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Letter to the Editor

Cannabis as a medicine. An update of the Italian reality

Cannabis and cannabinoids gained increasing attention for their possible clinical uses, as recently reported in a Special issue of this journal. The Mario Negri Institute recently organized a national conference on the therapeutic potential of clinical use of Cannabis, hosting lectures from main Italian stakeholders in the area. The goal was to clarify the current national regulations regarding production, prescription and availability in Italy, and to evaluate the current state on the clinical use of Cannabis.

The first question is if Cannabis and cannabinoids can really be treated as a drug. From a legislative point of view in Italy a medicine is: (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis [1]. And therefore, in this respect, they should be treated as such.

Drugs must follow well-defined research and regulatory paths to be allowed onto the market. They should demonstrate their activity, efficacy, and safety. Few commercial products containing cannabinoids, such as nabiximols (Sativex), dronabinol (Marinol), nabilone (Cesamet) and cannabidiol (Epidiolex), are available. In Italy only Sativex is available on the market. The other products must be imported in case of medical request. A large proportion of patients in Italy are treated quite exclusively with magistral preparations from the dried inflorescences [2]. Following an agreement between the Ministry of Defence and the Ministry of Health, and after an initial pilot project [3], the only Italian authorized manufacturer is “Stabilimento Chimico Farmaceutico Militare” (SCFM) which produces *Cannabis* FM2, grinded inflorescences with a balanced content of THC (5-8%) and CBD (7,5-12%) and *Cannabis* FM1 (THC 13-20%; CBD < 1%), with GMP certified compliance, according to an Active Substance Master File (ASMF) registered by the Competent authority for medicinal products (Italian Agency of the Drugs, AIFA). This is the active substance currently provided to pharmacies by the SCFM and is used without rigorous studies and without having established efficacy through controlled studies. A subsequent problem is the willingness of pharmacists to prepare the magistral products after prescriptions. The number of compliant pharmacies is limited and their distribution in the territory is not homogeneous. In addition, the properties of the magistral preparations depend on the pharmacy preparation, the technique of the preparations [4] and the different, sometimes precarious, consumption by the patients especially when an herbal decoction is administered. What is actually assumed by the patient? Which active substances present in the plant are taken? What is the dose [5]? These are the limits of the galenic preparation compared to a commercial product. Why was this choice made? *Cannabis* is supposed to function as an herbal-complex rather than single molecule, but this idea must be proven. The future availability of a standardized oil extract, with a well-defined route of administration (oral or transmucosal), could overcome most of these difficulties.

A further problem is that these preparations may be used in several disorders even if the Ministry of Health informs [6] that Cannabis for medical use does not cure those disorders but it can relieve the symptoms and support standard treatments: treatment of chronic pain and spasticity, nausea and vomiting related to chemotherapy, anorexia-cachexia in cancer and HIV patients, glaucoma and Tourette syndrome. These indications are widely shared by the members of the International Committee “The Health Effects of Cannabis and Cannabinoids” [7].This is not the case for the authorized commercial products, such as Sativex that is licensed in Italy for spasticity due to multiple sclerosis only [2]. Without the indications of AIFA, magistral preparations are all of-label, request a specific informed consent of the patients and may or not be reimbursed from the National Health Service depending on the local regulations of each region. Starting from these controversial positions, the clinical conditions suitable for the use of *Cannabis* depend on the free choice of clinicians who, according to their experience and the data of the literature, decide dosages and times in the prescription. Presently, physicians practice is a personal achievement, little supported by educational programs [5]. Literature conclusive evidences on health effects of *Cannabis* are still elusive [8,9] also in clinical field where the indications are substantial [10]. There are many potential biases and gaps that affect the results of the studies, such as differences in type of cannabinoids used, types of pathologies, research methodology and experimental designs. For instance, the comparative studies between cannabinoids and standard treatments are infrequent. The limits of the currently available literature do not help correct clinical practice.

In conclusion, to assess the clinical use of Cannabis as a drug in Italy is quite complex. While some aspects as the limits of the scientific and clinical evidence are common to other countries [11], other are specific to our context. The prevalent use of non-commercial preparations with uncertainty about the substances administered, the difficulties of finding pharmacies that are available to make magistral preparations after prescription, the sustained expense for the patients, preparation times, non-uniform regulations among regions, several counterposed positions among public authorities are real problems that need quick and specific responses. An improvement in the regulation may address some of the open questions described above. A strategic plan for research, particularly for clinical trials defining the pharmacokinetics, effectiveness and safety of *Cannabis* and cannabinoids could help inform these regulations and an appropriate clinical practice.

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