UPDATE IN RADIOLOGY

The addicted brain: Imaging neurological complications of recreational drug abuse

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KEYWORDS
Recreational drugs; Biochemical mechanisms; Magnetic resonance imaging; Functional imaging; Infarction; Hemorrhage; Leukoencephalopathy; Atrophy; Marchiafava–Bignami

Abstract  Recreational drug abuse represents a serious public health problem. Neuroimaging traditionally played a secondary role in this scenario, where it was limited to detecting acute vascular events. However, thanks to advances in knowledge about disease and in morphological and functional imaging techniques, radiologists have now become very important in the diagnosis of acute and chronic neurological complications of recreational drug abuse.

The main complications are neurovascular disease, infection, toxicometabolic disorders, and brain atrophy. The nonspecific symptoms and denial of abuse make the radiologist's involvement fundamental in the management of these patients. Neuroimaging makes it possible to detect early changes and to suggest an etiological diagnosis in cases with specific patterns of involvement.

We aim to describe the pattern of abuse and the pathophysiological mechanisms of the drugs with the greatest neurological repercussions as well as to illustrate the depiction of the acute and chronic cerebral complications on conventional and functional imaging techniques.

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PALABRAS CLAVE
Drogas de abuso; Mecanismo bioquímico; Resonancia magnética; Imagen funcional; Infarto;

El cerebro adicto: imagen de las complicaciones neurológicas por el consumo de drogas

Resumen  Las drogas constituyen un gran problema sociosanitario. Tradicionalmente, la neuroimagen ha tenido un papel secundario limitado a la detección de eventos vasculares agudos. En la actualidad, el radiólogo ha adquirido gran relevancia en el diagnóstico de las complicaciones neurológicas agudas y crónicas, debido al avance en el conocimiento de la enfermedad y al desarrollo de las técnicas de imagen morfológicas y funcionales. Las principales complicaciones son la patología neurovascular, la infección, los trastornos tóxico-metabólicos y

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Hemorragia; Leucoencefalopatía; Atrofía; Marchiafava–Bignami la atrofía cerebral. La sintomatología inespecífica y la negación del consumo hacen que la implicación del radiólogo pueda resultar fundamental en la atención de estos pacientes. La neuroimagen permite detectar alteraciones precoces y plantear el diagnóstico etiológico ante patrones de afectación específicos. Nuestro objetivo es describir el patrón de consumo y el mecanismo fisiopatológico de las drogas con mayor repercusión neurológica, así como ilustrar las complicaciones cerebrales agudas y crónicas mediante técnicas de imagen convencional y funcional.

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Introduction

Human kind has always wanted to experience new sensations, to reach different states of consciousness and, on occasion, to mask reality. The substances used with this purpose have targeted, whether intentionally or not, the central nervous system (CNS). Consumption patterns have changed and conditions of use have improved, but they all have deleterious effects that we can see and quantify.

Each substance has multiple forms of presentation which are modified all the time, the absorption pathways of the body are limited and they cause complications that overlap another. Neuro-imaging findings frequently pose the possibility of consumption, and even in view of characteristic patterns, it would be possible to suggest the specific type of drug. The role of the radiologist, therefore, is ever more relevant both finding urgent conditions and visualizing chronic effects.

Our goal is to describe the consumption pattern and the physiopathological mechanisms of the drugs that have the most neurological repercussion (cocaine, amphetamines, heroin, alcohol, cannabis and toluene), as well as to illustrate the acute and chronic cerebral complications through conventional and functional image modalities (positron emission tomography [PET], single photon emission computed tomography [SPECT] and perfusion by magnetic resonance [MRI]).

Cocaine

Cocaine is the main alkaloid obtained from the leaves of a shrub belonging to the family *Erythroxylon coca*, present in the Western regions of South America. There are two forms of presentation: hydrochloride (with the appearance of a fine powder) and alkaloid (also known as crack).1 The most popular route of administration is intranasal, which reaches concentrations in the CNS in 3–5 min. The main action of cocaine is summarized in the sympathomimetic effect due to the blockage of catecholamine reuptake.1–4 It also blocks the reuptake of serotonin and dopamine transmitters, increasing their extracellular concentrations, especially in the *accumbens* nucleus.2,5,6

