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Recommendations for the use of cannabidiol and cannabinoids (medical cannabis) in paediatrics – child neurology

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Recommendations for the use of cannabidiol and cannabinoids (medical cannabis) in paediatrics – child neurology

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1. INTRODUCTION

1.1. Overview

Declaration of Helsinki, 37th paragraph:
»In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available. «

https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

The interest of scientists, clinics and the general public as well in treatment with cannabinoids and extracts of natural cannabis has increased greatly in the last decade. At first, only relatively rare reports appeared on the possible efficacy of medical cannabis in children and adolescents with treatment-resistant epilepsies. Later, reports from open-label interventional studies were published (Devinsky et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol 2016; 15:270-8) and only recently there has also been confirmation of the efficacy with randomised, double-blind and placebo-controlled trials in children and adolescents with rare epilepsy syndromes (Devinsky O, Cross H et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 2017; 376:2011-20 AND Thiele EA et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome:

a randomised, double-blind, placebo-controlled phase 3 trial- Lancet 2018, published online Jan 2018).

Despite still quite contradictory views regarding the use of medical cannabis and its (synthetic or natural) active substances (mostly cannabinoids), the demand for these products has been increasing from year to year. Until the end of 2016, for example, more than 40 states in the USA had passed new decrees on the use of medical cannabis and cannabinoids (1). The number of countries in which the use of cannabinoids and medical cannabis are permitted is also increasing in the European Union (Netherlands, Croatia, Portugal, Italy, Czech Republic, Norway, Finland and Great Britain).

Many patients and the parents of sick children, who wish to help with treatment with an appropriate product from medical cannabis, are doomed to searching mainly on the still "black market", where unverified (not analysed) products are on offer. At the same time, it is significant that a great many clinics have become acquainted with the effects of cannabidiols and medical cannabis precisely from the parents and families of sick children. The voice of parents and the patients themselves is a powerful driver for the promotion of treatment and for exhortation and support to experts as well as the public (Varadakar S. Comment. The Lancet published online Jan 2018). Of course, there are, at the same time, still many publications on social networks, which are not always adequately peer-reviewed and in many cases, they attribute too much efficacy to such treatment without there being any expert or scientifically proven basis for it. Furthermore, many still do not know the difference between cannabidiols and medical cannabis (or cannabis for treatment). Cannabidiol (CBD) has no psychoactive properties because it does not contain tetrahydrocannabinol (THC). Some clinics and various health organisations are under greater and greater pressure to nevertheless prescribe unlicensed and unverified products of medical cannabis, especially those that can be located in some products for consumption (Vandrey R et al. Cannabinoid dose and label accuracy in edible medical cannabis products, JAMA 2015;313:2491-3). The use of pure cannabidiol is, however, certainly an exemplary case in which both the public and experts hit the nail on the head. The public and professional groups have recognised the potential value of this drug and have promoted the need for new clinical trials and contributed to the emergence of new information for the licencing and safe use of CBD. Appropriate instructions and recommendations are especially necessary where our target group is children. They are intended for all who provide health care for children and young people so that they can offer the patients and their parents or guardian the most appropriate recommendations for the use of safe and the most appropriate components made from medical cannabis.

Regarding the last report from Europe (2), since October 2015 the prescribing and supply of medical cannabis has been permitted for medical purposes in Croatia. In line with recommendations from neurologists, infectious disease specialists and oncologists, general/ family practitioners and doctors in the healthcare of children, young people and women can prescribe preparations that contain THC (delta 9-tetrahydrocannabinol), dronabinol (Marinol® - which is a trans-isomer of THC = synthetic THC)) and/or nabilone (Cesamet®, a synthetic preparation that imitates the effects of THC – an analogue of THC) on a prescription without repeats for the following conditions: multiple sclerosis, cancer, epilepsy and AIDS. On the prescription, the amount of THC in a single dose, the number of doses, the form of the drug, mode of application and (whenever necessary) the type of plant and /or plant extract must be written. All drugs containing THC can be prescribed for 30 days and they must not exceed 7.5 grams THC per 30 days.

1.2. Current state in Slovenia and the emergence of recommendations

On the initiative of the Ministry of Health (MH) and recently (June 2018) also on the initiative of the Medical Chamber of Slovenia (MCS), a group of experts was established to produce recommendations for the correct and safe use of cannabinoids in patients in oncology, neurology and paediatrics. Recommendations for the treatment of people with advanced cancer have already been made. Whenever already established medications for pain relief, nausea and vomiting during systemic oncological treatment, and anorexia are not effective enough, attempts can be made to alleviate these symptoms with cannabinoids (3,4,5).

In the editorial of the Medical Journal (Červek J. Cannabis – dangerous drug or miracle remedy? Zdrav Vestn | June 2015 | Volume 84) Dr Červek wrote:
"The debate over cannabis and its substances is difficult because of prejudices and ideological and moral differences on both sides. On one side there are the obsolete convictions about cannabis as a dangerous drug, while on the other side, they attribute miraculous effects to the action of cannabis. In the discussion on its use for medical purposes, debate on the legalisation of its use for recreational purposes, on the position of self-treatment etc, gets mixed in. In the sea of disinformation, it is important to separate scientific data from ideological questions. The duty of medicine is to focus on evidence-based data.
Cannabinoids certainly have therapeutic potential. There are ever-increasing scientific proofs of the clinical benefit both in symptomatic treatment and treatment of the underlying illness. By no means is it the drug for all diseases and it cannot replace all types of treatment. For the preparation of optimal clinical guidelines, additional pre-clinical and clinical trials are necessary, which gradually show the true picture of cannabis and cannabinoids; substances with therapeutic doses, which are in some cases exceptionally successful, as they have an effect on the until now medically completely unexploited, but omnipresent endocannabinoid system. In that way, the scientifically supported knowledge spreads and the myths of both the exaggerated and fictitious therapeutic effects and the exaggerated and fictitious undesirable effects are refuted."

1.3. Types of cannabinoids and other components of medical cannabis

Cannabis contains more than 100 different phytocannabinoids and other active substance, such as flavonoids and terpenes. The most important and the most researched cannabinoids are delta 9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC has psychotropic effects; hence its use is regulated and is controlled by legislation on prohibited drugs. It binds to the CB1 receptors, which are mainly present in the central nervous system, i.e. in certain brain centres that are important for executive functions and memory (including the prefrontal cortex, anterior cingulate, basal ganglia, hippocampus, amygdaloid and cerebellum - Burns HD, et al. [18F]MK-9470, a positron emission tomography (PET) tracer for in vivo human PET brain imaging of the cannabinoid-1 receptor. Proc Natl Acad Sci USA. 2007;104(23):9800–9805. In that way, it can work to decrease nausea and vomiting, increase appetite, improve sleep and decrease pain, the feeling of fear and the response to stress.

