Postmodernity, addictive societies, cannabis and suicidal behaviour: Towards a brave new world?

Posmodernidad, sociedades adictivas, cannabis y comportamiento suicida: ¿Hacia un mundo feliz?

Hilario Blasco-Fontecilla, M.D., Ph.D.*,**,***,****

* Servicio de Psiquiatría, Hospital Universitario Puerta de Hierro-IDIPHIM-Segovia de Arana, Madrid, España.
** CIBERSAM, Madrid, España.
*** Universidad Autónoma, Madrid, España.
**** Consulting Asistencial Sociosanitario (CAS), Madrid, España.

"Is happiness not merely the freedom to follow
the dictates of one's own will or desire?"

Critique of modernity, Alain Touraine

"The postmodern moment is much more than a fashion;
it reveals the process of pure indifference in which all tastes,
all behaviours can exist side-by-side without excluding one another;
everything can be had with ease, the most practical, the most esoteric things,
old as well as new, the simple-ecological life as well as the hypersophisticated life,
in a lifeless time with no stable reference points, with no guiding coordinates."

The age of emptiness, Gilles Lipovetsky

Suicidal behaviours - ideation, intent, and completed suicide - are a public health problem of the highest order (Saiz & Bobes, 2014). They generate significant economic expense in Western societies (Czernin *et al.*, 2012). More important than the economic impact, however, is the human cost: up to 20 million people attempt suicide, and about one million complete it annually worldwide (WHO, 1999); indeed, suicide is the second cause of death among the world's young population (WHO, 2014). Considering that substance use is a risk factor for suicidal behaviour, and that cannabis is consumed mainly by young people, it is striking that the role the endocannabinoid system (ECS) plays in suicidal behaviour has been relatively little studied.

Recently two "epidemics" linked to substance use have been of concern in the Spanish media: the "silent epidemic" on the one hand, in which a significant part of the general Spanish population takes anxiolytics or even opioids on medical prescription (Zuil, 2017); on the other hand, the imported epidemic of smoked heroin that claimed more than 33,000 lives in the US in 2015 and which, as expected, has reached on our shores (Rego, 2017). The opioid epidemic that devastated American society at the beginning of the century led the Obama administration to limit the legal prescription of opioids as of 2010. This led opioid addicts to begin using heroin and synthetic opioids, such as fentanyl, which are cheaper and easier to acquire. In other words, legal use was replaced by illegal use (Tedesco *et al.*, 2017). In Spain, the fact that the use of opioids had multiplied by a factor of 14 since 1992 had already been reported in 2008; the authors also pointed out how fentanyl was replacing morphine (Garcia del Pozo *et al.*,

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Send correspondence to:
Hilario Blasco-Fontecilla, M.D., Ph.D., Servicio de Psiquiatría, Hospital Universitario Puerta de Hierro-IDIPHIM-Segovia de Arana, Madrid, Spain. C/ Manuel de Falla 1, 28222, Majadahonda, Spain. E-mail: hmblasco@yahoo.es

2008). Unfortunately, it is only to be expected that the pattern of opioid use in the US - the transition from legal to illegal opioids - may be reproduced in Spain.

These two epidemics have at least two common elements: firstly, they are epidemics imported from the same country (US), one that has established itself as a social reference point for postmodern Western societies; secondly, it is possible that both epidemics are related to the existential void which is characteristic of postmodern societies (Blasco-Fontecilla *et al.,* 2015, Lipovetsky, 1986), and the inability of many of its inhabitants to endure it. It is possible that to face this void many citizens resort to taking different substances, whether legal or illegal. As Antonio, the protagonist of the article, points out to the El Mundo journalist after smoking a dose of heroin: "You see? This is peace, there are no bad thoughts or pain, only an immense tranquility ... " (Rego, 2017).

In addition to these two media concerns, cannabis is a new source of worry, at least in the health field. Cannabis is the third most widely used drug in the world, and the most heavily used illegal drug, with consumption increasing dramatically in the last two years (Casajuana *et al.,* 2017). It contains around 500 chemical substances and 100 cannabinoids, the most frequently found being delta-9-tetrahydrocannabinol (9-THC), up to 40%, which is a partial CB_1 agonist with a euphoric effect, and cannabidiol (CBD), a CB_1 receptor antagonist with analgesic and anti-inflammatory effects and without psychotropic effects but with modulators of other endocannabinoids (Casajuana *et al.,* 2017). Cannabis use has spread alarmingly in different countries, including ours, particularly among the youngest (see Figure 1).

