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Different drugs, different sides: injection use of opioids alone, and not stimulants alone, predisposes to right-sided endocarditis

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ABSTRACT

Objectives Many studies suggest that infective endocarditis (IE) in people who inject drugs is predominantly right sided, while other studies suggest left sided disease; few have differentiated by class of drug used. We hypothesised that based on differing physiological mechanisms, opioids but not stimulants would be associated with right sided IE.

Methods A retrospective case series of 290 adult (age ≥18) patients with self-reported recent injection drug use, admitted for a first episode of IE to one of three hospitals in London Ontario between April 2007 and March 2018, stratified patients by drug class used (opioid, stimulant or both), and by site of endocarditis. Other outcomes captured included demographics, causative organisms, cardiac and non-cardiac complications, referral to addiction services, medical versus surgical management, and survival.

Results Of those who injected only opioids, 47/71 (69%) developed right-sided IE, 17/71 (25%) developed left-sided IE and 4/71 (6%) had bilateral IE. Of those who injected only stimulants, 11/24 (46%) developed right-sided IE, 11/24 (46%) developed left-sided IE and 2/24 (8%) had bilateral IE. Relative to opioid-only users, stimulant-only users were 1.75 (95% CI 1.05 to 2.93; p=0.031) times more likely to have a left or bilateral IE versus right IE.

Conclusions While injection use of opioids is associated with a strong predisposition to right-sided IE, stimulants differ in producing a balanced ratio of right and left-sided disease. As the epidemic of crystal methamphetamine injection continues unabated, the rate of left-sided disease, with its attendant higher morbidity and mortality, may also grow.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It is known that people who inject drugs are at high risk of infective endocarditis (IE), that injection of hydromorphone increases the risk of IE due to injection drug use, and that there are current international epidemics of both opioid and methamphetamine misuse.

WHAT THIS STUDY ADDS

⇒ IE associated with injection drug use has largely been assumed in North America to be predominantly right sided, though some studies suggest left-sided disease predominates; overall, the majority of the literature on the association between injection drug use and IE considers drug use as a single homogeneous clinical entity. This study shows that opioid and stimulant injection must be considered separately, showing that injection use of opioids is associated with a strong predisposition to right-sided IE, stimulants differ in producing a balanced ratio of right-sided and left-sided disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This should change our understanding of injection drug use associated endocarditis, adding nuance based on the substances individual patients inject. There should be increased suspicion of left-sided endocarditis in people who inject stimulants. Given left-sided endocarditis's attendant risks of stroke, ischaemic limb and other embolic complications, as well as increased reliance on surgical management and increased risk of all-cause mortality, we hope that this result might also help to motivate dedication of greater attention and funds to development of multimodal harm reduction strategies and addiction treatments for stimulant use.

INTRODUCTION

Infective endocarditis (IE) has long been known to complicate injection drug use. Since a seminal case series in 1949, cataloguing IE in 11 patients using 'main line' opium,[1] the injection of opioids has been central to our understanding of injection drug-associated IE (IDaIE). As the opioid epidemic has accelerated in recent decades, a parallel rise in IDaIE has been clearly apparent.[2 3] This is associated with significant mortality—high-quality models suggest that population-level mortality attributable to IDaIE among people who inject drugs (PWID) approaches 20%, and between 2020 and 2030 approximately 257 800 people are expected to die from IDaIE

in the USA alone.[4] IE among PWID has come to be seen as predominantly right sided, affecting predominantly the tricuspid valve (the pulmonic valve is seldom affected in isolation).[5 6] This stands in contrast to IE in the general population, which is generally left-sided (approximately 85% of cases), affecting the aortic and mitral valves in roughly equal proportion.[7] While the majority of current literature finds a strong association between right-sided IE and injection drug use, this has not always been the case. A number of older cohort studies prior to the opioid epidemic, when cocaine was the dominant drug injected, showed a predominance of left-sided disease associated with injection drug use.[8] Similarly, in a very large recent cohort study in primarily European patients, the majority of IE in PWID was left sided.[9] In none of these studies was the association between particular drugs injected and site of disease explored.

Explanations of the general predominance of right-sided IE in PWID have frequently appealed to factors such as mechanical particle bombardment of the tricuspid valve endothelium and immunological suppression by malnutrition and coinfection, factors present regardless of the drug injected.[10] Certain injected opioids, however, can have direct, dose related, clinically significant immunosuppressive effects.[11] Moreover, some controlled-release prescription opioids prepared for injection have been shown to support growth of *Staphylococcus aureus*.[12] Injection of this preparation can therefore directly lead to *S. aureus* bacteraemia and to endocarditis, an association supported by population-level data.[13] Furthermore, the first-pass action of opioids directly on cardiac endothelia, which contain mu-opioid receptors, is specific to injected opioids.[14] This effect, strongest at the point of least dilution, that is, the tricuspid valve, has been hypothesised to include disruption of endothelial tight junctions via toll-like receptor 2, promoting bacterial translocation.[15] Bacteria (especially *S. aureus*) may then be better able to adhere to affected tissues.[16] Taken together, these factors appear to contribute to opioids in particular predisposing to right-sided endocarditis.

