Curr Neurol Neurosci Rep (2013) 13:325
DOI 10.1007/s11910-012-0325-0

STROKE (HP ADAMS JR, SECTION EDITOR)

Drug Abuse and Stroke

Ana Catarina Fonseca · José M. Ferro

Published online: 9 January 2013

Abstract Cerebrovascular disorders contribute to the morbidity and disability associated with illicit drug use. Drug abusers have an increased risk of both hemorrhagic and ischemic stroke. In geographic areas with a high prevalence of illicit drug use, drug abuse is a frequent cause of stroke in the young adult. The illicit drugs more commonly associated with stroke are psychomotor stimulants, such as amphetamine and cocaine. Less commonly implicated are opioids and psychotomimetic drugs, including cannabis. Toxicology screening for illicit drugs should be done in young patients with stroke with no obvious cause, or if suggested by history or examination. Although in some patients the mechanism of stroke is identified using neuroimaging and other modern diagnostic tools, in a sizeable fraction of cases the mechanism of stroke remains unclear. Further studies are needed to elucidate the role of hemodynamic and immunologic mechanisms in these cases.

Keywords Drug abuse · Illicit drugs · Ischemic stroke · Intracerebral hemorrhage · Subarachnoid hemorrhage · Doping · Cocaine · Heroin · Amphetamine · Pentazocine · LSD · Cannabis · Phencyclidine

Introduction

Illicit or illegal drugs are drugs which are under international control but which are produced, trafficked, and /or consumed illicitly. The United Nations estimates that some 200 million people (4.8 % of the world's population aged 15–64 years) use illegal drugs annually, with 25 million being classed as problem users. The major causes of death in drug users are overdose, suicide, AIDS, and violence. Cerebrovascular disorders, although less frequent, also contribute to the morbidity and disability associated with illicit drug use [1•]. A few studies investigating the causes of stroke in the young adult found that drug abusers had an increased risk (6.5 times) [2] of both hemorrhagic and ischemic stroke. In geographic areas with a high prevalence of illicit drug use, drug abuse is a frequent cause of stroke in the young adult. In the Baltimore-Washington Young Stroke Study, 12.1 % of young stroke victims had recent drug use and in 4.7 % it was considered the sole cause of stroke [3]. In a cross-sectional study of hospital discharges, amphetamine increased the risk of hemorrhagic stroke (4.95 times), whereas cocaine increased the risk of both hemorrhagic stroke (2.33 times) and ischemic stroke (2.03 times) [4]. The etiological attributable fraction of illicit drug use for stroke in the young may be even higher in some developing countries, particularly in those which are drug producers. For instance, in a series of stroke patients from Iran, 45.7 % were addicted to opium [5].

The illicit drugs more commonly associated with stroke are psychomotor stimulants, in particular amphetamine and cocaine. Less commonly implicated are opioids and psychotomimetic drugs, including cannabis.

Association of Stroke with Specific Drugs

Psychomotor Stimulants

Cocaine

Cocaine is originally extracted from an *Erythroxylon coca* plant from South America and is consumed in two chemical forms: cocaine hydrochloride and cocaine alkaloid. Cocaine hydrochloride is a water-soluble crystal powder that is

This article is part of the Topical Collection on *Stroke*

A. C. Fonseca · J. M. Ferro (✉)
Department of Neurology, Hospital de Santa Maria, Instituto de Medicina Molecular, University of Lisbon, Av. Prof. Egas Moniz, 1649-035 Lisbon, Portugal
e-mail: jmferro@fm.ul.pt

A. C. Fonseca
e-mail: catarinagfonseca@gmail.com

absorbed by mucous membranes. Its main administration is through intravenous injection or snorting. Cocaine alkaloid is produced by dissolving cocaine hydrochloride in water, ammonia, and ether to obtain "free base" or in water and baking soda to produce "crack." Both forms can be smoked [6].

The effects of cocaine in the central nervous system result from blocking of the reuptake of catecholamines such as dopamine, serotonin, norepinephrine, and epinephrine at nerve endings. These neuroanatomical actions result in a potentiation of sympathetic activity.

Stroke can occur with both cocaine hydrochloride and alkaloid crack and following any method of administration. Crack cocaine seems to be associated with both ischemic strokes and hemorrhage strokes, whereas cocaine hydrochloride results more often in hemorrhagic events [7].

The main peak in the description of cocaine-associated stroke happened in 1983 when "crack" was introduced and its use became almost epidemic.

Ischemic Stroke

Of all cocaine-associated strokes, 25–60 % are ischemic [8–10]. The majority (50–80 %) of infarcts involve the middle cerebral artery [11]. Reported ischemic strokes include hemispheric, subcortical, cerebellar, brain stem, retinal, and spinal infarcts [12].

Classic risk factors for ischemic stroke are usually absent in patients with cocaine-associated stroke, suggesting that these factors are not implicated in cocaine-related infarct [13]. Patients with cocaine-related stroke tend to be young, in the fourth decade of life [13, 14].

The causes of ischemic infarcts are diverse and include large-artery, small-artery, and cardioembolic strokes. These causes appear to be of relatively equal incidence [15•].

Multiple overlapping mechanisms may be responsible for ischemic stroke related to cocaine. Acutely, cocaine can induce vasospasm, sudden onset of hypertension, and myocardial infarction [7] with cardiac arrhythmias. In the longer term, cocaine may induce cardiomyopathy [16], endothelial dysfunction towards a prothrombotic condition and accelerated atherosclerosis [17], increased platelet activation [18], and vasculitis [12]. It has also been shown that cocaine doses within the range administered by drug abusers induce cerebral microischemia and that these effects are exacerbated with repeated use [19].

