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Review Article

Effect of drug use in the treatment of acute ischemic stroke: A scoping review

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ABSTRACT

Background: Drugs of abuse have been associated with ischemic stroke; however, the clinical presentation, outcomes, and treatment data in this population are limited. The overall safety and efficacy of thrombolytic therapy and thrombectomy in these patients remain unclear. This scoping review summarizes published complications and clinical outcomes in patients with recent abuse of cocaine, methamphetamine (MA), cannabis, decongestant, opioids, alcohol, and 3,4-methylenedioxymethamphetamine (MDMA) presenting with acute ischemic stroke.

Methods: We conducted a scoping review of the primary literature that assessed outcomes data of thrombolytic therapy or thrombectomy in drug users with acute ischemic stroke. We searched PubMed, Ovid Medline, and Web of Science. Demographic and stroke characteristics, treatment, complications, and clinical outcomes at last follow-up were collected and summarized.

Results: We identified 51 studies in this review. Drugs of abuse of interest were cocaine (14 studies), MDMA (one study), MA (eight studies), cannabis (23 studies), alcohol (two studies), decongestants (one study), and opioids (two studies). Clinical presentation and stroke presentation were most commonly described features. Thrombectomy outcomes were reported for four patients total (two studies), all with history of cocaine use. Thrombolysis treatment and outcomes were reported for 8851 patients (five studies) with history of cocaine, alcohol, or cannabis. Both treatments were pursued in three patients (three studies). Treatment complications included intracerebral hemorrhage, vasospasm, and cerebral edema.

Conclusion: Evidence for thrombolytic and thrombectomy treatment in drug users remains limited. Controlled studies are needed to examine complication profile and outcomes following thrombolytic and thrombectomy treatment in this population.

Keywords: Cerebrovascular accident, Drugs of abuse, Ischemic stroke, Thrombectomy, Thrombolysis

INTRODUCTION

Drug abuse has been a growing problem in the world associated with increased societal burden as well as short- and long-term health effects. According to the 2021 World Drug Report, the UN estimates that about 275 million people have used drugs worldwide annually with over 36 million people being classified as suffering from drug abuse disorders.[18,28] Drug abuse is most common among young males and is highest among persons between the ages of 18 and 25 at 39%.[14,28] In this cohort, drug abuse is associated with higher societal costs and appears to be increasing.[14]

Drugs of abuse have been found to weaken the integrity of the blood–brain barrier and affect vascular physiology. Specifically, several illicit drugs such as psychomotor stimulants – particularly amphetamine and cocaine – as well as opioids and psychotomimetic drugs have been found to cause vasospasm, vasculitis, accelerated atherosclerosis, and enhanced platelet aggregation.[14,18] These changes render the cerebrovasculature susceptible to the development of vascular insults. Correspondingly, drugs abusers have a 6.5 times increased risk of both hemorrhagic and ischemic stroke. However, the clinical presentation and stroke characteristics in this population have not been well elucidated.

In addition, while current treatment for ischemic stroke includes thrombolysis and mechanical thrombectomy, drug users may be at increased risk of complications such as iatrogenic vasospasm and hemorrhagic reperfusion injury following these therapies as a consequence of the damaging physiological changes on blood vessels provoked by substances of abuse.[30,34,40,42,53] Yet, no difference in stroke management guidelines exists for ischemic stroke in the setting of drug abuse.

Our scoping review aims (1) to describe the clinical presentation and treatment for patients with ischemic stroke associated with drugs of abuse including cocaine, MA, opioids, 3,4-methylenedioxymethamphetamine (MDMA), alcohol, and decongestants, and (2) to describe complications and outcomes related to thrombolysis therapy and thrombectomy in drug users, and (3) to identify areas for further research in the treatment of ischemic stroke in these patients.

MATERIALS AND METHODS

Search strategy and selection criteria

Electronic databases PubMed, Web of Science, and Ovid Medline were searched from inception to September 21, 2022. A keyword search using Boolean operators OR and AND with terms including but not limited to: "cocaine," "amphetamine," "cannabis," "3,4-methylenedioxymethamphetamine," "ephedrine," "heroin," "alcohol," and "ischemic stroke" [Supplement for full search terms]. These substances were included in the literature review, as they have been known to affect the cerebrovasculature.

Inclusion and exclusion criteria were determined a priori. We included randomized control trials, observational cohort studies (prospective or retrospective), case–control studies, and case series that included (1) patients with drug abuse of the aforementioned substances who presented with acute ischemic stroke regardless of etiology with relevant clinical, treatment, or outcomes data. Studies were excluded if (1) they did not include clinical, treatment, or outcomes data for ischemic stroke associated with drugs of abuse, (2) they did not include positive toxicology for drug of abuse during presentation, and (3) they were not in the English language.

References of included articles were also reviewed for consideration to identify articles potentially missed by the electronic literature search [Figure 1].

Data extraction

The following baseline data were collected: patient sex and age; previous medical history of hypertension, diabetes, or prior cerebral infarct; stroke characteristics such as mechanism of ischemic stroke and stroke location; hospital admission data, including clinical presentation; treatment data, including type of therapy administered (i.e., tissue plasminogen activator (tPA), thrombectomy); stroke-related complications, including reperfusion injury, vasospasm, and cerebral edema; and clinical follow-up such as last follow-up time and outcome. Stroke-related complications were defined as complications occurring during hospital course attributable to either stroke treatment (i.e., tPA or thrombectomy) or natural progression of stroke (i.e., paralysis, locked-in syndrome, and cerebral edema).

Data synthesis

The study outcome was a descriptive assessment of the clinical presentation, complications, long-term morbidity, and mortality related to ischemic stroke in drug users as well as a descriptive assessment of outcomes related to thrombolysis and thrombectomy in this population. In included studies with multiple patients, continuous variables such as age and last clinical follow-up were reported as medians. Crude estimates of related variables were reported as the total proportion of all included studies.

