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Staphylococcus aureus endocarditis associated with injecting new psychoactive substances

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Abstract

Background *Staphylococcus aureus* **infective endocarditis (IE) associated with injection of new psychoactive substances (NPS) in Edinburgh from 2014 to 2016 was observed. We compared these infections with a series of** *S. aureus* **IE cases in a non-injecting population within Edinburgh.**

Methods NPS-associated *S. aureus* **IE diagnosed between 1 January 2014 and 31 May 2016 in persons who inject drugs (PWID) were compared with a series of** *S. aureus* **IE cases from non-PWID.**

Results There was a fourfold increase in the annual incidence of *S. aureus* **IE, mainly due to NPS use in PWID. A larger vegetation diameter was seen on echocardiogram in PWID vs non-PWID (median 1.7 cm vs 0.65 cm; p = 0.009) with more embolic complications in PWID (15 PWID vs 1 non-PWID; p = 2.1 x 10^{-7}) but no difference in 90-day mortality (2 PWID vs 4 non-PWID; p = 0.39).**

Conclusions NPS-associated *S. aureus* **IE correlated with complications, such as deep organ embolic abscesses, that were different from non-PWID** *S. aureus* **IE. The alarming increase in incidence resolved with targeted public health and legislative measures.**

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Introduction

Infective endocarditis (IE) was first described in 1885 by William Osler as infection of the heart valves in individuals with rheumatic valve disease.[1] IE is now a major cause of morbidity and mortality with an annual incidence of approximately 3–10 cases per 100,000 patients and an in-hospital mortality of 20%.[2–5] More recently, there has been a marked change in the aetiology and demographics of IE globally.[6] Historically associated with oral streptococcal infections, IE is now most commonly associated with healthcare-acquired infections; *Staphylococcus aureus* being the most common causative organism in the industrialised world.[2,3,7] Degenerative valve disease, diabetes, malignancy, intravenous drug use and congenital heart disease are major risk factors for developing IE.[6] Clinical presentation of IE can often vary between individuals, with fever (90%) and cardiac murmurs (85%) being the most common presenting features, and cardiac failure and embolic phenomena being the more commonly encountered complications.[6,8,9] *S. aureus* often affects the native valves (70–80%) with left-sided valves being the most commonly targeted sites.[10] The outcome of *S. aureus* native valve IE is worse than non-*S. aureus* infections.[11] Mortality associated with left-sided *S. aureus* endocarditis ranges between 30 and 71%, and has remained high despite better diagnostic procedures, antimicrobial drugs and surgical intervention.[12] Comparatively, right-sided IE has lower mortality, reported at 17%.[12] IE commonly occurs in persons who inject drugs (PWID) with an annual incidence of 2–5%, usually affecting a younger age group compared to non-PWID IE.[13–17] *S. aureus* is the most frequently (over 50%) isolated pathogen in this group.[13,18–22] Approximately 10% IE involves the right-sided valves, of which the majority occur amongst PWID.[23]

More recently, there has been international concern about the growing use of 'new psychoactive substances' (NPS). Informally termed 'designer drugs' or 'legal highs', their widespread availability resulted in an alarming increase in use throughout Europe in 2014 as documented in the recent annual report from the European Monitoring Centre for Drugs and Drug Addiction.[24] Up to 8% of individuals aged 15–24 years have used NPS in the UK according to recent data from United Nations Office on Drugs and Crime.[24] More than 450 substances are currently being monitored by the

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European Union Early Warning System.[25] NPS use is an emerging social and medical problem in the UK.[26] In 2012, 52 deaths in England and Wales were directly attributable to NPS use.[27,28] Unfortunately, 'legal highs' initially fell outside the drug regulatory laws and escaped legislative bans as they were engineered to evade existing regulations. Furthermore, the ease of availability of these substances over the internet, in retail outlets known as 'head shops' and with local drug suppliers allowed rapid distribution within communities.