Although the reasons for this increase are certainly complex, among them we may find: 1) the trivialization of the potentially harmful effects of cannabis; 2) the magnification of the therapeutic potential of some of its components, which has led to the commercialization of Sativex®, an oromucosal spray with identical proportions of 9-THC

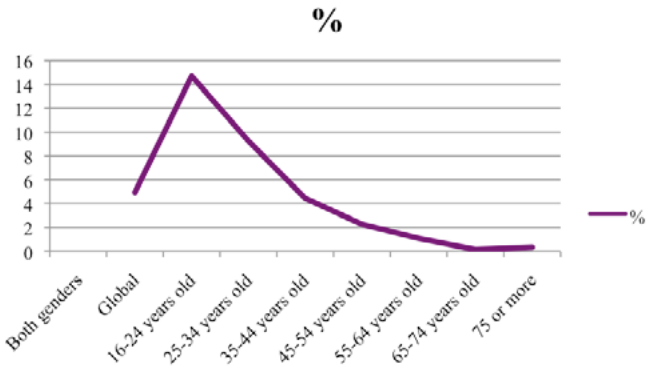

Figure 1. Cannabis use during the previous 12 months by sex and age group in % (population aged 16 and over) (year 2009, compiled by author, SOURCE: INE [Spanish Office for National Statistics]).

and cannabidiol; 3) the fact that it is a relatively poorly studied drug, linked to recreational use and to which severe effects are not attributed (Casajuana *et al.,* 2017); and 4) its legalization in different states of the US and countries around the world (Alvarez *et al.,* 2017). This legalization is a reflection of the trivialization regarding the use of cannabis. While in the early 1990s there was no legislation on the medicinal use of cannabis in the US, today more than a third of US states have some law in this regard, and perception of the risks of cannabis has been relaxed. It is clear that the medicinal use of marijuana may have benefits for some patients. But it is equally obvious that it is having negative outcomes at the public health level. Thus, in recent years there has been an increase in the illicit use of cannabis and disorders related to its use in the US (Hasin *et al.,* 2017). The authors of this study point out that this laxity in the laws resulted in an increase of 1.1 million adult "illicit" cannabis users from 1991 to 2012 and half a million adults with mental disorders derived from cannabis use in the US.

Among the potential therapeutic effects of cannabis in general, we can mention: 1) treatment of chemotherapy-induced nausea, or of chronic neuropathic pain in multiple sclerosis, diabetic neuropathy or other conditions [60], with Sativex® approved for the treatment of central neuropathic pain in multiple sclerosis and intractable cancer pain (Russo *et al.,* 2016); 2) reduction of positive symptoms and severity of symptoms in schizophrenia (Murray *et al.,* 2017, Zuardi *et al.,* 2012); 3) utility when treating epilepsy with animal (Huizenga *et al.,* 2017, Kaplan *et al.,* 2017b) and clinical models (Devinsky *et al.,* 2017, Kaplan *et al.,* 2017a); 4) treatment of some anxiety disorders, particularly post-traumatic stress disorder (Walsh *et al.,* 2017). Indeed, the authors postulate that rather than acting as a gateway for the use of other drugs, using cannabis could function as a way of getting off them; 5) CBD could attenuate the positive reinforcement exerted by opioids by interfering with the cerebral mechanisms responsible for the acute reinforcing properties of opioids except cocaine (Hurd, 2017); and 6) the chronic consumption of low doses of 9-THC has reversed cognitive decline in "mature or elderly" mice, doing so by a glutamatergic mechanism mediated by the CB_1 receptor and histone acetylation (Bilkei-Gorzo *et al.,* 2017).