RESULTS

A total of 51 studies were included in this review. Baseline patient and stroke characteristics, imaging findings at admission, treatment, and clinical outcomes of each included study are summarized for each drug of abuse in Tables 1-7.

Cocaine

Fourteen studies with a total of 45 patients (13 females [29%]) reported on ischemic stroke in patients with a positive cocaine toxicology screen on presentation [Table 1].[1,2,4,10,31,34,37,38,42,46,47,52,54,65] The median age at presentation was 46 years (range, 27–75). Patients presented with headache (3/16 [19%]), speech disturbance (10/16 [63%]), sensorimotor dysfunction (11/16, [69%]), and visual disturbance (5/16, [31%]). Six studies with six patients reported on the mechanism of ischemic stroke, which included embolic in two, thrombotic in three, and vasospasm

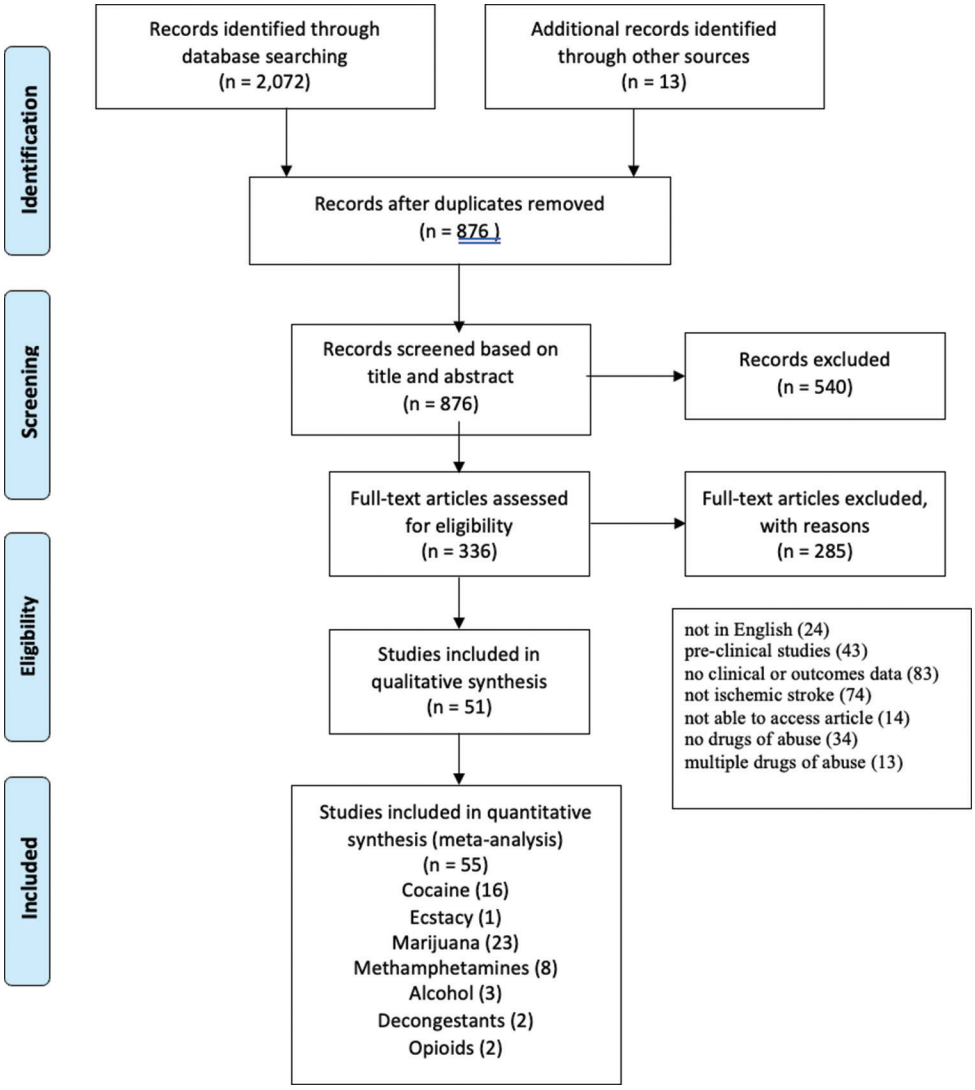

Figure 1: Flow diagram showing study selection process.

in one. There were 11 studies in which location of stroke was mentioned: middle cerebral artery (MCA) (7/12, [58%]), basilar artery (BA) (3/12, 25%), posterior inferior cerebellar artery (1/12, 8.3%), and posterior unspecified (1/12, 8.3%).

In six studies, patients with evidence of cocaine use were treated with either tPA and/or thrombectomy.[4,31,37,38,42,65] Martin-Schild *et al*. reported on 29 patients (female [17%], median age 48 [range 19–67]) with evidence of recent cocaine exposure, treated with tPA without complications, although clinical follow-up data were unavailable.[38] Baud *et al*. described two chronic cocaine users treated with tPA for ischemic stroke, both of which were complicated by hemorrhagic conversion subsequently.[4] At the 3-month follow-up, one patient remained bedbound and minimally responsive. In their case series, Memon *et al*. reported three patients (female [66%], median age 63 [range 51–66]) who underwent thrombectomy for MCA occlusion.[42] Hemorrhagic conversion occurred in two patients and vasospasm occurred in one. At the 3-month clinical follow-up, one patient died and all had a modified Rankin score >3. Konzen *et al*. reported one patient [female, age 35] who underwent thrombectomy for MCA occlusion without complications.[31] MacEwen *et al*. described one chronic cocaine user [male, age 40] who received tPA and underwent thrombectomy for BA stroke without complications.[37] At the 9-month follow-up, he had residual stroke deficits. Vidale *et al*. also reported on one patient (female, age 39) with ischemic stroke treated with tPA and thrombectomy without complications.[65]

In eight studies including eight patients, thrombectomy or tPA was not used for the treatment of ischemic stroke. Hemorrhagic conversion, resulting in death, occurred in one patient. Clinical follow-up (2 months) was available for two patients, at which time residual stroke deficits persisted.