Most NPS are derived from synthetic cathinones and cannabinoids and can be classed into several categories, a few being sedatives, hallucinogens and stimulants.[29] 'Bath salts' are a stimulant form of NPS and contain one or more synthetic derivatives of the naturally occurring cathinone, which targets plasma membrane monoamine transporters expressed on nerve cells and other cell types.[30] These NPS influence the uptake of several neurotransmitters, such as norepinephrine, dopamine and 5-hydroxytryptamine.[31] These products have no legitimate use as bath additives and are often labelled as 'not for human consumption' to circumvent laws governing their sale.[30] The emergence of 'bath salts' was first described in 2010 in the USA, and by 2011 a dramatic spike in emergency admissions with toxic exposures was seen. Patients intoxicated with 'bath salts' can present with severe and prolonged symptoms, including psychosis, combative behaviour, tachycardia and hyperthermia. A recent case series on cathinone-related emergency admissions showed that 51% of these patients were admitted to hospital and 21% of these cases required critical care input.[32,33] Infective complications can often occur at the site of injection and include cellulitis, abscesses or necrotising soft tissue infections. Blood stream infections are also common and can be associated with deeper infection, such as deep organ abscesses or complications including IE.[34]

Among PWID presenting with fever, 13% will have echocardiographic features suggestive of IE[35] with *S. aureus* being the most common pathogen.[7] Drug users have a higher rate of colonisation with *S. aureus*, which in turn, is a risk factor for infection and subsequent IE.[36]

A possible association between 'bath salt' injecting and *S. aureus* cardiac infection has been described in New York, USA.[17] A similar phenomenon has been observed in Lothian, Scotland, where a major increase in NPS injecting, particularly ethylphenidate-based 'bath salts', rapidly became a public health and public order issue in 2014 and 2015. The association in Lothian with a sharp increase in *S. aureus* bacteraemia has been published previously,[34] but, alarmingly, many instances of *S. aureus* bacteraemia were associated with an underlying diagnosis of IE. We report an increased annual incidence of *S. aureus*-associated IE as a result of a change in drug-taking behaviour within a large Scottish health board (NHS Lothian), and describe differences in clinical progression within this group when compared to the same disease in a non-PWID group.

Methods

Objectives

To compare presentations and outcomes of a cluster of *S. aureus* endocarditis associated with NPS with a series of *S. aureus* IE cases in a non-injecting population within a Scottish regional health authority covering a population of 850,000 from 2014 to 2016.

Design, setting and participants

The prospective component of the study was carried out between 1 January 2014 and 31 May 2016 in a single Scottish Health Authority, which has three acute adult hospitals covering a population of 850,000. Cases were defined as PWID who gave a recent history of injecting NPS and who were diagnosed as having *S. aureus* IE defined by the Duke criteria.[37] Data relating to PWID infections were collected and collated prospectively as part of a public health investigation of infections associated with injection of NPS. The control series consisted of all cases of *S. aureus* endocarditis diagnosed in a non-PWID population. These cases were also defined using the Duke criteria and were derived from the same health authority region between 2007 and 2016. A total of 14 *S. aureus* IE cases in a non-PWID population were identified retrospectively. Electronic case records were used to collate patient demographics, antimicrobial treatment, investigations and clinical outcomes, including duration of in-patient care, surgical interventions performed and mortality at 90 days (from the date of diagnosis of the *S. aureus* bacteraemia).

Echocardiograms were analysed by two cardiologists independently and the size of vegetations measured in at least two views using the calliper tool. A mean of the largest dimensions was used as the final vegetation size.

Statistical analyses

Data were analysed using Microsoft Excel 2010 (Microsoft, Redmond, WA, USA) and R 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Continuous data are presented as medians and interquartile ranges and were analysed using a Mann–Whitney U-test. Categorical data are presented as numbers and percentages and were analysed using Fisher's exact test. Spearman's rank-order correlation test using the Spearman's correlation coefficient was applied for correlations between continuous variables.

Ethical approval

Advice was sought from the South East Scotland Research Ethics Service regarding access to patient information. As this study was based on data obtained in the course of routine patient care, with no communication of identifiable patient data, no formal ethical review was required. All patient-related data was handled in accordance with Caldicott principles.