Cocaine may induce vasospasm by preventing the uptake of sympathomimetic neurotransmitters by nerve terminals, leading to sensitization to epinephrine and norepinephrine and accumulation of serotonin, which is one of the main cerebral vasoconstrictors. Vasospasm may remain for days after the last consumption of cocaine. Although cocaine has a half-life of approximately 1 h, it is metabolized into substances that have a vasoconstrictive effect that can last for days.

Cocaine in vitro enhances the response of platelets to arachidonic acid, leading to increased production of thromboxane and platelet aggregation, promoting thrombus formation [18].

Vasculitis is a controversial pathophysiological mechanism in cocaine-associated stroke (Fig. 1). Although vasculitis has been histologically demonstrated in isolated cases [20] and Moyamoya-like vasculopathy has been reported in cocaine addicts [21], some authors state that cocaine rarely causes evident vasculitis [10] and that vasculitis may be caused by another drug or inactive ingredients that may have been consumed at the same time as cocaine, namely, amphetamines. Others propose that vasculitis can be missed by angiography and can only be documented in a brain biopsy [22]. Most autopsies failed to show vasculitis, and when present it was mild without vessel wall necrosis. Recently, high-resolution contrast-enhanced vessel wall MRI demonstrated circumferential arterial wall thickening and enhancement compatible with inflammation in a case of cocaine vasculopathy [23]; however, there was no histologic confirmation. The blood-oxygen-level-dependent MRI vasomotor reactivity findings can be nonspecific and could be a manifestation of the hemodynamic effects of large-vessel involvement [24].

Although most ischemic strokes related to cocaine are documented in the first few hours after cocaine consumption, there may be a delay of up to several hours between cocaine intake and onset of stroke, owing to the vasoconstrictor effect of cocaine metabolites and to an extended endothelial dysfunction [17, 25].

Regarding the clinical evaluation of these patients, if the patient is reluctant or unable to report a history of cocaine intake, proof of cocaine intake can be achieved by documenting positive urine toxicology findings for cocaine or its metabolite benzoylecgonine. In one study, 21.6 % of patients had a positive toxicology screen despite an initial patient reported negative history [3].

A higher frequency of markedly elevated serum creatine kinase levels in ischemic strokes related to cocaine has been described, probably due to rhabdomyolysis associated with hyperthermia, adrenergic stimulation, or direct toxic action in muscular metabolism [13].

Bhattacharya et al. [26] reported that the disability resulting from cocaine-related stroke was not significantly different from that resulting from non-cocaine-related stroke. In a recent retrospective and prospective study of ischemic stroke in the young, cocaine addicts had a higher rate of complications (33.3 % vs 15.2 %) and mortality (11.1 % vs 3.8 %) ($p>0.05$) [13].

Cocaine abuse may contribute to cognitive sequelae following a stroke. Long-term cocaine use causes dopamine depletion, leading to depression and deficits in attention and initiation [27].