Table 1: Baseline characteristics, treatment, complications, and outcomes of ischemic stroke in cocaine users.

Author (Year)	No. of patients, n	Sex	Age (years)	Clinical presentation	Previous medical history	Mechanism of ischemic stroke	Stroke location	Treatment	Stroke-related complications	Last clinical follow-up (months)	Clinical outcome at last follow-up
Levine *et al.* (1987)[34]	--	M	27	L headache; R hemihypesthesia; aphasia	None	--	MCA	--	None	2	Poststroke residual deficits (mild anomia, intermittent headache)
Petty (1990)[52]	--	F	39	L hemiparesis; dysarthria	None	Embolic	MCA	--	None	--	--
Aggarwal and Byrne (1991)[1]	--	F	25	Abnormal gait; headache	None	Vasospasm	PICA	--	None	--	--
Konzen *et al.* (1995)[31]	--	F	35	L headache; dysarthria; L hemiparesis; L hemihypesthesia	None	Thrombotic	MCA	Thrombectomy	None	--	--
Anand *et al.* (2007)[2]	--	F	31	R hemiplegia; L hemiparesis	None	--	Posterior circulation	--	None	--	--
MacEwen *et al.* (2008)[37]	--	M	40	Athetosis; dysarthria; diplopia; L gaze paresis	Cerebral infarct	Thrombotic	BA	tPA, thrombectomy	None	9	Poststroke residual deficits (mild loss of dexterity in L hand, balance disturbance)
Martin-Schild *et al.* (2009)[38]	29	F (17%)	48 (19-67)	--	HTN (67.9%)	--	--	tPA	None	--	--
Morales *et al.* (2012)[46]	--	M	--	Disorientation	HTN	--	--	--	None	2	Poststroke residual deficits (memory impairment, impaired executive functioning secondary to poor

(Contd...)

Table 1: *(Continued).*

Author (Year)	No. of patients, n	Sex	Age (years)	Clinical presentation	Previous medical history	Mechanism of ischemic stroke	Stroke location	Treatment	Stroke-related complications	Last clinical follow-up (months)	Clinical outcome at last follow-up
											attention and memory disturbances)
Vidale *et al.* (2014)[65]	--	F	39	Aphasia; L gaze paresis; L facial hemiparesis; R hemiplegia	None	--	MCA	tPA, thrombectomy	None	--	--
Potolicchio (2015)[54]	--	M	75	Unresponsive	HTN	Thrombotic	BA	--	Early hemorrhagic conversion; development of locked-in syndrome; died at hospital before discharge	NA	NA
Connelly *et al.* (2015)[10]	--	M	44	Disorientation	None	--	--	--	--	--	--
Mullaguri *et al.* (2018)[47]	--	F	66	Aphasia	None	Embolic	Posterior circulation	--	None	--	--
Baud *et al.* (2020)[4]	--	M	55	L hemiparesis; L hemiataxia	None	--	--	tPA	Extravasation in the dorsal pons during tPA infusion, resulting in locked-in syndrome; died at hospital before discharge	NA	NA
	--	M	68	R hemiplegia; aphasia	None	--	--	tPA	30 min after tPA, pt. developed a headache, became nonverbal, and progressed to coma due to hemorrhage	3	Patient remained bedbound and minimally responsive
Memon *et al.* (2020)[42]	--	F	51	Dysarthria; L hemiplegia; R gaze deviation	None	--	MCA	Thrombectomy	Persistent complete occlusion of right M1 despite several MT passes; large infarct that required hemicraniectomy due to malignant MCA syndrome; hemorrhagic conversion	3	mRS 5

(Contd...)

Table 1: *(Continued).*

Author (Year)	No. of patients, n	Sex	Age (years)	Clinical presentation	Previous medical history	Mechanism of ischemic stroke	Stroke location	Treatment	Stroke-related complications	Last clinical follow-up (months)	Clinical outcome at last follow-up
	--	M	63	Aphasia; R hemianopsia; R hemiparesis; L gaze preference	None	--	MCA, BA	Thrombectomy	M1 segment stenosis 2 h postthrombectomy, resulting in dysarthria and R hemiplegia; repeat reocclusion of L MCA; malignant cerebral edema, requiring hemicraniectomy; hemorrhagic conversion	3	Patient died
	--	F	66	Aphasia; R hemianopsia; R hemiparesis; L gaze preference	None	--	MCA	Thrombectomy	Vasospasm	3	mRS 4; aphasia improved

BA: Basilar artery, L: Left, MCA: Middle cerebral artery, mRS: Modified Rankin score, PICA: Posterior inferior cerebellar artery, R: Right, tPA: Tissue plasminogen activator

MDMA

Hanyu *et al*. presented one patient with MDMA-associated ischemic stroke [Table 2].[23] This patient was a 28-year-old male with no significant medical history that presented with headache and abnormal sensation/motor function. The mechanism of ischemic stroke was from vasospasm of the MCA. No specific treatment was pursued with no stroke-related complications during the hospital course. Clinical follow-up for this patient was not available.

Methamphetamine (MA)

Eight studies described 21 patients [8 females (42%)] with a median age of 31.5 years [range, 19–45] presenting with acute ischemic stroke and MA use [Table 3].[12,24,25,36,41,49,51,55] There were seven studies that reported initial clinical presentation of these patients, which included headache (3/11, [27%]), speech disturbance (9/11, [82%]), abnormal sensation/motor function (10/11, [91%]), and visual disturbance (5/11, [45%]). Five studies reported mechanism of stroke, which included thrombotic (2/6, [33%]), embolic (2/6, [33%]), and dissection (2/6, [33%]). Seven studies mentioned location of stroke, consisting of the internal carotid artery (ICA) in three, MCA in five, and posterior cerebral artery (PCA) in one patient. One patient presented with stroke involving the ICA and MCA.

