ARE NEW PSYCHOACTIVE SUBSTANCES SHADOWING BIGGER THREATS?

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In recent years, a wide range of new substances of abuse have emerged, namely the so called 'New Psychoactive Substances' (NPS). Although they are not entirely new, these substances have been rediscovered and are entering the market under various names. Since they fall outside of many international conventions and laws on recreational drugs, and have emerged at a time where potential users are particularly internet savvy in identifying and obtaining drugs online, NPS have rapidly become a threat. Although data is still scarce, the literature indicates several reports that strongly support the risk associated with consumption of these compounds. However, despite being a "hot topic", NPS may be shadowing 'incoming threats'; namely the generalized trend towards legalization of medicinal and non-medicinal cannabis, as well as the dramatic increase in the misuse of prescription opioids and subsequent transition to heroin or non-pharmaceutical fentanyl. Both threats are discussed in this paper, highlighting not only the risk that they pose in general, but also their long-term implications.

1. Introduction

The term "drug of abuse" refers to a wide spectrum of substances with effects on perception, reasoning, and mood, presenting different abilities to produce dependence in consumers. Discussing the history of "drugs of abuse" is almost the same as discussing Mankind's own history, since drugs have always been an integral part of human culture and religious rituals and have evolved simultaneously with humans [1]. Indeed, historical records show that our ancestors as far back as the Neolithic era consumed drugs, in particular psychotropic substances (peyote, cannabis, poppy, coca, among others) [2]. Nevertheless, the impact of the abuse of such substances are long known [3]. According to the World Health Organization (WHO) [4], at least 15.3 million persons currently experience drug-use disorders.

In 2015, the United Nations (UN) approved a new agenda to be achieved by 2030, composed of seventeen goals and 169 targets towards sustainability. Under the umbrella of the third goal, "Good Health and Well-Being", the UN dedicated a single target (Target 3.5) to increase the promotion and strengthen the prevention and treatment of substance abuse, including narcotic drug abuse and harmful use of alcohol. It is important to stress however, that the implications related to the drugs of abuse (e.g. production and dealing) go far beyond the SDG's 3rd goal [5] .

2. New Psychoactive Substances (NPS)

In recent years, a wide range of new substances of abuse have emerged, namely the so called New Psychoactive Substances (NPS). Although many of these substances are not described in international drug control conventions and laws, NPS are not a novel phenomenon. Many of them were synthesized and, in many cases, patented in the early 1970s or even earlier. More recently, these substances have been rediscovered and their chemistry or process of synthesis slightly modified to produce effects similar to known illicit substances (e.g. cannabinoids). NPS can be found under various designations: from designer drugs, to legal highs, from bath salts to research chemicals (the later more recently). [6]. Among the widely varied group of NPS, is impossible not to highlight the synthetic cannabinoids, which are without doubt the largest group of NPS and the most highly consumed. As the name implies, the substances that

fall in this category produce effects similar to cannabis based products. Substances like "Spice" (JWH-018), ADB-PINACA or, more recently MDMB-CHMICA fall in this category [7]. Such substances, as well as their rate of appearance in the market (according to EMCDDA [8], two new substances hit the market each week) pose a dramatic challenge to those formulating drugs policy and related public health responses.

Increasing familiarity with navigating the Internet for illicit substances, providing more easily accessible information on their potential effects, has made the Internet a key source of information on NPS, particularly for young people. User-oriented drug information sites are often perceived to be trustworthy and are normally ranked higher in common search engines. The internet created space for a significant change in the drug-dealing paradigm: online sales. Creative marketing strategies (e.g. "research chemicals") feature broad disclaimers and questionable "safety advice". As a consequence, NPS have emerged in user repertoires, with self-experimentation and recreational drug use featuring commonly, as a result of enthusiastic user advertising. It is important to highlight that heavy drug users in general tend to be conservative and less open to experimentation of new substances. Manufacturers and wholesalers based in China have come to prominence as a suspected wholesale source of many of the precursors and bulk active substances for synthetic products [9].

The majority of current epidemiological indicators are poorly suited to monitor new substances, reflecting the complexity and the dynamic nature of the market, including the fact that many NPS products are mislabelled, i.e., the label does not contain the correct name of the substance. Nevertheless, it is possible to find in the literature several reports that strongly support the risk associated with the consumption of these compounds [10–12].

Due to prominent danger arising from the NPS, both EMCDDA and the United Nations Office for Drugs and Crime (UNODC) have implemented early-warning systems to detect this class of compounds. Additionally, from a purely academic/research point of view, NPS have become the "hot topic" amongst scientists; as demonstrated by the increasing number of publications and scientific communications dedicated to this theme [13].

