

2 Important new studies on methamphetamine and health

1. Methamphetamine Associated Heart Failure, a New Epidemic

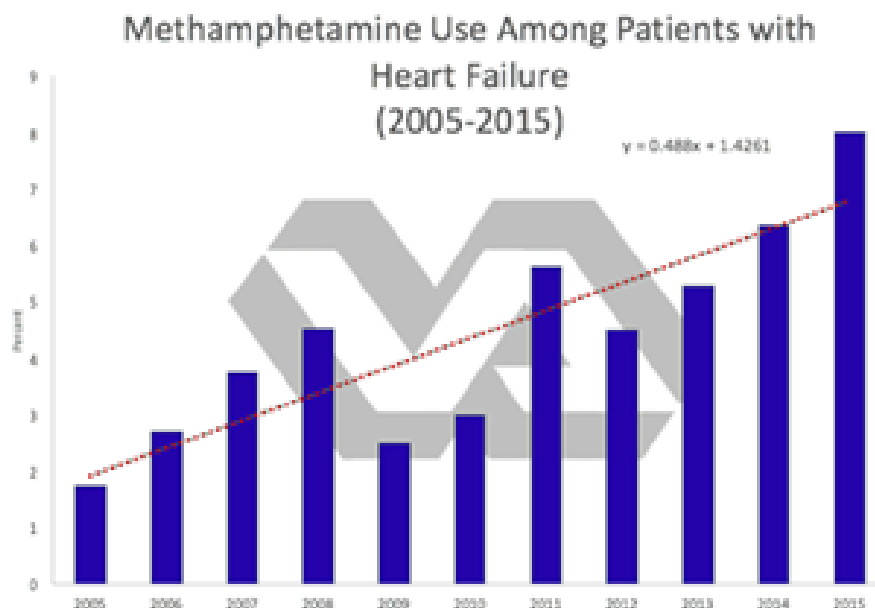
Marin Nishimura, Janet Ma, Isac C Thomas, Sutton Fox, Avinash Toomu, Sean Mojaver, Derek Juang, Alan Maisel

American Heart Association. Circulation. 2017;136:A14066

Methamphetamine is one of the most commonly abused illegal substances in the United States. Heart failure due to Methamphetamine use (MethHF) is a poorly characterized disease entity that appears to be on the rise. Among 9588 patients with diagnosis of heart failure treated at San Diego VA Medical Center in between 2005-2015, 480 were identified to have history of methamphetamine abuse as determined by ICD-9 diagnosis code and/or urine toxicology screen as well as a diagnosis code of heart failure. Demographic, diagnostic, and clinical characteristics of MethHF and heart failure patients without methamphetamine use (HF) were compared. Clinical outcomes of time to emergency room (ER) visit, all-cause readmission, and all-cause mortality were compared using Kaplan-Meier curves.

From 2005-2015, the prevalence of methamphetamine usage among patients with heart failure increased linearly (Figure 1). A preliminary cohort comparison demonstrated MethHF had similar ejection fraction and BNP levels but trends toward increased troponin levels, more atrial fibrillation, and a higher GFR. MethHF patients had a greater risk of ER visits (2.3 per year vs 0.5 per year, $p=0.01$) and a trend towards a greater risk of all-cause hospital readmission (1.3 per year vs 0.6 per year, $p=0.09$).

Heart failure due to methamphetamine use - or MethHF- is increasing in prevalence and appears to be a new phenotype of heart failure. MethHF and HF differ in multiple domains, including healthcare utilization.



2. Stroke and Methamphetamine Use in Young Adults: A Review

Julia M Lappin; Shane Darke; Michael Farrell

J Neurol Neurosurg Psychiatry. 2017;88(12):1079-1091.

Abstract and Introduction

Abstract

Background. Methamphetamine use and stroke are significant public health problems. Strokes among people aged below 45 years are much less common than in older age groups but have significant mortality and morbidity. Methamphetamine is a putative cause of strokes among younger people.

Methods. A review of methamphetamine-related strokes was conducted. Bibliographic databases were searched until February 2017 for articles related to methamphetamine and stroke. Both haemorrhagic and ischaemic strokes were considered.

Results. Of 370 articles screened, 77 were selected for inclusion. There were 81 haemorrhagic and 17 ischaemic strokes reported in case reports and series. Both types were approximately twice as common in males. Route of administration associated with haemorrhagic stroke was typically oral or injecting, but for ischaemic stroke inhalation was most common. Haemorrhagic stroke was associated with vascular abnormalities in a third of cases. One quarter of individuals completely recovered, and a third died following haemorrhagic stroke. One-fifth completely recovered, and one-fifth died following ischaemic stroke.