Injection use of stimulants continues to rise across North America in a 'methamphetamine epidemic' paralleling the opioid epidemic.[17] Factors that at baseline increase the likelihood of left-sided IE compared with right include greater turbulence of flow, oxygenation of blood, and prevalence of pre-existing valvular abnormalities (eg, bicuspid aortic valve, mitral prolapse, degenerative valvular heart disease).[18] There is reason to suspect that stimulants (eg, cocaine and methamphetamine) predispose to left-sided IE by exacerbating the factors which predispose the left side of the heart to IE in non-PWID: increasing cardiac output, turbulence and pressures.[19] If injection use of stimulants does predispose to left-side predominant IE, this would be highly concerning. Left-sided IE accrues higher mortality than right-sided IE, and is associated with high-morbidity embolic phenomena including stroke, while right-sided IE, though frequently complicated by septic pulmonary emboli, is less associated with overall morbidity and mortality, and may (sometimes) be treated with shorter courses of antimicrobials.[20]

We studied a large cohort of people with IE and self-reported injection drug use, including what we believe to be the largest extant data set of people who used exclusively one class of injection drugs (stimulant or opioid), as established by self-report and objective correlation. We hypothesised that people who injected only opioids who developed IE would show the expected right-sided predominance, and would be less likely to develop left-sided or bilateral IE than those who injected only stimulants.

METHODS

Study design

This retrospective cohort study was conducted across all three acute care hospitals in London, Ontario, Canada (population 511 000), from 1 April 2007 to 31 March 2018. Data analysis occurred from September to December 2020. Informed consent from study participants was waived for this retrospective collection of deidentified data. Patients and the public were not involved in the creation of this study, its conduct or dissemination planning. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies.[21]

Patient identification and data set design

The study population was generated by extracting from hospital medical records all inpatient stays including a code for IE from the International Classification of Diseases, Ninth Revision, Clinical Modification or International Statistical Classification of Diseases, 10th Revision, Clinical Modification (ICD-9 CM) or International Statistical Classification of Diseases, 10th Revision, Clinical Modification (ICD-10) among their discharge diagnoses; this approach has been previously validated.[22] The electronic patient care database in London, an integrated medical record complete with bloodwork, diagnostic imaging, microbiology and clinical notes, allowed comprehensive review and long-term follow-up data. Medical records were reviewed by two infectious diseases physicians (ES and MS) with standardised extraction of data to an anonymised data set. We *a priori* restricted cases to first episode, native valve IE, as prosthetic valves and sites of previous IE are higher risk for recurrent same-valve IE, potentially confounding the effect of drug class.[18]

Measures

Demographic information collected for each patient included age, sex and homelessness. Microbiological data captured included initial diagnostic blood culture results as well as operative cultures when available. Variables captured regarding injection drug use included self-reported substances used within 3 months before admission, urine toxicology screening results, opioid

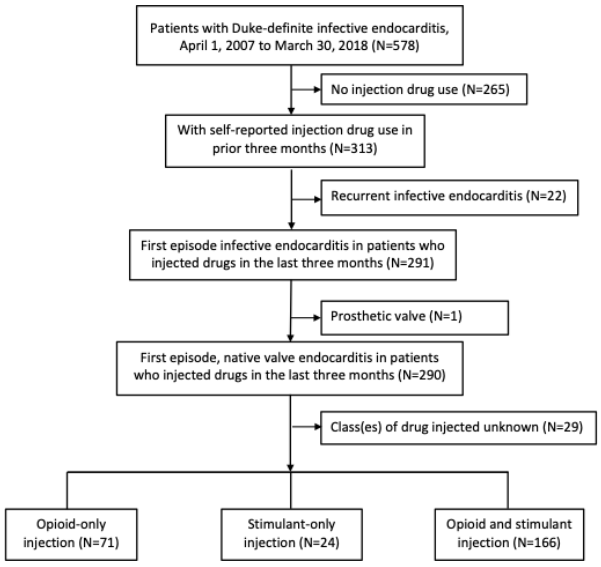

Figure 1 STROBE analysis. STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

substitution therapy at admission and referral to addiction services. Site of involvement as well as cardiac, vascular and infective complications were captured, as were medical and surgical treatment.

Patients were categorised as injecting exclusively opioids, exclusively stimulants or mixed injection use, based on self-reported drug use within 3 months of presentation, as reported within clinical documentation, and informed by drug screening (available in 66% of cases). If urine drug screening demonstrated substances that the patient denied using, the urine drug screen was used to define drugs used. Opioids included hydromorphone (controlled and immediate release), morphine, fentanyl, heroin and oxycodone. Stimulants included methamphetamine, cocaine, bupropion and methylphenidate. Reported use of methadone or buprenorphine orally for opioid substitution therapy for previous opioid use was not categorised as opioid use for the purpose of analysis, as these drugs were not generally injected.

Site of endocardial involvement was determined by review of echocardiography (transthoracic or transoesophageal); valvular involvement was unknown in cases where definite modified Duke criteria were met without clear visualisation of valvular vegetation. Right-sided IE was defined as infection involving only right heart structures (pulmonic and tricuspid valves, right atrium and ventricle), left-sided IE as infection involving only left heart structures (aortic and mitral valves, left atrium and ventricle) and bilateral infection as infection simultaneously involving both right and left structures.

