The role of cannabinoids and endocannabinoid system in the treatment of epilepsy

Monika Pędracka, Jacek Gawłowicz

Department of Neurology, State Specialist Hospital in Lublin, Poland

SUMMARY
Introduction. The treatment of epilepsy is still a major challenge. Despite the introduction of many new antiepileptic drugs, approximately 30% of patients still remain drug resistant. In the absence of a satisfactory therapy outcome, which is sometimes associated with numerous side effects, there is a need for new and effective drugs with low toxicity. Cannabinoids have been shown in preliminary animal model studies and in studies of patients with epilepsy to have antiepileptic activity.

Aim. The aim of this paper is to review current reports on the role of the endocannabinoid system and cannabinoids in the treatment of epilepsy.

Methods. Articles from PubMed and Scopus published up to 2015 concerning the role of cannabinoids and the endocannabinoid system in the treatment of epilepsy are reviewed.

Review and Discussion. Cannabis has been used for thousands of years in the treatment of various diseases. They contain cannabinoids, which act on the endocannabinoid system which regulates many biochemical and physiological processes. By affecting glutamate and gamma-aminobutyric acid (GABA) neurotransmission cannabinoids have the ability to affect seizure threshold. The best known cannabinoid is cannabidiol, which inhibits the occurrence of seizures without causing significant side effects in humans and animals. However, only a small number of double blind, randomized and placebo controlled studies have been published to date.

Conclusions. The role of cannabinoids in the treatment of epilepsy is not well defined because these substances have shown pro-convulsive actions in some animal studies and also there are not many randomized trials performed to date. The existing human data do not support the conclusion that cannabinoids are effective and safe in the treatment of epilepsy, but do encourage further studies on a larger group of patients.

Key words: cannabinoids • cannabidiol • tetrahydrocannabinol • marijuana • epilepsy

INTRODUCTION
Epilepsy is one of the most common neurological disorders which affects about 50 million people in the world (Goldenberg, 2010). According to the 2009 definition of Therapeutic Working Group of the International League Against (ILAE) epilepsy can be considered as drug-resistant in the event of failure of two successive properly selected patient regimens – based on the use of one or more preparation (Kwan et al., 2010). The resistance to treatment entails approximately 20–30% of patients with epilepsy. Its consequence can be worse quality of life and higher mortality. In the absence of satisfactory results of therapy, which is often associated with numerous side effects, there is a need for new, effective and safe drugs with different mechanisms of action.

Recently, cannabinoids arouse particular interest as substances that can modify the course of some neurological diseases in a positive way. Until now the efficacy of the formulations of cannabis in treating the neuropathic pain, nausea and vomiting in cancer, for the
treatment of spasticity in multiple sclerosis and spinal diseases has been demonstrated (Ożarowski et al., 2014). They probably have anti-inflammatory, anticonvulsant, neuroprotective, antipsychotic and sedative activities (Zhornitsky and Potvin, 2012; Gloss and Vickrey, 2014). Perhaps they could find application in the treatment of alcohol and nicotine addiction (Karabowicz et al., 2014). An interesting subject of many researches is the effect of cannabinoids on the proliferation, growth and apoptosis of cells. These properties can cause regression of brain tumors, especially gliomas. They inhibit neurodegeneration processes, which can produce a beneficial clinical effect in Parkinson’s disease, Huntington’s Chorea, or Tourette’s syndrome (Benbadis et al., 2014). Some of the isolated cannabinoids showed anticonvulsant properties in animal models, in particular cannabidiol (CBD) and its propyl derivative – cannabidivarin (CBDV) (Jones et al., 2010; Rymanowski, 2014; Hill et al., 2012).

Sativex, a drug based on cannabis and comprising of a mixture of CBD/tetrahydrocannabinol (THC) at a ratio of approximately 1:1, is approved for the treatment of spasticity in multiple sclerosis in over 20 countries (http://www.gwpharm.com). Another preparation – Epidiolex, a highly purified cannabis extract at a concentration of CBD approximately 98%, is currently being evaluated for the treatment of Lennox-Gastaut and Dravet syndromes, that constitute the so-called catastrophic epilepsies (https://clinicaltrials.gov).