Addiction caused by cocaine is due to its rapid action mechanism, since its effect is almost immediate after administration.1 A feeling of euphoria or high is experienced after its consumption mediated mainly by the occupation of dopamine receptors called DA-D2.1,3–5

The main cerebral complications derived from cocaine abuse are vascular ones, especially subarachnoid hemorrhages and intraparenchymatous hemorrhages; overall hemorrhagic events are twice as frequent as ischemic infarctions.1,7,8 Nevertheless, the form of the drug and the route of absorption influence on the type of adverse event. When cocaine is smoked in the form of crack the incidence of hemorrhagic events is greater, while there are no significant differences between ischemic and hemorrhagic events when the drug is sniffed.9,10

The physiopathological mechanisms involved in the production of ischemic cerebrovascular accidents are multiple and synergic, but vasoconstriction or vasospasm stand out among them2,11 (Table 1). This phenomenon can cause endothelial damage consisting of disruption of the tunica media and arteriolar fibrosis, among other alterations.11 However, the significant vasculitis component stands out, confirmed by the existence of focal stenoses of the vascular lumen and enhancement of vessel walls in angiographic studies.5,11

Ischemic infarctions commonly affect the territories of mid and posterior cerebral arteries (Fig. 1), and the border territories, the internal capsule and the hippocampus, without a specific disorder pattern.1,2,5 Mesencephalic infarction has been associated with the simultaneous use of cocaine and amphetamines.14 Since it does not show a characteristic distribution, concomitant findings are specially relevant, such as perforation of the nasal septum, accelerated atherosclerosis in young people without cardiovascular risk factors (Fig. 2) and generalized vasospasm.

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Figure 1  Acute ischemic cerebrovascular accident in the territory of the left medial cerebral artery associated with cocaine consumption. (A) CT without IV contrast showing hypodensity of the caudate head, the left lenticular nucleus and the insula (arrowheads). (B) Parametric map of the mean transit time (MTT) showing a large ischemic area with an increased MTT (in blue), mostly corresponding to salvable tissue (represented in green in C), and a small ischemic core of unviable tissue mass with diminished cerebral blood volume (red in C). (D) Diffusion-weighted images identifying restriction of the ischemic area in the Sylvian territory.

Figure 2  Thirty-eight-year-old man with accelerated atherosclerosis without the classical cardiovascular risk factors – usual cocaine consumer. (A) Doppler duplex ultrasound image of the cervical segment of the internal carotid artery showing a relatively homogeneous soft plaque (white arrows), with irregular surface, ulceration (arrowhead) conditioning a serious stenosis of the lumen with high-speed turbulent flow (black arrow) and peak systolic speed of approximately 300 cm/s. (B) CT volumetric reconstruction of both carotid arteries showing marked bilateral atherosclerotic damage (plaques marked with arrows). (C) Detail of the transversal image of a CT study in bone window where we can identify perforation of the nasal septum (arrow).
Figure 3 Thirty-three-year-old woman showing intense headache and left hemiparesis whose toxic urine analysis reveal cocaine consumption. (A) Transversal CT image without IV contrast showing right intraparenchymatous cortico-subcortical frontal parafalcine hematoma (arrows). (B) T2-weighted transversal MRI showing the markedly hypointense hematoma (arrows), vasogenic edema on its lateral edge and, on its medial edge, one tubular flow vacuum nidus corresponding to an arteriovenous malformation (arrow-heads). (C) T1-weighted sagittal MRI with IV contrast showing the nidus of the malformation (arrow) with drainage into the superior longitudinal sinus. (D) Digital subtraction arteriography sagittal image confirming the arteriovenous malformation (arrow).

Up to 50% of patients with cocaine-induced hemorrhagic complications show underlying vascular condition such as aneurysms and vascular malformations. The greater prevalence of aneurysms is explained by the maintained increase of blood pressure. The mechanism involved in aneurysmal rupture and arteriovenous malformations is high systolic peak and increase of heart rate after acute consumptions (Fig. 3). The combined abuse of cocaine and ethanol is not uncommon, which increases synergically the odds of suffering subarachnoid hemorrhages.

The intraparenchymatous hematoma is usually lobar and subcortical while there is greater incidence of bleeding in the encephalon. Hematomas are larger and they tend to spread themselves to the ventricles more easily than in non-users, which conditions greater neurological deficits. Hemorrhagic transformations of the ischemic areas is not uncommon due to damage to hematoencephalic barrier and increase of arterial pressure.