Statistical analysis

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean±SD. Univariable modified Poisson regressions were used to compare the relative risk of side of left or bilateral IE (relative to right-sided IE) among stimulant and opioid users. In a sensitivity analysis, the analysis was repeated after excluding patients with bilateral IE, comparing pure left-sided to pure right-sided IE. All statistical analyses were completed using R V.3.6.3 and the geepack package.

RESULTS

Following review to ensure definite IE by modified Duke criteria, the cohort initially included 578 individuals.[23] Of these, individuals with self-reported active injection drug use within 3 months of admission numbered 313; this cohort was previously reported in a study of blood stream infections in PWID with IE.[24] Censoring to limit to first episodes of IE left 291 cases. Removal of the single patient with a pre-existing prosthetic valve led to a final cohort of 290 cases (figure 1).

Of the 290 cases of first episode, native-valve, modified Duke criteria definite IE occurring in PWID included in our analysis, the majority occurred in people who injected both opioids and stimulants (166, 57%), while 29/290 (10%) did not have documentation of the substances they injected. Our cohort included 71 people who injected only opioids and 24 people who injected only stimulants. See table 1 for the descriptive characterisation of all patients, classified by drug(s) used, including demographics, clinical characteristics, endocarditis sites and microbiological breakdown. No clinically significant differences in baseline characteristics were noted between groups.

Patients who injected opioids alone showed the hypothesised right-sided predominance of disease (47/71 (66%) right sided, 17/71 (25%) left sided, 4/71 (6%) bilateral and 3/71 (4%) site unknown). Patients who injected only stimulants did not show a right-sided or left-sided predominance (11/24 (44%) right sided, 11/24 (44%) left sided, 2/24 (8%) bilateral, 0/24 (0%) site unknown). Patients known to inject both drug classes showed a right-sided predominance similar to opioid-only users (114/166 (69%) right sided, 35/166 (21%) left sided, 12/166 (7%) bilateral and 5/166 (3%) site unknown).

Modified Poisson regression showed that, compared with opioid-only users, stimulant-only users were 1.75 (95% CI 1.05 to 2.93; p=0.031) times more likely to have a left or bilateral IE, as opposed to a right IE. The sensitivity analysis excluding bilateral IE showed the robustness of this result, with stimulant-only users 1.88 (95% CI 1.05 to 3.37; p=0.034) times more likely to have left-sided IE, when compared with opioid-only users (table 2).

DISCUSSION

The majority of the literature on the association between injection drug use and IE considers drug use as a single homogeneous clinical entity. However, as detailed in the Introduction section, multiple physiological and microstructural factors led us to expect that opioid and stimulant injection might be associated with different clinical presentations of IE. Certainly, the

Table 1 Demographic and clinical characteristics of entire cohort

		Stimulant use only (n=24) n (%) or mean (SD)	Opioid use only (n=71) n (%) or mean (SD)	Both stimulant and opioid use (n=166) n (%) or mean (SD)	All injection drug use (n=290) n (%) or mean (SD)
Age at admission	Mean (SD)	38.2 (10.9)	37.1 (9.8)	33.7 (9.0)	35.1 (9.8)
Sex	Female	12 (50)	34 (48)	90 (54)	143 (49)
	Male	12 (50)	37 (52)	76 (46)	147 (51)
HIV status	Negative	17 (71)	53 (75)	117 (70)	207 (71)
	Positive	1 (4.2)	8 (11)	20 (12)	29 (10)
	Unknown	6 (25)	10 (14)	29 (17)	54 (19)
Hepatitis C status	Negative	5 (21)	17 (24)	24 (14)	54 (19)
	Positive	16 (67)	48 (68)	128 (77)	208 (72)
	Unknown	3 (12)	6 (8.5)	14 (8.4)	28 (9.7)
Homeless	No	20 (83)	64 (90)	132 (80)	241 (83)
	Yes	4 (17)	7 (9.9)	34 (20)	49 (17)
Site of IE	Right side	11 (46)	47 (66)	114 (69)	180 (62)
	Left side	11 (46)	17 (24)	35 (21)	79 (27)
	Bilateral	2 (8.3)	4 (5.6)	12 (7.2)	22 (7.6)
	Unknown*	0 (0)	3 (4.2)	5 (3.0)	9 (3.1)
Vegetation valve or site†	Aortic	9 (38)	16 (23)	13 (7.8)	49 (17)
	Mitral	5 (21)	7 (9.9)	35 (21)	60 (21)
	Tricuspid	12 (50)	50 (70)	123 (74)	198 (68)
	Pulmonic	0 (0)	2 (2.8)	2 (1.2)	4 (1.4)
	Non-valvular‡	0 (0)	0 (0)	1 (0.6)	2 (0.7)
	Unknown*	0 (0)	3 (4.2)	5 (3.0)	9 (3.1)
Congenital heart disease§	Yes	0 (0)	0 (0)	1 (0.6)	1 (0.3)
Other valve disease¶	Yes	1 (4.2)	0 (0)	2 (1.2)	4 (1.4)
Echocardiogram performed	Both TTE** and TEE¶	14 (58)	38 (54)	73 (44)	136 (47)
	TTE** only	10 (42)	32 (45)	93 (56)	152 (52)
	None	0 (0)	1 (1.4)	0 (0)	2 (0.7)
Cardiac complications†	Myocardial abscess	1 (4.2)	4 (5.6)	7 (4.2)	14 (4.8)
	Aortic root abscess	1 (4.2)	3 (4.2)	4 (2.4)	10 (3.4)
	Heart failure	4 (17)	15 (21)	21 (13)	47 (16)
	Conduction delay	3 (12)	1 (1.4)	1 (0.6)	6 (2.1)
Vascular complications†	Ischaemic stroke	5 (21)	10 (14)	21 (13)	46 (16)
	Intracerebral haemorrhage	2 (8.3)	6 (8.5)	9 (5.4)	24 (8.3)
	Mycotic aneurysm	1 (4.2)	3 (4.2)	5 (3.0)	13 (4.5)
	Septic pulmonary emboli	10 (42)	44 (62)	110 (66)	177 (61)
	Hepatic infarct	0 (0)	2 (2.8)	0 (0)	4 (1.4)
	Mesenteric ischaemia	0 (0)	1 (1.4)	0 (0)	2 (0.7)
	Renal infarct	0 (0)	4 (5.6)	0 (0)	14 (4.8)
	Limb ischaemia	0 (0)	0 (0)	0 (0)	2 (0.7)
Invasive infection†	CNS infection††	3 (12)	6 (8.5)	14 (8.4)	29 (10)
	Septic arthritis	2 (8.3)	7 (9.9)	21 (13)	32 (11)
	Osteomyelitis	2 (8.3)	5 (7.0)	15 (9.0)	25 (8.6)