3. Non-medical cannabis

Although NPS pose a significant threat to public health in general, due to the above-mentioned reasons, we believe that they may be shadowing emerging threats from other substances, including in particular cannabis and prescription opioids.

Cannabis and cannabis based products (e.g. hashish) are the most used drugs worldwide. According to the UNODC [14], in 2014, an estimated 182.5 million people aged 15−64 years used cannabis for nonmedical purposes globally. In Europe, cannabis is also the most commonly used illicit drug. It is estimated that at least one in every eight young adults (aged 15–34 years) used cannabis in the last year across the European Union [7]. It is important to note that in the last years, three major trends have been observed:

» A trend indicating an increase in cannabis users;

» An increasing demand for treatment of cannabis use disorders (CUD) and associated health conditions in high- and middle-income countries [15];

» An upward trend in the mean THC content of all confiscated cannabis preparations in the USA and in some European countries;

» The breeding of different strains towards the production of plants with much higher content of THC over the past decade (from around 3% to 12–16% or higher; % of THC weight per dry weight of cannabis).

Since the beginning of the twenty-first century, the usage of cannabis and cannabis-based products for medical purposes have been subject of major discussion worldwide, particularly in the USA. Although most of the so-called medical cannabis programs focus on the use of cannabis for symptoms associated with physical health disorders (e.g. cancer or chronic pain) [16], a substantial portion of cannabis medical use aims to address mental health concerns. Although evidence suggests that medicinal cannabis may carry the potential for the treatment of posttraumatic stress disorder (PSTD) and as a substitute for problematic use of other substances, the literature regarding this subject is limited [15,17]. According to Walsh et al. [17], users of medical cannabis report that cannabis may serve as a substitute for both pharmaceutical and recreational drugs and therefore, is preferred due to its perceived lack of harm and more acceptable side effect profile. Even so, extrapolation from reviews of non-therapeutic cannabis use suggests that the use of medical cannabis may be problematic among individuals with psychotic disorders [17]. Additionally, in a recent study published by Hasin et al. [18], the results showed a higher increase in cannabis use in the states were medicinal cannabis laws were passed, compared with the states with no medicinal cannabis laws. These increases are probably related to the increase in availability, potency and perceived safety/acceptability of the drug.

In the past five years, four jurisdictions in the United States and Uruguay (see page 4) have passed laws to allow the production, distribution and sale of cannabis for non-medical purposes (recreational use), which is contrary to the trend of international drug control conventions [14]. Even more recently, Canada also moved towards the legalization of recreational use of cannabis [19]. Nonetheless, a critical question still needs to be answered: what are the social and health implications of such regulations?

Although in some areas the literature is still scarce, we can divide the effects of cannabis use in two:

» Short-term effects;

» Long-term effects.

In terms of short-term effects, cognitive function impairment comes at the top the list. In 2011, Crean et al. [20] reviewed a broad spectrum of cognitive functions, designated as executive functions, and identified studies that reported that attention, concentration, decision-making, impulsivity, inhibition (self-control of responses), reaction time, risk taking, verbal fluency and working memory were highly impaired in a dose-dependent manner (though these effects were not consistently observed). Cannabis acutely impairs several components of cognitive function, with the most robust effects on short-term episodic and working memory, planning and decision-making, response speed, accuracy and latency [21] . Some studies also report increased risk-taking and impulsivity [20].

Less experienced cannabis users are more likely to experience stronger intoxicating effects on attention and concentration than heavy users that have established drug tolerance. Cannabis also impairs motor coordination, interferes with driving skills

Above: Are NPS shadowing bigger threats? cannabis (left), pharmaceutical opioids (centre) and designer drugs (adjacent page).

and increases the risk of injuries. In a recent review by Prashad and Filbey [22], the authors state that the literature indicates that users of cannabis exhibit cognitive impairments and the few existing studies show evidence of motor deficits. Together with the evidence that cognitive processes are critical for motor learning, it is probable that cannabis users also exhibit deficits in motor learning.

Evidence also suggests that recent cannabis smoking is associated with substantial driving impairment, particularly in occasional smokers, with implications for work in safety-sensitive positions or when operating a means of transportation (e.g. cars, trains or planes) [23–26]. Performance of the complex interactions between human and machine can be impaired as long as 24 hours after smoking a moderate dose of cannabis and the user may be unaware of the drug's influence [25].