Chronic addicts characteristically show structural atrophy in the frontal lobes and to a lesser extent, in the temporal ones, where reduction of metabolic activity has been confirmed in PET examinations with 18-fluorodeoxyglucose. Perfusion studies with SPECT with hexamethyl propylene or amino oxyme marked with metastable technetium 99 (99mTc-HMPAO) have shown a generalized reduction of 30% in global cerebral blood flow adding a specific reduction of the relative cerebral blood flow in the prefrontal cortex, anterior cingulate gyrus, the
thalami, the basal ganglia, the occipital cortex and the cerebellum.\textsuperscript{16}

In addition to the withdrawal syndrome, many users experience an intense crave to consume after it has gone (the so-called craving stage), which can be triggered by multiple stimuli. In this complex stage, there is a selective activation of the limbic system in perfusion studies,\textsuperscript{19} hypermetabolism in the orbitofrontal cortex\textsuperscript{19,20} and even involvement of the mu opioid system.\textsuperscript{21} Functional studies based on oxygen consumption (BOLD sequence) in active users confirm an increase of activity in the craving stage and dependence located in the limbic, paralimbic regions, the accumbens nucleus, the frontal and inferior frontal orbital circumvolutions and the anterior cingulum.\textsuperscript{22} This activation has also been shown during the craving for consumption when videos showing the drug were played.\textsuperscript{23} However, after administration of the substance, these regions are deactivated.\textsuperscript{22}

Amphetamines and derivatives

Amphetamine was synthesized for the first time in 1887 and it was the first substance of a group that shares properties, called the same way as a whole. Later there appeared methamphetamine and MDMA (3,4-methylenedioxymethamphetamine), commonly known as "ecstasy" or "crystal". There is rigorous legal control of amphetamine derivatives in research studies and for the treatment of disease (obesity and hyperactivity). The consumption profile of MDMA is associated with night-time leisure; it is the second most consumed illegal drug among young people after cannabis.\textsuperscript{24} The most common route of administration is orally, in the form of powder or "crystal" or pills. It causes a rapid feeling of euphoria and an increased sensory perception this is why it is considered both stimulant and hallucinogenic.\textsuperscript{5,25}

Amphetamines, as a whole, increase the synaptic concentrations of biological amines (dopamine, noradrenalin and serotonin/5-hydroxytryptamine); the main and most characteristic action of MDMA is the release of 5-hydroxytryptamine.\textsuperscript{5,11,25} This neurotransmitter is the amine with the greatest vasoconstrictor effect in the brain.\textsuperscript{5}

Although the biochemical mechanism of amphetamines causes long-term ischemia, the most common urgent complications are hemorrhages due to blood pressure increase. Just as it happens with cocaine consumption, blood pressure increases after consumption conditions greater risk of rupture of arteriovenous malformations and preexisting aneurysms.\textsuperscript{5,26}

Vasoconstriction in cerebral microcirculation ultimately causes necrosis of irrigated tissue.\textsuperscript{8,9,26} The areas that are more commonly affected by this ischemia are the globus pallidus (as it happens with heroin) and the occipital cortex, where the largest concentration of 5-hydroxytryptamine receptors are located (called 5HT 2A)\textsuperscript{6,9}; in fact, the most common finding in autopsies is necrosis of the globus pallidus\textsuperscript{16} (Appendix B Fig. S2 online). This spatial specificity explains why it is in these areas where structural and functional complications develop.

Another complication that stems from blood pressure increase is posterior reversible encephalopathy syndrome (Fig. 4). This is an unspecific disorder of cerebrovascular self-regulation showing a preference for posterior circulation and borderline cortical areas. On the computed tomography (CT), findings can be subtle, identifying hypodensity non-confluent cortical–subcortical, bilateral areas often located in the posterior parietal occipital lobes.