Continued

Table 1 Continued

		Stimulant use only (n=24) n (%) or mean (SD)	Opioid use only (n=71) n (%) or mean (SD)	Both stimulant and opioid use (n=166) n (%) or mean (SD)	All injection drug use (n=290) n (%) or mean (SD)
Secondary bacteraemia‡‡	Yes	1 (4.2)	22 (31)	36 (22)	58 (20)
Antimicrobial treatment	Wholly inpatient, wholly IV	11 (46)	41 (58)	94 (56)	162 (56)
	Wholly inpatient, part oral	0 (0)	7 (9.9)	18 (11)	26 (9.0)
	Part outpatient, wholly IV	11 (46)	19 (27)	31 (19)	72 (25)
	Part outpatient, part IM	0 (0)	0 (0)	2 (1.2)	2 (0.7)
	Part outpatient, part oral	2 (8.3)	4 (5.6)	21 (13)	28 (9.7)
Surgical treatment†	Any surgical intervention	6 (25)	16 (23)	17 (10)	49 (17)
	Device insertion or removal	1 (4.2)	4 (5.6)	5 (3.0)	5 (1.7)
	Valve repair	5 (21)	9 (13)	12 (7.2)	32 (11)
	Valve replacement, any	3 (12)	11 (15)	4 (2.4)	25 (8.6)
	Valve replacement, biologic	1 (4.2)	8 (11)	4 (2.4)	17 (5.8)
	Valve replacement, mechanical	2 (8.3)	3 (4.2)	0 (0.0)	9 (3.1)
	Valve repair and replacement	2 (8.3)	4 (5.6)	1 (0.6)	10 (3.4)
Length of stay	Mean days (SD)	21.5 (18.1)	32.4 (23.8)	31.7 (23.9)	29.7 (23.1)
Left against medical advice	Yes	4 (17)	10 (14)	46 (28)	62 (21)
Opiate used§§	Hydromorphone IR¶¶	0 (0)	51 ()	120 ()	171 (59***)
	Hydromorphone CR$^{\chi}$	0 (0)	21 ()	32	53 (18***)
	Morphine	0 (0)	11 (15)	35 (21)	46 (16***)
	Fentanyl	0 (0)	5 (7.0)	7 (4.2)	12 (4.1***)
	Heroin	0 (0)	3 (4.2)	11 (6.6)	14 (4.8***)
	Oxycodone	0 (0)	14 (20)	22 (13)	36 (12***)
	Oxycodone-acetaminophen	0 (0)	4 (5.6)	5 (3.0)	9 (3.1***)
Stimulant used§§	Methamphetamine	18 (75)	0 (0)	131 (79)	149 (51$^{\bullet}$)
	Cocaine	10 (42)	0 (0)	68 (41)	78 (27***)
	Crack	4 (17)	0 (0)	14 (8.4)	28 (9.7***)
	Bupropion	1 (4.2)	0 (0)	1 (0.6)	2 (0.7***)
	Methylphenidate	3 (12)	0 (0)	18 (11)	21 (7.2***)
Addictions counselling referral	Yes	6 (25)	29 (41)	66 (40)	103 (56)
Opioid substitution therapy†††	Yes	7 (29)	11 (15)	27 (16)	48 (17)
Death	No	18 (75)	49 (69)	127 (77)	209 (72)
	Yes, during this episode	5 (21)	9 (13)	18 (11)	43 (15)
	Yes, during full follow-up period	6 (25)	22 (31)	39 (23)	81 (28)
Microbiology†	Staphylococcus aureus	18 (75)	58 (82)	151 (91)	245 (84)
	MSSA	15 (62)	43 (61)	113 (68)	184 (63)
	MRSA	3 (12)	15 (21)	38 (23)	61 (21)
	Viridans-group strep	3 (12)	2 (2.8)	10 (6.0)	19 (6.6)
	Non-viridans strep	1 (4.2)	3 (4.2)	5 (3.0)	12 (4.1)
	Enterococci (all *Enterococcus faecalis*)	3 (12)	4 (5.6)	5 (3.0)	17 (5.9)

