articolo

Medical Cannabis and Epilepsy: Bioethical Aspects

Tiago Gurgeldo Vale - Alberto Carrara, L.C.

Medico, pediatra, licenza in Farmacologia, dottorato in Neuroscienze e dottorando in Bioetica, *Regina Apostolorum*, Roma.

Docente di filosofia dell'uomo e neuroetica, coordinatore del GdN, APRA, Fellow della Cattedra UNESCO in Bioetica e Diritti Umani di Roma.

Introduction

Anny, a five-year-old girl, Brazilian, carrier of a rare syndrome, CDKL5, which triggers a type of severe and intractable epilepsy. Her first seizure occurred when she was only 45 days old, in the arms of her mother. She began losing milestones, and at 5 years of age her family was very worried, since she was failing while on many antiepileptic drugs. She had significant cognitive and motor delays, struggled to walk and talk, and needed complete assistance for everyday activities. At this point Anny was experiencing up to 80 generalized tonic-clonic seizures a week[1]. In early October 2013, the Fischer's found out about cannabidiol through "The Hope 4 Harper," a Facebook support group.

In early November 2013, Renata Fischer, niece, living in Orlando, started to buy and send the product illegally by mail to the Fischers. In 9 weeks Anny Fischer was seizure free. The number of publications on this subject greatly increased in the media of the country, kindled a discussion and generated a great pressure on the Brazilian government to legalize the use of medical cannabis. On January 2015, the National Health Surveillance Agency (ANVISA) approved unanimously reclassification of cannabidiol as a controlled use of medication and no longer as a banned substance[2].

Childhood epilepsies beginning in the first few years of life are frequently characterized by seizures that are resistant to available treatments. A high seizure burden in early childhood likely contributes to the severe cognitive, behavioral, and motor delays common in these children. When indicated treatments fail to control their child's seizures, some parents turn to alternative treatments. Perhaps most desperate of all for new therapies have been parents of children with severe early life epilepsy. The data consist of anecdotal cases of children successfully treated with the medical marijuana, often cannabidiol-enriched preparations[3].

Cannabis as medicine

The *Cannabis* genus of flowering plants mainly comprises the *sativa* and *indica* species. It is among the most widely used of all psychoactive drugs. Indigenous to Central and South Asia, cannabis was used for millennia to produce hemp fiber for rope, clothing, bowstrings, and paper; it has been valued for its seeds and seed oils; as livestock feed; and for medicine, religious ceremonies, and recreation.

Regardless of new discoveries, the use of cannabis as a medicine was reported by the ancient Chinese in the world's oldest pharmacopoeia, the *pen-ts'aoching*,compiled in the first century but based on oral tradition passed down from the time of Emperor Shen-Nung, who lived around 2700 B.C.[4].

The medical indications of cannabis, in the beginning of the 20th century, were summarized in three areasin *Sajous's Analytic Cyclopedia of Pratical Medicine* (1924): sedative o hypnotic (insomnia, mania, hay fever, delirium

tremens, chorea, tetanus, rabies, and others), analgesic (headaches, migraine, neuralgia, gastric ulcer, menorrhagia, multiple neuritis, and others), other uses (to improve appetite and digestion, for the 'pronounced anorexia following exhausting disease', diarrhea, cardiac palpitation, and others)[5].

There are studies, in different phases, about the therapeutic effects of Δ^9-THC in conditions such as epilepsy, insomnia, vomits, spasms, pain, glaucoma, asthma, lack of appetite, Tourette's syndrome, and others. Evidence for the efficacy of cannabisvaries substantially for different indications, with the best data in painful HIV-associated sensory neuropathy[6], chronic pain[7], chemotherapy-induced nausea and vomiting[8], and spasms in patients with multiple sclerosis[9].

Other cannabinoids are also under investigation, such as Cannabidiol, which has evidence for therapeutic effects in epilepsy, insomnia, anxiety, inflammations, brain damage (as a neuroprotector), psychoses, and others[10].

Cannabis, cannabidiol and epilepsy

Epilepsy is a chronic disorder of the brain that affects people in every country of the world. It is characterized by recurrent seizures. Fear, misunderstanding, discrimination and social stigma have surrounded epilepsy for centuries. Some of the stigma continues today in many countries and can impact the quality of life for people with the disorder and their families. People with seizures tend to have more physical problems (such as fractures and bruising), as well as higher rates of other diseases or psychosocial issues and conditions like anxiety and depression.