Cannabinoids may have therapeutic potential in the treatment of many diseases, however, because of the actions of interest groups led by the environmentalists which support the legalization of marijuana, the subject entails a heated discussion not only in the world of medicine but also within the media.

AIM
The aim of this paper is to summarize data on the role of the endocannabinoid system and cannabinoids in the treatment of epilepsy.

METHODS
Articles from PubMed and Scopus published up to 2015, concerning the endocannabinoid system and treatment of epilepsy with cannabinoids were identified and reviewed. Keywords used: cannabinoids, cannabidiol, tetrahydrocannabinol, marijuana, epilepsy.

REVIEW OF LITERATURE AND DISCUSSION
Classification and properties of cannabinoids, history of cannabis use
Cannabinoids are organic compounds, which are divided into three groups:

1) phytocannabinoids, such as cannabidiol and Δ9-tetrahydrocannabinol,
2) endocannabinoids (e.g. anandamide and 2-arachidonylglycerol), and
3) synthetic cannabinoids (e.g. WIN55212-2, CP55940 or HU210).

Phytocannabinoids probably only occur naturally in plants of the species Cannabis. Endocannabinoids play a significant role in the human body, taking part in the regulation of many physiological phenomena, including immunological and hormonal phenomena (Karabowicz et al., 2014).

Hemp (cannabis) comes from Central Asia and is one of the oldest medicinal plants. Historical archives show that it has been used in the treatment of various diseases for approximately 5000 years (Mechoulam, 1986). Hemp was also used for the production of rope, fabric and paper. Emperor Shen Nong, the father of Chinese medicine (2700 BC), advocated marijuana in the treatment of rheumatism, malaria, constipation, menstrual disorders and beriberi. In India the use of cannabis for medicinal and probably religious purposes began approx. 1000 BC. These plants were used as analgesics, anticonvulsants, sedatives, hypnotics, antispasmodic, digestive and as appetizing aids (Zuardi et al., 2006). The tradition of using cannabis was transferred from India to Persia, Assyria and the whole Middle East and Africa. In Europe marijuana appeared most likely thanks to contemporary migration of peoples and trade. The precise time at which it appeared on this continent is not known (Jędrzejko, 2011).

The anticonvulsant properties of cannabis have been known for centuries. Between 9th and 10th century BC the Arabic scholar Al Mayusi described its anticonvulsant effect after nasal application of the juice from the leaves of Cannabis sativa. Persian physician Al-Badri, in the 15th century BC, described the efficacy of cannabis in the treatment of convulsions during its regular application (Lozano, 2001; Mechoulam, 1986). In the 19th century several articles on the efficacy of cannabis extract in controlling severe seizures were pub-
lished – e.g. O’Shaughnessy, 1842; Shaw, 1843 (Cunha et al., 1980). Irish physician William O’Shaughnessy in
forty pages described the healing properties of cannabis, including the ability to inhibit seizures (O’Shaughnessy, 1842). In this way, hemp was introduced to the western pharmacopoeia (Mikuriya, 1969).

There are several varieties of Cannabis – C. sativa, C. indica and sometimes C. ruderalis. Cannabis sativa contains more than 500 different chemical compounds, of which approx. 100 are the cannabinoids (Radwan et al., 2009; Hill et al., 2012; Szaflarski and Bebin, 2014). An important ingredient in cannabis is Δ9-tetrahydrocannabinol (Δ9-THC), which has psychoactive properties. This substance was first described in 1964 by a group of scientists from the Hebrew University in Jerusalem under the leadership of Gaoni and Mechoulam. Another important Cannabis compound is cannabidiol – isolated in the 1940’s. Its structure was determined in 1963 (Gloss and Vickrey, 2014). The tetrahydrocannabinol content in a plant depends on genetic properties, age, growing conditions, the process of collection, the type of soil and the climate. The most common cannabis products include: 1) marijuana, which is drought leaves and inflorescence (approx. 0.5%–4% THC) and 2), hashish (15% THC), dried and compressed resin extracted from plants. Hashish oil (30% THC) is also available on the drug market. In specially genetically modified plants tetrahydrocannabinol content can be very high. In the Netherlands, a variety of cannabis called Netherweed is grown, containing approximately 20% THC (Jędrzejko, 2011; Szukalski, 2005).

