Abstract. – This review illustrates some brief considerations of the medical use of cannabis recently issued in Italy. History and uses of cannabis throughout centuries and different countries are illustrated together with a description of botany and active phytocannabinoids. Then, medical use of cannabis anti-pain treatment for patients resistant to conventional therapies is described in case of chronic neuropathic pain, spasticity, for antiemetic and antiemetic effect in nausea and vomiting caused by chemotherapy, for appetite stimulating effect in cachexia, anorexia, loss of appetite in cancer patients or patients with AIDS and in anorexia nervosa, hypotensive effect in glaucoma resistant to conventional therapies and for reduction of involuntary body and facial movements in Gilles de la Tourette syndrome. Italian most recent legislation on medical cannabis is detailed with some law proposals, also showing the inconsistent legislation within European Union. Some final considerations of future studies are also reported.

Key Words: Cannabis, Cannabinoids, Treatment of pain, Medical use of cannabis, European and Italian legislation.

Introduction

In the current health context, health is meant in the largest sense of the term, as a condition of physical and psychological well-being. Even the code of medical deontology, in its last version of 2014, considers the well-being of the patient as a priority obligation for the physician. Also the society operates in this direction. An important example is that referred to the well-known events of the biological testament, that of medically assisted procreation with related problems and finally the issue of transplants. Indeed, the last years experimentation in the field of transplants are aimed not only to save lives, but also to improve the patients quality of life. A classic example is the transplantation of the hand and that of uterus.

However, the global economic crisis has obli-ged the prevalence of management and organiza-tional aspects, the implementation of some investigations at the expenses of others, affected by economic reasons, lack of resources and funding. More and more often, the autonomy of the professional in detecting the most appropriate for a patient has to be faced not only with financial constraints, but also with indications, recommendations or guidelines. These latter are issued at various levels by public bodies with the aim of observing predetermined financial constraints. In this perspective, with a reduction in costs or a simple resources rationalization, the goal of achieving the well-being of the patient risks to be hardly feasible.

Treatment of Pain and its Variables

In the medical experience, pain represents one of the most important manifestations of the disease. Moreover, it has to be said that, among the symptoms, it is the one that mostly compromises the quality of life. Inappropriate management of pain creates very important physical, psychological and social consequences, especially in the most debilitating forms of pain - such as chronic ones - in which patient assistance is a real emergency for the Italian health system. Even the Code of Medical Deontology, in the Article 3, clarifies that among the duties of the physician or medical surgeon there is the treatment of pain and the relief from suffering. The evolution of the concept of palliative care is found in the terminology currently used: in the new Code “the relief from suffering” is replaced by “pain therapy” (Article 39). The expression “pain therapy” underlies an important concept: pain has to be measured and treated not at the discretion of the physician (doctor), but on the basis of knowledge and protocols.
that allow to quantify and effectively treat it.

Therefore, by excluding disproportionate therapies and protecting the dignity of the person who has been assured on the resolution of pain, the treatments - as far as possible - have to be suitable in preserving the quality of life. Indeed, the “quality of life” corresponds to a certain degree of psycho-physical autonomy, cognitive qualities, residual work capacity, ability to recover relations with society, with the family and with the world of work that can qualify a life as qualitatively acceptable. Therefore, in addition to the doctor (physician) duty, adequate pain therapy has to be considered a right of the patient, which has to be accompanied, through multidisciplinary approaches, in the difficult path of a disease characterized by the presence of pain.