Several anecdotal reports suggest that cannabis has anticonvulsant properties and would be effective in treating partial epilepsies and generalized tonic-clonic seizures. They are based on the fact that in individuals who smoke marijuana to treat their epilepsy, stopping use of cannabis precipitates the reemergence of convulsive seizures, while resuming consumption of this psychotropic drug controls epilepsy; these results are reproducible[11]. However, a conflicting report suggested that the smoking of marijuana may be proconvulsant[12].

Cannabidiol, a nonpsychoactive compound of cannabis, is one of the 80 terpenophenolic substances called "cannabinoids", which are present in varying relative proportions depending on the strain of the plant (up to 40% of the cannabisextract)[13]. It was isolated in 1940 and its structure was elucidated in 1963[14].

The first pharmacological effects of cannabidiol described were antiepileptic and sedative. In 1973, a Brazilian group reported that cannabidiol was active in reducing or blocking convulsions produced in experimental animals by a variety of procedures[15], which was confirmed by another group a year later[16]. At the end of the decade, the same Brazilian group has tested cannabidiol as a treatment for intractable epilepsy in 16 grand-mal patients[17]. In a less successful study, no significant improvement in seizure frequency was observed among 12 epileptic patients who received 200-300 mg of cannabidiol per day, in addition to standard antiepileptic drugs[18].

In rats, cannabidiol was an effective and relatively potent anti-convulsant in the maximal electroshock (MES) and audiogenic seizure models[19]. In mice, cannabidiol pretreatment prevented tonic convulsions caused by either MES seizures, gama-aminobutyric acid (GABA) antagonists or inhibitors of GABA synthesis, in addition to reliably protecting against 3-mercaptopropionic acid-induced lethality, but was ineffective against strychnine-induce convulsions[20]. Cannabidiol inhibits epileptiform activity in vitro. In two different models of spontaneous epileptiform local field potentials (LFPs), decreased epileptiform LFP burst amplitude and duration, and reduced seizure severity and lethality in the pentylenetetrazole (PTZ) model of generalized seizures in vivo[21]. But in another study, cannabidiol had no effect on PTZ -induced or MES-induced seizures[22].

A Cochrane review identified four studies, published between 1978 and 1990, that met the inclusion criteria for being RCTs that were blinded (single or doubled) or un-

blinded. These studies were not adequately powered (they included between 9 and 15 patients), one of them being unpublished abstract. Therefore, they failed to provide evidence about cannabinoid efficacy in treating epilepsy[23].

A U.S. survey of 19 parents, 12 of whom had children with Dravet syndrome, explored the use of cannabidiol-enriched cannabis in pediatric treatment-resistant epilepsy[24]. Of parental respondents, 53% reported a >80% reduction in seizure frequency; 11% of children were seizure free during a 3-month trial. Among the 12 patients with Dravet syndrome, 42% reported a >80% reduction in seizures. The parents often reported improved alertness and none reported improved alertness and none reported severe side effects, although a few of them reported drowsiness and fatigue. Neither the doses nor the exact composition of the different cannabis extracts could be determined. Therefore, a possible placebo effects as well as the impact of the percentages of THC on both effects and side effects in this much selected population could be assessed.

Studies of synthetic cannabidiol and plant extracts, either isolated or in combination with Δ^9-THC, have likely provided sufficient human data on the pharmacology of the cannabidiol[25].

Bioethical Aspects

Prominent internet and national media attention has fueled a rapidly growing interest among parents to use cannabis derivatives to treat epilepsy. The data consists of cases of children successfully treated with medical marijuana, often CBD-enriched preparations. However, the lack of regulation and standardization in the medical cannabis industry raises concerns regarding the composition and consistency of the products that are dispensed. Most parents use cannabis extracts purchased from a dispensary or from a cannabis grower.

These artisanal preparations may contain different percentages of CBD and THC, as well as many other cannabinoids and other compounds. Their concentration can vary based on the plant clones, weather, soil, and other factors. Most importantly, there are no controlled data on the use of these preparations. It lacks blinded data on efficacy as well as safety. To access safety and efficacy of medical marijuana, the chemical mixture should be stable over time and by different growers. For example, a high CBD:THC clone by a grower in one area may have different ratios of these two cannabinoids as well as varying quantities of other cannabinoids when cultivated by another grower in another area. And there may be variability even for the same grower because soil nutrients, plant pathogens, and many other factors can vary even within the same greenhouse.