Figure 4  Forty-two-year-old woman–sporadic consumer of 3,4-methylenedioxymethamphetamine (MDMA) going to hospital with headache, visual alteration and hypertensive crisis due posterior reversible encephalopathy syndrome. The urine toxicology exam reveals 3,4-metilendioximetanfetamine (MDMA). (A) T2-weighted transversal MRI showing extensive confluent cortico-subcortical bilateral edema predominantly parieto-occipital posterior (arrows). (B) T2-weighted FLAIR coronal MRI showing the edema (arrows) and its mass effect with fissure collapse (arrowheads). The clinical manifestations and the radiological findings were resolved a few days later with support measures and blood pressure control.
The MRI is more sensitive for its diagnosis and findings are detected early, showing high signal intensity in T2-weighted/FLAIR sequences.

When it comes to long-term effects, selective atrophy in the occipital and frontal cortex, the left temporal lobe and the brainstem has been confirmed compared to users that abused other substances exclusively or jointly (polyaubuse). Methamphetamines can cause gray matter volume loss which can range from generalized to unilobar. However, an increase in the volume of the striatum has been confirmed (caudate and putamen) in adult methamphetamine consumers for over two years. Volume increase is due to mechanisms of initial response to neurotoxicity – above all swelling. This reaction evolves subsequently to atrophy if the neurotoxic dose continues to increase. In children exposed to methamphetamines in utero there is striatum volume loss initially, since there is no such compensation to dopaminergic damage.

With PET, it is possible to observe selective damage in serotonergic neurons and a reduction of its transmitters. When it comes to SPECT-measured perfusion we have been able to confirm a decrease of the relative cerebral blood flow in the visual cortex, the caudate, the superior parietal lobe and the dorsolateral region of the frontal lobe, associated with MDMA-induced vasoconstriction. Keeping with it, we have been able to detect reduction in relative cerebral blood volume of such dorsolateral region of the frontal cortex through MRIs as the first functional manifestation after the first contacts with MDMA in young subjects.

Heroin

Heroin or diacetylmorphine is the most widely consumed illegal compound within the opioid group. It was commercialized for the first time in 1898 as an analgesic substitute to morphine, but it was withdrawn after the physical and psychological dependence that it caused was confirmed. Its appearance is that of a white, fine crystalline powder, although it can vary. There are three main types: number two or freebase; number three, known as brown sugar due to its earthy aspect; and number four or Thai variety of a 90% purity. The IV is the most effective, filling route of administration with respect to its effect, and it was the most widely used until AIDS appeared. Today, the inhaled and smoked routes of administration are more widely used.

The mechanism of action of heroin is mediated by the activation of three types of receptors: mu, kappa and delta. Mu receptors are responsible for the feeling of euphoria and positive reinforcement, in addition to analgesia, respiratory depression and miosis. Kappa and delta receptors contribute to the analgesic effect, the feeling of dysphoria and the psychomimetic effect.

A sharp, positive feeling after the first contacts (honeymoon) occurs initially. When the state of intoxication advances, the effects fade. The degree of tolerance turns the drug into a means to avoid withdrawal syndrome and less and less often into a source of pleasure.

Ischemia is the most common neurovascular complication of the compounds derived from opioids and morphine. The physiopathological mechanisms involved are vasospasms due to smooth muscle contraction, vasculitis phenomena and embolisms due to additives. Borderline vascular territories are the most vulnerable ones, but the anatomical structure that is most commonly affected is the globus pallidus (up to 5–10% in chronic users). Chronic ischemia is common which is shown on the MRI as confluent hyperintensities in the periventricular and subcortical white matter. This finding gains special importance if patients are young and without any other risk factors.

A specific complication of the heroin addict who uses the inhaled route is a phenomenon known as chasing the dragon. This denomination comes from the way the smoke is inhaled when the heroin is heated over an open flame. It became popular as an alternative to IV administration to avoid HIV contagion. The neurological complication consists in a leuкоencephalopathy with edema. It is probably due to a mechanism of mitochondrial toxicity, triggered by impurities that are activated when heating aluminum foil. These manifestations can occur with cerebellar and extrapyramidal signs, and in the most serious cases pseudo bulbar manifestations, spasms, hypotonic muteness or even death occur. Anatomopathologically, a spongiform degeneration of the corticospinal tracts and of the cerebral and cerebellar white matter has been reported. T2/FLAIR MRI sequences show bilateral symmetric hypersignal of white matter in these locations. Cerebellar disorders and of the posterior limb of the internal capsule – not affecting the anterior limb, is the most characteristic sign. These findings are not exclusive to heroin-induced leukoencephalopathy and they can be secondary other substance abuse. Spectroscopy findings complement diagnosis and increase their specificity; they show an abnormal descent of the N-acetylaspartate peak, an increase of lactate and myoinositol, and stability of lipid peaks (Fig. 5). Resolution of the clinical disorder has been described when heroin use is interrupted though image findings can persist.