Results

A total of 15 PWID and 14 non-PWID with *S. aureus* IE were included in the study. All PWID gave a history of having injected

Table 1 Demographic details, blood parameters and vegetation size for the persons who inject drugs (PWID) and non-PWID groups

Demographics	PWID Median (IQR)	Non-PWID Median (IQR)	p-value
Total (n)	15	14	–
Age (years)	36 (33–40)	66 (64–77)	8.0×10^{-7}
Gender (male : female)	13 : 2	8 : 6	0.109
CRP (mg/l)	266 (230–300)	190 (135–333)	0.232
Albumin (g/l)	18.0 (16.0–21.0)	26.0 (23.0–28.0)	0.002
WCC (10^9/l)	15.2 (13.5–17.9)	11.8 (9.9–14.7)	0.247
Haemoglobin (mg/dl)	104.4 (97.8–114.0)	115.0 (95.0–139.8)	0.262
Vegetation size (cm)	1.7 (1.5–2.0)	0.65 (0.2–1.1)	0.009
Embolic complications	15	1	2.1×10^{-7}
Required valve surgery	3	7	0.13
Mortality at 30 days	1	0	1.00
Mortality at 90 days	2	4	0.39

CRP: C-reactive protein; IQR: interquartile range; WCC: white blood cell count

NPS substances (ethylphenidate, also known as 'Burst') prior to their presentation. Three PWID described concomitant heroin and NPS use immediately prior to presentation, with the rest describing NPS use only. Of this group, eight had previous, but not recent, exposure to heroin. No cases of IE were identified amongst PWID with exclusive heroin use in the time period examined. The median age of PWID was significantly lower than of non-PWID (36 [interquartile range (IQR): 33–40] vs 66 [IQR: 64–77] years; $p = 8.0 \times 10^{-7}$). A total of 87% of PWID and 57% of non-PWID were male. All patients in the PWID group were HIV negative and three were hepatitis C negative. Two PWIDs had a new diagnosis of hepatitis C and all the others had chronic hepatitis C. The demographic characteristics and blood markers for all patients are summarised in Table 1.

In the PWID group, there were eight (53.3%) patients with echocardiographic evidence of vegetations solely on the tricuspid valve, two (13.3%) with sole mitral valve involvement, one (6.7%) patient with sole aortic valve involvement, one (6.7%) patient with both tricuspid and pulmonary valve involvement, and three (20%) patients with both mitral and tricuspid valve vegetations. In contrast, exclusively left-sided heart valves were involved in the non-PWID group: mitral valve, n = 10 (71.4%); aortic valve, n = 4 (28.6%).

The vegetation dimensions on echocardiogram were significantly greater in the PWID group than in the non-PWID group [median: 1.7 (IQR: 1.5–2.0) vs 0.65 (IQR: 0.20–1.10) cm; p = 0.009], as summarised in Figure 1. There was an inverse correlation between vegetation size and albumin levels (Spearman's rank correlation rho: -0.42; p = 0.037) (Figure 2); however, vegetation size did not correlate with other blood markers, including C-reactive protein (CRP; rho = 0.30; p = 0.13).

Embolic complications secondary to infective endocarditis were more common in the PWID group [15 (100%) PWID and 1 (7.1%) non-PWID; $p = 2.1 \times 10^{-7}$].

A total of 12 (80%) patients in the PWID group had pulmonary emboli, of which four (26.7%) had CT evidence of both pulmonary and extrapulmonary emboli (e.g. splenic, renal and cerebral emboli) and three (20%) patients had extrapulmonary involvement only. In contrast, no pulmonary emboli were seen in the non-PWID group and only one patient had extrapulmonary emboli. Vegetation size was available for all the PWID-associated cases of *S. aureus* IE but only for 13 (92.8%) of the non-PWID cases. A vegetation size of ≥10 mm (n = 18) was associated with a higher number of embolic complications than with smaller vegetations (≤10 mm, n = 10; number with emboli, 15 vs 1, respectively; $p = 2.7 \times 10^{-4}$). Furthermore, in patients with small vegetations only one had embolic phenomena and this was an NPS user. A total of five PWIDs had lung abscesses, four had brain abscesses, three had splenic abscesses and five patients had no deep collections. There were no reported abscesses in the non-PWID group. For all the PWID patients with lung abscesses, there was evidence of tricuspid valve infection. The abscesses were predominantly basal and commonly in the right lung, although in one patient they were bilateral.

One patient required bilateral amputation of his feet that were infected and necrotic as a consequence of septic emboli in order to facilitate control of secondary sites of active infection and bacteraemia to optimise the chance of successful valve replacement surgery. Lung, brain and spleen abscesses were treated conservatively with antimicrobials and did not require drainage procedures. Three patients in the PWID group required valve surgery compared to seven in the non-PWID group (p = 0.13).