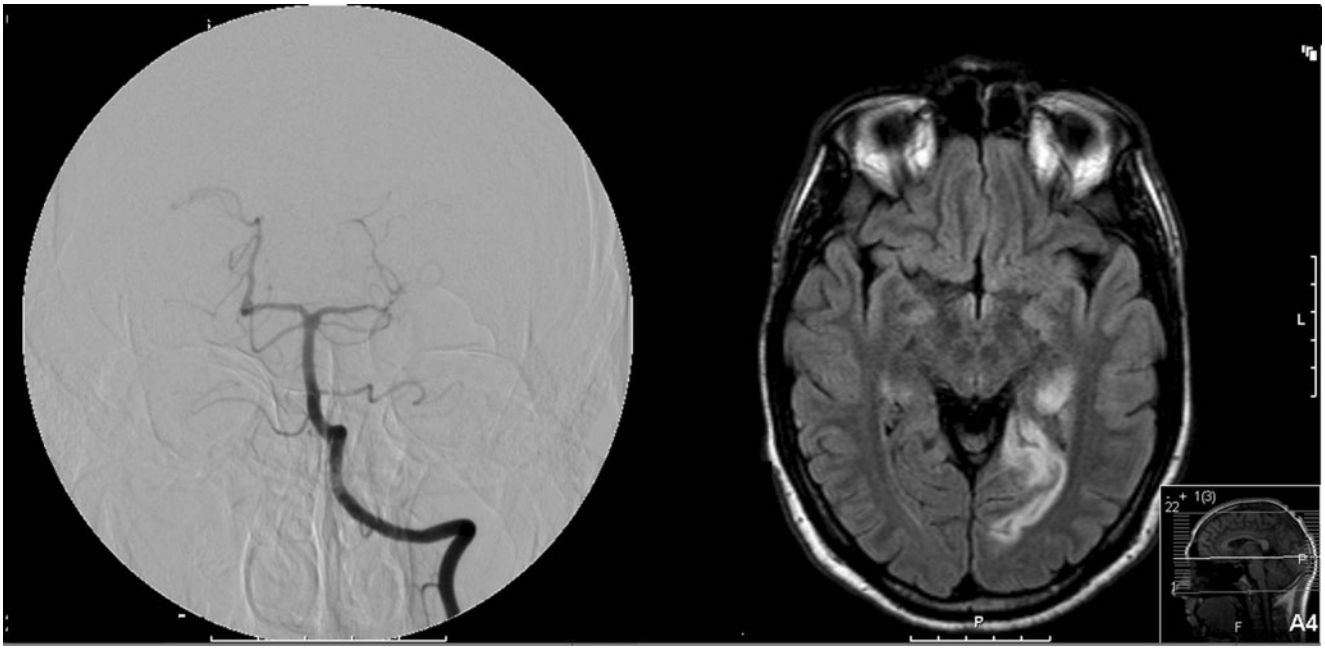

Fig. 1 Brain MRI T2 fluid-attenuated inversion recovery image showing a left posterior cerebral artery ischemic stroke in a cocaine user (*right*). Cerebral angiography showed irregularities and narrowing of the left P1 and P2 segments (*left*)

Regarding treatment, thrombolysis seems to be safe in cocaine-associated stroke. A retrospective studied found no complications in patients with cocaine-associated stroke treated with tissue plasminogen activator. Cocaine-positive and cocaine-negative treated patients had similar stroke severity and safety outcomes [15•].

Intracranial Hemorrhage

Cocaine users have a higher frequency of intracranial hemorrhages (ICHs) than non-cocaine users [14]. ICH is commoner in those actively consuming cocaine, perhaps owing to acute spikes in blood pressure. However, because of the short half-life of cocaine (less than 1 h), high arterial blood pressure may no longer be found in the initial evaluation of the patient [8].

Cocaine use has been associated with several types of ICH, including intraparenchymal hemorrhage, intraventricular hemorrhage, and subarachnoid hemorrhage (SAH) [10]. Headache following consumption of cocaine should alert the physician to the possibility of ICH.

There are four proposed mechanisms by which cocaine can induce a hemorrhagic stroke:

1. A sudden increase in arterial pressure may enhance the rupture of a vessel, often in association with an underlying aneurysm or arteriovenous malformation [14, 28], which provides weak sites for vascular rupture. Intraaneurismal pressure can equal mean systemic arterial pressure [29] and become many times greater than that registered in the cerebral arteries. Up to 41 % of patients presenting with a cocaine-associated cerebral hemorrhage were reported to have evidence of vascular abnormalities such as aneurysms or arteriovenous malformations. Arteriography should therefore be part of the investigation of young patients who are suspected of being drug abusers.
2. Hemorrhagic transformation of ischemic infarcts related to multifocal vasoconstriction [22].
3. Vasculitis.
4. Changes in cerebrovascular autoregulation. Cocaine causes vasodilatation and increases cerebral blood flow at blood pressures substantially higher than those resulting in vascular rupture in normotensive patients [30].

A retrospective study of a series of ICH found that cocaine-associated ICH patients had higher admission blood pressures, significantly more subcortical locations, and higher risk of intraventricular hemorrhage compared with patients with cocaine-negative ICH [31•]. Patients with cocaine-associated ICH also had a poorer prognosis (worse functional outcome, fewer discharged home or to inpatient rehabilitation, three times more likely to die during short-term hospitalization) [31•].

A retrospective analysis of patients with aneurysmal SAH related to cocaine reported that cocaine users were younger than controls (45.1 years vs 54.1 years; $P \leq 0.0003$), and were more likely to smoke tobacco, drink alcohol, and have renal dysfunction [32•].

Aneurysms have been reported to be significantly smaller and rupture at a younger age among cocaine users compared with nonusers [33].

There are contradictory data regarding the occurrence of vasospasm and outcome in patients with SAH associated with cocaine abuse. Alaraj et al. [32•] found no significant difference in SAH severity, unfavorable short-term outcome, incidence of symptomatic or radiologic vasospasm, stroke, or death between cocaine users and nonusers. Simpson et al. [34] documented that patients who consumed cocaine intravenously and had an SAH had a poorer outcome than other patients with SAH. This was hypothesized to be due to an increased intensity and duration of vasospasm related to the use of cocaine. Howington et al. [35] in a retrospective study reported that cocaine use was associated with a 2.8-fold greater risk of developing vasospasm in SAH (95 % confidence interval 1.86–4.22).

Amphetamines and Related Agents

Amphetamines are psychomotor stimulants and their effect on the central nervous system includes blocking the reuptake of dopamine and stimulating the release of dopamine and norepinephrine as well as possible involvement in the serotonergic and endogenous opiate systems. The systemic effects of amphetamines include sympathomimetic actions as elevation of systolic and diastolic blood pressure and tachycardia, cardiac dysrhythmias, and hyperpyrexia. 3,4-Methylenedioxyamphetamine and 3,4-methylenedioxymethamphetamine (Ecstasy) are amphetamine derivatives.

Methamphetamine is the most potent of amphetamines and is the most commonly abused. Cardiovascular responses caused by binge administration of methamphetamine include hypertension, vasoconstriction [36], and focal myocytes necrosis [37].

All forms of amphetamine administration have been related to stroke (oral, intravenous, nasal, and inhalation). Amphetamine use increases the odds of stroke by almost four times that of nonusers [38]. Most case series report a disproportionate rate of hemorrhagic stroke with amphetamine use, up to twice the risk with cocaine use (odds ratio 4.95 vs. 2.33) [4].

The use of amphetamines has been associated with ischemic strokes and hemorrhagic strokes, including intraparenchymal hematomas and SAHs [39].

