Cannabis therapy in neurological disorders: Recent advances and perspectives

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ABSTRACT

Both phytocannabinoids (Δ9-tetrahydrocannabinol, cannabidiol) and synthetic derivatives (nabilone, dronabinol) showed therapeutic benefits in some neurological disorders. Cannabis inhalation was reported to attenuate several symptoms (rigidity, bradykinesia, tremor) in Parkinson’s disease. A significant reduction in monthly seizures in patients with epilepsy has been noted for cannabidiol, while administration of Δ9-tetrahydrocannabinol resulted in benefits on psychomotor agitation in patients suffering from Alzheimer’s disease. Although there are clinical studies supporting the use of cannabis preparations as adjuvant therapy in neurological disorders, more investigations are needed to assess their safety and efficacy.

Keywords: cannabis, phytocannabinoids, neurologic disorders

INTRODUCTION

Since ancient times, Cannabis sativa L. (Cannabaceae, hemp) has been used for its medicinal benefits. Reduction in nausea, vomiting, orexigenic effects in patients with AIDS or patients receiving chemotherapy, reduction of intraocular pressure, as well as general analgesic effects are among its known pharmacological effects (1-5). Cannabis sativa is indigenous to Central Asia being cultivated both legally for fibers and seeds, and illicitly for the production of illegal drugs such as marijuana (dried flower buds from female plants), hashish (compressed plant trichomes) and oils (rich in cannabidiol, but containing less than 0.2% tetrahydrocannabinol). The most potent phytocannabinoids are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Also, two synthetic THC derivatives, nabilone and dronabinol, are used for medical purposes. THC is responsible for the psychoactive, undesirable effects whereas CBD, as well as nabilone and dronabinol, lack such effects (6).

The endogenous cannabinoid system was discovered in 1990. Since then, extensive research on the potential use of cannabinoids in neurodegenerative disorders has been done. Endocannabinoids activate the cannabinoid receptors (G-protein–coupled receptors) resulting in an inhibitory effect on glutamate release (7).

The cannabinoid receptors, namely CB1 (cannabinoid receptor type 1) and CB2 (cannabinoid receptor type 2), are present in the nervous and immune systems. Most of CB1 receptors are located in areas of pain signalling control in central nervous system (CNS), and, to a lesser extent, in the cerebellum and hippocampus, basal ganglia, neuromuscular junctions and peripheral nerves (8). Activation of CB1 receptors...
results in the inhibition of glutamate and gamma-aminobutyric acid (GABA) release from the presynaptic terminals, with subsequent influence on memory processing, nociceptive pathways, psychoactivity and motor control. CB1 receptor activation explains the benefits (reduced nausea and vomiting, pain alleviation, enhanced appetite, reduced dyskinesia and intraocular pressure) but also the side effects (somnolence, fatigue, possible hallucinations) reported by patients. CB2 receptor activation leads to attenuation of chronic inflammation and suppression of chronic pain, but the complete mechanism underlying the aforementioned effects is yet to be understood. CB2 receptors are present in peripheral nerves, brain microglia, keratinocytes, bone and liver. CB2, and to a lesser extent CB1 receptors, are also found in macrophages, polymorphonuclear neutrophils and lymphocytes, their activation supporting, in part, the anti-inflammatory potential of cannabinoids (8).

The endocannabinoid system is involved in tissue homeostasis after pathological alterations, thus being a potential therapeutic target in numerous diseases, including neurological ones. Animal studies showed alterations in the endocannabinoid system in different neurological disorders and efforts have been made to use these findings for the development of new treatments. These efforts made possible the approval of nabiximols (Sativex®, a mixture of THC and CBD, each spray of 0.1 ml containing 2.7 mg THC and 2.5 mg CBD) for the treatment of pain and/or spasticity in multiple sclerosis in 2005 in U.S.A. and Canada, which was a milestone in cannabis research (9).