Moreover, the belief that treatments derived from natural products are safer or more effective is common and potentially dangerous. For example, tetrodotoxin is a "natural" sodium channel blocker produced by fish, worms, octopi, crabs, and other animals. Many natural products and synthetic medications vary in their therapeutic versus toxic effect based on dose as well as genetic and non-genetic (e.g., medical) factors.

The human experience reported in patients with Dravet syndrome and Lennox-Gastaut syndrome[26] are with products containing primarily cannabidiol, often with CBD:THC ratios as high as >20:1. Nevertheless, the safety and efficacy of cannabidiol in patients with epilepsy need to be determined. In addition to THC and cannabidiol, there are >80 other cannabidiol and >300 non cannabidiol chemicals present in cannabis, with the remainder including potentially neuroactive substances such as terpenes, hydrocarbons, ketones, aldehydes, and other small hydrophobic compounds capable of crossing the blood-brain barrier[27].

The extraction method is also critical, as the conditions and solvents used to separate these phytocompounds may alter them in the process. The safety of these chemical should be studied. To assess safety and efficacy, it is necessary to define the precise chemical profile of a drug or botanical product. The data

currently available for medicinal marijuana do not meet these criteria[28].

Despite the fact that animal experimental data clearly suggest a potential benefit of cannabidiol as a potential treatment for epilepsy, supportive clinical data are quite sparse. Many reports suffer from a number of design flaws, including incomplete baseline quantification of baseline seizure frequency, indeterminate time periods for outcome determination and, in some cases, inadequate (or missing) statistical analysis in general, a lack of sufficient detail to adequately evaluate and interpret the findings. Using rigorous review methodology, Gloss and Vickery conclude that based on the low quality of the reports available; there is insufficient data available to draw any conclusions regarding the efficacy and/or long-term safety of cannabidiol in treating epilepsy[29].

Although many marijuana strains used for epilepsy treatment are reported to have high CBD: THC ratios, THC is more potent than cannabidiol, so low doses of THC can have adverse effects, especially in young children. The risk of negative effects of cannabis in the developing brain must therefore be considered. Recent studies suggest that cannabis has adverse effects in children younger than 15, including a risk for psychosis, and long term impairment of mobile/locomotive functions. In a meta-analysis of studies that investigated residual effects of cannabis on the neurocognitive performance of adult human subjects, chronic use was associated with a decrease in the ability to learn and remember new information, whereas other cognitive abilities were unaffected[30].

THC may produce as well cognitive impairment, dizziness and tachycardia, alterations in blood pressure, and a range of transient but potentially severe psychiatric effects such as mood change and panic attacks, hallucinations, and delusional beliefs[31]. Depending on the dose and the setting in which is taken, it can be either anxiolytic or anxiogenic. Amongst recreational users it has been incriminated as a risk factor for schizophrenia[32], but the level of risk remains controversial[33]. Pioneering early studies in healthy humans demonstrate that cannabidiol could inhibit the cognitive and psychotomimetic effects of THC[34].

THC may be teratogenic although the objective evidence for this in humans is not compelling. Despite the potential positive effects of cannabidiol, a large body of studies fails to reveal its teratogenic and mutagenic effects[35].

Over-activity of the endocannabinoid system may be associated with the development of obesity, metabolic problems including Type-2 diabetes mellitus, cardiovascular diseases, and some forms of liver disease. Rimonabant (also known as Acomplia), a synthetic drug that acts as an antagonist/inverse agonist at the CB1 receptor, was introduced for appetite suppression in obesity[36]. However, an intact endocannabinoid system is essential for normal mental health, yet Rimonabant has been associated with an increased risk of depression and suicidal ideation, anxiety, and aggression.

In vitro studies have shown that cannabidiol is a potent inhibitor of multiple CYP isozymes, including CYP2C and CYP3A[37]. In addition, given its metabolism via CYP3A4, clinical trials of cannabidiol in patients receiving enzyme-inducing antiepileptic drugs, such as carbamazepine or phenytoin, will require detailed pharmacokinetic studies. Since cannabinoids are strongly bound to proteins, interactions with other protein-bound drugs may also occur. Of greatest clinical relevance is the reinforcement of the sedating effects of other psychotropic substances (alcohol, benzodiazepines), and the interaction with substances that act on the heart and circulation (amphetamines, adrenaline, atropine, beta-blockers, diuretics, tricyclic antidepressants, etc.) [38]. In fact, adequate pharmacokinetics data are needed to inform dosage recommendations and identify interactions with antiepileptic drugs and other medications that can cause toxicity and impair efficacy.