Continued

Table 1 Continued

		Stimulant use only (n=24) n (%) or mean (SD)	Opioid use only (n=71) n (%) or mean (SD)	Both stimulant and opioid use (n=166) n (%) or mean (SD)	All injection drug use (n=290) n (%) or mean (SD)
	Enterobacterales	1 (4.2)	2 (2.8)	0 (0)	5 (1.7)
	Pseudomonas or acinetobacter	0 (0)	0 (0)	4 (2.4)	4 (1.4)
	Bartonella henselae	0 (0)	1 (1.4)	1 (0.6)	2 (0.7)
	Burkholderia cepacia	0 (0)	1 (1.4)	0 (0)	1 (0.3)
	Actinomyces odontolyticus	1 (4.2)	0 (0)	0 (0)	1 (0.3)
	Candida albicans	0 (0)	1 (1.4)	1 (0.6)	2 (0.7)
	Polymicrobial	3 (12)	5 (7.0)	14 (8.4)	22 (7.6)
	Culture negative	0 (0)	2 (2.8)	4 (2.4)	6 (2.1)

*Definite endocarditis by modified Duke criteria with no evidence of vegetation on echocardiogram.
†Sum to more than 100% because the categories are not mutually exclusive.
‡Includes atrial and right ventricular vegetations.
§Single included patient with congenital heart disease had coarctation of the aorta, without prosthesis.
¶All patients with underlying valvular disease had bicuspid aortic valves. The patient with coarctation also had bicuspid valve and is included in this count. We note that the patient who injected only stimulants and had a bicuspid aortic valve was diagnosed with mitral valve endocarditis.
**Transthoracic echocardiogram $^{\pi}$ transoesophageal echocardiogram.
††CNS infection, including meningitis, brain abscess, epidural abscess or paraspinal abscess; septic emboli leading to stroke are captured separately as 'ischaemic stroke' above.
‡‡As defined in Tan *et al*[24] identification of a microorganism in blood culture, not secondary to an infection at another body site, different from that grown on index blood cultures at the time of infective endocarditis diagnosis; obtained at least 48 hours after index blood cultures and while the patient was receiving parenteral antimicrobials; not associated with a new vegetation; presumed to be due to direct inoculation.
§§Use within 3 months of admission.
¶¶Hydromorphone immediate release, most commonly sold by brand name dilaudid$^{\chi}$hydromorphone controlled release, most commonly sold by brand name Hydromorph Contin.
***Percentages are of known use among all patients; denominator includes 29 patients with unknown substance use.
†††Methadone, suboxone, naloxone.
CNS, central nervous system; CRχ, continuous-release; IM, intramuscular; IR, immediate-release; IV, intravenous; MRSA, Methicillin-resistant *Staphylococcus aureus*; MSSA, Methicillin sensitive *Staphylococcus aureus*.

present North American literature, in which injection drug use is closely correlated with right-sided IE, differs from data obtained prior to the opioid epidemic and from present European data in ways which demand explanation. Here, we have shown that the strong predisposition to right-sided IE is best understood as specifically related to injection of opioids, while injection of stimulants differs in predisposing to significantly more left-sided IE, leading to a balanced proportion of left-sided and right-sided disease in those within our cohort using only stimulants. The opioid epidemic has been a phenomenon primarily seen in the USA and Canada, with Europe being much less affected.[25] The presence of relatively more stimulant users, especially users of cocaine, could account for the difference in predominant site of IE found in the early studies from North America cited in the Introduction (which predate the opioid epidemic), as well as Pericás *et al*[9], which primarily drew from a European catchment, where stimulant use in general outpaces opioid use and couse in injection is common.[25] The single cohort study which is most frequently cited to support cocaine leading to left-side predominant IE, Chambers *et al*[8], has significant weaknesses: it was small, with only 23 episodes of IE captured; many patients had localisation of IE by clinical assessment only, with echocardiography localising 'abnormality' on only 13 patients; and cocaine use was significantly confounded by heroin use, with the majority of cocaine used in combination with heroin (a 'speedball'). Similarly, while Pericás *et al* suggested a left-side predominance to IE among PWID generally, many variables of great import were not

Table 2 Comparing side of IE and drug use

	Right IE	Left IE	IE both sides	Total
Opioid Only	47 (69%)	17 (25%)	4 (6%)	68
Stimulant Only	11 (46%)	11 (46%)	2 (8%)	24
Total	58	28	6	92