In addition to the complications derived from the substance itself, both the impurities (lipophilic substances) used in the mixture and the unsterile conditions in the IV administration make infections be relatively common and especially important. Half the users develop endocarditis, occlusion of small vessels due to septic emboli and formation of abscesses. In the MRI, abscesses are shown as rounded lesions that are enhanced in a ring shape after the administration of contrast, they show perilesional vasoergic edema and its purulent content restricts diffusion (Fig. 6). The organism involved in most cases is Staphylococcus aureus, which enters the blood stream from the skin through the needle.

The chronic consumption of heroin leads to encephalic atrophy, hypometabolism and hypoperfusion. Gray-matter loss, confirmed through volumetry on the MRI, prevails in the prefrontal bilateral cortex, the temporal lobes and the insulae, with a correlation between the duration of use and the degree of atrophy suggestive of a cumulative effect. White matter has been assessed in image studies through diffusion tensor imaging, in which it has been possible to observe a reduction in the fractional anisotropy translating a disruption of fibers in bilateral frontal regions, the right
Studies and-Based Delayed

The perfusion main acute takenly and the ometabolism intoxication progressively beverages years.

Alcohol

Figure 5 Man with predominantly supratentorial leukoencephalopathy associated with heroin consumption—typically known as chasing the dragon. (A) and (B) CT transversal images without IV contrast showing generalized white matter hypodensity of the corona radiata (asterisks) spreading throughout the corticospinal tracts into the posterior limbs of the internal capsules (arrowheads). (C) and (D) T2-weighted transversal MRIs in the same locations where we can more clearly see white matter damage with signal increase. (E) The single-voxel spectroscopy study with short echo time showed a decrease of the N-acetylaspartate peak and a slight increase of lipids and lactate.

There are three main neurological damage mechanisms: direct toxicity, derivative-mediated damage (methanol and acetaldehyde) and effects secondary to cirrhosis and nutritional deficits. There are multiple direct damage mechanisms proposed, but the common outcome is greater susceptibility of N-methyl-D-aspartate receptors of excitement and glutamate cytotoxicity, the so-called upregulation.

Wernicke’s encephalopathy is one of the main complications of chronic alcoholics due to deficit of thiamine coenzyme (vitamin B1). Wernicke’s encephalopathy causes the classic triad of ophthalmoplegia, confusion and gait disorder though the complete clinical manifestations only occur in one third of the patients. Delayed diagnosis and treatment can lead to Korsakoff’s psychosis, characterized by memory alterations and confabulation. Osmotic changes due to thiamine reduction cause intracellular and extracellular edema, especially in areas near the cerebrospinal fluid, where the hematoencephalic barrier is more patent. Lesions are commonly located around the third ventricle and the lateral ventricles, the thalamus dorsomedial

precentral gyrus and the left cingulum. Studies in chronic addicts have confirmed a global decrease of perfusion\(^{[1]}\) and ometabolism\(^{[1],[4]}\) and a greater reduction of both parameters in the frontal and temporal lobes (Fig. 7). When it comes to acute effects, it has been confirmed that there is a drop in perfusion quantified through ASL (arterial spin labeling) in the anterior left cingulate cortex, the left prefrontal cortex and the insulæ.\(^{[2]}\)

Alcohol

Alcohol is a socially accepted legal drug. Excessive, chronic consumption of alcohol is associated with an increase of morbimortality and it reduces life expectancy in up to 15 years.\(^{[3]}\) Based on its process of manufacturing, alcoholic beverages are divided into fermented and distilled. The main component of alcohol is ethanol, a CNS depressor that progressively numbs brain and sensory functions. It is mistakenly confused with a stimulant because at the onset of intoxication there is lack of behavioral inhibition.
Figure 6  Habitual IV heroin consumer going to the ER with disorientation. (A) CT without IV contrast where we can identify multiple subcortical supratentorial abscesses (arrows)—predominantly right and mesencephalic. (B) T2-weighted transversal MRI confirming the findings and showing an important vasogenic perilesion edema. (C) In the diffusion sequence, the content of the abscesses shows restriction since it consists of purulent material. (D) After the administration of contrast the abscesses are totally enhanced looking like ring shapes. The microorganism involved is Staphylococcus aureus.