Experimental and clinical evidence suggests methamphetamine has a direct toxic or immunological effect in the cerebral vessels [40]. Cerebral vasculitis is a commonly described histologic and radiological finding in abusers of methamphetamine with either hemorrhagic or ischemic stroke [41]. Histology of cerebral vessels of patients with strokes associated with methamphetamine intake has shown necrotic lesions in small and large cerebral arteries, with moderate to extensive medical necrosis with minimal inflammatory cells [40, 42]. Some authors proposed the use of immunosuppressants in vasculitis associated with methamphetamine [37].

Amphetamine-associated ICH has been attributed to acute hypertension and to cerebral vasculitis. Both subcortical and lobar hematomas have been described [39, 41]. Intracerebral hemorrhage has been described after a single dose. Patients with intracerebral hemorrhage related to the short-term use of amphetamine-like psychostimulants may present with fever and acute hypertension. ICH after a long period of amphetamine use can result from vessel damage that occurred during exposure. Amphetamine-related SAHs mostly frequently report underlying aneurysms [2, 39].

Amphetamine abuse was associated with increased risk of death after a hemorrhagic stroke [4].

Ecstasy

Ecstasy has been linked to the occurrence of cerebrovascular accidents. Ecstasy alters brain serotonin concentrations, and brain postsynaptic 5-HT_2 receptors play a role in the regulation of brain microvasculature. There are reports in the literature of ischemic and hemorrhagic strokes including SAH occurring within hours of ingestion of Ecstasy [43–45]. Infarcts caused by Ecstasy are frequently seen in the occipital cortex and globus pallidus. These correspond to brain areas with a high expression of serotonin receptors [46].

An acute sympathetic stimulation has been proposed as the cause of aneurysm rupture after intake of Ecstasy. Nevertheless, Ecstasy is a synthetic amphetamine derivative, and it has been hypothesized that it can probably cause cerebral vasculitis [47].

There is a case report of stroke 48 h after intake of a variant of Ectasy, the designer drug 4-bromo-2,5-dimethoxyphenethylamine. In this case, magnetic resonance angiography and cerebral angiogram imaging demonstrated profound vascular abnormalities of large-caliber, medium-caliber, and small-caliber vessels with watershed infarction [48].

Ephedrine

Ephedrine is a sympathomimetic drug derived from ephedra and may cause vasculitis, like methamphetamine. Wooten et al. [49] reported late vasculitis related to ephedrine abuse. Recently, there have been more reports that show ephedrine increases the risk of strokes [50]. Legal dietary supplements contain ephedra.

Opioids

Opioids or narcotics are natural or synthetic drugs that have pharmacologic proprieties similar to those of morphine. Morphine is one of the alkaloids derived from the exudate

of seed from the poppy plant. Heroin is made by acetylation of morphine.

Heroin binds to endogenous opiate receptors, namely, the mu receptor, which is responsible for the actions of central nervous system and cardiovascular system. Heroin causes hypotension, bradycardia, and respiratory depression and several ECG changes [51]. When injected, its psychic effect peaks at 10 min and is followed by profound sedation lasting for 1 h.

There are few reports of stroke associated with the use of heroin. Most strokes occurred after intravenous use, but there are reports of stroke after inhalation [52–54]. Almost all strokes are ischemic.

The most frequent mechanism of stroke in heroin addicts is multiple cardioembolism due to infective endocarditis [55, 56•]. Other sources of embolism are cardiac arrhythmias and foreign substances added to "cut the product," such as aspirin, caffeine, the cleaning power Ajax, lidocaine, mannitol, quinine starch, sugar, strychnine, and talcum powder. Adulterants can embolize directly to the brain or be caught in the lungs, where they cause a granulomatous reaction, leading to pulmonary hypertension, and right-to-left shunting, by opening pulmonary fistulae or through a permeable patent foramen ovale.

Another potential stroke mechanism is global brain hypoperfusion and hypoxia, in the setting of profound hypotension, bradycardia, and respiratory depression or seizures [57, 58]. In these circumstances an additional factor is the compression of the carotid artery caused by the prolonged lateral neck flexion in a comatose intoxicated addict [59]. Infarcts are typically located at the border zone between major cerebral arterial territories or at the globus pallidus [46, 60].

The role of vasculitis in heroin-associated stroke is controversial. In some cases there were angiographic abnormalities such as vessel occlusion, segmental narrowing [57] or scattered narrowing [61] or "beading," which were interpreted as vasculitis, but which can be due to embolism or vasoconstriction in subjects using multiple types of drugs. In favor of an immune mechanism is the fact that most cases occurred after the first intake of heroin or the resumption of the habit after abstinence. However, there is no pathological proof of vasculitis in these cases.

Pentazocine

In the 1970s, drug users combined pentazocine (brand name Talwin, slang name "Ts") with tripelennamine (an antihistamine typically sold as blue tablets) to produce a euphoric sensation. This combination received the slang name "Ts and Blues." Several cases of stroke, both ischemic and hemorrhagic, were reported in association with the intravenous use of Ts and Blues. In some patients stroke was related to bacterial endocarditis or to embolization of foreign material [55, 62].

Misuse of these substances declined after naloxone was mandatorily added to pentazocine preparations.