Other important compounds isolated from Cannabis are: cannabiol (CBN), cannabigerol (CBG), cannabichromene (CBC), cannabidivarin (CBDV) (Izzo et al., 2009; Russo, 2011; Jones et al., 2010).

Tetrahydrocannabinol, which has psychoactive properties, is a partial agonist of the CB1 and CB2 receptors (Pertwee, 2008; Szaflarski and Bebin, 2014). In the central nervous system it has the ability to both stimulate and inhibit the secretion of neurotransmitters. It can activate or block the CB1 receptors, which explains the anticonvulsant and proconvulsant properties in different models of epilepsy (Pertwee, 2008; Wallace et al., 2003).

The mechanism of the action of cannabidiol is not known (Wallace et al., 2003; Santos et al., 2015). This compound has a very weak affinity for the CB1 receptors, it affects other mechanisms – it is the antagonist of 5-hydroxytryptamine receptor (5HT1α), N-methyl-D-aspartate receptor (NMDA) and GABA receptors. It inhibits the reuptake of adenosine, serotonin, dopamine, GABA, norepinephrine (Szaflarski and Bebin, 2014; Maa and Figi, 2014; Agar, 2015). Other receptors associated with CBD that are putative endothe
cannabinoid receptors (Cbe), are paroxysmic proliferator-activated receptors gamma (PPAR-γ), alpha adrenergic receptors and opioid (μ) receptors (Gloss and Vickrey, 2014; Stanley et al., 2015). Cannabidiol may act indirectly on CB1 receptors by inhibition of fatty acid amide hydrolase activity (Stanley, 2015). It is the enzyme responsible for the degradation and destruction of anandamide – endocannabinoid that through the affinity to the CB1 receptors compete with THC for binding sites. Therefore, cannabidiol causes an increase of N-arachidonylethanolamine (AEA), thereby reducing the psychoactive effect of THC in the preparations of the CBD, causing their better tolerability. These compounds may act synergistically in the treatment of pain, inflammation, epilepsy and cancer (Russo, 2011).

Endocannabinoid receptors, endocannabinoid system

Substantive research on the endocannabinoid system began in 1988, after the isolation of cannabinoid receptors from the rat’s brain. They are a part of the endocannabinoid system that also includes endogenous ligands anandamide (AEA) and 2-arachidonylglycerol (2-AG), as well as transporters and enzymes involved in the biosynthesis and degradation (Pertwee et al., 2010). The endocannabinoid system is involved in many physiological processes (Pacher, et al., 2006; Karabowicz et al., 2014).

So far known cannabinoid receptors CB1 and CB2 close-coupled to G-proteins – are activated by endocannabinoids, which are emitted on the request in response to neuronal agitation (Lutz, 2004). This leads to inhibition of extracellular calcium influx into the cytoplasm, which in turn blocks the production of cyclic adenosine monophosphate (cAMP).

CB1 receptors, which are responsible for the psychotropic activity of THC, are mainly located at the ends of CNS neurons, and to a lesser extent in the peripheral system. Most are present in the hippocampus, cerebellum, striatum and basal ganglia (Ameri, 1999; Szaflarski and Bebin, 2014). They have also been identified in the internal organs, tonsils and skin (Karabowicz et al., 2015). Postsynaptic increase in intracellular calcium induced by neurotransmitters can cause the biosyn-
thesis and release of endocannabinoids in the synapse. Activation of CB1 receptors inhibits the release of, in-
ter alia, glutamate and GABA – it is important in mod-
ulating the seizure threshold (Pertwee, 2008).

CB2 receptors were mainly found in immune cells, neurons of peripheral terminals, microglia and in the
cerebral vascular endothelium. They have an effect
on the cardiovascular system and processes of cellular
immunity, also they regulate the secretion of cyto-
kines and the migration of immune cells (Sugiura and
Waku, 2002).