Cannabis: history and Uses of a Much-Discussed Plant

Cannabis, also known as marijuana, ganja, pot, kif, hemp, is one of the oldest psychoactive plants known to mankind. It is native to the regions of Central Asia, but is spread all over the world. It is believed that the name derives from the Assyrian “qunnubu” or “qunnabu”\(^7\). The most ancient human artifact, a piece of hemp fabric, was discovered in Mesopotamia and dates back to the 8\(^{th}\) century BC. Numerous ancient writings dealt with the pharmacological and psychoactive properties of cannabis. In the 1\(^{st}\) century AC, Plinius the elder described in his “Natural Stories” that a decoction of the cannabis root could be used to alleviate the stiffness of the joints, gout and related conditions\(^7\). The medical use of cannabis comes from the ancient times: in this regard there is documentation in Chinese medical texts dating back to 2800 BC, where its consumption is indicated for the intake for a wide range of diseases\(^8\). In Europe, the spread Cannabis dates back to the 19\(^{th}\) century, on the occasion of Napoleon’s military campaigns in Egypt. The first scientific studies date back to 1839: O’Shaughnessy, an Irish doctor, administered cannabis to patients suffering from various diseases, from epilepsy to rheumatism, finding an anticonvulsant, analgesic, anti-epileptic efficacy. During the 19\(^{th}\) and the early years of 20\(^{th}\) century, cannabis was a medical product commonly used in clinical practice. Its success, as an active pharmacological compound, also arrived to America. Nevertheless, at the beginning of the 20\(^{th}\) century more effective treatments came into force: vaccines against cholera and tetanus, antibiotics for gonorrhea, which prevented or treated the cause of the disease instead of its symptoms, psychotropic drugs such as barbiturates, which replaced cannabis in the psychiatric area. Furthermore, in the treatment of pain, acetylsalicylic acid and more generally analgesics, started to be more effectively used\(^8\). In any case, the cause of the decline in the pharmacological use of cannabis was its pharmacological instability whereby the plant effects were difficult to predict and standardize. The active principle delta-9-tetrahydrocannabinol (THC) had not yet been isolated and the effects of the galenic preparations, in terms of pharmacological potency, were closely related to the concentration of this compound. Many variables influenced its concentration: e.g. the origin of the plant, its freshness, as well as its storage. Furthermore, to limit its use, there was also a factor of an economic nature. Indeed, the importation of hemp had becoming increasingly difficult and expensive in relation to the conflicts with India and, more generally, to the two world conflicts.

As a result, the use of cannabis for therapeutic purposes was increasingly limited up to the prohibition of its use with the Single Convention on Narcotic Drugs of 1961\(^{10}\). Only several decades later, at the beginning of the 21\(^{st}\) century, cannabis has been re-admitted as a pharmacological active drug and “medical cannabis” used and legalized for therapeutic purposes in many countries.

Botany and Active Ingredients

According to the official modern taxonomy, cannabis belongs to the Cannabaceae family, together with hop. It is a dioecious plant (there are separate male and female plants) and the female flowering tops are the ones to produce the largest amount of the resinous substance containing the psychoactive ingredient, THC. There are more than 460 chemical components of the plant, and more than 60 presenting the typical structure of cannabinoids. Among these, THC, presents at about 1.5% total flowering tops weight, is the only one with psychoactive properties. Research on its potential use in the medical field has recognized it as the main responsible for the pharmacological properties of the plant, although other compounds contribute to some of these effects. In particular cannabidiol, without psychoactive effects, but with antipsychotic, analgesic and anti-inflammatory ones. When THC is given together with CBD, there is a reduction in anxiety, dysphoric and potential effects on the memory. The pharmacokinetic properties of cannabis vary depending on the administered dose and route of administra-
tion. In his discretion, the doctor decides the route of administration and the doses to be used taking into account the therapeutic needs of the patient. The doctor should discuss with patients the potential benefits and risks of cannabis since the decision to prescribe and use cannabis preparations have to be shared with the patient, who must give written informed consent. Again, the doctor has to inform the patient of the main drawbacks, underlining that the use of cannabis may lead to positivity to Antidrug tests (Decree 309/90), doping tests (Law 376/2000)11,12 tests indicated in the Highway Code (Article 187 of the Highway Code: Guide in state of psycho-physical alteration due to the use of drugs). The patient should inform the doctor if he/she is taking any other medication, so that the doctor can evaluate the possible drug interactions before prescribing cannabis-based preparations.

**Medical Use of Cannabis**

The use of compounds with therapeutic activity has to comply with quality and safety standards. These standards are guaranteed by scientific studies and scrupulous monitoring of the drug used in the experiments. Let’s start from the available scientific data we have. Recently, controlled and observational clinical studies have been conducted and systematic and meta-analysis of international indexed literature have been reported to evaluate cannabis therapeutic effects 13. The majority of the controlled studies have been carried on synthetic cannabinoids (dronabinol, nabilone, levonantradol, not available in Italy) or nabiximols (an oromucosal spray with specific THC and CBD dosage available in Italy). Only two studies used smoked or vaporized marijuana, five studies used smoked THC, seven oral preparations of THC.

