Mini Review

Medicinal Cannabis: Cultural, Societal and Regulatory Challenges in the Americas

Victor M. Rivera*

Department of Neurology, Baylor College of Medicine, USA

Abstract

Utilization of cannabis for recreational purposes in its smoked form (marijuana) along with its potential habit forming properties and effects in the central nervous system (CNS), are issues provoking considerable current international legal and scientific debate. The appearance of the plant in the Americas in the 16th Century initiated complex popular concepts of its effects, not just on the psychological sensations experienced by the user, but its mythically assumed curative effects as well. The plant cultivation and its consumption remained clandestine thus favoring an aura of attractive prohibition, particularly in Mexico where it has had a folkloric role, being popularly utilized in the 20th Century by troops and bohemian intellectuals, and later illegally exported by increasing demand in the United States. Recent knowledge on the biochemistry and pharmacological properties of non-psychoactive cannabinoids has initiated the era of medicinal cannabis. There are few agents approved by international licensing agencies. These products exert their effect in the CNS treating neuropathic pain, spasms and spasticity in Multiple Sclerosis (MS), chemotherapy-associated intractable nausea/vomiting and anorexia and weight loss in HIV infected patients. A realistic challenge faced by government derived regulatory agencies, particularly in areas in development like most of Latin American countries, is the lack of analytical infrastructure and access to informational resources affecting regulators. This handicaps not only access to products based on evidentiary clinical trials but it may allow entrance to agents that simply have an anecdotal proposal. Remedial measures are suggested.

INTRODUCTION

Anatomical elements of the plants Cannabis *indica* and *sativa* are the source of marijuana and hashish, the former using the pulverized leaves while the latter is acquired by using resins manufactured to be smoked in blocks. The legal implications of liberating marijuana for recreational use by the public, or for industrial production of medicinal products, remain under undecided and careful observation in most places of the world, despite that some of the metabolites and derivatives (cannabinoids) have shown compelling evidence of medical benefits. Health licensing agencies such as the Food and Drug Administration (FDA), European Medicine Agency (EMA) and diverse governmental offices globally, encounter substantial challenges distinguishing between anecdotal adjudications of curative properties and real efficacy based on evidence. This situation is confounded by the paucity of controlled clinical trials and by strong cultural and political factors. This paper discusses some of the challenges faced by regulatory agencies in Latin America when involved in the process of evaluating proposed medicinal agents based-on-cannabis, once a distinct difference between recreational smoked marijuana, some edible products, and specific forms proposed for therapeutic purposes is established.

DISCUSSION

Considering the social impact that liberating marijuana for universal utilization would imply: its recreational use, potential medical therapies, and biological research, the complex legalities of the process and the public perceptions in these different areas condition the need for adequate information, education and consensus. Data based on scientific evidence is primordial. A particular concern present in different regions of the continent, is the limited capabilities for the proper analytical process of potential medicinal agents.

Historical aspects

The cannabis plant has been known and used from over two millennia in China, India and North Africa where the hemp was utilized to produce fabrics, paper and ship ropes. Smoking leaves of pulverized cannabis *indica* was found to produce attractive sensations. The plant was first brought to the Americas

by Hernán Cortéz in 1521 after the completion of the conquest of Mexico. Its cultivation in 1545 was initially sanctioned by the Spaniards as a source of cordage [1]. African slaves arrived to Mexico between the seventeenth and nineteenth centuries smoking cannabis in occult spiritual and curative rituals. Throughout the course of time traditional healers were called "*Marias*" and "*Juanas*", the conjunction of words evolving into the common term "Marijuana". Particularly in Mexico during the first decades of the 20th century consumption of marijuana turned to a recreational habit favored by its psychological stimulating properties among groups in the economically low sociological strata and soldiers [2]; later on the use was adopted by affluent classes and intellectuals [3]. The folkloric attraction of its use in Mexico was enhanced by the 'forbidden' aura that surrounded its acquisition [4]. Despite that cannabis cultivation in Mexico remains illegal the demand for marijuana in the US (despite its legalization for recreational and medical use in several states) has resulted in criminal transnational traffic. Intense congressional debate is being carried out in Mexico regarding approval of medicinal cannabis derivatives although universal liberation for recreational purposes is no longer in the agenda [5].

The major suppliers to the US are at present Mexico and Jamaica, while Paraguay is the main source of illegitimate exportation in South America [6]. Cannabis use for all or several purposes has been approved in many countries in Europe, Canada, almost half of the states and the District of Columbia in the US [7], and more recently for medicinal indications in Argentina, Colombia, Chile and Uruguay [8].