Psychotomimetic Agents

Cannabis

Cannabis, also known as marijuana, in addition to its psychotropic effects may induce systemic cardiovascular effects such as postural hypotension, decubitus hypertension, tachycardia, and an increase in the concentration of carboxyhemoglobin [63]. Although cannabis use is widespread worldwide, it has only exceptionally been associated with cerebrovascular disease. There are some case reports of ischemic, hemorrhagic stroke and transient ischemic attacks in cannabinoid users that are inconclusive as to causality [64, 65]. Although most patients were long-term cannabis users, there are also reports related to random consumption [63]. A case–control study reported an odds ratio for ischemic stroke with marijuana use of 1.76 (95 % confidence interval 1.15–2.71), controlling for other risk factors [2]. In a prospective cohort of 48 consecutive young patients with ischemic stroke, 13 patients consumed cannabis. Ten of these patients showed a specific pattern of multifocal intracranial stenosis that seemed to be associated with cannabis use [66•].The main radiological characteristics of the angiopathy were involvement of multiple intracranial arteries and reversibility of vasoconstriction after cannabis withdrawal. In this study, ischemic strokes were more frequent in the vertebrobasilar territory [66•]. A case series of 17 patients with ischemic stroke who were cannabis consumers also reported a preponderance of infarcts in the posterior circulation, suggesting a susceptibility of posterior circulation [67]. In this case series no evidence of structural vasculopathy was found.

Mechanisms that have been hypothesized but not proven for marijuana-associated stroke include altered cerebral autoregulation, hypotension, vasospasm, cerebral vasoconstriction syndrome, vasculitis, and cardioembolism (resulting from arrhythmia, namely, atrial fibrillation or myocardial infarction) [68, 69]. It is also possible that cannabis, being an illegal drug not subject to sanitary control, may be mixed with other substances that may increase the risk of stroke [70].

Phencyclidine

Phencyclidine, also known as "angel dust," can be smoked, eaten, or injected. Phencyclidine has sympathomimetic effects. It is a vasoconstrictor and has been associated with acute hypertension and delayed hypertensive crisis days

after its use [71]. There have been reports of hemorrhagic strokes including SAH after phencyclidine abuse [72]. There is no reference to vasculitis in this context.

Lysergic Acid Diethylamide

Lysergic acid diethylamide (LSD) is an ergot derivative and is a vasoconstrictor. There are only a few reports in the literature of ischemic stroke following the ingestion of LSD tablets. Carotid vasoconstriction was the proposed cause of these strokes [73, 74]. The last case of ischemic stroke resulting from ingestion of LSD was reported in 1974 [73], which reflects the decline in the use of this illicit drug.

Doping in Sports

A number of substances are illegally used in sports to enhance performance. Doping substances include hormones, such as anabolic–androgenic steroids, corticosteroids, ACTH, HCG, growth hormone, erythropoietin, and

Table 1 Type and mechanisms of stroke related to illicit drug use

Drug	Type of stroke	Mechanism
Cocaine	Ischemic	Vasospasm
		Cardioembolism—myocardial infarction, arrhythmia, cardiomyopathy
		Prothrombotic state—endothelial dysfunction, platelet activation
		Vasculitis
	Hemorrhagic (SAH, IVH, parenchymal)	Hypertensive spikes
		Underlying aneurysm or arteriovenous malformation rupture
		Vasculitis
		Changes in cerebrovascular autoregulation
Amphetamines	Ischemic	Vasculitis—toxic or immunological effect
	Hemorrhagic (parenchymal hematomas, SAH)	Vasculitis
		Hypertensive spikes
		Underlying aneurysm or arteriovenous malformation rupture
Opioids	Ischemic	Cardioembolism—infective endocarditis, arrhythmias
		Embolization of foreign substances
		Global hypoperfusion and hypoxia—hypotension, bradycardia, respiratory depression
		Compression of carotid artery
		Vasculitis
Pentazocine	Ischemic	Bacterial endocarditis
	Hemorrhagic	Embolization of foreign substances
Cannabis	Ischemic	Changes in cerebral autoregulation
	Hemorrhagic	Hypotension
		Vasospasm
		Cerebral vasoconstriction syndrome
		Vasculitis
		Cardioembolism—arrhythmia, myocardial infarction
Phencyclidine	Hemorrhagic (SAH, parenchymal)	Sympathomimetic effect—acute hypertension
LSD	Ischemic	Carotid vasoconstriction
Anabolic steroids	Ischemic	Enhanced atherogenesis —decreased HDL levels, increased LDL levels, hypertension
		Prothrombotic effect—platelet and procoagulant enhancement
		Hemorheologic effect—impaired endothelial function, increased viscosity
		Cardioembolism—arrhythmia

SAH subarachnoid hemorrhage, *IVH* intraventricular hemorrhage, *LSD* lysergic acid diethylamide, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

precursors, β blockers, narcotics, diuretics, and probenecid. Anabolic–androgenic steroids increase the risk of a vascular event through several mechanisms. They are atherogenic, as they decrease the levels of HDL cholesterol and increase the levels of LDL cholesterol and promote hypertension. They have a prothrombotic effect, by increasing platelet count and function and the activity of procoagulants, while decreasing fibrinolysis. They also have a hemorheologic effect, impairing endothelial function and increasing viscosity. Furthermore, anabolic–androgenic steroids cause myocardial injury, namely, ventricular hypertrophy and decreased myocardial relaxation, and are proarrhythmic. Erythropoietin and derivatives are prothrombotic and have a hemorheologic effect through an increase in viscosity.