1.3.1. In Slovenia at present we have at our disposal the following synthetic preparations:

a) Magistral prescription medicine from dronabinol and cannabidiol in the form of drops: Dronabinol 0.25 g, Cannabidiol 0.25 g in Miglyol ad 27.78 g –
1 drop contains 0.25 mg THC and 0.25 mg CBD. It is mainly used for alleviating symptoms associated with advanced cancer, nausea and vomiting during chemotherapy, anorexia and weight loss and chronic pain. In clinical practice, a dose of 10 drops three times daily (TDS), which is 7.5 mg THC per day, has been found to be effective. If necessary, the dose can be titrated to 30 drops TDS), which is 22.5 mg THC per day.

b) Cannabidiol – one-molecular (Bionorica) in the form of pure CBD (98.9%) and therefore without psychotropic effects of THC, which is mainly used for the treatment of epilepsies.

In the pharmacy of the University Medical Centre, natural pure CBD (Vakos XT®) has been available since the beginning of February 2018.

c) Natural CBD (with a permitted THC content < 0.2%) from the manufacturers like Hempika, Be-Hempy, HempTouch, CBD oil and others are available in Slovenia in health food shops (See also: Table 1).

<u>Other natural preparations:</u>
By interventional import it is possible to order an extract of medical cannabis - THC/CBD together with other extracted substances from cannabis (nabiximols) in an oral spray – Sativex, which is available in Austria. One spray is 100 µL and contains 2.7 mg THC + 2.5 mg CBD, administered in two to 16 doses per day (43.2 mg THC + 40 mg CBD). It is used for treating spasticity and pain caused by spasms, mainly in patients with multiple sclerosis.

For medical purposes, about 14 types of flowers and cannabis products with varying THC content (from one to 22 per cent) and varying CBD content (from 0.05 to nine per cent) can be used. They must be of pharmaceutical quality. http://www.formularium.si/fileadmin/fs.zaf.si/pdf331/CvetKonop.pdf.

Otherwise, in the European market and outside of Europe (mainly in the USA and Canada) the follow preparations from natural cannabis exist:

BEDROCAN (Netherlands)
Bediol (THC 6.3%, CBD 8%)
Bedrolite (THC < 1%, CBD 9%)
Bedica (THC 14%, CBD 1%)
Bedrocan (THC 22%, CBD 1%)
TILRAY (Canada, also accessible in Portugal and Croatia)
THC 25%, THC 10%, THC/CBD: 25%/25%, CBD 100% and CBD 25%
CannaKids (Canada – preparations mainly/only for children)
CBD/THC tincture (5 mg/ml THC and 5 mg/ml CBD)
THC flavoured tincture (50 mg/ml THC and 0.1 mg/ml CBD)
THCA tincture (25mg/ml THCA)
THC tincture (5 mg/ml THC, 0.25 mg/ml CBD)
CANNATOL Rescue nasal spray = 5% THC (57 mg/ml THC, 1.3 mg/ml THCA) – 1 spray in 1 nostril, repeat after 20 seconds (for termination of seizures)
CHARLOTTE'S WEB (for children)
CW Extra Strength
CW Maximum Strength

HALEIGH'S HOPE (for children)
Ratios CBD:THC 30:1, 20:1, 15:1 and 10:1 (60 ml = 2400 mg CBD)

TABLE I
List of current foreign and local (Slovenian) products for paediatric use

Foreign		
Charlotte's web	https://www.cwhemp.com/	USA/EU
Haleigh's Hope	https://haleighshope.com/	USA /EU
Elixinol	https://elixinol.com/	USA /EU
Kannaway	https://kannaway.com	USA /EU
Palmetto Harmony	https://palmettoharmony.com/	USA
RSHO	https://shop.medicalmarijuanainc.com/	USA
CannaKids	http://cannakids.org	USA
Myriamshope	https://myriamshope.org	USA
Epidiolex	https://www.gwpharm.com	USA
Pure Spectrum	https://www.purespectrumcbd.com	USA
ENDOCA	https://www.endoca.com/	EU-USA
Tikun Olam	http://www.tikun-olam.info/Edibles	ISRAEL
TilRay	https://www.tilray.ca	CANADA
Enecta	https://www.enecta.com	ITALY
Blue Bird Botanicals	https://bluebirdbotanicals.com/	USA
MGC Pharmaceuticals	https://mgcpharma.com.au	Australia
Bedrocan	https://bedrocan.com	EU
PureEurope	http://www.pureeurope.eu	EU
Medihemp	https://medihemp.eu	EU
CannabiGold	https://cannabigold.pl	EU
Greenzania	https://www.greenzania.com	EU
Pharmahemp	https://pharmahemp.ie	EU
Love Hemp	https://love-hemp.com	EU

Local (Slovenian)		
Hempika	https://hempika.si/	SLO
Be Hempy	https://be-hempy.si	SLO
Canadoc	http://www.slovenska-konoplja.si	SLO
Hemptouch	https://www.zeleni-dotik.si	SLO
Konoplja osvobaja	http://www.konoplja-osvobaja.si	SLO
Posestvo Sončni Raj	http://www.posestvosoncniraj.si	SLO
EkoKor	http://ekokor.si	SLO
Cannamedis	https://www.cannamedis.si	SLO
Agrosloven	https://www.agrosloven.com	SLO
Eko-sol	https://www.ekosol.si	SLO

2. INDICATIONS IN CHILD NEUROLOGY

2.1. EPILEPSY

2.1.1. Introduction

In the treatment of treatment-resistant epilepsy in children, the first choice is always antiepileptic drugs (AED), for whose use there are clear guidelines. AED are usually classified – as drugs of first choice, alternative drugs of first choice and in supplementary drugs (for treatment in combination). At the end of such guidelines, there are usually instructions, which procedures must be done, whenever combined treatment is also ineffective, or the child cannot tolerate it (6). In cases, when the child is not a candidate for surgical treatment of epilepsy, so-called non-pharmacological and other approaches and procedures are usually used, some of which have already been known for centuries or even from Biblical times. These are, for example, the ketogenic diet and other similar diets, the use of various minerals (e.g. magnesium) and food supplements (e.g. vitamin B6 – pyridoxine and folic acid). Recently, various forms of cannabinoids (especially those from natural medical cannabis) and some synthetic substances produced from them - mainly cannabidiol, have also been used (7).

In the last few years, a large number of studies dedicated to cannabidiol (CBD), the main component of cannabis (Cannabis sativa), which is not a psychoactive and has already been used for centuries for every possible affliction, from the treatment of anorexia and other psychosomatic illnesses to relief of various, particularly chronic pains, and as an effective means against nausea and vomiting and against various types of attacks of spasms in people with epilepsy (9). They also studied the possible effects of treatment with CBD in certain psychiatric disorders like anxiety and schizophrenia and the results of the published studies on them have confirmed the good results (10).

Plants contain more than 180 phytocannabinoids, although we hardly know anything about their medicinal effects. More is known only about two substances, the psychoactive tetrahydrocannabinol (THC) and CBD. Over the last few years, there has been a lot of interest from the public about the efficacy of unrefined medical cannabis, which contains a high ratio of the two components (CBD:THC), for the treatment of epilepsy in children, especially for treatment of treatment-resistant child epilepsies and/or the so-called epileptic encephalopathies such as Dravet and Lennox-Gastaut syndromes (see below).