Conclusions. There is a preponderance of haemorrhagic strokes associated with methamphetamine use in young people, and methamphetamine-related stroke is associated with poor clinical outcomes. Mechanisms of methamphetamine-associated stroke include hypertension, vasculitis, direct vascular toxicity and vasospasm. In a period of rising worldwide methamphetamine use, the incidence of methamphetamine-related stroke will increase, with a consequent increase in the burden of disease contributed by such events.

Introduction

Methamphetamine use is a significant public health problem, particularly in countries around the Pacific rim (North America, East/Southeast Asia and Oceania), with an estimated 35 million stimulant users worldwide, predominantly of methamphetamine.^[1-3] Harmful physical and mental health consequences are common, including cardiovascular and cerebrovascular pathology, psychosis, suicide and premature mortality.^[4-8] The stimulants methamphetamine and amphetamine have been available in various forms since the middle of last century.^[7]

Methamphetamine use has changed over years: in 1950s and 1960s, it was popular as benzedrine, later amphetamine became the preferred form, while most recently there has been a substantial global increase in the availability and use of high potency, crystalline methamphetamine.^[1,3,9] Routes of methamphetamine administration include oral, inhalation (smoking), intranasal and intravenous use.^[7]

Stroke too is a major public health problem, with high mortality rates and high levels of subsequent disability.^[10,11] Between 1990 and 2010, stroke has risen from the fifth to the third leading cause of disability-adjusted life years, with increase of 19%.^[10] Moreover, the incidence of stroke has been rising among younger persons.^[12] While stroke incidence rises with age and is less common in people aged below 45 years, stroke among young people has significant health sequelae and societal costs.^[12]

Stroke in Young People

In all-age stroke populations, ischaemic strokes (cerebral infarction) are more common.^[13] In younger people (<45 years), this remains the case, but a greater proportion are haemorrhagic (eg, 33.5% in those 20–44 years vs 23.1% in those 45–54 years).^[13] Haemorrhagic strokes in those aged 20–44 years are subarachnoid or intracerebral in approximately equal proportion.^[13] In young people, subarachnoid haemorrhages are most frequently due to an underlying cerebral aneurysm or arteriovenous malformation (AVM).^[14] Non-traumatic intracerebral haemorrhage (ICH) is associated with hypertension in 70% of all-age stroke, but in young people it may account for as little as 20%, with a high preponderance of other causes such as AVM, ruptured saccular aneurysm and sympathomimetic drug use.^[15]

Risk factors for ischaemic stroke include dyslipidaemia, smoking and hypertension.^[16,17] As is the case for haemorrhagic stroke causation differs in young people (<45 years), with a higher preponderance of females, recent illicit substance use and use of the contraceptive pill/oral contraceptives than in those even slightly older (45–49 years).^[17]

Substance Use and Stroke in Young People

The prevalence of illicit drug use is highest among younger people.^[9,18,19] There is increased relative risk for both ischaemic and haemorrhagic stroke associated with all drug use^[20] and drug use as a cause of stroke is significantly more common among young people.^[17] Intravenous use of any illicit drug increases the risk of ischaemic stroke through thromboembolic mechanisms.^[21] Stroke risk factors are different among users of illicit substances, with higher rates of smoking and lower rates of hypertension and diabetes compared with those with ischaemic stroke in the absence of substance use.^[21] Alcohol has also been demonstrated to increase risk of stroke.^[17] One class of drugs that has been associated with stroke incidence is the psychostimulants.^[11] Cocaine, in particular, has been associated with a substantially increased risk of haemorrhagic stroke.^[11] Methamphetamine shares pharmacological characteristics and physiological effects in common with cocaine, and both are associated with hypertension and coronary disease.^[5,7,22,23] Methamphetamine, however, has a longer half-life than cocaine,^[7] and there is subsequently a longer exposure to systemic hypertension. Moreover, methamphetamine also substantially increases the risk of stroke.^[24–26] It is important to note that methamphetamine is also strongly associated with the development of ischaemic heart disease and accelerated atherosclerotic coronary artery disease.^[7]

Despite its widespread use and potential clinical significance, however, the features and pathogenesis of methamphetamine-related stroke are poorly understood. This is of particular relevance in a period of large increases in worldwide methamphetamine use, when the incidence of methamphetamine-related stroke, particularly among young people, would be expected to increase in conjunction with use. In the context of increased use of methamphetamine, and thus

of increased stroke risk, the current study aimed to review the literature on methamphetamine-related stroke among young people (defined as <45 years).