Biopharmacological and molecular aspects

The major pharmacological component, present mainly in the leaves and unfertilized female flowers of the marijuana plant, is also the main psychoactive element of cannabis: *Δ-9 tetrahydrocannabinol* (THC). Since it is possible to botanically manipulate the concentration of THC, current techniques have raised the concentration in marijuana plants from 3% in 1980 to 20% in the last decade. This chemical can also be reproduced synthetically [9]. More than 113 cannabinoid derivatives have been identified, *cannabidiol* (CBD) accounting for up to 40% of the plants extract. CBD is present in a smaller proportion in the leaves with most of its concentration found in the stem (hemp) which is mostly devoid of THC. Other cannabinoids without apparent psychoactive effects are *cannabigerol* and *cannabinol*, both being explored for therapeutic possibilities [10,11]. *Nabiximol* is a specific extract of cannabis with specific CNS effects reducing hypertonic muscle tone and spasms, albeit only shown so far in inflammatory demyelinating disease [12]. Endocannabinoid receptors CB1 are located in brain structures related to behavior, impulse control, coordination and other functions, and are activated by the diverse derivatives from marijuana. This may explain temporary symptoms of dysphoria, depersonalization, disinhibition and ataxia experienced by most of the users [13]. In the other hand, in the therapeutic area, *nabilone (dronabinol),* a synthetic cannabinoid that mimics THC appears to specifically activate neuronal networks located in the *area postrema* located in the dorsal area of the brain stem's medulla. This central effect is pharmacologically utilized to inhibit nausea and vomiting induced by cancer chemotherapy as well as

improving weight loss and appetite in patients with HIV infection [14]. There is scant information on the effect by cannabinoids on the endocannabinoid receptors identified in immune cells (CB2)**,** but it appears that by interaction of these molecules, cytokine upregulation of the Th1 pro-inflammatory system theoretically would have deleterious effect in autoimmune disorders. Activation of CB2 receptors by cytokine release may also be responsible for the vasospastic phenomena observed in some individuals after exposure to smoked cannabis [15]. THC concentration in the CNS concentrations after marijuana inhalation triggers after a few minutes (peak effect ≥ 30 minutes; average duration 3.0 hours) a temporary complex set of physiological and neuropsychological reactions associated to activation of both CB1 and CB2 receptors. THC plasma concentrations of 2 to 5 ng/ml are associated with measurable impairment of neuropsychological functions synergistically confounded when cannabis is associated to alcohol and other CNS acting substances [16].

Therapeutic evidence for medicinal marijuana

The official regulatory processes to approve a proposed medicinal agent requires of objective data on efficacy acquired through specifically designed and adequately controlled study protocols. The results of each study should provide statistical significance and scientific evidence to support and justify its safe availability to the public. There are very few cannabinoids that have met these challenges [17]. While several clinical trials have shown *Nabinol* to be effective in the control of intractable chemotherapy-associated nausea and vomiting, and management of cachexia and anorexia in people with HIV infection, extension of these effects to other conditions has not been granted (although *Nabinol* has also been licensed for management of pain, but only in Mexico) [18]. Independent systematic reviews by the American Academy of Neurology, the Swiss Federal Office of Public Health and the Division of Drug Abuse and Alcohol of Harvard Medical School drew similar conclusions and recommendations in regards of the evidentiary status of therapeutic cannabinoids [19]. *Oral Cannabinoid Extract* is considered effective in the management of spasticity, spasms and neuropathic central pain in MS. *Nabiximol* and other CBD have weaker levels of evidence as treatments for several neurological conditions and neurogenic symptoms, fluctuating from "ineffective", to "probably ineffective". At present time, no study involving CBD for therapeutic purposes has provided a Level 1 of evidentiary power with a recommendation a degree; hence these products are not acceptable for those diverse proposed indications. Smoked marijuana used as therapy has been classified as of "uncertain efficacy" by these systematic analyses [20].

Regional regulatory challenges

The FDA has established a strict set of guidelines to approve chemicals and molecules for medicinal purposes. These regulations are not necessarily adopted by other licensing institutions, particularly in Latin America. This is due in part by the different health laws followed in the region as well as by lack of adequate resources for proper evaluation exerted on licensing offices. Although US dispositions may be adopted in some cases, independent assessments may reach at times similar conclusions. An example of this coincide is offered by *Nabilone* which is

considered a controlled substance (Schedule III (C III) in the US and, similarly in Mexico is classified within the frame of Section I for 'Narcotics', according to the Mexican General Health Law. Regulatory agencies in countries in development nevertheless face the challenges of lack of analytical infrastructure and methodology, and access to informational resources affecting officials and regulators. This concern is particularly notorious in Latin America where marijuana has been approved in several countries for medicinal purposes. A realistic preoccupation derived from insufficient technological resources and appropriate analytical support is the potential handicap of safe and efficacious products, while in the other hand allowing entrance to the market to agents proposed strictly on anecdotal basis or with uncertain safety profile. Unified, comprehensive instructional programs across the region supported by international organizations, i.e. the Panamerican Health Organization, may be considered to provide educational tools to regulatory health institutions in Latin America.

CONCLUSIONS

Availability of medical marijuana in the Americas is impacted by diverse factors including public reservations, inherent to a historical protracted perception. Complicated regional licensing issues confound the concern of insufficient methodological means available to the local regulators. While knowledge on the molecular and pharmacological properties of cannabinoids continues to progress, clinical studies designed to provide evidence are strongly needed.

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