A systematic review done by the American Academy of Neurology, evaluating publications from 1948 to 2013 regarding cannabinoids use in multiple sclerosis, motor diseases, and epilepsy, revealed that only THC in combination with CBD or CBD alone (oral administration) seemed to alleviate spasticity in multiple sclerosis (10). Other formulations seemed to be effective against the aforementioned disorders, but with less evidence. Proof was insufficient to conclude on the efficacy of smoked cannabis. There was no conclusive evidence regarding the effectiveness of cannabis and cannabis-derived products in other neurological disorders, such as Huntington’s disease and Tourette syndrome (11).

HUNTINGTON’S DISEASE
Huntington’s disease affects the dopaminergic neurons in globus pallidus with consequent locomotor, mood and/or mental impairments. Pharmacological interventions in the endocannabinoid metabolism protected neurons in different models of Huntington’s disease. Endocannabinoid reuptake inhibitors had anti-hyperkinetic effects in animals treated with 3-nitropropionic acid, mostly via activation of TRPV1 (transient receptor potential cation channel subfamily V member 1, a capsaicin-like receptor, also activated by endocannabinoids in pain sensation) (20).
One double-blind, randomized, controlled study assessed the effects of CBD (10 mg/kg/day, oral administration for six weeks) in patients with Huntington’s disease. No clinically significant improvements were observed in chorea sensitivity, functional ability or information recall in comparison with placebo (21). The latter findings were confirmed by a double-blind, placebo-controlled, randomized, crossover, pilot study initiated by Lopez-Sendon Moreno et al. (2016) on 26 patients with Huntington’s disease. The study investigated the potential benefits of nabiximols and revealed that while nabiximols (Sativex®) were well tolerated, they did not improve the clinical outcomes (22).

MULTIPLE SCLEROSIS

Spasticity is the main cause of disability in patients with multiple sclerosis. Cannabinoids reduce glutamate release, thereby regulating glutamatergic excitability and consequently spasticity (23). In mice models with autoimmune encephalomyelitis which recreates multiple sclerosis in humans, CBD seemed to ameliorate disease symptoms. The mechanisms underlying the reduction in spasticity are the decrease in pro-inflammatory mediators and activation of PPARγ (peroxisome proliferator-activated receptor gamma, also known as glitazone receptor) and PI3K-AKT-mTOR pathway (regulator of cell cycle) (24).

The MUSEC trial (2012), a double-blind, placebo-controlled, phase III study, involving 279 patients, assessed the effects of oral administration of a standardized Cannabis sativa extract (0.8-1.8 mg CBD and 2.5 mg THC) on spasticity, pain, but also sleep quality in multiple sclerosis. The study revealed the capacity of Cannabis sativa standardized extract to alleviate muscle stiffness in multiple sclerosis. Authors also concluded that there was an effective pain remission in patients, especially in patients having high baseline pain score (25). In a randomized, placebo-controlled, crossover trial, Corey-Bloom et al. (2012) showed that inhaled cannabis reduced the treatment-resistant spasticity in mutiple sclerosis (26). A placebo-controlled, double-blind, between-groups study on 493 patients with progressive multiple sclerosis, did not find any effect on disease progression when receiving a daily oral cannabis extract (standardized in 0.8-1.8 mg CBD and 2.5 mg THC), dose-adjusted for each patient to a maximum of 28 mg of THC daily for ten weeks (27). As noted elsewhere, 40-60% of individuals with multiple sclerosis manifest some degree of cognitive dysfunction, therefore the use of cannabis products may further compromise cognitive functions (28).

AMYOTROPHIC LATERAL SCLEROSIS

The main symptoms of amyotrophic lateral sclerosis are miastenia, spasticity, and respiratory difficulties. The disease is fatal and affects the upper and lower motor neurons originating in the motor cortex in brain and spinal cord, respectively. Cannabinoids are supposed to act in the aforementioned regions, thus being potentially useful in alleviating symptoms such as spasticity, dysphagia, negative mood and pain (29). As the immune cells express CB2 receptors, cannabis might play a role in downregulating cytokine and chemokine production, hence reducing neuroinflammation associated with amyotrophic lateral sclerosis pathogenesis. Additionally, cannabis may provide neuroprotection by modulating glutamatergic transmission (30).