There are three reports of ischemic stroke associated with the use of anabolic–androgenic steroids in bodybuilders. The stroke mechanism was thought to be cardioembolic in one patient [75] and was unknown in the remaining patients [76, 77]. Ephedrine and extract of ma huang (a Chinese ephedra) were associated with stroke in two sportsmen [78, 79].

Conclusion

Illicit drugs can cause both ischemic and hemorrhagic stroke and therefore contribute to the burden of stroke in the young adult, particularly in cities and regions with high prevalence of drug consumption. Toxicology screening for illicit drugs should be done in young patients with stroke with no obvious cause, or if suggested by history or examination [80]. Although in some patients the mechanism of stroke is identified using neuroimaging and other modern diagnostic tools (Table 1), in a sizeable fraction of cases the mechanism of stroke remains unclear. Further studies are needed to elucidate the role of hemodynamic and immunologic mechanisms in these cases.

Disclosure No potential conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. • Esse K, Fossati-Bellani M, Traylor A, Martin-Schild S. Epidemic of illicit drug use, mechanisms of action/addiction and stroke as a health hazard. Brain Behav. 2011;1:44–54. *A comprehensive review of the epidemics of drug abuse and its medical complications, focusing on stroke*.
2. Kaku DA, Lowenstein DH. Emergence of recreational drug abuse as a major risk factor for stroke in young adults. Ann Intern Med. 1990;113:821–7.
3. Sloan MA, Kittner SJ, Feeser BR, et al. Illicit drug-associated ischemic stroke in the Baltimore-Washington Young Stroke Study. Neurology. 1998;50:1688–93.
4. Westover AN, McBride S, Haley RW. Stroke in young adults who abuse amphetamines or cocaine: a population-based study of hospitalized patients. Arch Gen Psychiatry. 2007;64:495–502.
5. Iranmanesh F. Prognostic value of electrocardiography and electroencephalography in patients with ischemic stroke. Acta Neurol Taiwan. 2008;17:228–32.
6. Velasquez EM, Anand RC, Newman 3rd WP, et al. Cardiovascular complications associated with cocaine use. J La State Med Soc. 2004;156:302–10.
7. Brust JC. Clinical, radiological, and pathological aspects of cerebrovascular disease associated with drug abuse. Stroke. 1993;24 (12 Suppl):I129–33.
8. Daras M, Tuchman AJ, Koppel BS, et al. Neurovascular complications of cocaine. Acta Neurol Scand. 1994;90:124–9.
9. Brown E, Prager J, Lee HY, Ramsey RG. CNS complications of cocaine abuse. Prevalence, pathophysiology, and neuroradiology. AJR Am J Roentgenol. 1992;159:137–47.
10. Levine SR, Brust JC, Futrell N, et al. Cerebrovascular complications of the use of the `crack' form of alkaloidal cocaine. N Engl J Med. 1990;323:699–704.
11. Bartzokis G, Goldstein IB, Hance DB, et al. The incidence of T2-weighted MR imaging signal abnormalities in the brain of cocaine-dependent patients is age-related and region-specific. AJNR Am J Neuroradiol. 1999;20:1628–35.
12. Daras M, Tuchman AJ, Marks S. Central nervous system infarction related to cocaine abuse. Stroke. 1991;22:1320–5.
13. Carcelén-Gadea ME, Pons-Amate JM, Climent-Díaz B, et al. Involvement of cocaine in cerebral vascular pathology. Rev Neurol. 2012;54:664–72.
14. Klonoff DC, Andrews BT, Obana WG. Stroke associated with cocaine use. Arch Neurol. 1989;46:989–93.
15. • Martin-Schild S, Albright KC, Misra V, et al. Intravenous tissue plasminogen activator in patients with cocaine-associated acute ischemic stroke. Stroke. 2009;40:3635–7. *A retrospective review that studied safety outcomes (symptomatic intracerebral hemorrhage, mortality, and modified Rankin Scale) of intravenous thrombolysis in ischemic stroke cocaine-positive patients*.
16. Sauer CM. Recurrent embolic stroke and cocaine-related cardiomyopathy. Stroke. 1991;22:1203–5.
17. Sáez CG, Olivares P, Pallavicini J, et al. Increased number of circulating endothelial cells and plasma markers of endothelial damage in chronic cocaine users. Thromb Res. 2011;128:e18–23.
18. Pereira J, Sáez CG, Pallavicini J, et al. Platelet activation in chronic cocaine users: effect of short term abstinence. Platelets. 2011;22:596–601.
19. Ren H, Du C, Yuan Z, et al. Cocaine-induced cortical microischemia in the rodent brain: clinical implications. Mol Psychiatry. 2011; In press.
20. Fredericks RK, Lefkowitz DS, Challa VR, Troost BT. Cerebral vasculitis associated with cocaine abuse. Stroke. 1991;22:1437–9.
21. Storen EC, Wijdicks EF, Crum BA, Schultz G. Moyamoya-like vasculopathy from cocaine dependency. AJNR Am J Neuroradiol. 2000;21:1008–10.
22. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 27–1993. A 32-year-old man with the sudden onset of a right-sided headache and left hemiplegia and hemianesthesia. N Engl J Med. 1993;329:117–24.