pulvinar nuclei, the mammillary bodies, and the pineal and periaqueductal region. In the most serious cases, the deep white matter and even the cortex can also be affected. In the affected areas, the MRI will show hyperintensity in T2/FLAIR, and after the administration of contrast they can be enhanced due to rupture of hematoencephalic barrier, and intense enhancement of mammillary bodies is pathognomonic of this disorder in acute stages and even in the absence of T2 hyperintensity (Fig. 8).

Another manifestation of chronic alcohol abuse is Marchiafava–Bignami disease, consisting of corpus callosum demyelination and necrosis. A toxic agent from red wine has been identified that, in conjunction with vitamin deficiency, can be the cause of these manifestations. The disorder begins in the trunk and it can spread to the knee and even the splenius. The corpus callosum necrosis occurs in three stages characteristically (layer necrosis), typical of this disease. There are two subtypes: A, where there is complete damage of the corpus callosum showing greater impairment of consciousness and leading to worse prognosis; and B, where damage of the corpus callosum is partial showing less impairment of consciousness and more favorable evolution. MRIs are especially important due to the fact...
Figure 7  Forty-eight-year-old man chronic heroin male consumer showing cognitive impairment and behavioral alterations. (A) T1-weighted transversal MRI where we can identify an important frontal bilateral atrophy with anteroposterior damage gradient. See dilation of the subarachnoid spaces of frontal convexities and Sylvian fissures (arrows). (B) PET transversal image with 18F-fludeoxyglucose where we can see frontal bilateral hypometabolism (arrows) with the same distribution as the atrophy in the structural image.

that clinical manifestations are unspecific. Hyperintensity in T2/FLAIR without mass effect in the central region of the corpus callosum is the common presentation (Fig. 9); it can be enhanced peripherally after the administration of contrast on the acute stage.\textsuperscript{55} The white matter in the brain hemispheres can also be damaged – a finding described in up to 40% of necropsies of patients with Marchiafava–Bignami disease. Spread to the cortex – known as Morel’s cortical laminar sclerosis consists of gliosis of the third cortical layer in the frontal and lateral regions.\textsuperscript{56} In PET studies with FDG it has been possible to confirm a metabolic reduction in the cortex frontal of temporoparieto-occipital association due to the disruption of commissural fibers that alter this association network.\textsuperscript{55,57}

Chronic hepatic encephalopathy is due to and inadequate cleansing of nitrogenated compounds and other toxins that accumulate in the brain parenchyma. Image findings of this disease are practically undetectable through CT and MRI T2-weighted sequences. In the T1-weighted sequences there is bilateral and symmetrical hyperintensity compatible with manganese deposits, located in the base ganglia (in particular in the globus pallidus), the hypothalamus, the mesencephalon and the adrenohypophysis (Appendix B Fig. S1 online). MRI spectroscopy study obtained with short echo time is characteristic in patients with chronic hepatic encephalopathy, who show a significant reduction of myoinositol and choline, and an increase of glutamine/glutamate peaks.\textsuperscript{51}

Lastly, chronic alcoholism is associated with neuronal loss and atrophy, especially of the frontal superior and motor cortex, and with white matter, bridge, thalamus, mammillary body and cerebellum volume loss, and greater damage of the vermis superior.\textsuperscript{51} Concomitant use of alcohol with other drugs, in particular with cocaine, contributes to greater white matter loss, due to the formation of a long-lasting vasoactive metabolite, cocaethylene, resulting from the co-administration of both substances.\textsuperscript{11}

Cannabis

Cannabis is the most consumed illegal drug worldwide.\textsuperscript{58} It is obtained from Cannabis sativa, a dioecious herb. Its main psychoactive component is a lipophilic substance called delta-9-tetrahydrocannabinol. The products obtained from cannabis are marihuana (prepared with dry leaves), hashish (derived from its resin) and hashish oil (obtained from distilling organic solvents).