Synthetically, the results were the following:

- Nauseas and vomiting following chemotherapy (37 reports - 1772 participants). In 14 studies nabilone was used, in 6 ones THC in capsules, in 4 ones levonantradol, in 3 ones dronabinol, in 1 nabiximols. In all these studies cannabinoids resulted to be effective 14.
- Stimulation of appetite in HIV patients (4 reports - 255 participants). All studies involved dronabinol and the effect of marijuana smoke or dronabinol intake compared with placebo was studied: weight gain was demonstrated in both types of administration15.
- Chronic pain (28 reports - 2454 participants). 13 studies involved nabiximols, 4 smoked THC, 5 nabilone, 3 oromucosal THC sprays, 1 vaporized cannabis, 1 ajulemic acid and 1 THC oral. A study compared nabilone with amitriptyline, all the others compared active compound with placebo. The treated pain had different origins: neuropathic pain, tumor pain, diabetic neuropathy, fibromyalgia, HIV neuropathy, multiple sclerosis, and rheumatoid arthritis. The patients enrolled were treated with cannabinoids and the pain symptomatology improved in all cases16.
- Spasticity caused by multiple sclerosis or paraplegia (33 reports - 2280 patients). 6 studies involved nabiximols, 4 THC/CBD (2 together with dronabinol), 3 dronabinol, 1 nabilone, 1 ECP002A and 1 THC. Cannabinoids, in all their formulations and without significant differences between them, provided improvements in spasticity.
- Anxiety disorders. The data came from some studies whose primary outcome was chronic pain. In any case they showed a decrease in anxiety17.
- Sleep disorders (5 studies - 54 participants). All the studies involved nabilone, which has been shown to improve the sleep apnea/hypopnea index. In other studies with different primary outcome, the quality of sleep was assessed, with improvement reported for all cannabinoid formulations (best outcomes for nabiximols)18.
- Glaucoma (6 participants). No differences between placebo and cannabinoids treatment19.
- Tourette syndrome (2 studies - 36 participants). Improvement in the severity of tics in patients taking THC in capsules when compared to placebo20.

Severe adverse events were more frequent in cannabinoid-treated populations than in controls. To date, no data on long-term adverse events of cannabinoids used for medical purposes are available.

Taken together, the presented data show a moderate efficacy of cannabinoids in chronic pain and spasticity, a lower efficacy in all other indications.

Other possibilities of medical use of cannabis with minor importance have been reported in the literature and, among these, there are antitumor effects21. Nevertheless, from an epidemiological point of view, the treatment of chronic pain is an indication that has the greatest impact on population therapeutic needs and, consequently, on cannabis production. Recent studies22-24 report that 45-80%
of patients using cannabis-based products use them for pain management. As for all the other drugs, cannabis provides side effects\textsuperscript{25,26}.

**Italian Legislation on Medical Cannabis and Cannabinoids**

In Italy, doctors have been able to prescribe cannabis products and synthetic cannabinoids for therapeutic use since 1998, with a non-repeatable prescription. The Ministerial Decree of 18 April 2007\textsuperscript{27} include natural and synthetic cannabinoid derivatives in the Table of substances with therapeutic activity, correcting a coarse error of Law 49/2006 (so-called Fini-Giovanardi) that placed these substances among those lacking of this activity. It is, therefore, possible at moment to prescribe such products. Since 2007, Italy has recognized the therapeutic use of THC, the active ingredient of cannabis, and of two other similar substances of synthetic origin, dronabinol and nabilone.

Subsequently, with the Ministerial Decree dated 23\textsuperscript{rd} January 2013\textsuperscript{28}, the Ministry of Health included in the B section of the Medicinal Table active compounds of cannabis plant origin: compounds and preparations, including extracts and dyes. The doctor can, therefore, prescribe cannabis products for therapeutic purposes and any pharmacy, if properly supplied, can distribute cannabis products in the form and dose as prescribed by the doctor.