Specifically, the study aimed to:

- summarise the features of stroke in young amphetamine users; and
- determine the evidence for the pathogenesis of methamphetamine-related stroke.

References

1. Degenhardt L, Hall W. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. *Lancet* 2012;379:55–70.
2. Degenhardt L, Whiteford HA, Ferrari AJ, *et al.* Global burden of disease attributable to illicit drug use and dependence: findings from the global burden of disease study 2010. *Lancet* 2013;382:1564–74.
3. United Nations Office on Drugs and Crime. World Drug Report 2016. New York: United Nations. 2016.
4. Callaghan RC, Cunningham JK, Verdichevski M, *et al.* All-cause mortality among individuals with disorders related to the use of methamphetamine: a comparative cohort study. *Drug Alcohol Depend* 2012;125:290–4.
5. Darke S, Kaye S, McKetin R, *et al.* Major physical and psychological harms of methamphetamine use. *Drug Alcohol Rev* 2008;27:253–62.
6. Darke S, Torok M, McKetin R, *et al.* Patterns of psychological distress related to regular methamphetamine and opioid use. *Addict Res Theory* 2011;19:121–7.
7. Karch SB. *Karch's Pathology of Drug Abuse*. 4th edition. Boca Raton: CRC Press, 2009.
8. Lappin JM, Roxburgh A, Kaye S, *et al.* Increased prevalence of self-reported psychotic illness predicted by crystal methamphetamine use: evidence from a high-risk population. *Int J Drug Policy* 2016;38:16–20.
9. European Monitoring Centre for Drugs and Drug Addiction. *Exploring methamphetamine trends in Europe EMCDDA Papers*. Luxembourg: Publications Office of the European Union, 2014.
10. Murray CJ, Vos T, Lozano R, *et al.* Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the global burden of disease study 2010. *Lancet* 2012;380:2197–223.
11. Sordo L, Indave BI, Barrio G, *et al.* Cocaine use and risk of stroke: a systematic review. *Drug Alcohol Depend* 2014;142:1–13.
12. Griffiths D, Sturm J. Epidemiology and etiology of young stroke. *Stroke Res Treat* 2011;2011:209370.
13. Kissela BM, Khoury JC, Alwell K, *et al.* Age at stroke: temporal trends in stroke incidence in a large, biracial population. *Neurology* 2012;79:1781–7.
14. Zebian B, Critchley G. Spontaneous intracranial haemorrhage. *Surgery* 2012;30:136–41.
15. Toffol GJ, Biller J, Adams HP. Nontraumatic intracerebral hemorrhage in young adults. *Arch Neurol* 1987;44:483–5.
16. Phillips MC, Leyden JM, Chong WK, *et al.* Ischaemic stroke among young people aged 15 to 50 years in Adelaide, South Australia. *Med J Aust* 2011;195:610–4.
17. Putaala J, Haapaniemi E, Kaste M, *et al.* How does number of risk factors affect prognosis in young patients with ischemic stroke? *Stroke* 2012;43:356–61.

18. Center for Behavioral Health Statistics and Quality. *Behavioral health trends in the United States: results from the 2014 National Survey on Drug Use and Health*. Rockville: US Department of Health and Human Services, 2015.
19. Lader D. *Drug Misuse: findings from the 2015/16 crime survey for England and Wales*. Second edition. London: Home Office, 2016.
20. 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.
21. 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.
22. Neeki MM, Kulczycki M, Toy J, *et al*. Frequency of Methamphetamine Use as a Major contributor toward the severity of Cardiomyopathy in adults ≤ 50 Years. *Am J Cardiol* 2016;118:585–9.
23. V oskoboinik A, Ihle JF, Bloom JE, *et al*. Methamphetamine-associated cardiomyopathy: patterns and predictors of recovery. *Intern Med J* 2016;46:723–7.
24. Petitti DB, Sidney S, Quesenberry C, *et al*. Stroke and cocaine or amphetamine use. *Epidemiology* 1998;9:596–600–600.
25. 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.
26. Huang MC, Yang SY, Lin SK, *et al*. Risk of Cardiovascular Diseases and Stroke events in Methamphetamine Users: a 10-Year Follow-Up study. *J Clin Psychiatry* 2016;77:1396–403