Is medical marijuana or cannabidiol safe and effective for children with epilepsy? It is not yet known. Are some children particularly vulnerable to the effects of tetrahydrocannabinol (THC)? Evidence suggests that early

exposure to THC increases the risk of cognitive, addictive, and psychotic disorders. Are there subgroups of children for whom THC, cannabidiol, or other compounds may exacerbate seizures? Many questions remain unanswered. Hence, it is quite difficult for the physician choose to use medical marijuana or cannabidiol. There is great controversy among physicians regarding the use of medical cannabis.

Medical care is a kind of human act and is therefore subject to the laws and principles, that is, to moral evaluation. It is an act that arises directly from man's higher faculties, the intellect and the will, and for which he is responsible. Morality belongs to the inner life of the individual, which he expresses in his acts. But the decisive importance of the action itself is not to be forgotten, since it has an impact on the person and on society, either positive or negative. Otherwise, we risk falling into a type of morality that only regards "intention," and that is, therefore independent of the action. It is important to consider the "end". However, this does not mean that the end justifies the means, especially if these means are not good. In order for an act to be good, it is necessary that the whole process be good.

But what can we say about the patient's right to decide for himself whether or not to use medical cannabis? Isn't the patient autonomous? The concept of autonomy in moral philosophy and bioethics recognizes the human capacity for self-determination, and puts forward the principle that the autonomy of persons must be respected.

And who should make decisions for children, who clearly are not responsible for their quality of life and who need help in making prudent decisions? In the case for assessing medical cannabis and cannabidiol in epilepsy, mainly in children with Lennox-Gastaut syndrome and Dravet syndrome and severe mental impairment, Cilio*et al* (2014)[39] has written in a very important scientific article in which he states that autonomy is not a compelling argument in these situations. Although combination therapies such as cannabidiol and THC are effective for disorders such as spasms in patients with multiple sclerosis, there is little controlled data for efficacy in any disorder using whole plant extracts. Autonomy is a step backward for medical care if it becomes dissociated from rigorous and unbiased study.

Most physicians are keenly aware that available antiepileptic drugs often fail to control seizures and often have disabling side effects, and that the morbidity and potential mortality of severe epilepsy is horrific. But those truths do not provide objective data on the safety and efficacy of medical cannabis. They can influence decisions, informed by the principles of autonomy, beneficence, and nonmaleficence[40], about what is a reasonable course of action with limited scientific data. But they do not elevate the available data anywhere near the level of proof of efficacy and safety.

On October 21, 1985, Pope John Paul II said to the scientists of the Pontifical Academy of Sciences that it is the task of doctors and medical workers to give the sick the treatment which will help to cure them and which will aid them to bear their sufferings with dignity[41]. Even when the sick are incurable they are never untreatable: whatever their condition, appropriate care should be provided for them. Appropriate care should be thought in terms of principle of proportion risk, that is, in term of proportion between the advantages and foreseeable risks of a treatment. In the former case, even high-risk procedures might be employed if all safe medicine has been exhausted and great respect for the subject is preserved. In the latter, only a narrow scope of risk may be authorized, which is to say that it cannot exceed the risk of any insubstantial physical impairment.

Conclusion

Basic research studies have provided strong evidence for the safety and anticonvulsant properties of cannabidiol. However, the lack of pure, pharmacologically active compounds and legal restrictions have prevented clinical research and confined data on effi-

cacy and safety to anecdotal reports. Pure cannabidiol appears to be an ideal candidate among phytocannabinoids as a therapy for treatment-resistant epilepsy. A first step in this direction is to systematically investigate the safety, pharmacokinetics, and interactions of cannabidiol with other antiepileptic drugs and obtain an initial signal regarding efficacy at different dosages. These data can then be used to plan double-blinded placebo-controlled efficacy trials involving children with catastrophic epileptic syndromes.
Despite all of the challenges of medical cannabis as a potential therapy for epilepsy, what is not controversial is the need for a calm approach to this matter, an approach which requires thoughtful and thorough pharmacological and clinical investigation into cannabis and its many constituent compounds. And thus the scientific community will be able to either confirm or disprove its safety and antiepileptic potential.

NOTE

[1] C. Almeida, «Maconha: Remédio proibido», *Super Interessante*, 338(2014), 34-43.

[2] O. Nin, «CBD Timeline Brazil», in https://prezi.com/cw8znkrqimxm/cbd-timeline-brazil/ [12-04-15].