There was no significant difference in median CRP values between PWID and non-PWID groups [266 (IQR: 230–300) vs 190 (IQR: 135–333) mg/l; p = 0.23]; however, albumin was significantly lower in the PWID group than in the non-PWID group at the time of diagnosis of IE [18 (IQR: 16–21) vs 26 (IQR: 23–28) g/l; p = 0.002].

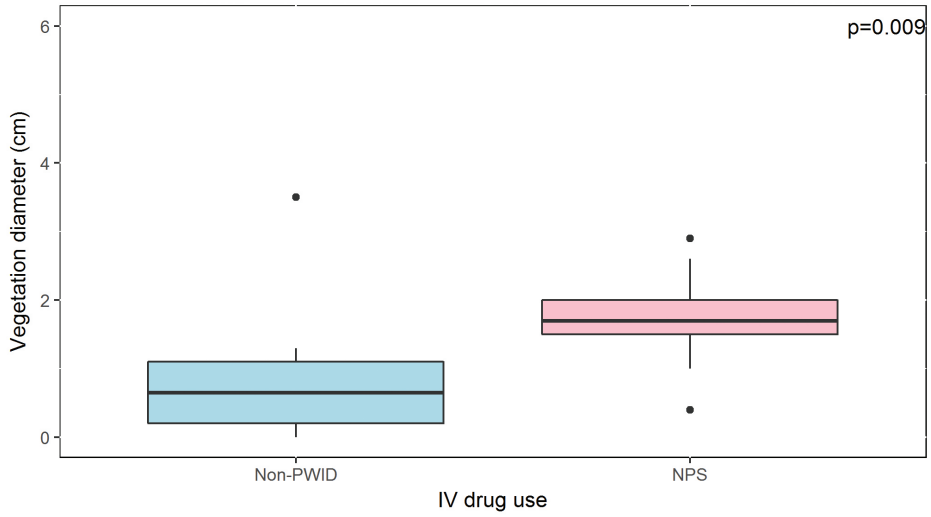


Figure 1 Differences in vegetation size at echocardiogram in patients who injected intravenous (IV) new psychoactive substances (NPS) vs those who did not inject drugs. PWID: persons who inject drugs

Although all the PWID IE cases were due to methicillin-susceptible *S. aureus*, a range of subtypes were identified (spa types t062, t084, t127, t131, t267, t571, t605, t1509, t1548, t3609 and t8272). All isolates were negative for the gene coding the Panton–Valentine leukocidin toxin.

There was one death at 30 days in the PWID group. At 90 days there were four deaths in the non-PWID group and two in the PWID group, which, owing to the relatively small numbers, was not statistically significant (p = 0.39).

Discussion

While there is a well-established association between injecting recreational drugs and IE, the incidence of IE in PWID is considered low at 1.5–20 cases of endocarditis per 1,000 person-years.[38] In our study, we identified 15 cases of bacterial endocarditis in PWID within 28 months and this correlated with a period of intense NPS injecting behaviour in our healthcare region. This dramatic increase in cases impacted on local healthcare services, including cardiology, cardiothoracic surgery, orthopaedic surgery, vascular surgery, plastic surgery, general surgery, critical care, infectious diseases and microbiology. During our period of prospective surveillance of cases of *S. aureus* IE in PWID from 2014 to 2015 there were no cases of IE identified in exclusive heroin injectors who did not inject NPS, suggesting a strong association between injecting NPS and the risk of subsequent *S. aureus* IE. It is plausible that the pattern of IE seen in our cohort of patients was substance specific, linked to NPS and not heroin. During this period, NPS injecting was dominated by ethylphenidate-based substances that were sold legally with names such as 'Burst', 'Blue Stuff', 'Blue' and 'Quack.'