2.1.2. Efficacy and unwanted effects

An open-ended study by Orinsky et al. on the use of pure CBD demonstrated that they were successful in significantly decreasing the number of seizures in young patients (11). In addition, they established a suitable safety profile for patients with severe, treatment-resistant epilepsies as only five of 162 patients (3%) stopped treatment because of undesirable effects. The efficacy of CBD, therefore, looks very promising, but the authors state that further studies will be needed. As far as the use of CBD in other conditions is concerned, natural cannabis and CBD have proven to be effective, especially as an antiemetic, as an analgesic and for decreasing intraocular pressure (21). The same author also states that medical cannabis is safe as far as potentially exceeding the dose is concerned, but there may be some undesirable effects, such as clumsiness on walking and movement, light-headedness' and vertigo, dry mouth and fast heartbeat. He also stresses the need for further trials to establish the most appropriate dose and what is the best way or method of administering cannabis.

In another study, which was carried out using a questionnaire for parents in a Facebook group for exchanging opinions about the efficacy of medical cannabis for treating their children with treatment-resistant epilepsies, 150 parents answered the 24 questions (22). With the study they found out that before that, on average, 12 AED had been consumed without any real effect, whereas after using medical cannabis with a high CBD content, in 84% of children the number of seizures decreased (42% of children had more than an 80% reduction), while in 11% the seizures stopped completely (22). In addition, the parents also mentioned additional positive effects (similar to those in our group – see below), namely, increased attention/alertness, a better mood and improved sleep. Among the side effects, drowsiness and tiredness were detected.

A similar study published in 2018 comprising mainly parents of children with two of the worst epilepsy syndromes (infantile spasms and Lennox-Gastaut syndrome), showed that medical cannabis with a high CBD content was very effective. The questionnaire was answered by 117 parents, who indicated an 85% reduction in the number of seizures, and of these, 14% of children were completely seizure free (23). Among the side effects, the parents indicated only an increased appetite (? A positive effect in most of these children). Again, they stated the positive effects: improved sleep in 53% of children, better attention in 71% and improved behaviour in 63% of children (23).

2.1.3. Dosing CBD – our experience:

In children in our study (see below) we used effective doses of cannabidiol, from 5 mg/kg/day to 16 mg/kg/day (on average, 8 - 10 mg/kg/day), the starting dose was always 1 - 2 mg/kg/day. In babies and toddlers, the drug was given in three doses, in older children, in two doses daily. The parents were always taught that they must give the child CBD separately to the other AED, at least one hour before or one hour after the child's standard AED.

2.1.4. Results and discussion

We began treatment with cannabidiol (CBD), a non-psychotropic substance in cannabis at the beginning of 2015. For that reason, we imported the first product from the Bionorica firm. The clinical trial (approval of the Medical Ethics Committee – no. 103/10/13, dated 18. 11. 2013) does not have a comparison group, but its primary purpose was to determine the frequency of epileptic seizures during the introduction of CBD and after its introduction in comparison with the frequency of epileptic seizures before entry into the trial, to determine the dose of CBD that the children could tolerate well and that would be effective (at least a 50% reduction in the frequency of epileptic seizures) and to monitor potential undesirable effects (Neubauer D, Perkovic-Benedik M, Osredkar D. Cannabidiol for treatment of refractory childhood epilepsies: experience from a single tertiary epilepsy centre in Slovenia. Epilepsy & Behavior. 2018; 81:79-85).
In a retrospective data analysis (1 February 2015 - 31 July 2017), 66 children, aged from 6 months to 24 years, median 8 years (ratio of boys: girls 1.3: 1), were included. The product was 98% pure crystalline cannabidiol powder, which was prepared as an oily solution (100 mg CBD = 1 ml) in the hospital pharmacy. This substance was used exclusively as a supplementary treatment to existing AED. CBD was added to 1 - 4 AED (average 2), before that, however, the children had already been treated with two to 14 drugs. Before treatment started, basic blood tests (full blood count, urea, electrolytes and creatinine, liver function tests and ammonia) were carried out. The starting dose was 1 mg/kg per day, which we gradually increased (weekly) until the desired effect of complete seizure control was achieved, or to the maximum dose of 16 mg/kg/day. The therapeutic effect was most often achieved at a dose of 8 mg/kg/day.

Thirty-two children (48.5%) had more than a 50% improvement in seizures, 14 (21.2%) of whom were completely seizure free (100% improvement). No child suffered a deterioration in seizures, while in 15 (22.7%) there was no effect. Besides seizure reduction, the parents also observed improvement in behaviour (in seven), better sleep (in seven), improved gross motor functions (in five), more alertness and better cognitive functions (in five and three), improved appetite (in three), a happier frame of mind (in three), improved speech (in three), better eye-to-eye contact (in two) and improved communication (in two).

Side effects were noted in 7% (five children). These were transient eosinophilia (9%), a mild increase in liver tests and a yellowness of the skin (which normalised after a reduction in dose), abdominal pain (which soon disappeared), excessive sleepiness and the appearance of »being on a high« (which we eliminated with a lower dose) and nocturnal enuresis (which disappeared after a dose reduction). We also realise the limitations of our study: the analysis was retrospective, there was no control group (double blind with a placebo), the parents themselves judged the effectiveness and we did not measure

the concentration of CBD in the blood (in those with side effects we determined the concentration of AED, which were always within the therapeutic values).

Since we did not have a comparative group, we assessed that it was appropriate, that we also follow children whose parents told us that they had started to treat them with medical cannabis (in most cases with a preparation in the form of an oil or resin, which also contains a high amount of CBD, and also THC in a low ratio - in Slovenia the ratio of CBD/THC in medical cannabis ranges between 20:1 and 15:1, in two of the three children from Macedonia, we succeeded in analysing the components). There were 20 children in this group, whom we are still following, and the results are very similar regarding the reduction in the number of epileptic seizures. Of the ten, for whom we already have results, seven (70%) became completely seizure free, in one there was no effect, while in two the effect was less than 50% (20%). Many parents also mentioned the child's improved cooperation, better behaviour and cognitive functioning and better motor functions (less spasticity).