Two patients in two articles underwent invasive intervention for ischemic stroke.[36,41] Loewenhardt *et al*. reported on one patient with a history of chronic MA use with MCA occlusion who was treated with balloon angioplasty without complications.[36] At the 1-month follow-up, the patient had residual poststroke deficits. McIntosh *et al*. described one patient with MCA ischemic stroke treated with angioplasty without complication and with residual stroke deficits at the 4-month follow-up.[41] Seven articles described 19 patients who did not undergo surgical intervention or treatment with thrombolysis. No complications were noted for these patients. At the median follow-up time of 4 months for seven patients, residual stroke deficits remained in all patients.

Cannabis

There were 23 studies identified that included patients presenting with cannabis induced ischemic stroke [Table 4].[3,6,11,16,17,19,21,27,29,39,44,50,57-59,61,63,64,67-69,71,72] Demographic information was available in 22 articles for a total of 44 patients (10/44 [23%] female) with a median age of 28 years. All included studies described clinical presentation for the 184 total patients, which consisted of headache (2%), speech disturbance (64%), abnormal sensation/motor function (38%), and visual disturbance (14%). In seven articles, mechanism of stroke was specified in eight total patients, which included embolic in two, thrombotic

Table 2: Baseline characteristics, treatment, complications, and outcomes of ischemic stroke in MDMA users.

Author (Year)	Sex	Age (years)	Clinical presentation	Previous medical history	Mechanism of ischemic stroke	Stroke location	Treatment	Stroke-related complications	Last clinical follow-up (months)	Clinical outcome at last follow-up or discharge
Hanyu *et al.* (1995)[23]	M	28	Headache; R hemiparesis	None	Vasospasm	MCA	None	None	--	--

MCA: Middle cerebral artery

Table 3: Baseline characteristics, treatment, complications, and outcomes of ischemic stroke in methamphetamine users.

Author (Year)	Sex	Age (years)	Clinical presentation	Previous medical history	Mechanism of ischemic stroke	Stroke location	Treatment	Stroke-related complications	Last clinical follow-up (months)	Clinical outcome at last follow-up or discharge
Rothrock *et al.* (1988)[55]	M	35	L headache; dysarthria; R hemiparesis; aphasia	None	--	ICA	--	None	30	Poststroke residual deficits (aphasia and R hemiparesis)
	--	22	Headache; dysarthria; L gaze palsy; L homonymous hemianopia; L hemiplegia	None	--	MCA, ICA	--	None	12	Poststroke residual deficits (mild L hemiparesis)
	--	23	Aphasia, R hemiplegia	None	--	ICA	--	None	20	Poststroke residual deficits (aphasia and R hemiparesis)
Heye and Hankey (1996)[24]	M	35	Dysphagia; R homonymous hemianopia	None	Embolic	MCA	--	None	1	Poststroke residual deficits
Perez *et al.* (1999)[51]	M	36	Dysarthria; R hemiplegia; R facial droop	None	--	--	--	None	--	--
	F	29	Gait disturbance; aphasia; R hemiplegia	None	Thrombotic	MCA	--	None	8	Poststroke residual deficits (aphasia)
Ohta *et al.* (2005)[49]	F	19	Headache; L hemihypesthesia; blurred vision on L side	None	--	PCA	--	None	4	Poststroke residual deficits (L superior quadrant hemianopia)
De Silva *et al.* (2007)[12]	F	30	Aphasia; R neglect; R hemiparesis	None	Thrombotic with distal embolism	MCA	--	None	--	--

(Contd...)

Table 3: *(Continued)*.

Author (Year)	Sex	Age (years)	Clinical presentation	Previous medical history	Mechanism of ischemic stroke	Stroke location	Treatment	Stroke-related complications	Last clinical follow-up (months)	Clinical outcome at last follow-up or discharge
Ho *et al*. (2009)[25]	F (3/10) M (7/10)	45	--	HTN (5/10), Diabetes (3/10), prior cerebral infarct (3/10)	--	--	--	--	--	--
Loewenhardt *et al*. (2013)[36]	M	33	L hemiplegia; L neglect	None	Embolic	MCA	Balloon angioplasty	None	1	Poststroke residual deficits (L hemiparesis and L neglect)
McIntosh *et al*. (2006)[41]	F	36	Speech difficulty; R-sided weakness	None	Dissection	ICA	--	None	4	Poststroke residual deficits (mild aphasia)
	F	29	Global aphasia; R hemiparesis	None	Dissection	MCA	Angioplasty	None	4	Poststroke residual deficits (moderate aphasia)

BA: Basilar artery, ICA: Internal carotid artery, L: Left, MCA: Middle cerebral artery, mRS: Modified Rankin score, PCA: Posterior cerebral artery, R: Right

in two, severe constriction in one, and vasospasm in three. In 15 studies, location of stroke was available for 32 total patients: ICA (9%), MCA (53%), PCA (9%), pontine artery (3%), anterior circulation not otherwise specified (3%), and posterior circulation not otherwise specified (22%).

There were four case reports in which these patients were treated with thrombolysis or thrombectomy.[57,58,61,67] Shere and Goyal described a 55-year-old female chronic cannabis user with acute ischemic stroke who developed intracranial hemorrhage (ICH) following tPA administration that resulted in death.[57] Takematsu *et al*. reported on a 33-year-old male with MCA stroke who had no complications following tPA therapy.[61] Viswanathan *et al*. presented on a 31-year-old male chronic cannabis user with acute ischemic stroke who also was without complications following tPA.[67] At the 6-month follow-up, the patient had no residual deficits. Šimůnek *et al*. reported on a 28-year-old male chronic cannabis user treated with both tPA and thrombectomy for ischemic stroke, which resulted in no complications.[58]

Sixteen studies with a total of 39 patients reported complications in nonthrombolysis or thrombectomy treated strokes. Two patients developed cerebral edema and survived. Four patients died (cause unknown). In this cohort, clinical follow-up information was available for 26 patients (median time 6 [range 1–24]), of which 14 had residual deficits and 12 had no deficits.