Nevertheless, the use of cannabis, particularly when regular, and in large high-strength doses (with high levels of 9-THC), has been linked to the following detrimental effects: 1) reduction in bone mineralization, which could increase the risk of osteoporosis and bone fractures in adulthood (Sophocleous *et al.,* 2017); 2) periodontal disease in adulthood (Meier *et al.,* 2016); 3) greater likelihood of death below the age of 60 (Manrique-Garcia *et al.,* 2016); 4) prenatal cannabis exposure has been linked to greater frontal cortex thickness among children and adolescents, affecting the development of executive functions (El Ma-

rroun *et al.,* 2016), and generating greater aggression and attention problems among 18-month old girls (El Marroun *et al.,* 2011); 5) damage to the white matter of the corpus callosum, which may lead to diminished inter-hemispheric communication (Rigucci *et al.,* 2016); 6) greater susceptibility to false memories and less activity in the brain regions associated with the processing of attention and performance (parietal and frontal regions), and memory (temporal and medial temporal areas) (Riba *et al.,* 2015); 7) an increase in accidental poisoning among children. In a retrospective multicenter study conducted in France with 235 children aged under 6 who came to the hospital emergency department for accidental cannabis poisoning between 2004 and 2014, the authors noted that the rate of accidental poisoning by cannabis among young children had increased by 133%, and that calls to poison control centres had increased by 312% (Claudet *et al.,* 2017). The authors pointed out that the proportion of serious cases had risen from 7% in the period 2004-2009 to 19% during 2010-2014, and attributed this to the increasing concentrations of THC in cannabis, which rose from 9.3% (2004) to 20.7% (2014); 8) THC increases the risk of negative feelings such as anxiety, depression, worry, and negative self-evaluation, a reduced working memory, and paranoia (Freeman *et al.,* 2015); 9) the use of cannabis, especially in adolescence and early youth, a period in which brain maturation is still taking place, would increase the risk of psychosis. But not only this. A recent prospective study conducted with 245 patients who were followed for two years after their first psychotic episode found that the continued use of cannabis was associated with a poor prognosis and an increased risk of relapse, which was linked to the poorer treatment adherence of the patients involved (Schoeler *et al.,* 2017); 10) In another study, with a follow-up of 130 men and 90 women conducted for two years after their first psychotic episode, the authors reported that the relapse rate was higher among patients who had continuously used cannabis after the first psychotic episode, (59.1%), compared to those who had done so intermittently (36.0%) or had not used it (28.5%) (Schoeler *et al.,* 2016); and 11) contrary to what many people think, the regular consumption of high-strength cannabis generates dependency (Freeman & Winstock, 2015).

In terms of anxiety, this is regulated biphasically by the ECS, which could explain why cannabis can have a relaxing effect in certain situations, while generating anxiety in others. An example of the regulation of the biphasic response to anxiety is that THC has an anxiolytic effect in the prefrontal area, while it can be anxiogenic in the basolateral amygdala (Ruehle *et al.,* 2012). Since the action of CB_1 agonists inhibits the release of GABA, a simplistic assumption would be that CB_1 agonists could trigger an anxious response (Ruehle *et al.,* 2012), but as these authors point out, CB_1 agonists also inhibit the release of glutamate, and regulate the action of other receptors. Thus, anxiety regulation mediated by CB_1 receptors has to do with three factors: localization, basal activation, and sensitivity. Because the ECS also mediates monoaminergic neurotransmission, ECS stimulation could increase the neurotransmission of noradrenaline, which would be linked to increased anxiety. Furthermore, through the serotonergic system, mild stimulation of the ECS would have an anxiolytic effect, while strong stimulation would have an anxiogenic effect (Ruehle *et al.,* 2012). In situations of emotional stress, for example, when a patient is faced with a life event that can trigger suicidal behaviour, there is a glutamatergic excitatory excess. This would result in a down regulation of the CB_1 receptor exclusively in GABAergic neurons, which would in turn moderate the hyperactivation of the glutamatergic system. In conclusion, the effect of cannabis on anxiety can be very variable depending on the subject and their emotional state in different circumstances, as well as the composition of cannabis, among other factors.