We are preparing a study (approval of the Medical Ethics Committee 62/0616 No. 0120-314/2016-2, dated 31 August 2016), in which we would give one group first synthetic CBD for six weeks and the other a combination of CBD/THC of natural cannabis, after six weeks the groups would swap the drugs – which would certainly provide us with new insights (and perhaps scientific findings) into the properties of one and the other substances. Since some studies already exist that show that the use of medical cannabis (with all the range of cannabinoids and other very beneficial components – terpenes, various waxes, flavonoids and other biologically active substances) gives even better results, especially in those children in whom just the addition of pure CBD was not effective. Therefore, we believe that the Health Insurance Agency (ZZZS) should refund parents the cost of the purchase of medical cannabis abroad (from licenced and approved manufacturers – see Table I), whenever it is shown, that in children with treatment-resistant epilepsy (where there is no success with two or more AED), a 6-week trial of treatment with pure CBD does not have the desired effect. We recommend a six-month trial period of the effect of medical cannabis (because it is necessary to introduce it at least once more slowly than CBD). For the scale of efficacy, we propose the internationally - recognised scale on parents' impression regarding improvement of the condition (Clinical Global Impression Scale-Improvement – CGI-I – Busner J, Targum SD, 2007), where 1 means very much improved, 2 means much improved, 3 means minimally improved, 4 means no change, 5 means minimally worse, 6 means much worse and 7 means very much worse from the start of the introduction of treatment.

2.2. OTHER CONDITIONS IN CHILD NEUROLOGY

2.2.1. Birth hypoxia

Birth hypoxia is the name for a group of conditions, which happen just before birth, during birth and immediately afterwards and detrimentally affect brain development. The main cause is lack of oxygen, which is very often accompanied by insufficient blood flow in the brain, but the consequences are worse because, with this, a large number of substances that are very harmful to the developing brain are released. The most harmful effects, against which we try to fight, are oxidative stress, neuroinflammation and the toxicity of some substances that invade the cell.

The endocannabinoid system is an endogenous neuromodulatory system, which influences numerous functions of the central and peripheral nervous system. Modulation of the endocannabinoid system has proven to be a very effective neuroprotective strategy for the prevention (or at least reduction) of neonatal brain damage on brain models (24). The incidence of birth hypoxia is 2-3/1000 live births, which means, that in Slovenia 40-60 children are affected every year. Today, the only effective method of treatment is immediate (within six hours after birth) hypothermia. In Slovenia, since 2006, whole body cooling (to a temperature of 33 to 34 °C) (25) has been used. This method of neuroprotection was first introduced in the Clinical Department of Paediatric Intensive Care and Paediatric Surgery at the University Medical Centre in Ljubljana and it then quickly spread to all larger neonatal units around Slovenia. In such cases, cannabinoids are also promising as so-called neuroprotective substances, as they work as inhibitors of the uptake of calcium ions into the cell, which is one of the main mechanisms of damage to brain cells. It also acts as an antioxidant and anti-inflammatory substance and stimulates myelinisation (26). In addition, it has been proven to increase the level of the body's own endocannabinoids in birth hypoxia and other brain injuries. It is interesting that cannabinoids also act neuroprotectively when they are used only 12 hours after hypoxic brain damage in newborns (15).

2.2.3. Mental conditions

It has been proven that cannabinoid and especially CBD have an antipsychotic mode of action (27). In volunteers, it was demonstrated that CBD can inhibit the psychotic symptoms that appear with the use of THC. In a comparative study between CBD and standard antipsychotic drugs, it was shown that CBD was more effective because it improved the negative symptoms more, as well as having fewer side effects, especially extrapyramidal signs. Furthermore, the most recent studies also demonstrate improvement in cognitive functions after taking CBD (15). It has also proven very effective in the treatment of bipolar disorders in adolescents (28).

2.3.3. Autism

There are some preliminary studies that show that treatment with CBD – enriched medical cannabis – is very successful in eliminating the resistant behavioural problems in autism (Aran A et al. Cannabidiol-rich cannabis in children with autism spectrum disorder – a retrospective feasibility study – poster displayed at the international congress of INSAR-International Society for Autism Research, Rotterdam 2018). A similar observation was made by Stolar et al, who were the first to describe parents' experiences in treating the symptoms of autism with cannabinoid extract (ratio CBD:THC is 20:1): hyperactivity improved (in almost 70%), self-harm and anger outbursts decreased (65%) and there were fewer sleep disturbances (72%) and mood changes /swings (47%). (Stolar OE et al. Medical cannabinoids for children with autism spectrum disorder: parents' perspective, poster displayed at the International Congress of the ISFAR, Rotterdam 2018).
The latest excellent review article about the treatment of autism, attention deficit and hyperactivity disorder and severe behavioural symptoms only with the non-psychoactive cannabidiol, has been pubished in August 2018: Cannabidiol as a suggested candidate for treatment of autism spectrum disorder. Progress in Neuropsychopharmacology & Biological Psychiatry 2019; 89:90-96.
There are few reports on the safety of the use of medical cannabis for that purpose, hence two clinical, randomised trials are being run (NCT02956226, NCT03202303), and we await their results. In March 2019 Aran A et al. published preliminary results (Aran A, Cassuto H, Lubotzky A, Wattad N, Hazan E. Brief Report:
Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems-A Retrospective Feasibility Study. J Autism Dev Disord. 2019 Mar;49(3):1284-1288), where they stated that following the cannabis treatment, behavioural outbreaks were much improved or very much improved in 61% of patients.

2.3.3. Addiction

It has been established that CBD does not cause any addiction, but on the contrary, it acts against the behavioural pattern of addiction because of drugs, heroin and THC. Research is now underway on the potential of treating human addiction with THC.

2.3.4. Spasticity and dystonia in neurodegenerative diseases and cerebral palsy (CP)

Cannabinoids (with low THC content) have been shown to be successful in the treatment of numerous symptoms and signs due to neurodegenerative diseases in childhood. Low daily doses of THC (starting with 0.04 to 0.09 mg/kg body weight, average 0.33 mg/kg and maximal dose 1mg/kg) reduce spasticity and dystonia, increase interest in the surroundings, have an anticonvulsive effect and improve memory and thinking (13, 29).

In the pharmacological treatment of spasticity in children and young people, it raises to some extent a similar question to the pharmacological treatment of treatment-resistant epilepsy: when to try preparations of cannabinoids/medical cannabis. In the treatment of epilepsies, it quite quickly became clear that such treatment can be introduced after two unsuccessful attempts with standard (of course, appropriately chosen) antiepileptic drugs (22). In the treatment of spasticity, the determination of the standard is, of course, harder, particularly because there are no evidence-based models that would guide us in the choice of therapy or specified doses in the treatment of spasticity. Therefore, some recommend using the algorithm formulated by Valerie Stevenson, consultant neurologist at Queen Square Hospital in London (23). According to that algorithm, first it is necessary to establish whether spasticity even exists, then the proven spasticity must be assessed (for the assessment in children it is best to use one of the following scales: for gross motor, GMFCS, for fine motor of the upper extremity, BFMF, for spasticity, the modified Ashworth – Bohannon scale and for the assessment of abilities and the assessment of the effects of treatment/intervention, GMFM), which must be appropriately documented. At that time, we can also assess possible trigger factors and factors that can worsen the spasticity (skin ulcers, infections, constipation, pain, etc). After a longer time after physiotherapy (and/or appropriate rehabilitation) was initiated, we ask ourselves, whether further treatment of the spasticity is necessary. If the spasticity is only in one part – focal, we need to think about treatment with botulin and/or orthoses. Whenever the spasticity is diffuse (widespread), we begin treatment with one of the drugs of first choice (baclofen/gabapentin or vice versa). If there is no improvement, the drug of first choice is stopped and one of the drugs of second choice is started (gabapentin/baclofen, tizanidine, benzodiazepines, tiagabine, clonidine). If that drug is also not successful, a combination of THC/CBD can be used to try to treat the spasticity.