23. Mandell DM, Matouk CC, Farb RI, et al. Vessel wall MRI to differentiate between reversible cerebral vasoconstriction syndrome and central nervous system vasculitis: preliminary results. Stroke. 2012;43:860–2.
24. Koch S, Sacco RL. Cocaine-associated stroke: some new insights? Nat Clin Pract Neurol. 2008;4:579.
25. Havranek EP, Nademanee K, Grayburn PA, Eichhorn EJ. Endothelium-dependent vaso relaxation is impaired in cocaine arteriopathy. J Am Coll Cardiol. 1996;28:1168–74.
26. Bhattacharya P, Taraman S, Shankar L, et al. Clinical profiles, complications, and disability in cocaine-related ischemic stroke. J Stroke Cerebrovasc Dis. 2011;20:443–9.
27. Tolat RD, O' Dell MW, Golamco-Estrella SP, et al. Cocaine-associated stroke: three cases and rehabilitation considerations. Brain Inj. 2000;14:383–91.
28. Oyesiku NM, Colohan AR, Barrow DL, Reisner A. Cocaine-induced aneurysmal rupture: an emergent factor in the natural history of intracranial aneurysms? Neurosurgery. 1993;32:518–25.
29. Ferguson GG. Direct measurement of mean and pulsatile blood pressure at operation in human intracranial saccular aneurysms. J Neurosurg. 1972;36:560–3.
30. Kibayashi K, Mastri AR, Hirsch CS. Cocaine induced intracerebral hemorrhage: analysis of predisposing factors and mechanisms causing hemorrhagic strokes. Hum Pathol. 1995;26:659–63.
31. • Martin-Schild S, Albright KC, Hallevi H, et al. Intracerebral hemorrhage in cocaine users. Stroke. 2010;41:680–4. *A retrospective analysis of patients admitted with nontraumatic ICH. Patients with positive screens for cocaine were compared with patients with negative screens for cocaine. The location, disease, and outcome of patients with cocaine-associated ICH were analyzed.*
32. • Alaraj A, Wallace A, Mander N, et al. Effect of acute cocaine use on vasospasm and outcome in aneurysmal subarachnoid hemorrhage. World Neurosurg. 2010;73:357–60. *A retrospective study that aimed to investigate the effect of short-term cocaine use on response to vasospasm treatment and neurologic outcome in patients with aneurysmal SAH.*
33. Vannemreddy P, Caldito G, Willis B, Nanda A. Influence of cocaine on ruptured intracranial aneurysms: a case control study of poor prognostic indicators. J Neurosurg. 2008;108:470–6.
34. Simpson Jr RK, Fischer DK, Narayan RK, et al. Intravenous cocaine abuse and subarachnoid haemorrhage: effect on outcome. Br J Neurosurg. 1990;4:27–30.
35. Howington JU, Kutz SC, Wilding GE, Awasthi D. Cocaine use as a predictor of outcome in aneurysmal subarachnoid hemorrhage. J Neurosurg. 2003;99:271–5.
36. Salanova V, Taubner R. Intracerebral haemorrhage and vasculitis secondary to amphetamine use. Postgrad Med J. 1984;60:429–30.
37. Varner KJ, Ogden BA, Delcarpio J, Meleg-Smith S. Cardiovascularresponses elicited by the “binge” administration of methamphetamine. J Pharmacol Exp Ther. 2002;301:152–9.
38. Petitti DB, Sidney S, Quesenberry C, Bernstein A. Stroke and cocaine or amphetamine use. Epidemiology. 1998;9:596–600.
39. Ho EL, Josephson SA, Lee HS, Smith WS. Cerebrovascular complications of methamphetamine abuse. Neurocrit Care. 2009;10:295–305.
40. Shibata S, Mori K, Sekine I, Suyama H. Subarachnoid and intracerebral hemorrhage associated with necrotizing angitis due to methamphetamine abuse. An autopsy case. Neurol Med Chir Tokyo. 1991;31:49–52.
41. McGee SM, McGee DN, McGee MB. Spontaneous intracerebral hemorrhage related to methamphetamine abuse: autopsy findings and clinical correlation. Am J Forensic Med Pathol. 2004;25:334–7.
42. Brust JCM. Vasculitis associated with substance abuse. Neurol Clin. 1997;15:945–57.
43. Hughes JC, McCabe M, Evans RJ. Intracranial haemorrhage associated with ingestion of 'ecstasy'. Arch Emerg Med. 1993;10:372–724.
44. Gledhill JA, Moore DF, Bell D, Henry JA. Subarachnoid haemorrhage associated with MDMA abuse. J Neurol Neurosurg Psychiatry. 1993;56:1036–7.
45. Manchanda S, Connolly MJ. Cerebral infarction in association with Ecstasy abuse. Postgrad Med J. 1993;69:874–5.
46. Hagan IG, Burney K. Radiology of recreational drug abuse. Radiographics. 2007;27:919–40.
47. Auer J, Berent R, Weber T, et al. Subarachnoid haemorrhage with "Ecstasy" abuse in a young adult. Neurol Sci. 2002;23:199–201.
48. Ambrose JB, Bennett HD, Lee HS, Josephson SA. Cerebral vasculopathy after 4-bromo-2,5-dimethoxyphenethylamine ingestion. Neurologist. 2010;16:199–202.
49. Wooten MR, Khangure MS, Murphy MJ. Intracerebral hemorrhage and vasculitis related to ephedrine abuse. Ann Neurol. 1983;13:337–40.
50. Blamk-Reid C. How to have a stroke at an early age: the effects of crack cocaine and other illicit drugs. J Neurosci Nurs. 1996;28:19–27.
51. Lipski J, Stimmel B, Donoso E. The effect of heroin and multiple drug abuse on the electrocardiogram. Am Heart J. 1973;86:663–8.
52. Bartolomei F, Nicoli F, Swiader L, Gastaut JL. Ischemic cerebral vascular stroke after heroin sniffing. A new case. Presse Med. 1992;21:983–6.
53. Adle-Biassette H, Marc B, Benhaiem-Sigaux N, Durigon M, Gray F. Cerebral infarctions in a drug addict inhaling heroin. Arch Anat Cytol Pathol. 1996;44:12–7.
54. Benoilid A, Collongues N, de Seze J, Blanc F. Heroin inhalation-induced unilateral complete hippocampal stroke. Neurocase. 2012; doi:10.1080/13554794.2012.667125.
55. Caplan LR, Hier DB, Banks G. Current concepts of cerebrovascular disease–stroke: stroke and drug abuse. Stroke. 1982;13:869–72.
56. • Barbieux M, Véran O, Detante O. Ischemic strokes in young adults and illegal drugs. Rev Med Interne. 2012;33:35–40. *A recent update of the cerebrovascular complications of the different illicit drugs, their management, and treatment.*
57. Niehaus L, Meyer BU. Bilateral borderzone brain infarctions in association with heroin abuse. J Neurol Sci. 1998;160:180–2.
58. Daras MD, Orrego JJ, Akfirat GL, Samkoff LM, Koppel BS. Bilateral symmetrical basal ganglia infarction after intravenous use of cocaine and heroin. Clin Imaging. 2001;25:12–4.
59. Jensen R, Olsen TS, Winther BB. Severe non-occlusive ischemic stroke in young heroin addicts. Acta Neurol Scand. 1990;81:354–7.
60. Büttner A, Mall G, Penning R, Weis S. The neuropathology of heroin abuse. Forensic Sci Int. 2000;113:435–42.
61. Brust JC, Richter RW. Stroke associated with addiction to heroin. J Neurol Neurosurg Psychiatry. 1976;39:194–9.
62. Caplan LR, Thomas C, Banks G. Central nervous system complications of addiction to "T's and Blues". Neurology. 1982;32:623–8.
63. Mateo I, Pinedo A, Gomez-Beldarrain M, et al. Recurrent stroke associated with cannabis use. J Neurol Neurosurg Psychiatry. 2005;76:435–7.
64. Lawson TM, Rees A. Stroke and transient ischaemic attacks in association with substance abuse in a young man. Postgrad Med J. 1996;72:692–3.
65. Zachariah SB. Stroke after heavy marijuana smoking. Stroke. 1991;22:406–9.
66. • Wolff V, Lauer V, Rouyer O, et al. Cannabis use, ischemic stroke, and multifocal intracranial vasoconstriction: a prospective study in 48 consecutive young patients. Stroke. 2011;42:1778–80. *A 2-year prospective study evaluating the relationship between cannabis use and ischemic stroke in young stroke patients.*