Despite the growing use of cannabis worldwide, its role in suicidal behaviour has scarcely been explored. As we have noted in a systematic and as yet unpublished review focusing on the relationship of cannabinoid receptors and suicidal behaviour (Colino *et al.,* 2018), the ECS is involved in the regulation of pain, and since pain may be considered an intermediate endophenotype of suicidal behaviour (de Leon *et al.,* 2015), this suggests that the ECS could play a role in suicidal behaviour. The first suspicion that the ECS could be involved in suicidal behaviours came via *rimonabant*, a CB_1 receptor antagonist that produced anxiety, dysphoria and autolytic ideation in some obese patients (Christensen *et al.,* 2007), leading to its withdrawal from the market in 2008. Furthermore, when comparing identical twins who had used cannabis and those who did not in a recent study of 13,986 twins (6,181 monozygotic, 7,805 dizygotic), the authors found that cannabis use was linked to: 1) a 100 times greater risk of suicidal ideation; and 2) an almost 7 times greater risk of attempted suicide (Agrawal *et al.,* 2017). An alarming statistic revealed by this study was that the use of cannabis had increased from 30.4% in the 1st wave (1992-1993) to 69% in the 3rd wave (2005-2009). At the same time, average onset age had fallen, while frequent use had risen. Finally, in the aforementioned review we suggested that cannabinoid agonists could be tested as potential treatments for suicidal behaviour (Colino *et al.,* 2018) given that: 1) the majority (>90%) of people who attempt suicide speak of mental (psychological) pain (Blasco-Fontecilla *et al.,* 2015); 2) mental pain is what unifies and gives meaning to suicidal behaviour (de Leon *et al.,* 2015); and 3) Sativex® has been approved for the treatment of different types of chronic pain (Hauser *et al.,* 2017, Russo *et al.,* 2016). Moreover, given that the ECS appears to have a certain regulatory role over the opioid system (Hurd, 2017), this role and the potential use of Sativex® could be particularly interesting in

the context of the theory of addiction in suicidal behaviours (Blasco-Fontecilla, 2012, Blasco-Fontecilla *et al.,* 2014, Blasco-Fontecilla *et al.,* 2016). Either way, any approach in this regard has to be cautious because the use of Sativex® could also increase the risk of suicidal behaviour among some patients (Etges *et al.,* 2016).

In conclusion, cannabis use has become widespread in much of the world, particularly among young people, who are precisely those most vulnerable to its negative effects. Indeed, scientific evidence in animal models suggests that the potential benefits at brain level would only occur if used in adulthood or old age (Bilkei-Gorzo *et al.,* 2017). In addition, it is important to remember that there are more than 100 different cannabinoids (Casajuana *et al.,* 2017). While it is true that some cannabinoids, such as CBD, may play a therapeutic role in some clinical situations, it is no less true that other cannabinoids, such as 9-THC, have psychotropic effects and are related to increased psychiatric morbidity. In addition, while it is possible that some cannabinoids may play a therapeutic role in suicidal behaviour, the limited evidence available suggests that we should be prudent, since it could also increase the risk of suicidal behaviour. It is worth reflecting on the fact that suicidal behaviour has been associated both with the use of a CB_1 antagonist (rimonabant) (Christensen *et al.,* 2007) and with a drug (Sativex®), which is a mixture of an agonist and a CB_1 antagonist (Russo *et al.,* 2016).

I would like to conclude by saying that the high rates of all types of drug use - particularly cannabis - and of suicidal behaviour among young people are likely to be related to the kind of hedonistic and consumption-addicted societies that we construct together. We live in the age of emptiness (Lipovetsky, 1986) - in the age of "anything goes", in which there are hardly any valid reference points for young people aside from consumerism, in societies characterized by haste, lack of limits and low tolerance of frustration because of hyperabundance and oversaturation of the senses. We believed that living under the affirmation *I have, therefore I am* would make us happier. But this has not been the case and emptiness has been our punishment. Given this vacuum, it is not surprising that some young people resort to cannabis or suicidal behaviour. Postmodernism has also brought us an expansion of the "traditional" limits of medicine and the psychiatrization of everyday life (Blasco-Fontecilla, 2014, 2017). Because at the end of the day, "*society still looks to the medical profession for help and for hope during difficult times*" (Murthy, 2016). We are heading towards the ironically brave new world that Huxley predicted in his masterpiece; or are we perhaps we already living in his dystopia? One wonders if this is the kind of society that we would wish for ourselves, our children, and the generations to come. Because remember, as I point out in the essay *Hacia un mundo feliz* "in the brave new world of Huxley, Shakespeare was an author yet to be civilized" (Blasco-Fontecilla, 2017).

Conflict of interest

The author has received financial compensation for scientific talks for AB-Biotics, Praxis Pharmaceuticals, Rovi, and Shire in the last two years.

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