2.3.4.1 Studies on the effect of medical cannabis on spasticity (in adults and children)

Such studies are extremely rare; we must do more with some anecdotal reports or case presentations (level of evidence IV or V). In an abstract from the Congress for Physical Medicine and Rehabilitation in 2016, improvement in spasticity in an adult male with damage to the cervical spine is mentioned. He did not want to increase the level of baclofen in the baclofen pump, so he began self-treatment with cannabidiol (CBD). In the end, the author concludes, that the efficacy of 50 micrograms of CBD daily was equivalent to 183 micrograms of baclofen (30). Somewhat more patients are described who used CBD for the treatment of dystonia (31). After six weeks of treatment with a dose of 100 to 600 mg/day, they found improvement in the dystonia in all five patients,

with an improvement of 20 to 50%. In two patients, who had Parkinson Disease as well as dystonia, CBD worsened the hypokinesis and tremor (31). There is also a study with placebo from 1981. In this study, they attempted to treat the spasticity with 5 mg or 10 mg synthetic THC in nine patients (32). The results showed, that compared to the placebo, the spasticity in those who received THC statistically significantly decreased ($p<0.01$), and in four patients the spasticity even decreased by two standard deviations on the scorer for spasticity. The authors used quite a simple scorer for spasticity, assessing the magnitude of tendon reflexes (knee, ankle in adductor) with points from 0 – 4 points dividing the number of points by the number of examined reflexes. In that way, they obtained »spasticity points«. The only study that until now exists in childhood is the already above-mentioned recent study with a trial of dronabinol (21).

The recent International Conference on Cannabis in Poland (Cannabinoids in Theory and Practice, Wroclaw, February 3 - 4, 2017) saw the participation of some respected scientists who have more than ten years' experience in the use of cannabis for medical purposes. These were Prof. Uri Kramer, Prof. David Meiri and Prof. Silviu Brill from Israel, Dr Michael Lee from Oxford and Dr Michael A. Kowal, one of the scientific colleagues from the Bedrocan company, which already produces six preparations of ecologically grown medical cannabis for numerous EU countries - Finland, Macedonia, Poland, Germany, Croatia, Estonia, Great Britain and Norway. This medical cannabis is appropriately standardised and certified and will be the first product to be registered in the Netherlands as a prescription drug. Patients also spoke a lot about their own experience with self-treatment. Of interest was the personal story of a 24-year-old, who had suffered spinal trauma eight years previously, which caused paraplegia below the level of T7; for the last six months he had taken a combination of CBD/THC in the ratio of 20:1 and half a tablet of fluoxetine three times daily. During this time, some skin sensations returned, clonus disappeared, muscles became more developed /trophic again, he no longer had bedsores (even the tracheostomy scar was no longer visible), he regained control of his urine and faeces, his sexual power returned, he had erections again and could ejaculate (33).

Our own experience of treatment with natural cannabis is minimal and based on information, which we obtained from parents who purchased natural cannabis to help their child from local producers or online (mostly two products from California, Haleigh's Hope and Charlotte Web – the first has a ratio of CBD/THC 20:1, the second, 24:1), three children were from Macedonia (38).

In Slovenia, we are still waiting on appropriate legislation that would enable the use of cannabis for medical purposes (39-42). In this way, for the needs of scientific - research studies, and later also for patient treatment, quality and standardised products with a known origin and a GMP/ISO certificate of analysis (for example, the Bedrocan company - 43), could be used. In addition, we also have our own initial experience with analysing various samples of medical cannabis, which we analysed with the permission of parents

who brought us samples of cannabis, with the intent, that they would ensure safe use of these sorts of products, of which there are already many on the Slovene market, their composition, however, is largely unverified (44). We also described the use of medical cannabis in children with cerebral palsy and for improving spasticity in the magazine of the Cerebral Palsy Society (45).

2.3.4.2 Preparation for the study on the improvement of spasticity with medical cannabis

i) Design:

The prospective study will comprise 60 children, who are followed in our department or in outpatients (tertiary level – University Clinical Centre, Children's Hospital, Department of Child, Adolescent and Developmental Neurology, Bohoričeva 20, Ljubljana, Slovenia), for a period of one year.

Children and adolescents with confirmed cerebral palsy (CP), assessed by the GMFCS scale as level IV or V (non-ambulatory cases), aged between 5 and 25 years, will be included in the study. The included children will have the following forms of CP: spastic, dystonic or spastic-dystonic and the following distributions: unilateral, bilateral, diplegic.

In all children, we will document previous therapies and treatments/rehabilitation procedures, as well as any other medicinal products that they will take in addition to medical cannabis.

Prior to the use of medical cannabis and six weeks after its use, spasticity will be assessed using the modified Ashworth scale according to Bohannon and Smith (6) and functionality/activity will be measured using the GMFM-66 scale. The quality of life of the children with CP will be determined by the Disabkids scale, with which we already have experience (46, 47). The children's parents will also receive a special questionnaire, in which they will make notes of all additional/side/positive effects, which they observe during the therapy, especially concerning pain and sleep.

The other group will comprise children with aetiologically confirmed neurodegenerative diseases or with signs of an advanced encephalopathy in which the main clinical sign is spasticity and/or dystonia. The modified Ashworth scale according to Bohannon and Smith (6) will be used to assess spasticity, while disability will be assessed by the GMFCS scale (8). Only children who have grade IV or V will be included. We will also attempt to assess cognitive functions using scales that were used by C. Cans et al. within the SCPE study (1).

For the purpose of the study, an extract of medical cannabis with a ratio of CBD:THC 10:1 will be used. All samples will be appropriately analysed and standardised to the same ratio in advance.

In this study we will also use the efficacy scale, which is an internationally recognised scale on the impression of parents regarding improvement in the condition (Clinical Global Impression Scale-Improvement – CGI-I – Busner J, Targum SD, 2007), where 1 means distinct improvement, 2 means considerable improvement, 3 means minimal improvement, 4 means no change, 5 means minimal deterioration, 6 means considerable deterioration and 7 means distinct deterioration since the start of treatment.

ii) Expected results

We expect that with the use of medical cannabis in children who have spasticity and dystonia as the main signs, there will be an improvement, as already proven in one of the previous pilot studies (21).In comparison with that study, our group will be larger, children will be included from two of the worst groups of disabilities, for the measurement of efficacy, we will use a more objective measurement – already well-established scales of spasticity and functioning. At the same time, we will try to assess pain reduction, as it is known that with the use of medical cannabis there is not only just an indirect reduction in pain because of a reduction in spasticity, but also a direct effect on pain reduction, and establish whether there are also other positive effects that we observed in our preliminary studies with cannabinoids (improved sleep, appetite, attention, cognitive functions), which are important additional positive effects for these children.
This study also has the approval of the Medical Ethics Committee - KME (KME 61/04/17 no. 0120-162/2017-3, dated 28 August 2017).

iii) Administering THC

The only study that exists until now in childhood is a recent study with a trial of dronabinol (a synthetic preparation of pure THC) by Kuhlen M et al. Effective treatment of spasticity using dronabinol in paediatric palliative care. EJPN 2016; 20:898-903. In this study in children aged from 1.3 years to 18 years (average 12.7 years), THC was administered in a dose of 0.08 mg/kg/day (starting dose) to 1 mg /kg/day (maximal dose) - mean 0.3mg/kg/day – without finding moderate or severe side effects, even with use for more than 180 days. The initial daily dose in most of the children was, on average, 0.83 mg THC twice daily.