67. Singh NN, Pan Y, Muengtaweeponsa S, et al. Cannabis-related stroke: case series and review of literature. J Stroke Cerebrovasc Dis. 2011; In press.
68. Thanvi BR, Treadwell SD. Cannabis and stroke: is there a link? Postgrad Med J. 2009;85:80–3.
69. Renard D, Taieb G, Gras-Combe G, et al. Cannabis-related myocardial infarction and cardioembolic stroke. J Stroke Cerebrovasc Dis. 2012;21:82–3.
70. Mateo I, Infante I, Gomez-Beldarrain M, et al. Cannabis y patologia vascular cerebral. Neurologia. 2006;21:204–8.
71. McCarron MM, Schulze BW, Thompson GA, et al. Acute phencyclidine intoxication: clinical patterns, complications, and treatment. Ann Emerg Med. 1981;10:290–7.
72. Boyko OB, Burger PC, Heinz ER. Pathological and radiological correlation of subarachnoid hemorrhage in phencyclidine abuse. J Neurosurg. 1987;67:446–8.
73. Lieberman AN, Bloom W, Kishore PS, et al. Carotid artery occlusion following ingestion of LSD. Stroke. 1974;5:213–5.
74. Sobel J, Espinas O, Friedman S. Carotid artery obstruction following LSD capsule ingestion. Arch Intern Med. 1971;127:290–1.
75. Shimada Y, Yoritaka A, Tanaka Y, et al. Cerebral infarction in a young man using high-dose anabolic steroids. J Stroke Cerebrovasc Dis. 2012;21:906.e9–906.e11.
76. Frankle MA, Eichberg R, Zachariah SB. Anabolic androgenic steroids and a stroke in an athlete: case report. Arch Phys Med Rehabil. 1988;69:632–3.
77. Santamarina RD, Besocke AG, Romano LM, Ioli PL, Gonorazky SE. Ischemic stroke related to anabolic abuse. Clin Neuropharmacol. 2008;31:80–5.
78. Foxford RJ, Sahlas DJ, Wingfield KA. Vasospasm-induced stroke in a varsity athlete secondary to ephedrine ingestion. Clin J Sport Med. 2003;13:183–5.
79. Vahedi K, Domigo V, Amarenco P, Bousser MG. Ischaemic stroke in a sportsman who consumed MaHuang extract and creatine monohydrate for body building. J Neurol Neurosurg Psychiatry. 2000;68:112–3.
80. Ferro JM, Massaro AR, Mas JL. Aetiological diagnosis of ischaemic stroke in young adults. Lancet Neurol. 2010;9:1085–96.