Currently there is a lack of clinical data to support cannabinoids use in amyotrophic lateral sclerosis. However, there is only one randomized, double-blind, placebo-controlled, crossover trial that investigated the benefits of dronabinol in 27 patients. It has been noted that even though 5 mg of dronabinol is well-tolerated, there was no alleviation in the number or intensity of cramps, quality of life, appetite, sleep, or mood (31).

EPILEPSY AND SEIZURES

Epilepsy affects 50.4 per 100,000 people per year, being one of the most frequent neurological disorders. Approximately 30% of the patients with epilepsy have a drug-resistant form, that is failure to control one’s seizures with the adjusted dose of at least two antiepileptic drugs (32). CBD showed anticonvulsant effects in the pentylentetrazole-induced epilepsy model, pilocarpine temporal lobe epilepsy model and penicillin-induced partial seizure model most probably via G-protein-coupled receptor 55 (GPR55) antagonism and TRPV1 desensitization (33).

Only two randomized, placebo-controlled studies done by Devinsky et al. (2016, 2017), evaluated the potential benefits of CBD as adjuvant therapy in epilepsy. In the 2016 study, Devinsky et al. evaluated the efficacy of CBD (2-5 mg/kg/day for 12 weeks) as an add-on therapy to the classical treatment (antiepileptic drugs) on 137 patients with Dravet and Lennox-Gastaut syndromes, which are severe forms of epilepsy. Authors noted a reduction in monthly
seizures frequency in 36.5% of patients, with the most significant reduction in patients with focal and atonic seizures (34). In 2017, Devinsky et al. performed a double-blind, randomized clinical study on 120 patients (both children and adults) suffering from Dravet syndrome and drug-resistant epilepsy, split into two groups, control and placebo. The control group received 20 mg/kg/day CBD for 14 weeks as adjuvant therapy. 43% of patients in the control group had more than 50% reduction in seizures frequency. Also, in the control group, 5% of patients had no seizures (35).

ALZHEIMER’S DISEASE
Tau proteins, essential for microtubule assembly, integrity of cytoskeleton and signal transport in neurons, are the main protagonists in this disease, developing fibrillary tangles. In a model of Alzheimer’s disease-related neuroinflammation (intrahippocampal injection of the human amyloid-β in mice), CB1 agonists showed promising effects against neuronal tau hyperphosphorylation and behavioral impairments (36). Additionally, cannabinoids inhibit acetylcholinesterase and β amyloid aggregation, while agonism on CB1 and 2 receptors results in a significant increase of β amyloid clearance across the blood-brain barrier (37-39).

Casajeros et al. (2013) noted that nabiximols reduced tangleing of tau proteins in mice, improving dopamine metabolism, glial function and oxidative stress, as well as reduction in anxiety and self-injury (40).

In 2006, Walther et al. initiated an open-label, two-week study, on five Alzheimer’s disease patients and one patient with vascular dementia. Patients presented improvements in the nocturnal motor activity, hunger, agitation, and irritability with no adverse events when receiving 2.5 mg THC at 19:00 h, on a daily basis (41). However, a randomized, controlled trial conducted by van den Elsen et al. (2015) on 50 patients with dementia receiving 1.5 mg THC (three times a day, for three weeks), failed to show any benefit in comparison with placebo. Authors also noted that a total absence of adverse reactions might be due to inadequate dosage regimens (42).

NEUROPATHIC PAIN
Cannabis has been used to alleviate pain since 2900 b.C., as mentioned in ancient Chinese texts. The cause of neuropathic pain are inadequate messages sent to pain centers by damaged spinal and/or sensory nerves. In diabetic patients with neuropathy, for example, pain sensation is not in the foot tissue per se, being localized in the peripheral nociceptors. As the disease affects them, the brain misinterprets the incoming signals as pain in the affected tissues.

Cannabis plants per se are rarely used as painkiller medicine, patients using instead NSAIĐs, GABA agonists (gabapentin, pregabalin) and opioids (43,44).