Furthermore, according to the cooperation agreement between the Ministry of Health and the Ministry of Defense of 18 September 2014, Italy started the production of national cannabis, previously imported from Dutch crops through the Office of Medicinal Cannabis. Indeed, starting from December 14, 2016, cannabis-based FM2 product, produced by Military Pharmaceutical Chemical Works of Florence, Italy in agreement to the Good Manufacturing Practices (GMP) of the European Union, is available to be prescribed. FM2 cannabis consists of unfertilized, dried and milled female inflorescences containing 5-8\% tetrahydrocannabinol (THC) and one of cannabidiol (CBD) of 7.5-12\%\textsuperscript{29,30}. There are also cannabigerol, cannabichromene and tetrahydrocannabivarin in percentage <1\%. FM2 cannabis, grown in Good Agricultural and Collecting Practices (GACP) and produced according to GMP, is manufactured in accordance with the European Union directives on active substances for the production of medicines. The technical documentation of the product is registered at the Italian Drug Agency.

Following the coming into force of the Ministerial Decree of 9 November 2015\textsuperscript{31}, the General Directorate of Medical Devices and the Pharmaceutical Service of the Ministry of Health issued a circular with all the information that doctors and pharmacists have to follow for the use of FM2 cannabis for therapeutic purposes: prescription

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<th>Table I. Indications for medical cannabis (as reported in the Official Gazette n. 279 from 30-11-2015).</th>
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<tr>
<td>• Analgesia in diseases involving spasticity associated with pain (multiple sclerosis, spinal cord injury) resistant to conventional therapies.</td>
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<td>• Analgesia in chronic pain (with particular reference to neurogenic pain) in which treatment with non-steroidal anti-inflammatory drugs or with cortisone or opioid drugs has proved to be ineffective.</td>
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<td>• Anticinetosic and antiemetic effect in nausea and vomiting, caused by chemotherapy, radiotherapy, HIV therapies, which cannot be obtained with traditional treatments.</td>
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<td>• Appetite stimulating effect in cachexia, anorexia, loss of appetite in cancer patients or patients with AIDS and in anorexia nervosa, which cannot be obtained with standard treatments.</td>
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<td>• Hypotensive effect in glaucoma resistant to conventional therapies.</td>
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<tr>
<td>• Reduction of involuntary body and facial movements in Gilles de la Tourette syndrome, which cannot be achieved with standard treatments.</td>
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<th>Table II. Side effects of medical cannabis.</th>
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<td>Tachycardia</td>
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<td>Hypotension</td>
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<td>Paranoia</td>
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<td>Dizziness</td>
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<td>Reduction of cognitive development and psychomotor performance, alteration of attention and memory</td>
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<td>Psychiatric disorders</td>
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<td>Damage to the airways and lungs</td>
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<td>Risk of addiction weight reduction at newborn birth if used during pregnancy</td>
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and reimbursement, monitoring of prescriptions, indications, dosage and method of administration, methods of decoction preparation, pharmacodynamics and pharmacokinetic properties, contraindications, side effects, special warnings and precautions for use, interactions with other medicinal products and other forms of interaction, the creation of phytosurveillance system for safety monitoring. The circular reiterates that “cannabis cannot be considered a proper therapy, but a symptomatic treatment to support the standard ones, when these latter ones have not produced the desired effects or have caused non-tolerable secondary effects or require dosage increases that could determine the appearance of side effects”.

**Law Proposal S.2947 “Provisions Concerning the Cultivation and Administration of Medical Cannabis**

During 2017 in Italy the use of cannabis for therapeutic purposes was at the center of the political and social debate. In particular, on 30 October 2017 the Senate approved the Law Decree S.2947 “Provisions concerning the cultivation and administration of medical cannabis” 32.