Alcohol

Two studies included clinical, treatment, or outcomes data related to ischemic stroke in patients with alcohol use [Table 5].[13,20] Ducroquet *et al*. reported on the mechanism of ischemic stroke on 60 patients (female 4 [6.67%], median age 59 [53–67]) with a history of chronic alcohol consumption: arthrosclerosis in 10, cardioembolism in 13, and cryptogenic in 37.[13]

Gattringer *et al*. compared ischemic stroke outcomes in 4215 and 43,207 of patients with a history of acute or chronic alcohol use and those without these factors, respectively.[20] Among alcohol users, 698 patients (17%) received tPA. There were a reported 1095 stroke-related complications in this cohort, which included symptomatic ICH (36 patients, 0.9%), extracerebral bleeding (20, 0.5%),

Table 4: Baseline characteristics, treatment, complications, and outcomes of ischemic stroke in cannabis users.

Author (Year)	Sex	Age (years)	Clinical presentation	Previous medical history	Mechanism of ischemic stroke	Stroke location	Treatment	Stroke-related complications	Last clinical follow-up (months)	Clinical outcome at last follow-up or discharge
Cooles and Michaud (1987)[11]	M	27	Dysarthria	None	--	--	--	--	--	--
	M	28	L gaze deviation	None	--	--	--	--	--	--
Barnes *et al.* (1991)[3]	M	30	Speech disturbance; R hemiplegia	None	Vasospasm	MCA	--	None	--	--
Zachariah (1991)[72]	M	34	Dizziness; L hemiplegia; dysarthria	None	Vasospasm	--	--	None	1	Poststroke residual deficits (hemiparesis)
	M	32	R hemiplegia; dysarthria	None	--	--	--	None	--	--
White *et al.* (2000)[69]	M	15	Headache; unsteady gait	None	--	--	--	--	--	--
Geller *et al.* (2004)[21]	M	16	Headache; R hemiparesis; R hemihypesthesia; dysarthria	None	--	--	--	Suffers cardiopulmonary arrest during hospital course; death before discharge	NA	NA
	M	17	Visual disturbance; gait disturbance; disorientation	None	--	--	--	Death before discharge	NA	NA
	M	15	Headache; ataxia	None	--	Posterior circulation	--	None reported	--	--
Finsterer *et al.* (2004)[17]	M	37	L hemiparesis; L hemihypesthesia, and recurrent double vision	None	--	PCA	--	None reported	--	Poststroke residual deficits (blurred vision)
Mateo (2005)[39]	M	36	Aphasia	None	--	MCA	--	None reported	--	--
	M	36	Aphasia; R hemiparesis	Prior ischemic stroke	--	MCA	--	None reported	--	--
	M	36	Auditory agnosia	Prior ischemic stroke	--	MCA	--	None reported	24	No poststroke residual deficits
Trojak *et al.* (2011)[63]	F	24	Unresponsive	None	--	Anterior circulation	--	None reported	18	No poststroke residual deficits
Singh *et al.* (2012)[59]	M	15	Dysarthria; ataxia	None	--	Posterior circulation	--	None	--	No poststroke residual deficits by discharge
	M	16	Ataxia	None	--	Posterior circulation	--	Death prior to discharge	NA	NA

(Contd...)

Table 4: *(Continued).*

Author (Year)	Sex	Age (years)	Clinical presentation	Previous medical history	Mechanism of ischemic stroke	Stroke location	Treatment	Stroke-related complications	Last clinical follow-up (months)	Clinical outcome at last follow-up or discharge
	M	17	Ataxia	None	--	--	--	Death prior to discharge	NA	NA
	M	22	Dysarthria; ataxia	None	--	Posterior circulation	--	None	--	Poststroke residual deficits (ataxia)
	F	27	Aphasia	None	--	MCA	--	None	--	No poststroke residual deficits by discharge
	F	28	Wallenberg's syndrome	None	--	Posterior circulation	--	None	--	No poststroke residual deficits by discharge
	M	37	Aphasia; R hemiparesis	None	--	MCA	--	None	--	No poststroke residual deficits by discharge
	M	44	Dysarthria; ataxia	None	--	Posterior circulation	--	None	--	Poststroke residual deficits (ataxia)
	F	44	Aphasia; R hemiparesis	None	--	MCA	--	None	--	No poststroke residual deficits by discharge
	M	49	Dysarthria; L hemiparesis	None	--	MCA	--	None	--	No poststroke residual deficits by discharge
	F	52	Dysarthria; L hemiparesis	HTN	--	ICA	--	None	--	No poststroke residual deficits by discharge
	M	50	Dysarthria; ataxia	HTN	--	Posterior circulation	--	None	--	Poststroke residual deficits (ataxia)
	M	56	L hemianopsia; L hemiparesis	None	--	PCA	--	None	--	Poststroke residual deficits (L hemiparesis)
	M	58	Aphasia	None	--	MCA	--	None	--	No poststroke residual deficits by discharge
	M	59	R hemiparesis	HTN, prior cerebral infarct	--	Pontine	--	None	--	No poststroke residual deficits by discharge
	M	61	R hemiparesis	Prior cerebral infarct	--	PCA	--	None	--	Poststroke residual deficits (R hemiparesis)
	M	63	Dysarthria; R hemiparesis	HTN, prior cerebral infarct	--	MCA	--	None	--	--
Freeman *et al.* (2013)[19]	M	26	Dysarthria; aphasia, R hemiparesis	None	Thrombotic	MCA	--	None reported	--	--
	F	19	Dyskinesia; aphasia; R hemiplegia; R hemihypesthesia	None	Embolic	MCA	--	None reported	--	Poststroke residual deficits (R hemiparesis, aphasia)

(Contd...)