When damage is inflicted, all cells synthesize anandamide (an endogenous cannabinoid derived from arachidonic acid) which modulates pain signals transmission by CB receptors agonism, in turn leading to a reduced inflammation and sensitization. THC also acts as an agonist on CB receptors. CB1 receptors control the release of neurotransmitters in CNS; they are present in sensory neurons of the dorsal basal ganglia and trigeminal ganglion. To a lesser extent, CB2 receptors are found in CNS and dorsal basal ganglia, being up-regulated in response to peripheral nerve injuries. They modulate neuronal and immune interactions and inflammatory hyperalgesia (43).

A recent systematic review and meta-analysis examined 28 randomized trials involving 2,454 patients with chronic pain and noted that administration of cannabinoids was associated with a greater reduction in pain compared with placebo (37% vs. 31%). According to Whiting et al. (2015), moderate evidence emerged in supporting cannabinoids use in the chronic pain treatment, especially in the neuropathic pain (45). A placebo-controlled trial (not included in Whiting’s meta-analysis), using aerosolized cannabis, showed attenuation of the conventional analgesics-resistant pain in patients with diabetic neuropathy; the analgesic effect was dose-dependent (46). The randomized, placebo-controlled, crossover study of Wilsey et al. (2013), involving 39 patients with central neuropathic pain (related to spinal cord damage and disease) using vaporized cannabis, showed dose-independently reductions in neuropathic pain scale ratings (47). Literature examination showed no conclusive studies regarding cannabis benefits in different headache disorders, though it appears that cannabis may emerge as a potential treatment.

SAFETY
The use of cannabis is subjected to concerns regarding THC and CBD concentrations, as they might vary with species and extraction methods. In addition, common adverse reactions similar to other CNS depressants (barbiturates, benzodiazepines, neuroleptic medication) might occur.
## TABLE 1. Summary of clinical trials involving cannabis, phytocannabinoids and synthetic cannabinoids