Relative to opioid-only users, stimulant-only users were 1.75 (95% CI 1.05 to 2.93; p=0.031) times as likely to have a left or bilateral IE, as opposed to a right IE.
Relative to opioid-only users, stimulant-only users were 1.88 (95% CI 1.05 to 3.37; p=0.034) times as likely to have a left IE, as opposed to a right IE.
IE, infective endocarditis.

reported, including what drugs were used and indeed how injection drug use was attributed to patients.[9]

This is the largest cohort study to date of modified Duke-definite IDUaIE including detailed chart review capturing both drugs injected and sites of valvular involvement. A smaller study from Jain *et al*, involving patients who injected heroin, specifically noted predominance of right-sided disease in those who used 'any heroin' vs those who used primarily stimulants.[26] However, that study had noteworthy weaknesses: patients with a history of previous IE were not excluded, such that previous valvular damage may have impacted the findings; prescription opioid injection was not documented; and 39% of heroin-only users and 50% of stimulant-only users did not have the site of involvement identified, limiting the ability to identify trends in localisation in the smaller number of patients who used these substances in isolation. In this study, we drew from a baseline population with a very high rate of injection-associated IE—313 of 578 cases of definite IE between 2007 and 2018 were in PWID. This high rate has not gone unremarked on, leading as it did to declaration of a public health emergency in London, Ontario in 2016.[27] While clearly higher than seen in many previous registries, many North American centres have similarly noted recent extreme increases in the rate of IDUaIE.[28–31] In this paper, we limited the analysed cohort to only first episodes of IE; drug use was documented and captured for the vast majority of patients (90%); and 99.6% underwent transthoracic and/or transoesophageal echocardiography to clarify the site of involvement. Because of these differentiating strengths, we show here for the first time a statistically significant trend towards more left-sided IE associated with stimulant use.

The great strength of our study is the incorporation of history of particular substances used, which was allowed by our local integrated electronic health record and local medical personnel who took careful social histories on admission to hospital. Where possible, these data were also correlated with urine toxicology, available in approximately two-thirds of cases. There are limitations to these methods, as they rely on retrospective findings and, crucially, on patient report, which relies both on human memory and on the self-disclosure of patients who have many reasons not to be forthcoming about stigmatised activities. However, there does not seem to be any reason that this limitation should undermine our conclusion, as the different substances are, to the limits of our ability to discern, approximately equally stigmatised. This is also by necessity a cohort study and is retrospective in design. A study of a larger prospective cohort, questioned and tested regularly regarding their injection use including characterisation of substances used, followed until development of a first episode of IE, would clearly be superior—yet would be highly challenging to conduct, due not least to the difficulties in long term study retention in this population.

A majority of our patients (166, 57%) are known to have used both stimulants and opioids. This is consistent with previous studies which have demonstrated that methamphetamine use has been surging among opioid users, with the rate of use of both together doubling between 2011 and 2017.[32] Methamphetamines are less expensive than opioids and are accessible substitutes for opioid users when opioids are not available.[32] Mortality directly associated with this co-use has been clearly demonstrated in national cohort overdose data.[33] In many patients, opioid use is the dominant phenomenon, with methamphetamine use occurring opportunistically or when opioids are harder to obtain. Moreover, as detailed above, injection of opioids may induce changes in the valvular endothelium, predisposing to right-sided IE even when stimulants are also used. This may explain the right-sided predilection of IE in those who use both classes, which appears similar to that in opioid-only users.

While analysis of underlying microbiology was not an objective of this study, we note that on qualitative review the microbiology of the different groups appears well matched, with a predominance in all classes of *Staphylococcus aureus* infections and only isolated instances of fungal infections. We have previously demonstrated that fungal IE is more common in recurrent IE than in initial episodes, explaining the low incidence of fungal IE in this cohort restricted to first episode IE.[34]

One limitation of our study is that while patients were stratified by use of stimulant or opioid drugs, allowing analysis of class effects, the majority of individuals who used only a single class nonetheless used multiple members of that class, for example, opioid users variously injecting hydromorphone, fentanyl, and heroin, and stimulant users injecting methamphetamine and cocaine. Thus, our analysis is limited to class effects alone and cannot comment on specific drug effects. In particular, long-acting hydromorphone has been shown to increase the risk of IE to a greater extent than other opioids, but in this study the effect of that medication on especially right-sided IE is not individually discernible.[13] A factor analysis to decompose the effects of individual agents including long-acting hydromorphone remains a target for future study.