The law of the article 1 regulates the use of medicinal products of cannabis vegetable origin. 2) It guarantees uniform criteria on the national territory to access these products. 3) It promotes scientific research on possible further uses of medical cannabis. 4) It supports the development of cannabis production and processing techniques, to simplify the methods of administration cannabis-based medicines. The article 2 explains that ‘medical use’ means the administration of cannabis-based medicines prescribed after a suitable patient assessment and diagnosis, to provide appropriate treatment. The doctor may prescribe magistral preparations based on cannabis for the treatment of pain, in agreement to the law of 15 March 2010, n. 38, at the charge of the National Health Service. In the prescription, the doctor has to indicate the alphanumeric code assigned to the patient, the prescribed dose, the dosage and the methods of consumption. The prescription should also report the date of issue, the duration of the individual treatment, which in any case cannot exceed three months, as well as the signature and the stamp of the doctor who issued it (Article 3). The regions and the autonomous Provinces of Trento and Bolzano annually provide the data on prescriptions of medical cannabis, aggregated by disease and by patients age and gender without indication of the identity of patients (D. L. 30 June 2003, No. 196) (Article 4). Each year, the regions have to communicate, by 31 May, to the Cannabis State Organization, the amount of cannabis-based active substance they need for the following year. If further amount of cannabis are needed beyond those cultivated by Military Pharmaceutical Chemical Works of Florence, Italy, by decree of the Minister of Health, one or more companies can be identified, and authorized for cannabis cultivation as well as for processing by “Good agricultural and collecting practices” (GACP), in accordance the President of the Republic Decree of 9 October 1990, n. 309.

**Article 4.** In order to facilitate the use of cannabis-based preparation, Military Pharmaceutical Chemical Works provide for the development of new preparations for subsequent distribution to pharmacies, which dispense them on the basis of a non-repeatable medical prescription.

**Article 7 (Information campaigns).** The Ministry of Health, as Cannabis State Organization, publishes on its institutional website the contributions that are sent every six months by the Italian Drug Agency and the National Institute of Health on the state of scientific evidence on the medical use of cannabis, aimed at promoting knowledge and disseminating information to physicians and pharmacists on the use of cannabis-based products.

**Article 8 (Training of medical, health and social care personnel).** Following to article 8, paragraph 2, of Law March 15, 2010, n. 38, a periodic updating of medical, health and social care staff is organized and achieved through the attainment of training credits. These latter are intended to acquire specific professional knowledge on the therapeutic potential of cannabis-based herbal preparations in the various diseases and in particular on the treatment of pain (research promotion). As part of research activities, universities and medical-scientific societies can promote pre-clinical, clinical, observational and epidemiological studies on the appropriate use of cannabis-based medicinal products, carried out according to the current legislation on clinical trials, through the resources of the Italian Drug Agency, referred to the Article 48, paragraphs 18 and 19, letter b), number 3). Magistral preparations based on FM2 cannabis can be prescribed by any qualified doctor registered in the Order of Physicians, by non-repeatable prescription, where the reim
bursement is established by each Region and Autonomous Provinces of Trento and Bolzano.

**The Use of Cannabis for Therapeutic Purposes is Widespread at European Level**

European legislation is inconsistent on the use, cultivation and possession of cannabis. The three United Nations conventions on drugs - to which the EU adheres - authorize the use of psychotropic drugs only for medical or scientific purposes. The 1988 Convention considers “detention for personal use” as a crime. The signatory countries are then asked to adhere to international legislation on the possession of drugs, but it remains de facto free on the local policies to be adopted. From here it comes the variety of systems conceived in the EU. Cannabis is illegal in France, Italy, Poland, Bulgaria, Cyprus, Denmark, Croatia, Finland, Great Britain, Luxembourg, Malta, Romania, Sweden, Austria, Latvia, Slovakia, Slovenia, Lithuania, Belgium, Hungary. It is legal in the Netherlands. It is decriminalised in: Germany, Portugal, United Kingdom, Czech Republic, Spain, Estonia.

**Conclusions**

Since the last thirty years, cannabis has been the most studied plant in the field of medicine for its therapeutic properties in a wide range of medical conditions, including chronic neuropathic pain management. Central neuropathic pain is a medical challenge, due to its serious impact on the lives of patients and the difficulties in its management. For this reason, cannabinoids may represent an extra opportunity in the therapeutic luggage of the doctor. Therefore, further studies are needed to better define the therapeutic role of cannabis and its preparations. Indeed, the results on the medical effectiveness of cannabis are still controversial and the medical community continues to be not in agreement with the possibility to appeal at this type of treatment. However, given that the costs of cannabis for therapeutic use will be supported by the National Health Service, it is essential both to avoid unrealistic expectations in patients and to conduct further studies to make the best possible use of public money.

**Conflict of Interest**

The Authors declare that they have no conflict of interest.
care part D. Health Aff (Millwood) 2016; 35: 1230-1236.