<table>
<thead>
<tr>
<th>Neurological disorder</th>
<th>Type of study</th>
<th>Patients</th>
<th>Treatment</th>
<th>Study medication</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s disease</td>
<td>survey</td>
<td>339</td>
<td>Yes</td>
<td>oral cannabis leaves</td>
<td>improvement in cardinal motor symptoms and dyskinezia</td>
<td>Venderova et al. (2004)</td>
</tr>
<tr>
<td></td>
<td>placebo-controlled, double-blind trial</td>
<td>21</td>
<td>75 to 300 mg CBD, 6 weeks</td>
<td>no effects on motor functioning</td>
<td>Chagas et al. (2014)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>open-label observational</td>
<td>22</td>
<td>No</td>
<td>inhaled cannabis</td>
<td>reduced effect on bradykinesia small improvement in tremor, rigidity and posture</td>
<td>Lotan et al. (2014)</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>double-blind, crossover, randomized, controlled trial</td>
<td>15</td>
<td>No</td>
<td>10 mg/kg/day CBD for 6 weeks</td>
<td>no improvements in disease symptoms</td>
<td>Consroe et al. (1991)</td>
</tr>
<tr>
<td></td>
<td>double-blind, placebo-controlled, crossover, pilot trial</td>
<td>24</td>
<td>Yes</td>
<td>Nabiximols (Sativex®) oral spray, 12 sprays/day for 12 weeks</td>
<td>no overall treatment effect on clinical disease progression</td>
<td>Lopez-Sendon Moreno et al. (2016)</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>open-label, pilot</td>
<td>5</td>
<td>-</td>
<td>2.5 mg Dronabinol (THC) daily for 2 weeks</td>
<td>improvement in nocturnal motor activity, agitation, appetite, and irritability</td>
<td>Walther et al. (2006)</td>
</tr>
<tr>
<td></td>
<td>randomized, double-blind, placebo controlled-trial</td>
<td>50</td>
<td>Yes</td>
<td>1.5 mg THC thrice a day for 3 weeks</td>
<td>no significant improvements in NPS* score, agitation, and quality of life</td>
<td>van den Elsen et al. (2015)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>double-blind, placebo controlled</td>
<td>279</td>
<td>Yes/No</td>
<td>oral cannabis extract (max. 25 mg THC daily for 12 weeks)</td>
<td>significant reduction in muscle stiffness</td>
<td>Zajicek et al. (2012)</td>
</tr>
<tr>
<td></td>
<td>placebo controlled, double-blind crossover study</td>
<td>30</td>
<td>No</td>
<td>smoked cannabis (4%THC) for 3 days</td>
<td>significant reduction in spasticity and pain</td>
<td>Corey-Bloom et al. (2012)</td>
</tr>
<tr>
<td></td>
<td>placebo-controlled, double-blind, between-groups</td>
<td>493</td>
<td>Yes</td>
<td>oral THC (dose-adjusted, max 28 mg daily) for 36 months</td>
<td>no overall treatment effect on clinical disease progression</td>
<td>Zajicek et al. (2013)</td>
</tr>
<tr>
<td>Amyotrophic lateral disease</td>
<td>randomized, double-blind, placebo controlled, crossover trial</td>
<td>27</td>
<td>No</td>
<td>5 mg THC twice a day for 2 weeks</td>
<td>no significant improvement in cramp intensity</td>
<td>Weber et al. (2010)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>open-label trial</td>
<td>214</td>
<td>Yes</td>
<td>2-5 mg/kg/day oral CBD for 12 weeks</td>
<td>possible reduction of seizures frequency</td>
<td>Devinsky et al. (2016)</td>
</tr>
<tr>
<td></td>
<td>double-blind, placebo-controlled trial</td>
<td>120</td>
<td>Yes</td>
<td>20mg/kg oral CBD for 14 weeks</td>
<td>reduction in convulsive-seizure frequency; higher rates of adverse events</td>
<td>Devinsky et al. (2017)</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>placebo-controlled, double-blind, crossover study</td>
<td>39</td>
<td>-</td>
<td>inhaled, cannabis (1.29%/ 3.53% THC)</td>
<td>reduction in pain; dose-independent efficacy</td>
<td>Wilsey et al. (2013)</td>
</tr>
<tr>
<td></td>
<td>placebo-controlled, double-blind, between groups trial</td>
<td>246</td>
<td>Yes</td>
<td>sublingual, nabiximols (Sativex®) 24 sprays/day for 14 weeks</td>
<td>significant improvements in pain and sleep quality</td>
<td>Serpell et al. (2014)</td>
</tr>
<tr>
<td></td>
<td>meta-analysis</td>
<td>6462 (79 trials)</td>
<td>Yes/No</td>
<td>different formulations of cannabis or derivatives</td>
<td>benefits associated with cannabinoids but without statistical significance</td>
<td>Whiting et al. (2015)</td>
</tr>
</tbody>
</table>

*NPS – neuro-psychiatric symptoms

While some evidence suggests that there may be a small reduction in the hippocampal volume in cannabis users vs. non-users, but with no clinical manifestations, other data show that chronic, heavy use of smoked cannabis is associated with a decline in some cognitive abilities (decision-making and conceptual planning) (48, 49).
Unlike THC, CBD seems to have little influence on vital signs such as blood pressure and respiratory function. However, as Devinsky et al. (2017) noted, patients with Dravet syndrome treated with CBD reported significant adverse events such as somnolence (36%), diarrhea (31%), fatigue (20%), vomiting (15%), fever (15%), lethargy (13%) (35). Another potential concern regarding CBD use in different neurological disorders is drug-drug interactions, as CBD may inhibit several CYP450 enzymes (CYP2C9, CYP2D6), in turn leading to a delay in the metabolism of common OTC and prescription drugs that are metabolized by the aforementioned enzymes (50).

CONCLUSIONS

Although some clinical studies underline beneficial effects of cannabis formulations as an adjuvant therapy in different neurological disorders, research in this field is in its beginnings. Therefore, more studies should be performed to draw a solid conclusion regarding any medical therapy.

More research is needed to answer important questions regarding the safety profiles of either cannabis plant or its different pharmaceutical formulations and potential medical indications, especially in neurological diseases such as amyotrophic lateral sclerosis, multiple sclerosis, epilepsy and Alzheimer’s disease.

Author contributions

Alexandru Mandici – conceptualization, original draft preparation; Daniel Cojocariu – collection of data; Anca Miron – conceptualization, supervision, review, editing.

REFERENCES