[3] B.E. Porter - C. Jacobs on, «Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy», *Epilepsy Behav*. 29 (2013), 574-577.

[4] H.L. Li - H. Lin, «An archaeological and historical account of cannabis in China», *Econ. Bot.* 28/4 (1974), 437-447; E.L. Abel, *Marijuana, the first twelve thousand years,* Plenum Press, New York 1980.

[5] M. Aldrich, «History of therapeutic cannabis», in: M.L. Mathre (ed.), *Cannabis in medical practice*, N.C. Jefferson, Mc Farland 1997.

[6] T.J. Phillips - C.L. Cherry - S. Cox, «Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials», *PLoS ONE* 5 (2010), e14433.

[7] E. Martin-Sanchez - T.A. Furukawa - J. Taylor, «Systematic review and meta-analysis of cannabis treatment for chronic pain», *Pain Med.* 10 (2009), 1353-1368.

[8] F.C. Machado Rocha - S. Stefano - R. De Cassia Haiek, «Therapeutic use of Cannabis sativa on chemoterapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis», *Eur. J. Cancer Care* 17 (2008), 431-443.

[9] P. Flachenecker, «A new multiple sclerosis spasticity treatment option: effect in everyday clinical practice and cost-effectiveness in Germany», *Expert Rev. Neurother.* 13 (2013), 15-19.

[10] R. Mechoulam - L.A. Parker - R. Gallily, «Cannabidiol: an overview of some pharmacological aspects», *J. Clin. Pharmacol.* 42/11 (2002), 11S-19S; A.W. Zuardi - J.A. Crippa - J.E. Hallak et al, «Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug», *Braz. J. Med. Biol. Res.* 39/4 (2006), 421-429.

[11] P. Consroe - J.C. Wood - H. Buchsbaum, «Anticonvulsant nature of marihuana smoking», *Journal of the American Medical Association* 234 (1975), 306–307; J.M. Ellison - E. Gelwan - J. Ogletree, «Complex partial seizure symptoms affected by marijuana abuse», *Journal of Clinical Psychiatry* 51 (1990), 439–440; L. Grinspoon - J.B. Bakalar, *Marihuana. The Forbidden Medicine,* Yale University Press, New Haven 1997; R.J. Gurley - R. Aranow - M. Katz, «Medicinal marijuana: a comprehensive review», *Journal of Psychoactive Drugs* 30 (1998), 137–147.

[12] E.A. Carlini - J.R. Leite - M. Tannhauser et al, «Cannabidiol and Cannabis sativa extract protect mice and rats against convulsive agents», *J. Pharm. Pharmacol.* 25 (1973). 664–665.

[13] R. Mechoulam - L. Hanus, «A historical overview of chemical research on cannabinoids», *Chem. Phys. Lipids* 108 (2000), 1-13; R.G. Pertwee, «The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin», *Br. J. Pharmacol.* 153 (2008), 199-215.

[14] R. Mechoulam - Y. Shvo, «Hashish - I: the structure of cannabidiol», *Tetrahedron* (1963) 2073-2078.

[15] *Ibid.*; I. Izquierdo - O.A. Orsingher - A.C. Berardi, «Effect of cannabidiol and other Cannabis sativa compounds on hippocampal seizures discharges», *Psychopharmacologia* 28/1 (1973), 95-102.

[16] S.A. Turkanis - W. Cely - D.M. Olsen et al, «Anticonvulsant properties of cannabidiol», *Res. Communic. Chem. Pathol. Pharmacol.* 8/2 (1974), 231-46.

[17] J.M. Cunha - E.A. Carlini - A.E. Pereira et al, «Chronic administration of cannabidiol to healthy volunteers and epileptic patients», *Pharmacology* 21/3 (1980), 175-85.

[18] F.R. Ames - S. Cridland, «Anticonvulsant effect of cannabidiol», *S. Afr. Med. J.* 69/1 (1986), 14.

[19] P. Consroe - A. Wolkin, «Cannabidiol–antiepileptic drug comparisons and interactions in experimentally induced seizures in rats», *Journal of Pharmacology and Experimental Therapeutics* 201/1 (1977), 26–32.

[20] P. Consroe - M.A.C. Benedito - J.R. Leite et al, «Effects of cannabidiol on behavioral seizures caused by convulsant drugs or current in mice», *European Journal of Pharmacology* 83/3-4 (1982), 293–298.

[21] N.A Jones - A.J. Hill - I. Smith et al, «Cannabidiol displays antiepileptiform…», 569–577.