Endocannabinoids are synthesized in neurons of both
GABA and glutamate; by the stimulation or inhibition
of transmission of the transmitters they can cause a pro-
and anti-convulsant effect (Maa and Figi, 2014).

The high density of CB1 receptors in the cerebral
cortex, basal ganglia, hippocampus and cerebellum
is associated with the impact of cannabinoids on the
seizure threshold and adverse effects on memory pro-
cesses and cognitive and motor skills. A small number
of CB1 receptors are located in the brainstem, medulla
and thalamus and is the reason that relatively high dos-
es of Δ9-THC are associated with low toxicity (Herker-
ham et al., 1990; Szukalski, 2005).

The existence of other cannabinoid receptors can-
not be excluded. The GPR 55 receptor associated with
G protein is considered by some researchers to be the
third cannabinoid receptor (Brown, 2007; Ryberg et al.,
2007). However, for many researchers, it is not classi-
fied to any family of receptors and is called the orphan
receptor. GPR 55 has similar structure to the canna-
binoid receptors, it can interact with agonists of CB1/
CB2, as well as other ligands (Shore and Reggio, 2015).

Cannabinoids in animal models
Except for cannabidiol and THC, other ingredients of
cannabis (cannabinol, kannabidivarin and tetrahydro-
cannabidivarin) have also shown anticonvulsant prop-
erties in animal models (Gloss and Vickrey, 2014; Jones
et al., 2012). Wilkinson et al. (2003) reported that THC-
free extract, although devoid of antispastic properties,
still had anticonvulsant characteristics. Cannabidi-
ol inhibited the occurrence of tonic-clonic seizures in
mice in models of acute seizures induced by the max-
imal electroshock (MES). It was also active in models
based on the inhibition of GABA, with picrotoxin, iso-
niazid, bicuculline, pentylentetrazol (PTZ) and 3-mer-
caaptopropionic acid (Hill et al., 2012). CBD has shown
anticonvulsant properties in the pilocarpine model of
temporal lobe epilepsy, the penicillin model of partial
seizures in rats (Jones et al., 2010), electrical kindling
(Turkanis et al., 1979) and the audiogenic model (Con-
sro and Wolkin, 1977). There was no inhibition of sei-
zures induced by strychnine (Consroe et al., 1982) and
secondarily generalized seizures induced by cortical
implantation of cobalt in the model of chronic epilep-
sy (Colasanti et al., 1982). Tetrahydrocannabinol was
effective inter alia in models with MES, PTZ, strych-
nine, nicotine and in the model of temporal lobe epi-
lepsy (Devinsky et al., 2014).

Preclinical studies show that the CBD and other can-
nabinoids are effective in models of acute seizures, but
there are little data on their effectiveness in chronic
epilepsy models that are most useful in testing drugs
(Loscher, 2002).

Studies with the use of cannabinoids in human
epilepsy
To date only a small number of clinical trials of can-
nabinoids in the treatment of epilepsy have been pub-
lished. In the “Cochrane Systematic Review” (Gloss
and Vickrey, 2014) only four studies with blinded, ran-
domized, placebo-controlled study design were identi-
fied: Mechoulam (1978), Cunha et al. (1980), Ames and
Cridland (1985), Trembly and Sherman (1990). They are
summarized in table 1.

Summarizing the above trials, it must be concluded
that the study group was small (up to 15 people). Two
studies were presented in an incomplete form (abstract
and letter to the editor). There was no toxicity or sig-
ificant side effects at doses of 200–300 mg of CBD
for up to several months. The most common side ef-
fect was somnolence.

The American Academy of Neurology analyzed the
existing publications (1948–2013) on the use of canna-
bis preparations in treating various neurological disor-
ders. The results indicate a likely effectiveness in reduc-
ing spasticity in multiple sclerosis and inefficiencies in
the treatment of dyskinesias induced by levodopa. The
role of cannabis preparations in the treatment of epi-
lepsy, chorea and tics remains unclear (AAN Subcom-
mittee Koppel et al., 2014).