2.3.5. Tics and Gilles de la Tourette

Many adolescents and young adults have reported improvement in symptoms of Gilles de la Tourette syndrome and other resistant tics. As is known, these involuntary movements initially get worse in the preteen period, reach a peak in adolescence and then stabilise in adulthood. In adults with tics, THC is the recommended treatment, whenever first-line drugs do not help (30). We do not have any of our own studies, nor are there individual reports on this method of treatment in Slovenia. 1.4.

3. ENDOCANNABINOID SYSTEM IN CHILDREN

The classical endocannabinoid system contains the cannabinoid receptors CB1 and CB2, ligands and metabolic enzymes. There are more and more reports of the existence of signs and symptoms of a so-called deficiency in the endocannabinoid system, which causes migraine, fibromyalgia, irritable bowel syndrome and many psychiatric disorders - all having their onset in adolescence (31). It is known that children with autism have a so-called dysregulation of the immune system and that the endocannabinoid system is a key regulator of immunity through CB2 receptors, which is particularly expressed on macrophages. In children with autism, changes have been confirmed in the macrophage system and in those macrophages are dependent on a sufficient level of vitamin D in the body. Therefore, scientists believe that it is likely that it will soon be possible to show that cannabinoid receptors of the CB2 type have a therapeutic effect in the treatment of children with autism (32).

It is worth emphasising that, for the present, these modest experiences are only in the treatment of epilepsy, although it has been known for quite some time that CBD, particularly a high CBD / THC ratio, is also an effective drug for the treatment of other symptoms and signs in childhood neurology - spasticity, tics, attention deficit and some psychosomatic diseases (fibromyalgia, headaches, etc.).

EXTRACTS FROM CANNABIS (suitable for paediatric use):

- are diluted preparations made from concentrates or cannabis extracts,
- contain from 10 to 100 ml of total volume in which there is a varying amount/ combination of cannabinoids, which varies according to the supply of each manufacturer
- contain a varying concentration of cannabinoids, e.g. 2% CBD, 5% CBD etc. or a varying number of milligrams of cannabinoids (300 mg CBD, 500 mg CBD, 1000 mg, 5000 mg, …)
- in the field of paediatrics, they usually enter the body by the oral route (see below) using drops or by accurate dosing with needleless syringes (1 ml)
- they are kept in dark areas, cold (up to 25 degrees) or, according to the manufacturer's instructions, in the refrigerator.

Quality of the products:

- TYPE OF EXTRACTION: ethanol, CO2, … It is recommended that products obtained with toxic substances be avoided. Safer products are those made with safer and more effective methods of obtaining cannabis extracts, for example, supercritical CO2 extraction.

It is also important that products are supplied with certain certificates (eco certificates, GMP, GAP, etc.)

Endocannabinoid system in children

4. MODES OF APPLICATION OF CBD/THC
and other cannabinoids (45, 46)

A) INHALATIONS

On inhaling, the maximum concentration of THC occurs in a few minutes, the peak is reached after 30 minutes, and the effect disappears after 1 - 4 hours (depending on the dose). For medical use, vaporisation is recommended much more than smoking, but it is necessary to buy a vaporiser (there are many types of different vaporisers - usually from companies that have a licensed medical cannabis product - for example, Bedrocan in the Netherlands). However, when vaporisation or inhalations are used, it is difficult to determine the exact dose in milligrams, but adult patients themselves determine what is the most effective dose for them that does not cause an overdose **(which is why this mode of application is unsuitable for children and those with an intellectual disability/motor disability).**

B) ORAL ROUTE/INGESTION

The effect can be expected after 30 to 90 minutes, but it can vary from person to person. The maximum effect is achieved after 2 - 3 hours and usually lasts 6 to 8 hours, depending on the dose. THC is absorbed through the gastrointestinal tract and then passes through the liver (the first-pass effect), where it is broken down into 11-OH-THC, which is the "real" psychoactive substance. Metabolism from THC to OH-THC is dependent on CYP2C9 enzymes (cytochrome P 450 2 C9) and CYP3A4 (cytochrome P 450 3 A4). The CYP2C9 gene and certain genetic variants (polymorphisms) can also reduce the activity of the CYP2C9 enzyme and in some people cause excessive sensitivity to THC, as the modified enzyme can reduce the degradation of THC (into the inactive form) and hence it remains active in the body for longer. In the general population, it is therefore difficult to predict the extent of the impact in a particular person. In fact, the ingestion of an overdose of THC in medical cannabis is the most common reason for overdose with cannabis and for unwanted effects. 11-OH-THC is eventually metabolised/oxidised into an inactive form - 11-nor-9-carboxy THC (THC-COOH) acid, which occurs in the blood and urine. The most common side effects are increased heart rate, anxiety, excessive sleepiness, hallucinations and paranoia. In most products from abroad, the number of components from THC and CBD, as well as other cannabinoids: cannabinol (CBN), cannabidivarin (CBV), cannabichromene (CBC) and acid forms - THCA, CBDA, etc. are clearly written. and even the terpenic profile and the content of flavonoids. Such preparations for oral ingestion (oral route), which in addition to CBD and THC in various proportions, also contain other components (other cannabinoids, terpenes, flavonoids) **are the most suitable mode for children.**

C) SUBLINGUAL TINCTURE

Tinctures are concentrated liquids, based on alcohol, although sometimes that name can also be used for an oily solution. If a true, alcoholic tincture is used, it is usually taken under the tongue (sublingual) and the effect is reached in 15 - 60 minutes. The tincture can also be in the form of a spray. The good side is, that in that way smoking can be avoided, the tincture is quickly absorbed (quicker than by ingestion) and the effect of metabolising in the liver is negligible. It is necessary that the quantity of CBD and THC in one spray be written. **Children and particularly intellectually and physically disabled people cannot ingest medical cannabis in all ways, so perhaps this method is the most appropriate for them** (especially whenever it is an urgent condition – for example, frequent seizures or status epilepticus) and it can be given to the patient via a gastrostomy. That mode is also better because tinctures are more concentrated, and several milligrams of THC or CBD can be given in a small amount/volume in millilitres.