Table 4: *(Continued).*

Author (Year)	Sex	Age (years)	Clinical presentation	Previous medical history	Mechanism of ischemic stroke	Stroke location	Treatment	Stroke-related complications	Last clinical follow-up (months)	Clinical outcome at last follow-up or discharge
Bernson-Leung *et al.* (2014)[6]	F	22	Dysarthria; gait disturbance; drowsiness; L hemiparesis; L hemianesthesia	None	Embolic	MCA	--	None reported	--	Poststroke residual deficits (limited ambulation, no use of L arm)
	F	26	L facial hemiparesis; L hemianesthesia; dysfluency	Prior hemorrhagic stroke	--	MCA	--	None reported	--	--
Inal *et al.* (2014)[29]	M	23	R hemiparesis	None	--	MCA	--	Cerebral edema	--	Poststroke residual deficits (no resolution of stroke symptoms)
Oyinloye *et al.* (2014)[50]	M	26	Dysarthria; R hemiparesis	None	--	MCA	--	None reported	--	Poststroke residual deficits (minimal improvement of neurologic deficits)
Takematsu *et al.* (2014)[61]	M	33	R hemiparesis; aphasia	None	--	MCA	tPA	None	--	--
Wolff *et al.* (2015)[70]	--	--	Motor deficit (30), aphasia (90), visual disorders (20)	--	--	--	--	--	3 (n=58)	Mortality (2/58); mRS 0–2 (47/58), mRS>3 (11/58)
Moeller *et al.* (2017)[44]	M	25	L hemiparesis; dysarthria; visual disturbance; L hemianesthesia	None	--	MCA	--	Cerebral edema and hemorrhagic transformation during hospital course	--	Poststroke residual deficits (R arm paresis, paresis of R leg)
Shere and Goyal (2017)[57]	F	55	L hemiparesis	HTN	severe constriction	--	tPA	After tPA, development of new hemorrhage, resulting in loss of brain function; death prior to discharge	NA	NA
Šimůnek *et al.* (2017)[58]	M	28	L-sided homonymous hemianopsia, L-sided hemiparesis, L-sided hemianesthesia	None	--		tPA, thrombectomy	None	--	--
Volpon *et al.* (2017)[68]	F	14	Tonic clonic seizure	None	--	--	--	--	--	--
Faroqui *et al.* (2018)[16]	M	36	R hemiparesis; aphasia	None	Thrombotic	MCA	--	None	--	Poststroke residual deficits (speech, R-sided movement disturbances)

(Contd...)

Table 4: *(Continued).*

Author (Year)	Sex	Age (years)	Clinical presentation	Previous medical history	Mechanism of ischemic stroke	Stroke location	Treatment	Stroke-related complications	Last clinical follow-up (months)	Clinical outcome at last follow-up or discharge
Ugradar *et al.* (2019)[64]	M	21	R visual disturbance	None	--	ICA	--	None	--	No poststroke residual deficits by discharge
Viswanathan *et al.* (2019)[67]	M	31	L hemiparesis; L facial hemiplegia; dysarthria	Prior cerebral infarct	--	--	tPA	None	6	No poststroke residual deficits
Amor *et al.* (2021)[27]	M	32	R hemiplegia; aphasia	None	Vasospasm	ICA	--	None	3	Poststroke residual deficits (hemiplegia)

BA: Basilar artery, ICA: Internal carotid artery, L: Left, MCA: Middle cerebral artery, mRS: modified Rankin score, PCA: Posterior cerebral artery, R: Right, tPA: Tissue plasminogen activator

recurrent stroke (49, 1.2%), progressive stroke (211, 5%), epileptic seizure (45, 1.1%), cardiac decompensation/arrhythmias (222, 5.3%), and infection (483, 11.4%). Mortality before discharge was 1.2% (52/4215). Among nonalcohol users, 8132 patients received tPA. In this cohort, there were 11,092 stroke-related complications, which included symptomatic ICH (630 patients, 1.5%), extracerebral bleeding (152, 0.4%), recurrent stroke (425, 1%), progressive stroke (1736, 4%), epileptic seizure (450, 1%), cardiac decompensation/arrhythmias (2263, 5.2%), and infection (4820, 11.4%). Mortality before discharge was 2.6% (1097/43,207).

Opioids

There were two articles identified that described patients with evidence of opioid use presenting with acute ischemic stroke [Table 6].[26,66] All patients presented with abnormal motor function, and one patient had aphasia. In one patient, the mechanism of stroke was specified to be embolic. In 2 patients (67%), the location of stroke was MCA. No patients underwent thrombolytic therapy or thrombectomy. In two patients, no stroke-related complications, and, at 9-month follow-up for one patient, there were no poststroke residual deficits.

Decongestants

Montalban *et al.* described two male patients, aged 35 and 40, presenting with acute ischemic stroke and recent decongestant use [Table 7].[45] In both patients, speech disturbance and abnormal sensation/motor function were present, and mechanism of stroke was thrombotic. Location of stroke included the MCA in one patient, BA in one patient, and ICA in one patient. No treatment information, stroke-related complications, or clinical follow-up data were available.

DISCUSSION

In this scoping review, we present the clinical presentation, treatment, complication profile, and clinical outcomes related to ischemic stroke in patients with at least recent history of drugs of abuse. Data evaluating the clinical and stroke characteristics, complications, and outcomes in drug users presenting with ischemic stroke are lacking. While the average age of ischemic stroke is 69.6 years with most strokes occurring in the >65 age group, our review found that drug users with ischemic stroke were overall relatively younger, ranging from 28 years to 59 years, depending on the drug of abuse.[14] However, the clinical presentation, etiology of stroke, and location of stroke in this population remain comparable to that of overall patients presenting with ischemic stroke. In drug users overall, embolus, thrombus,

Table 5: Baseline characteristics, treatment, complications, and outcomes of ischemic stroke in alcohol users.