M. Hamerle et al. conducted an interesting study on
people suffering from epilepsy who had experienced
the use of illicit drugs; both cannabis and non-canna-
bis drugs. Cannabis was used by the group consisting
of 310 patients with epilepsy, from whom 13 were ac-
tive cannabis users and 297 were non active cannabis
users. The results show that in the vast majority of cases of cannabis consumption there was no affect significant effect on epilepsy (Hamerle et al., 2014).

Currently, there is too little research proving that cannabinoids are effective in the treatment of epilepsy. Only performing double-blind, placebo-controlled, randomized clinical trials with one or several cannabinoids can provide reliable information on their safety and efficacy (Friedman and Devinsky, 2015).

Anecdotal reports
Among the Facebook community of parents of children suffering from severe epilepsy syndromes (such as Dravet, Doose and Lennox-Gastaut), a survey consisting of 24 questions concerning the clinical picture of epilepsy and the use of cannabis preparations rich in CBD (without precisely defining the product composition, dosage) was conducted. Inclusion criteria (diagnosis of epilepsy and current use of cannabis) entailed 19 people. In the survey, 84% of respondents (16/19) stated that was a reduction in number of seizures in their children, 42% (8/19) reported a reduction in the frequency of attacks by more than 80% and in 2 patients (11%) seizures did not appear. Some parents reported improved attention, mood, and sleep in children, some experienced minor side effects such as fatigue and sleepiness (Porter and Jacobson, 2013).

Marijuana addiction and epilepsy
A separate theme is the dependence of severity of epilepsy patients who smoke marijuana. The data are inconclusive and sometimes contradictory. In a study (Ng et al., 1990) smoking marijuana reduced propensity to first seizure in men. Other findings may be based on the results of the interview carried out among 215 patients with epilepsy who smoked marijuana (Gordon and Devinsky, 2001). Among this group of respondents, 90% stated no association between the use of cannabis, and the impact on the frequency or severity of seizures. In some patients, with primary generalized epilepsy, marijuana exacerbated the illness. Unfortunately, both of these studies do not include reliable data on the regular use of anti-epileptic drugs and patient compliance.

A single publications describe the possible proconvulsive effects of marijuana after withdrawal. In the case of two patients treated for refractory epilepsy with chronic useing of marijuana, smoking cessation resulted in the numerous seizures occurring within 24 hours (Hegde et al., 2012).

The above-mentioned studies highlight how ambiguous the role of cannabinoids in epilepsy is. We do not know their interactions potential with other drugs. Enhancing the anticonvulsant effects by the CBD for older antiepileptic drugs, such as phenobarbital and phenytoin, while decreasing the efficacy of clonazepam and ethosuximide has been observed (Consroe, 1977).

### Table 1. Controlled study evaluating the anticonvulsant effects of cannabinoids in humans

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Type of study</th>
<th>Product and dosage</th>
<th>Efficacy</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechoulam and Carlini (1978)</td>
<td>9 adults</td>
<td>Randomized and blinded study</td>
<td>CBD 200mg/day for 3 months</td>
<td>3/4 CBD and 0/5 placebo improved</td>
<td>No toxicity</td>
</tr>
<tr>
<td>Cunha et al. (1980)</td>
<td>15 adults</td>
<td>Double-blind, placebo-controlled trial</td>
<td>CBD 200–300 mg/day for 3–18 weeks</td>
<td>4/8 CBD full seizure control, 3/8 CBD partial improvement 1/8 placebo improved</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Ames and Cridland (1986)</td>
<td>12 adults</td>
<td>Randomized and blinded. This was a letter to the editor, limited information</td>
<td>CBD 200–300 mg/day</td>
<td>No significant change to seizure incidence</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Trembly and Sherman (1990)</td>
<td>10 or 12 adults</td>
<td>Randomized and blinded. Results presented at conference, limited information</td>
<td>CBD 300 mg/day</td>
<td>Significant improvement</td>
<td>No toxicity</td>
</tr>
</tbody>
</table>

Data based on articles (Mechoulam and Carlini, 1978; Cunha et al., 1980; Trembly and Sherman, 1990), letter to the editor (Ames and Cridland, 1986) and complemented with the publication Gloss and Vickrey, 2014.