All the parts of the plant contain delta-9-tetrahydrocannabinol. The most commonly used form of cannabis abuse is smoked marihuana. Its resin is used in food for oral consumption; this form of administration causes a great amount of intoxications since the user does not control the time elapsed between ingestion and effects. Chronic consumption increases the risk of schizophrenia and behavioral changes.\textsuperscript{11}

After its consumption a feeling of wellbeing is obtained due to the activation of cannabinoid receptors CB1, present in the black matter, the hippocampus, the limbic cortex and the cerebellum.\textsuperscript{5,5}

Its wide use and polyconsumption are factors that make it difficult to establish a direct connection between cannabis and cerebrovascular disease.\textsuperscript{9,58} It causes orthostatic hypotension, which in people with little cerebral blood
Figure 8  Chronic alcoholic man with manifestations of confusion and ataxia due to Wernicke’s encephalopathy. (A) T2-weighted transversal MRI where signal hyperintensity is identified around the Sylvian aqueduct (arrowheads). (B) T2-weighted coronal FLAIR MRI where periventricular signal hyperintensity of the third ventricle can be easily identified (arrowhead). (C) and (D) Sagittal and transversal MRIs with IV contrast showing bilateral enhancement of mammillary bodies (arrowheads and arrow).

Figure 9  Chronic red wine male consumer with Marchiafava–Bignami’s disease in subacute stage. (A) and (B) T2-weighted FLAIR coronal and sagittal MRIs showing marked hyperintensity of the corpus callosum trunk posterior portion (arrowheads). No enhancement after the administration of contrast.
reserve can cause cerebral infarctions—being this is the main mechanism of ischemic cerebrovascular accidents⁵⁹ (Fig. 10). In addition to high blood pressure that acts as a trigger, there are other predisposing vascular alterations; in this sense, the presence of intracranial stenosis has been confirmed in 31% of cannabis consumers who have developed ischemic cerebrovascular accidents.⁶⁰ Vasospasms, vasculitis, development of arrhythmias and high concentrations of carboxyhemoglobin are other factors that predispose to adverse cerebrovascular events.⁸,⁹,⁶¹,⁶² The location of these ischemic infarctions is not specific: basal ganglia predominate, as well as periventricular white matter, the cerebellum and the temporal, parietal and occipital lobes.

Perfusion studies through PET and SPECT confirm an increase of relative cerebral blood flow with acute consumption.⁶³ However, there is reduction of generalized relative cerebral blood flow among chronic users that can be reverted with abstinence.³¹,⁵⁸ Glucose metabolism in sporadic users is usually diminished except for the cerebellum, probably due to the large number of cannabinoid receptors in this area.³¹

### Conclusion

Drugs are a serious social health issue, because they have important short and long-term repercussions on the CNS. The main acute complications are ischemia and hemorrhages whose early detection and urgent treatment is especially important for the prognosis of the patient. At times image findings are specific like the spectroscopic profile of leukencephalopathy due to heroin consumption, T₁ hyperintensity in chronic hepatic encephalopathy or contrast uptake in mammillary bodies in Wernicke’s encephalopathy. However in most cases diagnosis comes from integrating the images with the clinical context, such as the posterior reversible encephalopathy syndrome in young
patients without other cardiovascular risk factors or pallidus necrosis in heroin or MDMA addicts (Appendix B Table S2 online). Functional modalities such as PET and MRI perfusion play an ever more important role by showing the deleterious effects that have spatial specificity in some substances.

Ethical disclosure

Protection of people and animals. The authors declare that no experiments with human beings or animals have been performed while conducting this investigation.

Confidentiality of data. The authors confirm that they have followed their center protocol on the publication of data from patients.

Right to privacy and informed consent. The authors confirm that in this article there are no data from patients.

Authorship contribution

1. Manager of the integrity of the study: AMF and MM.
2. Study idea: AMF and MM.
3. Study design: AMF and MM.
4. Data mining: AMF and MM.
5. Data analysis and interpretation: N/A.
6. Statistical analysis: N/A.
7. Reference: AMF and MM.
8. Writing: AMF and MM.
9. Critical review of the manuscript with intellectually relevant remarks: AMF and MM.
10. Approval of final version: AMF and MM.

Conflicts of interests

The authors declare no conflict of interests associated with this article whatsoever.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.rxeng.2016.12.003.

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