[22] G.B. Cheser - D.M. Jackson, «Anticonvulsant effects of cannabinoidsin…», 255-264.

[23] D. Gloss - B. Vickrey, «Cannabinoids for epilepsy», *Cochrane Database Syst. Rev*, 6:CD009270, 2012.

[24] B.E. Porter - C. Jacobson, «Report of a parent…», 574-577.

[25] A. Ohlsson - J. Lindgren - S. Andersson, «Single dose kinetics of cannabidiol in man», in. S. Agurell - W.L. Dewey - R.E. Willette (edd.), *The cannabinoids: chemical, pharmacologic, and therapeutic aspects*, Academic Press, Orlando 1984; G. Hawksworth - K. McArdle, *Metabolism and pharmacokinetics of cannabinoids*, Pharmaceutical Press, London 2004.

[26] B.E. Porter - C. Jacobson, «Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy», *Epilepsy Behav.* 29 (2013), 574-577.

[27] M.A. Elsohly - D. Slade, «Chemical constituents of Marijuana: the complex mixture of natural cannabinoids», *Life Sci.* 78 (2005), 539-548.

[28] J.W. Miller, «Slim evidence for cannabinoids for epilepsy», *Epilepsy Curr.* 2 (2013), 81-82.

[29] D. Gloss - B. Vickrey, «Cannabinoids for epilepsy…», CD009270.

[30] P.A. Fried - B. Watkinson - R. Gray, «Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana», *Neurotoxicol. Teratol.* 20/3 (1998), 293-306.

[31] B. Costa, «On the pharmacological properties of delta-9-tetrahydro-cannabinol (THC)», *Chem. Biodivers.* 4 (2007), 1664-1677.

[32] D.C D'Souza - R.A. Sewell - M. Ranganathan, «Cannabis and psychosis/schizophrenia: Human studies», *Eur. Arch. Psy. Clin. N.* 259/7 (2009), 413-431.

[33] M. Frisher - I. Crome - O. Martino et al, «Assessing the impact of cannabis use on trends in diagnosed schizophrenia in the United Kingdom from 1996 to 2005», *Schizophr. Res.* 113 (2009), 123-128.

[34] I.G Karniol - I. Shirakawa - N. Kasinski et al, «Cannabidiol interferes with the effect of Δ9-tetrahydrocannabinol in man», *Eur. J. Pharmacol.* 28/1 (1974), 172-177; A. Zuardi - I. Shirakawa - E. Finkelfarb et al, «Action of cannabidiol on the anxiety and other effects produced by delta 9- THC in normal subjects», *Psychopharmacology (Berl)* 76/3 (1982), 245-250.

[35] S. Dalterio - R. Steger - D. Mayfield et al, «Early cannabinoid exposure influences neuroendocrine and reproductive functions in male mice: I. Prenatal Exposure», *Pharmacol. Biochem. Behav.* 20 (1984), 107-113.

[36] M. Bifulco - C. Grimaldi - P. Gazzero et al, «Rimonabant: Just an anti-obesity drug? Current evidence on its pleiotropic effects», *Mol. Pharmacol.* 71/6 (2007), 1445-1456.

[37] S. Zhornitsky - S. Potvin, «Cannabidiol in humans - The quest for therapeutic targets», *Pharmaceuticals* 5 (2012) 529–552; S. Deiana - A. Watanabe - Y. Yamasaki et al, «Plasma and brain pharmacokinetic profile of cannabidiol (CBD), cannabidivarine (CBDV), Δ9-tetrahydrocannabivarin (THCV) and cannabigerol (CBG) in rats and mice following oral and intraperitoneal administration and CBD action on obsessive–compulsive behavior», *Psychopharmacology (Berl)* 219 (2012), 859–873.

[38] F. Grotenhermen, «Cannabinois», *Current Drug Targets - CNS & Neurological Disorders* 4 (2005), 507-530.

[39] M. R. Cilio - E.A. Thiele - O. Devinsky, «The case for assessing cannabidiol in epilepsy», *Epilepsia* 55/6 (2014), 787-790.

[40] E. Sgreccia, *Manuale di Bioetica*, Vita e Pensiero, Milano 2007. 69-70.

[41] John Paul PP. II, «Address to the scientists of the PONTIFICAL ACADEMY OF SCIENCES, on 21 October 1985», in: https://w2.vatican.va/content/john-paul-ii/en/speeches/1985/october/documents/hf_jp-ii_spe_19851021_pontificia-accademia-scienze.html [21/04/2015].