced the benefits of cannabis in neuropathic pain and suggested an improved safety profile as an extract without undesirable neurological effects when containing low THC concentrations (< 4%) produced therapeutic benefits without undesirable neurological effects [415, 419]. Nabiximols mouth spray (Sativex®) contains CBD and THC that are currently available in the UK, Canada, and several European countries for treating the spasticity and neuropathic pain in MS patients [416–418]. The US Food and Drug Administration (FDA) approved a CBD-based liquid medication called Epidiolex® for the treatment of two forms of severe childhood epilepsy [417, 418], as well as THC-based pills, dronabinol (Marinol®) and nabilone (Cesamet®), for the treatment of nausea in cancer patients undergoing chemotherapy and to stimulate appetite in AIDS patients with marked weight and muscle loss [417, 418]. In fact, with the rising concern over opioid epidemic, cannabis and cannabinoids are emerging as strong alternatives for pain relief [413]. However, a complete understanding of action of cannabis should be desired as THC-mediated relief in chronic radicular neuropathic pain is associated with altered brain connectivity among anterior cingulate and dorsolateral prefrontal cortex with somatosensory cortex [420].

The risks and benefits of cannabinoid should be weighed carefully as marijuana, like all drugs, has potential risks. For example, cannabinoid not only increased appetite in cancer patients but also declined the quality of life, which may be due to the side effects of cannabinoid [469]. Further, oral cannabinoids have shown many adverse effects, e.g., dysphoria, dizziness, depression, or hypotension compared with conventional antiemetic therapy [1]. In addition, efficacy of cannabinoids is still unknown in neurologic conditions, e.g., dyskinesia in patients with Parkinson's disease, non-chorea-related symptoms of Huntington's disease, Tourette syndrome, cervical dystonia, and epilepsy [1, 414]. Common side effects include dizziness, dry mouth, nausea, disorientation, euphoria, confusion, sedation, and cardiac arrhythmia in people who are already at risk. Regular smoking of marijuana can be addictive and is associated with breathing problems and lung infections [470].

Insufficient literature and varied composition of cannabis products lead to inconclusive evidence of cannabinoid use and their efficacy in many diseases. Further, the prevalence of a wide range of adverse events associated with medical marijuana (ranging from dry mouth to patient death) is a potential

question that need to be addressed [415, 471]. As the scientific and medical world advance in the field of medical uses of marijuana, evidences suggest that marijuana may be an effective treatment for chronic pain, neuropathic (nerve) pain, and muscle spasms due to multiple sclerosis or paraplegia. Now as marijuana's use as a treatment for certain medical indications has taken focus, patients and physicians both have to learn about its potential risks and benefits [472].

Conclusions and future PPPM strategies: innovative approach by predictive diagnostics, targeted prevention, and personalization of medical services

One of the most significant features of medicinal cannabis is its ability to be considered as personalized medicine by allowing individuals to control over their own treatment (e.g., dose, time, and type of cannabis). This aspect of medicinal cannabis is more meaningful in CNS-related diseases. All neurodegenerative diseases need great medical support from early diagnosis and prognostic evaluation to personalized therapeutic regimes and a better prediction of treatment outcomes. Brain imaging along with advanced data acquisition and analysis has become a major important tool to identify disease and proper treatment benefits clinically [473]. However, lack of specific biomarkers to identify persons at risk for neurodegenerative disorders is an avenue for major improvement in the field. The first step would be to invent new preclinical models for neurodegenerative diseases that depict initiation and progression of diseases more accurately. Then identifying key molecular pathways relevant for pathophysiology of neurodegenerative diseases maybe considered a novel and viable perspective for both predictive as well as individualized medicine and targeted therapeutic modality. In light of systemic alteration, because it may seem that the impact of mechanistic approach would be diminished, at least in the short-term, therefore, the multi-omics at DNA and protein (both expression and activity) levels would be highly recommended and useful. An established biomarker panel is considered as a powerful tool for personalized medicine as for an individualized patient profiling and improved multi-level diagnostics, in a predictive, preventive, and prognostic fashion. A major requisite to achieve this is an increased interaction between basic scientists and clinicians with respect to preventive, predictive, and personalized medicines (PPPM) in neurodegenerative diseases [473].

The ECS has been shown to influence a range of CNS diseases as detailed in this review and numerous other systemic pathologies as well. The current literature is only just starting to scratch the surface on how the ECS can be targeted and modulated for therapeutic benefit. The future seeks to further understand CB2Rs due to their highly inducible feature making them a great therapeutic target [32]. The use of selective CB2R agonists shows promising targets to manipulate drug-seeking behavior, reward, dependence, and addiction pathways [28, 29, 474]. A primary target for future research would be to develop more selective CB2R agonists with less CB1R adverse activation. Another strategy would be to develop tissue specific activator/inhibitor of CBRs to limit peripheral side effects [475]. Additional options to be further explored are combination treatment plans in which FAAH modulators are used with agonists to control effect of metabolism and synthesis of natural endocannabinoids while implementing effects of synthetic agonists [32, 33].

Cannabis or cannabis-based compounds are becoming common in treating medical conditions. Since there is a definite lack of conclusive data on efficiency and side effects of cannabinoids in clinical conditions, treatment with cannabis or its products must be proceeded cautiously. Health care professionals serve as the most frequent source of information regarding cannabis risks and benefits. As more and more states have adopted medical cannabis laws, medical professionals must be trained for cannabis effect and health outcomes and must provide awareness about cannabis to concerned patients. Planned and standardized training could ensure that health care professionals are prepared to identify medically appropriate symptoms and conditions for use of cannabis [476].

The endocannabinoids show great promise for future therapeutics; however, a rational approach is necessary to develop specific agonist/antagonist régimes and to avoid unwanted health outcomes. In order to inform policymakers, practitioners and users more clearly, future studies should be performed by following uniform guidelines and reporting of patient outcomes [477]. In addition, better understanding of mechanisms responsible for the pathophysiology of neurodegenerative diseases and involvement of cannabinoid system would establish more certain platform for PPPM effectively [478]. Hence, further studies are needed to identify functional links between neurodegenerative diseases and endocannabinoid system and to translate them according to PPPM-guidelines [478] to provide higher standards of health care to affected patient.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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