Possible explanations for this apparent association with NPS injecting are complex. Often NPS injectors exhibited increased daily frequency of injecting (compared to opiate injectors) leading to increased probability of bacteraemia through many more skin punctures per day. A preferred anatomical site for injecting was the groin, which is an area where *S. aureus* may be commensal flora that could facilitate the direct inoculation of *S. aureus* into the bloodstream. Once in the bloodstream there is an opportunity for *S. aureus* to attach to heart valves. Another difference in NPS use was the practice of injecting from communal pots, and NPS was not heated or dissolved in citric acid unlike heroin.[39] Multiple areas of necrotic-looking skin lesions

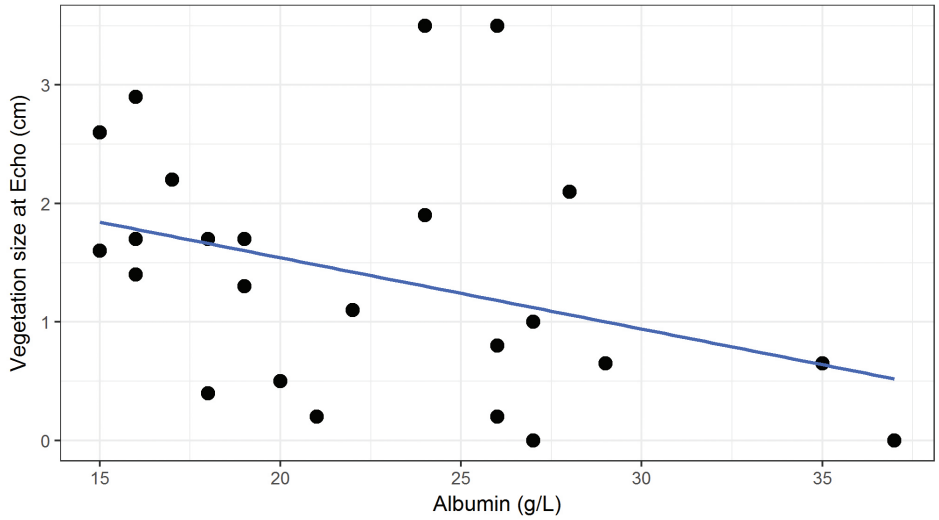
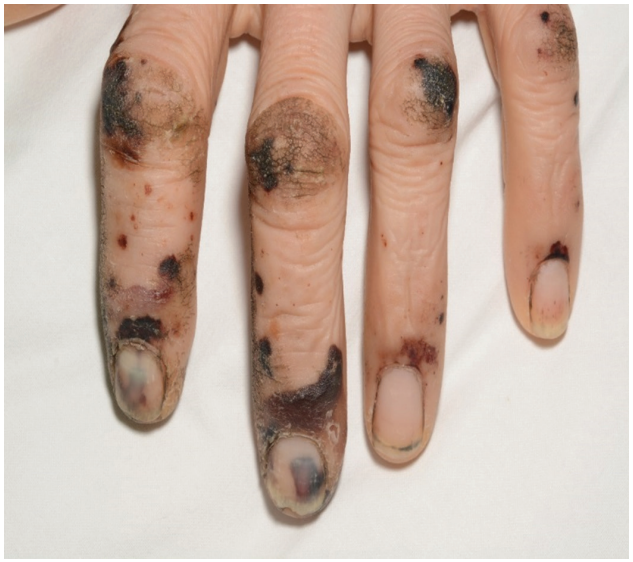


Figure 2 Correlation between albumin levels and vegetation size at echocardiogram

Figure 3 Skin lesions observed in a person who injected drugs (PWID) with new psychoactive substances *S. aureus* infective endocarditis (IE). Multiple necrotic lesions located in the peripheries of digits that resemble embolic phenomena were commonly seen in PWID with *S. aureus* IE. Similar such lesions, however, were also observed in PWID in other anatomical locations and in PWID who did not have a diagnosis of IE and so may not be specific to *S. aureus* IE



(Figure 3) were characteristic of ethylphenidate-based NPS injecting resulting in multiple skin sites of potential entry of *S. aureus* to bloodstream. These may have arisen owing to residual particulate matter in injected NPS that may have caused vascular damage and local necrosis. Extravasated NPS solutions are often corrosive to soft tissue and this may facilitate entry of commensal skin organisms, such as *S. aureus*, again from superficial skin damage with progression to deeper soft tissue infection or bacteraemia.[34] A direct cardiac toxic effect of 'bath salts' on heart valves is also a possibility, leading to deposition of an adulterant on cardiac valves that could facilitate attachment of *S. aureus*.[17] Other factors linked to NPS use could include *S. aureus* contamination of the drug solution, which, unlike heroin, does not require heating prior to injecting, thus increasing the chance of *S. aureus* survival in the injected drug solution.