The findings of this study should raise significant public health concern. Opioids have been devastating to our healthcare systems, including through an increasing burden of IE. A mitigating factor in the resultant morbidity and mortality has been that, as we have shown, opioids lead to primarily right-sided IE, which leads to fewer catastrophic outcomes than does left-sided IE. However, epidemic drug use continues across North America, and public health measures to control the opioid epidemic may have unintended consequences. As measures to reduce the availability of opioids for injection use progress, it is likely that more users will turn to the less-expensive, highly available methamphetamine, as we have seen occur opportunistically within our region, and a subsequent rise in left-sided IE can be anticipated to follow.[35] Left-sided IE increases patients' risks of stroke, ischaemic limb and other embolic

complications, as well as leading to increased reliance on surgical management and increased risk of all-cause mortality.[18] High mortality associated with IDUaIE was noted in this study, with 15% of subjects dying from the initial episode of IE and 28% total mortality captured during the follow-up period (see table 1). While tragic, this is not unexpected. The high mortality associated with IDUaIE has been previously documented, including a strong association with mortality attendant on left-sided or bilateral IE.[36] Indeed, the population-level attributable fraction of 10-year mortality from IE among all PWID was recently estimated to be 20%.[4] One protective factor in previous analysis was undergoing surgery, necessarily implying having been accepted by a surgeon for intervention.[36] However, many patients with IDUaIE are deemed poor surgical candidates for reasons including high risks of lost to follow-up with continued injection drug use leading to high rates of reinfection leading in turn to reoperation or death.[37] Similarly, most patients with IDUaIE are young, with guideline recommendation for mechanical valve replacement with its attendant need for long-term vitamin K antagonist therapy and therefore close monitoring.[38] This leads to challenges in follow-up, raising the risks of poor outcomes. Many PWID with left-sided IE do suffer poor outcomes post surgery, while in turn some who might have had good outcomes were they offered surgery may be denied that chance due to poor odds of abstinence and survival free from reinfection.[39] Shifting of those odds is therefore crucial. While good addictions service involvement can help mitigate risk, even at our centre only 56% of patients with IDUaIE were referred, a clear target for process improvement. Certainly, evidence-based measures to treat opioid use disorder, including but not limited to pharmacological approaches using substitution and partial-agonist therapies (eg, methadone and buprenorphine), require greater uptake. Unfortunately, there is currently limited evidence supporting any pharmacological therapy for methamphetamine or cocaine use disorders, although some agents, including naltrexone, bupropion and stimulant agonists, show promise as directions for future research.[40 41] Further work is called for in the development of multimodal harm reduction strategies and addiction treatments for stimulant use.

CONCLUSION

The predisposition to IE due to injection drug use is not a homogeneous process, but rather can and should be considered stratified by drug class used. While opioids alone are associated with a strong predisposition to right-sided IE, stimulants differ in producing a balanced ratio of right and left-sided disease. The rate of left-sided IE, with its higher incidence of systemic complications and mortality, may increase should the epidemic of crystal methamphetamine use continue unabated.

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REFERENCES

1 Luttgens WF. Endocarditis in main line opium addicts; report on 11 cases. *Arch Intern Med* 1949;83:653–64.
2 Weir MA, Slater J, Jandoc R, *et al*. The risk of infective endocarditis among people who inject drugs: a retrospective, population-based time series analysis. *CMAJ* 2019;191:E93–9.
3 Schranz AJ, Fleischauer A, Chu VH, *et al*. Trends in drug Use-Associated infective endocarditis and heart valve surgery, 2007 to 2017: a study of statewide discharge data. *Ann Intern Med* 2019;170:31–40.
4 Barocas JA, Eftekhari Yazdi G, Savinkina A. Long-Term infective endocarditis mortality associated with injection opioid use in the United States: a modeling study. *Clin Infect Dis* 2020;9:ciaa1346.
5 Moss R, Munt B. Injection drug use and right sided endocarditis. *Heart* 2003;89:577–81.
6 Ramadan FB, Beanlands DS, Burwash IG. Isolated pulmonic valve endocarditis in healthy hearts: a case report and review of the literature. *Can J Cardiol* 2000;16:1:1282–8.
7 Khan MZ, Munir MB, Khan MU, *et al*. Contemporary trends in native valve infective endocarditis in United States (from the National inpatient sample database). *Am J Cardiol* 2020;125:1678–87.
8 Chambers HF, Morris DL, Täuber MG, *et al*. Cocaine use and the risk for endocarditis in intravenous drug users. *Ann Intern Med* 1987;106:833–6.
9 Pericás JM, Llopis J, Athan E. International collaboration on endocarditis (ICE) Investigators. prospective cohort study of infective endocarditis in people who inject drugs. *J Am Coll Cardiol* 2021;77:544–55.
10 Frontera JA, Gradon JD. Right-Side endocarditis in injection drug users: review of proposed mechanisms of pathogenesis. *Clin Infect Dis* 2000;30:374–9.
11 Edelman EJ, Gordon KS, Crothers K, *et al*. Association of prescribed opioids with increased risk of community-acquired pneumonia among patients with and without HIV. *JAMA Intern Med* 2019;179:297–304.
12 Kasper KJ, Manoharan I, Hallam B, *et al*. A controlled-release oral opioid supports S. aureus survival in injection drug preparation equipment and may increase bacteremia and endocarditis risk. *PLoS One* 2019;14:e0219777.
13 Silverman M, Slater J, Jandoc R, *et al*. Hydromorphone and the risk of infective endocarditis among people who inject drugs: a population-based, retrospective cohort study. *Lancet Infect Dis* 2020;20:487–97.
14 Cadet P, Bilfinger TV, Fimiani C, *et al*. Human vascular and cardiac endothelia express mu opiate receptor transcripts. *Endothelium* 2000;7:185–91.