D) TOPICAL USE

Cannabis can be used in creams, lotions and in skin preparations, especially for the alleviation of local pain and spasms and/or for various skin diseases (for which it has been used in India and South America for over 1,000 years) and for bacterial skin infections (e.g. MRSA). Some people use this method for treating arthritis (especially of smaller joints), bursitis, fasciitis and muscular and joint pains and dermatitis, psoriasis, eczemas etc. and in (more anecdotally) at-risk precancerous skin lesions. Topical products, however, are not usually well standardised and it is necessary first to test them on a small area of skin and with a small amount. **Not recommended for younger children.**

E)RECTAL USE

Some people report good results from using medical cannabis in the form of suppositories, but we must be aware, that it is not proven that THC can be absorbed through the rectal mucosa. However, if THC is in combination with hemisuccinate, absorption is twice that obtained by ingesting the preparation. For now, rectal products are only used experimentally and are not yet available on the market. Their use will probably be very limited anyhow, mainly to intestinal diseases (for example colitis). In children, this method is not recommended, because it is not clear what proportion of the substance will reach the bloodstream.

F)TRANSDERMAL PLASTERS

Plasters are interesting because when they are used, metabolism does not go through the liver and their method of use is very simple. The only difficulty is that most of the components in medical cannabis do not mix with water (cannabinoids are fat-based components) and the water layer of the skin can prevent the absorption of the substance into the bloodstream. There are, however, means for accelerating penetration through the skin into the blood (so-called »permeation enhancers«), but mostly only for research purposes. When finally, a good substance is found, this will probably also become a recommended method for children.

IMPORTANT:

It is important, in particular, that the preparations are accessible in appropriate aggregate form, which enables 100% control of the dosing, which are, according to the course of the therapy (from a small starting dose to the target dose), the only appropriate and must be in some appropriate ratios that allow dosage accuracy and at the same time provide a sufficiently large amount of effects (e.g. in mg of CBD). It is also extremely important that add-on treatment with cannabis preparations is separated from other (mostly antiepileptic) drugs by at least one hour (ideally 2 hours).

RATIOS AND CONCENTRATIONS

The CBD:THC ratio must always be written on substances made from medical cannabis. Ratios higher than 10: 1 (for example, 15: 1, 20: 1 and 30: 1) do not usually cause psychoactivity, while ratios below 10:1 can cause a psychoactive effect in some people. However, the concentration shows how much CBD or THC in milligrams there is per millilitre (for example, 10% = 100 mg/ml) and from these concentrations (CBD and THC) the ratio can always be calculated.

DOSING

Treatment is always started with low doses and very slowly increased (the "start low and go slow" rule). In addition, the rule "one amount is right for everyone" is not applicable for cannabis dosing, and the dosage for each person is very individual and specific. First, we decide on the mode or the route of entry of medical cannabis into the body. Then, we decide which effect of medical cannabis is most important (preventing convulsions, preventing spasms, better sleep and/or appetite, preventing vomiting/nausea, etc.).

Depending on the desired effect, we decide on the composition (ratio). High CBD:THC ratios mean a low content of THC and therefore very little (or no) psychoactive effects are expected (the effects are therefore expected primarily from the CBD - for example, for prevention of epileptic seizures). Such ratios are highly recommended for children, especially as an anticonvulsant, for pain relief, an antiemetic, against anxiety, for improving mood and for spinal cord injuries (neuroprotective).

Low ratios of CBD:THC (for example, 8:1, 4:1, 2:1 or 1:1) are not recommended for children. They are however good for pain relief, they have an anti-inflammatory action, are good muscle relaxants, have an antidepressive action, and act against nausea and vomiting and anxiety.

Dosage of CBD: low doses are around 10 mg daily (0.5 mg to 1.0 mg/kg/day), high doses are around 200 mg daily (up to 10 mg/kg/day).

Dosage of THC: The initial dose is 1.0 - 2.5 mg daily to a maximum of 5 mg daily (we can begin with significantly lower doses - for example, 0.05 mg/kg/ day - in one study, very good results were achieved in improving spasticity at a THC dose of around 0.3 mg/ kg/ day). Whenever substances have a low CBD: THC ratio we always choose the dosage based on THC to avoid potential adverse effects due to too much THC. Overdosing is most common with oral administration because the breakdown product of THC is psychoactive and long-acting. There is, however, no risk of possible respiratory arrest or death because there are no THC receptors in the brainstem.

The most common unwanted effects of THC overdosage are rapid heart rate, orthostatic hypotension, altered perception of time, paranoia and anxiety, dysfunctional motor coordination, delusional thinking, excessive sleepiness and a sense of fear that one will die. The means of reducing these unwanted effects are: cold lemonade, pine nuts, pepper and real calamus (Acorus calamus - similar to ginger). All these substances contain terpenoids, which are an antidote to the undesirable effects of overdosing with THC. Best of all, the effects of overdosing with THC can be stopped by pure CBD or by CBD-enriched medicinal cannabis.

Table 3: Comparison of the most frequent methods of taking the drug

INHALATION	ORAL	SUBLINGUAL	TOPICAL
Effect in a few minutes	Effect in 30 - 90'	Effect in 15 - 60'	Only for external use
Peak effect: 30'	Peak effect: 2 - 3 h	Peak effect: 1 - 2 h	Spread on the skin according to need
Lasts: 1- 4 h	Lasts: 6 - 8 h	Lasts: 1 - 6 h	CBD is better absorbed through the skin than THC
Vaporizers are better than smoking		Available in the form of a tincture or as an extract	
Dosing is easier because the effect is immediate	More difficult to dose: start with a low dose and repeat the dose after 90 ' (start low and go slow)		Doses can be repeated; first, try on a small part of the skin to avoid possible allergic reactions
	After ingestion, THC changes to 11-OH THC, which is very psychoactive - a small amount can be very potent in terms of (undesirable) psychoactive effects		
Vaporiser required	No aids required, no smell, discrete mode of use	No aids required, no smell, discrete mode of use	

5. CONCLUSIONS

As can be seen from the above, there is still considerable disagreement regarding the use of cannabidiol, and especially cannabinoids and medical cannabis (with a high CBD / THC ratio) for the treatment of epilepsies and other neurological conditions in children and adolescents (34). It is also interesting that the greatest resistance to this kind of treatment is among medical specialists (neurologists, epileptologists), while general practitioners, researchers, and in particular the patients themselves and the public, approve of this kind of treatment and consider it to be very effective. In view of the above, there is some evidence that a small percentage of the psychoactive substance (THC) is medicinal and does not cause convulsive side effects or addiction. This could put medical cannabis alongside synthetic cannabinoids, although it must be kept in mind that medicinal cannabis has an additional effect - i.e. the "entourage" effect, which means that the combination of cannabinoids in the plant is that which can be effective and it is certainly more effective than its individual components for most of the conditions that we treat today (35)

Preparations of medical cannabis could, therefore, today represent a potential for "compassionate use" in severe neurological problems in children and adolescents. Perhaps in certain circumstances, it is easier to decide for their use in those children in whom the desired effect is not achieved with standard procedures; in any case, with increasing research in this field and quality clinical studies on the usefulness and efficacy, the use of cannabinoids and medical cannabis show promise of a significant expansion.