Author (Year)	Number of patients, n	Female	Mean age (SD), years	Clinical presentation	Previous medical history	Mechanism of ischemic stroke	Stroke location	Treatment	Stroke-related complications	Last clinical follow-up (months)	Clinical outcome at last follow-up or discharge
Ducroquet *et al.* (2013)[13]	60	4/60 (6.67%)	59 (53-67)	--	HTN (35/60, 58.3%), diabetes (13/60, 21.67%), heart disease (8/60, 13.3%), prior cerebral infarct (6/60, 10%)	AS (10), cardioembolism (13), unknown (37)	--	--	--	--	--
Gattringer *et al.* (2015)[20]	4215a	619/4215 (15%)	65.8	--	HTN (3410/4215), diabetes (1183/4215), heart disease (466/4215), prior cerebral infarct (886/4215)	--	--	tPA (16.6%)	ICH (0.9%); extracerebral bleeding (0.5%); recurrent stroke (1.2%); progressive stroke (5%); epileptic seizure (1.1%), cardiac decompensation/ arrhythmia (3.5%); myocardial infarction (0.7%); infection (11.4%); death (1.2%)	--	--
	43,207b	22,108/43,207 (51%)	74.8	--	HTN (34,973/43,207), diabetes (11,043/43,207), heart disease (4098/43,207), prior cerebral infarct (9979/43,207)	--	--	tPA (18.9%)	ICH (1.5%); extracerebral bleeding (0.4%); recurrent stroke (1%); progressive stroke (4%); epileptic seizure (1%); cardiac decompensation/ arrhythmia (5.2%); infection (11.4%); myocardial infarction (0.8%); death (2.6%)	--	--

AS: Atherosclerosis, HTN: Hypertension, ICH: Intracerebral hemorrhage, tPA: Tissue plasminogen activator, a-acute alcohol use, b-chronic alcohol use

Table 6: Baseline characteristics, treatment, complications, and outcomes of ischemic stroke in opioid users.

Author (Year)	Sex	Age (years)	Clinical presentation	Previous medical history	Mechanism of ischemic stroke	Stroke location	Treatment	Stroke-related complications	Last clinical follow-up (months)	Clinical outcome at last follow-up or discharge
Vila and Chamorro (1997)[66]	M	34	Dyskinesia	None reported	--	MCA	--	None	9	No poststroke residual deficits
	M	19	L dyskinesia	None reported	Embolic	MCA	--	None	--	--
Hsu *et al.* (2009)[26]	M	33	Aphasia; hemiplegia	None reported	--	--	--	--	--	--

L: Left, MCA: Middle cerebral artery

Table 7: Baseline characteristics, treatment, complications, and outcomes of ischemic stroke in decongestant users.

Author (Year)	Sex	Age (years)	Clinical presentation	Previous medical history	Mechanism of ischemic stroke	Stroke location	Treatment	Stroke-related complications	Last clinical follow-up (months)	Clinical outcome at last follow-up
Montalban *et al.* (1989)[45]	M	35	Dysarthria; R hemiparesis	None	Thrombotic	MCA	--	--	--	--
	M	40	Dysarthria; R hemiparesis	None	Thrombotic	ICA	--	--	--	--

ICA: Internal carotid artery, MCA: Middle cerebral artery, R: Right

and vasospasm were etiologies of stroke, with embolic stroke occurring relatively more. The MCA was found to be the most common location of occlusion in this population followed by the ICA and BA.

However, while thrombolytic therapy and mechanical thrombectomy have revolutionized stroke care, their safety in drugs users is unclear. Risks occur with both thrombolytic therapy and mechanical thrombectomy. ICH and reperfusion injury can occur in up to 6% and 4.4% of patients undergoing tPA and endovascular thrombectomy, respectively.[35,48] Although often without clinical sequelae, cerebral vasospasm can occur in 3.9–23% of patients undergoing thrombectomy.[22] As certain drugs of abuse physiologically alter the neurovasculature, there is theoretical risk that increased complication risk associated with these common stroke treatments in patients with recent history of drug use. However, the available literature remains sparse and cannot adequately guide practice. Below, we include a discussion highlighting evidence-related thrombolytic therapy and thrombectomy in cocaine, amphetamine, cannabis, alcohol, and opioid users.

Thrombolysis and thrombectomy in cocaine users

Chronic cocaine use has been found to cause acute hypertensive episodes as well as cerebral small vessel disease, which are risk factors for intracranial bleeding.[7,62] It is hypothesized that increased development of hemorrhagic transformation can occur following alteplase administration in cocaine users as a result of the pharmacodynamic effects of cocaine or its induction of endothelial dysfunction.[60] Siniscalchi *et al.* proposed that potentiation of sympathetic activity through cocaine-associated inhibition of norepinephrine and dopamine reuptake in sympathetic neurons may explain this pharmacodynamic mechanism.[60] However, in their retrospective study, when Martin-Schild *et al.* compared tPA outcomes between patients with and without evidence of cocaine use (n = 29 and n = 75, respectively), there were no differences in the number of ICH events or mortality, despite the presence of a significantly severe clinical presentation in the cocaine use group.[38] Our pooled analysis of all reported cases of stroke in the setting of cocaine abuse indicates that 3.2% (1/31) of patients experienced hemorrhagic conversion following

IV thrombolysis and 50% (2/4) following thrombectomy. This finding suggests that mechanical thrombectomy in cocaine users is associated with a relatively increased risk of hemorrhagic reperfusion injury, a finding that warrants further investigation with larger sample size.