15 Khatri R, Sharma U, Roy S. Hydromorphone exposure exacerbates inflammatory bowel disease in a mouse model. *J Am Coll Surg* 2015;221:S30. 2015.
16 Bassareo PP. Hydromorphone and risk of infective endocarditis. *Lancet Infect Dis* 2020;20:651–2.
17 Jones CM, Compton WM, Mustaquim D. Patterns and Characteristics of Methamphetamine Use Among Adults - United States, 2015-2018. *MMWR Morb Mortal Wkly Rep* 2020;69:317–23.
18 Que Y-A, Moreillon P. Infective endocarditis. *Nat Rev Cardiol* 2011;8:322–36.
19 Lange RA, Hillis LD. Cardiovascular complications of cocaine use. *N Engl J Med Overseas Ed* 2001;345:351–8.
20 Baddour LM, Wilson WR, Bayer AS, *et al*. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American heart association. *Circulation* 2015;132:1435–86.
21 Vandenbroucke JP, von Elm E, Altman DG, *et al*. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Int J Surg* 2014;12:1500–24.
22 Tan C, Hansen M, Cohen G, *et al*. Accuracy of administrative data for identification of patients with infective endocarditis. *Int J Cardiol* 2016;224:162–4.
23 Li JS, Sexton DJ, Mick N, *et al*. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;30:633–8.
24 Tan C, Shojaei E, Wiener J, *et al*. Risk of new bloodstream infections and mortality among people who inject drugs with infective endocarditis. *JAMA Netw Open* 2020;3:e2012974.
25 European Monitoring Centre for Drugs and Drug Addiction. *European drug report 2021: trends and developments*. Luxembourg: Publications Office of the European Union, 2021.
26 Jain V, Yang M-H, Kovacicova-Lezcano G, *et al*. Infective endocarditis in an urban medical center: association of individual drugs with valvular involvement. *J Infect* 2008;57:132–8.
27 Shah M, Wong R, Ball L, *et al*. Risk factors of infective endocarditis in persons who inject drugs. *Harm Reduct J* 2020;17:1):1–0.
28 Gray ME, Rogawski McQuade ET, Scheld WM, *et al*. Rising rates of injection drug use associated infective endocarditis in Virginia with missed opportunities for addiction treatment referral: a retrospective cohort study. *BMC Infect Dis* 2018;18:1–9.
29 Kadri AN, Wilner B, Hernandez AV, *et al*. Geographic Trends, Patient Characteristics, and Outcomes of Infective Endocarditis Associated With Drug Abuse in the United States From 2002 to 2016. *J Am Heart Assoc* 2019;8:e012969.
30 Day S, Patel N, Maffett S. Infective endocarditis trends amongst intravenous drug users: an examination of practice patterns in a mid-western tertiary care center. *J Am Coll Cardiol* 2019;73:21.
31 Fleischauer AT, Ruhl L, Rhea S, *et al*. Hospitalizations for Endocarditis and Associated Health Care Costs Among Persons with Diagnosed Drug Dependence - North Carolina, 2010-2015. *MMWR Morb Mortal Wkly Rep* 2017;66:569–73.
32 Ellis MS, Kasper ZA, Cicero TJ. Twin epidemics: the surging rise of methamphetamine use in chronic opioid users. *Drug Alcohol Depend* 2018;193:14–20.
33 Hedegaard H, Miniño AM, Warner M. Co-involvement of opioids in drug overdose deaths involving cocaine and psychostimulants. *NCHS Data Brief* 2021;406:1–8.
34 Rodger L, Shah M, Shojaei E, *et al*. Recurrent endocarditis in persons who inject drugs. *Open Forum Infect Dis* 2019;6:ofz396.
35 Scheim A, Rachlis B, Bardwell G, *et al*. Public drug injecting in London, Ontario: a cross-sectional survey. *CMAJ Open* 2017;5:E290–4.
36 Rodger L, Glockler-Lauf SD, Shojaei E, *et al*. Clinical characteristics and factors associated with mortality in first-episode infective endocarditis among persons who inject drugs. *JAMA Netw Open* 2018;1:e185220.
37 Shrestha NK, Jue J, Hussain ST, *et al*. Injection drug use and outcomes after surgical intervention for infective endocarditis. *Ann Thorac Surg* 2015;100:875–82.
38 Bonow RO, Carabello BA, Chatterjee K. 008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American heart association Task force on practice guidelines (writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease) endorsed by the Society of cardiovascular Anesthesiologists, Society for cardiovascular angiography and interventions, and society of thoracic surgeons. *J Am Coll Cardiol* 22008;52:e523–661.
39 An KR, Luc JGY, Tam DY, *et al*. Infective endocarditis secondary to injection drug use: a survey of Canadian cardiac surgeons. *Ann Thorac Surg* 2021;112:1460–7.
40 Siefried KJ, Acheson LS, Lintzeris N, *et al*. Pharmacological treatment of methamphetamine/amphetamine dependence: a systematic review. *CNS Drugs* 2020;34:337–65.
41 Trivedi MH, Walker R, Ling W, *et al*. Bupropion and naltrexone in methamphetamine use disorder. *N Engl J Med* 2021;384:140–53.