The range of spa types of *S. aureus* suggests that the organisms may have been arising from the individual commensal flora of the affected PWID, although there were three cases of t127, two cases of t131 and two cases of t605, which might indicate a link between cases and possible person-to-person transmission or infection from the same source. No epidemiological links were known that might account for such transmission and it should be recognised that these are common spa types in the UK and may have arisen through coincidence. Although there is a clear association between NPS use and *S. aureus* IE, the clinical features of the IE differ between PWID and non-PWID groups. *S. aureus* IE in NPS users was associated with larger valve vegetations and significant embolic phenomena complicating both antimicrobial and surgical management. This was because the presence of concurrent deep abscesses needed to be taken into consideration when planning the timing of valve replacement, the need for drainage and the duration of intravenous antibiotic treatment. In addition, the coexistence of deep organ abscesses caused by embolism of infected material was considered to present a risk of *S. aureus* reinfection to newly placed valve replacements inserted as emergency procedures owing to native valve failure. The larger size of vegetations seen in the PWID group may explain the higher incidence of embolic complications in the NPS users as a larger vegetation may be more able to release bacteria into blood given its larger surface area. Studies report that in patients with left-sided native-valve IE, the risk of embolism is increased with a vegetation size ≥10 mm.[40,41] We found a similar increased risk of embolic complications in patients with a vegetation size ≥10 mm, although this is not restricted to left-sided IE in the NPS injecting PWID population where a new pattern of left-sided IE is emerging in PWID.[42,43] This is consistent with our findings of IE in right- and left-sided valves in the PWID group.

The tricuspid valve is most frequently involved in opiate injectors and left-sided valvular involvement is uncommon.[42,43] We here report a new pattern of valve involvement in NPS injectors with exclusive left-sided valve involvement in 3/15 (20%) and a further 3/15 with both mitral and tricuspid involvement at presentation.

There is interest in identifying biomarkers to predict outcomes in patients with infective endocarditis.[44,45] It has been shown that detecting a high CRP and low albumin within 48 hours of admission is associated with higher mortality rates from IE.[44] Patients with IE-associated emboli have also been reported to have higher CRP and lower albumin levels.[45] Although a small cohort, we also found that in PWID with NPS-associated IE there was an association between a lower albumin and increased incidence of embolic events but not increased mortality. We also identified a moderate negative correlation between albumin levels and vegetation size, another factor that has been shown to predict embolic risk in IE.[45]

IE caused by *S. aureus* is associated with a less favourable prognosis in a non-PWID population than in a PWID population.[46] In our study, despite a greater embolic risk, we observed a lower 90 day mortality in the PWID group than in the non-PWID population. The higher median age of the non-PWID group could be influencing the higher mortality, possibly as a consequence of comorbidities associated with increased age.[46]

Our study has certain limitations. Firstly, we compared a prospective case series with a retrospective cohort of endocarditis and the patient cohorts were small. There were no prospective cases of non-PWID *S. aureus* IE recorded during the study period. In order to identify

a similar number of cases of *S. aureus* IE in non-PWID patients we had to screen medical records covering a 9-year period, illustrating how much more common *S. aureus* IE had become in the NPS-injecting PWID population. Secondly, the groups compared differed in their age, which may influence the outcomes seen. However, it is worth noting that *S. aureus* endocarditis in the non-injecting population is very rare and there were no cases of non-NPS endocarditis identified during the study period. Septic pulmonary emboli are typically recognised on CT by wedge-shaped septic infarcts and subpleural nodular lesions, with or without necrosis and cavitation, and are often seen in the lower zones and peripheries of the lungs.[47] It is worth noting that only one non-PWID patient had a CT chest and three patients from the non-PWID group had CT head. However, CT investigations within our group are probably reflective of their clinical presentation and assessment by the medical teams at the time.

Although the association with *S. aureus* IE and injecting recreational drugs is well known, this is usually described in the context of opiate injecting. The radical shift in injecting behaviour away from opiates and towards ethylphenidate-based NPS in Lothian during 2014–16 when NPS was legally available resulted in a clear impact on the clinical presentation of PWID *S. aureus* IE requiring the expertise of a variety of medical and surgical disciplines to manage its associated morbidity. Interestingly, in the months since trade in NPS was rendered illegal by the Psychoactive Substances Act 2016, there has been a reduction in cases of PWID-associated *S. aureus* infection locally.

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