Cocaine use is also associated with induced vessel wall hyper-reactivity that can enhance the severity of iatrogenic vasospasm in the neurovasculature during mechanical thrombectomy.[42] Biochemical mechanisms including cocaine-induced blockage of monoamine reuptake, increased cytokine activity, and endothelin release have been thought to cause both vessel spasm and subsequent occlusion.[42,62] There are currently no retrospective or controlled studies that have investigated and compared thrombectomy complications and outcomes between patients with and without evidence of cocaine use. In our review, thrombectomy-related vasospasm occurred in 75% of patients (3/4) with a history of cocaine abuse, suggesting that this occurs relatively more often in this population. Although our sample size was small, this finding necessitates further investigation, and more controlled studies with sub-stratification based on severity of stroke and length of cocaine use are needed to establish the safety of current ischemic stroke treatments in these patients.

Thrombolysis and thrombectomy in amphetamine-type stimulant users

Amphetamines, such as MA, are psychostimulants that are associated with causing systemic hypertension and vasculitis, increasing baseline risk of intracranial bleeding compared to nonusers.[18,53] Studies have suggested that chronic MA use can destroy endothelial cells that line the BBB by elevating the production of reactive oxygen species and direct cytotoxic effects.[5] In addition, MA has been reported to weaken vascular wall integrity by fibrinoid necrosis of the tunica intima and media, leading to vessel rupture.[5,32] As such, MA use could potentiate the risk of ICH after thrombolytic therapy. To date, there are no case reports or retrospective studies that detail tPA or TNK use in MA users for ischemic stroke. In our review, there was one MA user treated with heparin without complications, suggesting that heparin may be safe in this population.[36] There are no reports to outline the complication profile and outcomes for the use of thrombolytic therapy in MA users.

Amphetamine use has also been associated with provoking endothelial dysfunction that perpetuates the development of iatrogenic vasospasm, similar to cocaine.[32,56] To date, there are no retrospective or controlled studies comparing complications and outcomes between MA and non-MA users treated with thrombectomy to explore this. More controlled studies with larger sample are needed to further investigate this observation and determine the safety of such therapy on MA users.

Thrombolysis and thrombectomy in cannabis users

Chronic cannabis use can also induce dysfunction of the BBB by provoking transient arterial hypertension and inhibition of thrombin-driven clot formation that can increase risk of intracranial bleeding.[9,70] Cannabis use can also be associated with reversible cerebral vasoconstriction syndrome, which can lead to vasospasm of cerebral arteries.[43] However, the clinical significance of these physiologic changes in response to ischemic stroke treatment remains largely unknown. There are no current controlled studies to investigate outcomes between cannabis and noncannabis users exposed to tPA or thrombectomy for ischemic stroke to assess risk. In our review, there were three cannabis users treated with thrombolysis, two of which suffered no complications and one of which presented with severely elevated blood pressure (256/112) and developed ICH resulting in death.[57,61,67]

Thrombolysis and thrombectomy in alcohol and opioid users

Alcohol has been found to compromise the structural integrity of the neurovasculature through disruption of the tight junctions and promotion of oxidative stress.[8] However, these physiologic changes may be dose dependent. In animal models, low-to-moderate alcohol consumption has been shown to be protective against ischemia/reperfusion (I/R) injury by suppressing inflammation through activation of PPARγ.[73] Heavy alcohol consumption, conversely, can worsen I/R injury by promoting inflammation.[8,73] Similarly, acute opioid administration in low doses before cortical ischemic insult has been found in mice to be neuroprotective by mitigating oxidative stress and inflammation.[15] However, in animal models, chronic opioid use in which tolerance and dependence are present can alter BBB homeostasis through a pro-inflammatory mechanism and ROS-mediated toxicity.[18,53]

Chronic alcohol consumption associated with reduced hepatic function has also been hypothesized to worsen clinical outcome following thrombolytic therapy based on animal model studies.[33] Lemarchand *et al*. found that mice exposed to 10% alcohol for 6 weeks experienced worse ischemic lesions following tPA administration compared to controls and that this effect is dependent on the level of liver impairment.[33] The authors suggested that the clearance of tPA may be delayed in the liver in mice exposed to alcohol, which could result in an increase in tPA passage into the brain parenchyma.

In our review, we identified one study in which Gattringer *et al*. compared IV thrombolysis outcomes in patients with chronic or acute alcohol consumption to those without reported alcohol consumption.[20] Although they found no differences in symptomatic ICH between these two groups,

further studies comparing complication risk and outcome between acute, chronic, and nonalcohol users are needed. Future studies should also further explore the dose-related effects of alcohol consumption and opioid use on ischemic stroke specific therapies and should sub-stratify based on severity of presentation and stroke.

Limitations

We acknowledge that there are a number of limitations in this review. For one, our review was mostly limited to case reports with small sample sizes that did not detail all clinical data, treatment administered, complications, and clinical outcome with follow-up. There is also potential for selection bias with these studies that can compound the small sample sizes. Importantly, we were also unable to sub-stratify based on severity of stroke and presentation, chronic versus acute use of the respective drugs, and the quantitative amount of drug the patient consumed.

CONCLUSION

In this scoping review, we present the clinical presentation, outcomes, and treatment of ischemic stroke in drug users to highlight areas for further research. Data regarding clinical presentation and outcomes of ischemic stroke in drug users were available; however, evidence of the safety and efficacy of thrombolytic and thrombectomy treatment in these patients is severely lacking. The risk of hemorrhagic transformation and vasospasm as a result of these treatment modalities exist, yet the extent to which they are present in drug abusers, particular cocaine and cannabis users, is unknown. Controlled single and multicentered studies with large populations are needed to further examine complication profile and clinical outcomes data following thrombolytic and thrombectomy treatment in users of all drugs of abuse presented in this review.

Declaration of patient consent

Patients' consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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