Regarding the long-term effects of cannabis usage, we must refer to cognitive performance. During the 1990s, scientists began to investigate the potential correlation between cannabis use and poorer cognitive performances. The challenge was to understand if cannabis use impaired cognitive performance, or if persons with poorer cognitive functioning were more likely to become regular cannabis users, or both [27]. After this study and in the years since, better-controlled case-control studies have consistently found deficits in memory, verbal learning and attention in regular cannabis users [28–31]. These deficits have been correlated with the duration and frequency of cannabis consumption, the age of initiation and the estimated cumulative dose of THC. Thus, it is still not clear if cognitive function fully recovers after cessation of cannabis use, especially given that there is no agreement between different studies [32–34]. With reference to teenage users in particular, according to the many existing studies (e.g. Ellickson et al. [35], Horwood et al. [36]), cannabis use before the age of 15 years predicts early school-leaving and is typically associated with lower college degree completion, lower income, unemployment, a greater need for economic assistance, and use of other (and probably "heavier") drugs [37–39]. In a recent study, Goldenberg et al. [40] showed that the effects of regular cannabis use and its impact in the quality of life (QoL) are comparable, since frequent cannabis use has been associated with adverse social and health effects. According to the authors, there seems to exist a correlation between these two factors, showing an increased probability of frequent users reporting a reduction of their quality of life. Additionally, these studies indicate that quitting cannabis (in the case of these users) did not return their QoL to the level of non-users.

Another interesting study is presented by Vicent et al. [41]. According to these authors, the average cannabis user tends to be price sensitive and to purchase high quality marijuana rather than poor quality. At this point it becomes clear that, the legalization of recreational cannabis will result in a higher availability and, as consequence, to a decrease of the price and an increase of the users.

In Europe, there is currently no movement towards legislating cannabis. However, there has been a clear increase in social movements and the development of associations across the continent to pressure its legalization [42]. Although it is still too early to evaluate the impact of new cannabis policies, the evidence collected to date in the USA points to an increase in cannabis use in states where referendums have led to the legalization of recreational marijuana use. New challenges have emerged in some states of the USA (notably Colorado), including the marketing of unregulated cannabis products (edibles) with a high content of tetrahydrocannabinol (THC). Moreover, there is evidence of an increasing number of cannabis users driving under the influence, as well as an increase in cannabis-related emergency room visits and hospitalizations. An increase in the overall consumption of marijuana, in turn, can potentially lead to an increase in the health burden of marijuana use [19].

4. The threat of prescription opioids

In the late 1990s, state medical boards in the USA began reducing restrictions on the laws governing the prescribing of opioids for the treatment of chronic non-cancer pain [43]. As a result, a dramatic increase in opioid prescriptions was observed. This new position, together with the introduction of the new pain management standards for in-patient and out-patient medical care implemented by the Joint Commission on the Accreditation of Health Care Organizations (JCAHO) in 2000 [44], and with a continuously increasing aggressive marketing by the pharmaceutical industry, led to an even more dramatic increase of prescription of opioids for treatment of chronic non-cancer pain across the USA. Between 2000 and 2011, the prescription of opioids (oxycodone and fentanyl in particular) increased between 8-14 fold across US and Canada [45,46]. The increase of education and public awareness regarding the use of prescribed opioids, as well as local and regional interventions, have led to a subsequent decrease in opioid prescriptions; however this has been associated with increasing diversion of prescription drugs. This decrease was also followed in parallel by a dramatic increase in heroin and other opioid (e.g. non-pharmaceutical fentanyl) consumption and overdose

death rates, especially since 2010 [47,48].

Keeping in mind the trend observed in the USA, what should we expect in Europe?

It is not surprising that in Europe, the prescription of opioids has also increased in recent years, although at a slower rate than in the USA, with tramadol the most prescribed opioid across Europe [46]. To date, consumption of these drugs has not resulted in an alarming increase in terms of morbidity and mortality in Europe. Nevertheless, more preventive measures and more effective monitoring systems must be implemented to prevent similar problems as those observed in North America [46].

5. Conclusions

Within this paper, three major threats are addressed: NPS, cannabis and prescription opioids. Although at the moment, NPS are the substances of most focus (also in terms of research), they should not shadow other emerging and existing problems. The trend towards the liberalization of both medical and non-medical cannabis results in a generalized increase of cannabis users which, sooner or later, will translate to a greater health burden. On the other hand, the dramatic increase of the use of prescription opioids and potential transition to heroin [48] pose a significant threat as well, not only in North America, but also to Europe and eventually, to the other continents.

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