### ADVERSE EVENTS OF CANNABINOIDS

There is little published data on the adverse effects caused by medical preparations of cannabis. However,
numerous references highlight the negative health effects of smoking cannabis, especially with chronic use. These effects are probably related with the action of THC, which causes mood disorders, depression, anxiety and psychosis. There are also reports of psychotic episodes after a single use of marijuana (Dąbrowska et al., 2012). Cases of psychological and physical addiction during chronic use have been described (Hall and Dagenhardt, 2009). Smoking cannabis can cause: dry mouth, conjunctivitis, mood disorders, dizziness, dysphoria, impaired memory, hallucinations, psychomotor retardation, amotivational syndrome, tachycardia and hypotension (Gordon and Devinsky, 2001). Cardiovascular effect can be particularly troublesome among those who have an earlier diagnosed of heart problems (Dąbrowska et al., 2012).

Reports of a potential association of the use of cannabis with cerebrovascular incidents are disturbing. Dozens of cases of stroke in people addicted to marijuana have been described. However, risk factors for cerebrovascular diseases have not been identified. The possible pathogenic effects of cannabis include an antihypertensive effect and pro-arrhythmia, which could trigger toxic and immunological mechanisms of damaging within the brain. The consequence of these processes may be multifocal cerebral vasospasm. In 2013 Wolff and colleagues published a prospective study conducted among 48 people smoking marijuana. Study patients underwent magnetic resonance angiography (MRA), which revealed the existence of the characteristic highlighted above, the pattern of multifocal cerebral artery stenosis – multifocal intracranial stenosis (MIS). A feature of this angiopathy is the location of many cerebral changes are reversible after discontinuation of cannabis. In the case of young people with stroke, smoking marijuana, without the identification of other risk factors, – MRA studies should be considered.

SUBJECTIVE OPINIONS ON THE USE OF CANNABIS IN EPILEPSY
An interesting result of a survey conducted among 776 people was published by Mathern et al. in 2014. They presented the differences in expectations in relation to the preparations of cannabis therapy in patients with refractory epilepsy. Nearly all patients and the public were of the opinion that there was sufficient evidence of the efficacy and safety of this therapy and would recommend its use. Clearly less trust in this form of therapy occurs among general physicians, basic researchers, nurses, and other medical personnel – about 83% would recommend treatment with cannabinoids.

In the group of epileptologists and neurologists only 50% would advise using this therapy for severe cases of refractory epilepsy. These results, in the face of the current lack of substantial evidence on the safety and efficacy of cannabis, show how large an impact of the environmental and media lobbying for the legalization of marijuana for the public review is.

CONCLUSIONS
Cannabinoids, substances naturally present in cannabis, probably regulate many biochemical and physiological processes. By stimulating or inhibiting the synthesis of GABA, glutamate and other neurotransmitter, they may affect the seizure threshold and the occurrence of seizures. Several of these compounds showed anticonvulsant properties in experimental animal models. Cannabidiol inhibited seizures in models of acute seizures, there is less data concerning the use in chronic epilepsy models. Tetrahydrocannabinol in preclinical animal studies was associated with both pro- and anticonvulsant effects.

Unfortunately, not many randomized, blinded and controlled studies of cannabinoids in the treatment of epilepsy have been undertaken. Cannabidiol was mainly used to provide data on small groups of patients in a short period of observation. It cannot be ruled out that to achieve a good clinical effect, apart from the CBD, the presence of the other ingredients of cannabis is necessary. An important issue is therefore the precise optimal composition, standardization and certification of medicinal preparations. Significant issues are also bioavailability, pharmacokinetics of tested substance and interactions with other drugs.

In conclusion, it can be said that there is little evidence regarding the safety and efficacy of cannabinoids in the treatment of epilepsy. Perhaps, they constitute a new therapeutic path, but it requires an execution of properly designed studies over a long period of time and on a larger group of patients.

CONFLICT OF INTEREST
Doctor Jacek Gawłowicz and doctor Monika Pędracka are involved in planning randomized controlled trials of CBD supplied by GW Pharmaceuticals: The study to investigate the efficacy and safety of Cannabidiol as an adjunctive treatment for seizure associated with Lennox-Gastaut Syndrome in Children and Adults.
REFERENCES