In the last two years, there have been several scientific studies that have proven the effectiveness of treatment with cannabinoids in child epileptology, studies supporting the level of evidence grade I.

These include:

Devinsky O et al: *Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial,* Devinsky O, Cross H et al: *Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome* and the recent article of Thiele et al.

Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial.

All three articles contribute to the fundamentals of evidence-based medicine on the treatment of children and adolescents with resistant epilepsies and especially severe epileptic syndromes, such as Dravet and Lennox-Gastaut syndromes. After many years of waiting for a successful cure for these syndromes, this is certainly very exciting and good news for clinical experts and for patients. An ongoing study on the medium- and long-term effects of tolerance and the maintenance effect of the use of CBD in epilepsies (NCT02224573 and NCT02224560) has already been reported. Studies are also underway

on the efficacy of CBD in tuberous sclerosis (NCT02544763) and the treatment of infantile spasms (NCT02953548 and NCT02955887).

The recent article *(Szaflarski JP et al: Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies:Expanded access program results* – accepted for publication May 2018 – available before printing: DOI:101111/epi.14477) also validates the efficacy and safety and good tolerance, since within the scope of an extended programme of treatment of epilepsy with cannabidiols (CBD) in 607 paediatric patients and follow-up, which until now has already run for 146 weeks, demonstrated an even and lasting efficacy throughout the period of follow-up, without important side effects.

Similar good effects have also been recently shown in two studies (Canadian and Israeli), where they used medical cannabis, in the ratio CBD/THC 20:1 (Hausman-Kedem M et al. *Efficacy of CBD-enriched medical cannabis for treatment of refractory epilepsy in children and adolescents – An observational, longitudinal study* – Brain & Development 2018 (in press – September 2018) AND

McCoy B. et al. *A prospective open-label trial of a CBD/THC cannabis oil in Dravet syndrome* – Annals of Clinical and Translational Neurology, 2018 – accepted for publication June 2018 – available before printing doi: 10.1002/acn3.621).

A recently published review paper has provided an overview of recent clinical trials registered on

ClinicalTrial.gov. These trials used different CBD formulations in patients affected by severe forms of drug-resistant epilepsy. All the studies were approved by local ethics committees and published in PubMed. The results of scientific studies (14) obtained so far claim that the use of CBD in clinical applications could represent hope for patients who are resistant to all conventional anti-epileptic drugs. (Silvestro S, Mammana S, Cavalli E, Bramanti P, Mazzon E. Use of Cannabidiol in

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7. GLOSSARY OF CANNABINOID TERMS

CANNABIS, cannabis (Cannabis Sativa L.), an annual herb of the family of cannabis, is a bicameral or one-necked bloom. There are three types of cannabis, Sativa, Indica and Ruderalis, which differ in form, content and ratio of cannabinoids.
INDUSTRIAL CANNABIS: all types of cannabis, whether industrial or medical, are of the same genus, cannabis (Cannabis Sativa L.). The designation of the plant depends on the cultivation method and the purpose of its use. The term for industrial cannabis is most often used to produce food, oils, ointments, cosmetics, textiles and in construction. The proportion of THC in the whole plant should not exceed 0.3%, or in Slovenia 0.2%.

MEDICAL CANNABIS: we speak of cannabis from which we can extract therapeutic potentials. Since all types of cannabis contain cannabinoids, it means that any type of cannabis can be classified as medical cannabis, including industrial cannabis. The concept of medical cannabis has not yet been definitively defined in both the legal and medical fields, and it is likely that in the future the difference between medical and other cannabis will be primarily in the composition itself and in the standards of quality.

COMPONENTS IN CANNABIS: up to August 2016, 1249 different components had been identified in cannabis: 144 cannabinoids, terpenes, waxes, flavonoids and other biologically active molecules, proteins, fatty acids, B and D group vitamins, calcium, -iron, in smaller traces of phosphorus, magnesium, zinc, copper and manganese. Of the 1249 identified components, 1105 remaining ingredients were recorded in addition to cannabinoids.

CANNABINOIDS: polycyclic hydrocarbons found in cannabis and in smaller quantities in some other plants; more than 144 different cannabinoids of plant origin are known, which are typical of cannabis and do not appear in any other plant (THC, CBD, CBG, CBC, CBL, CBV, THCV, CBDV etc.).

PHYTOCANNABINOIDS: natural compounds found in the plant itself (cannabis flowers, leaves and pollen).

SYNTHETIC CANNABINOIDS: molecule of cannabinoid, which is produced/synthesised in a laboratory by a chemical reaction.

TERPENES: they have a wide spectrum of biological and pharmacological activities and can interact synergistically. They occur in living beings and plants in order to deter parasites and emit a strong smell and have a strong taste. More than 200 different terpenes in cannabis have been recorded, which define its smell and various potential actions of terpenes.

FLAVONOIDS: as terpenes, they have a wide spectrum of biological and pharmacological activities. They occur in many different plants and have a unique smell and taste.

ENDOCANNABINOIDS: cannabinoids produced by our own body. The human body has its own compound which is nastajajo formed in? mammalian tissues.

ENDOCANNABINOID SYSTEM: signal system, which is composed of endocannabinoids, cannabinoid receptors and enzymes. They maintain our homeostasis, participate in regulating and adjusting the function of the cardiovascular, digestive, musculoskeletal, nervous and immune systems.

CANNABINOID RECEPTORS: CB1 receptors are mostly expressed in the central nervous system and are found in brain cells, lungs, kidneys prostate, liver. CB2 receptors are found in the peripheral nervous system, in cells of the immune system, in the central nervous system and in the digestive system.

ENTOURAGE EFFECT (freeloader effect): synergistic therapeutic action of cannabinoids, terpenes and flavonoids, extracted from cannabis, where the effect is stronger than the therapeutic effects of individual components.

ACIDIC FORMS OF CANNABINOIDS found in fresh, raw (?) cannabis. Basic cannabinoid acids have the sign (THC-A, THCV-A, CBD-A, CBG-A, etc.). This is an acronym of cannabinoids, which have the sign A (acid) at the end. The acid forms of cannabinoids are not meant to be psychoactive.

DECARBOXYLATION: the process of heating by which the neutral variants of cannabinoids, THC, CBD, CBG etc. are made from the acidic forms

CANNABIS OIL / EDIBLE OIL: extracted from the seeds of industrial cannabis, which has a THC content of less than 0.2% and in such oil can be bought in general food shops.

CANNABIS RESIN, TINCTURE, CBD OIL, THC OIL, HASH OIL, CBD RESIN, CBD/THC PASTE, CANNABIS EXTRACT, EXTRACT, AGGREGATE FROM CANNABIS etc.: natural obtained extract from cannabis flowers (not seeds), they are usually in higher concentrations.