Explaining the Differences in Opioid Overdose Deaths between Scotland and England/Wales: Implications for European Opioid Policies

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Keywords

Opioids · Drug dependence · Problem drug use · Drug-related death · Polydrug use · Injecting drug use · Incarceration

Abstract

Backgrounds: Between 2009 and 2018, the number of opioid-related deaths (ORDs) in Scotland showed a dramatic increase, whereas in England and Wales, a much lower increase in ORD was seen. This regional difference is remarkable, and the situation in Scotland is worrisome. Therefore, it is important to identify the drivers of ORD in Scotland.

Methods: A systematic literature review according to PRISMA guidelines was conducted to identify peer-reviewed studies about key drivers for the observed differences in ORDs between Scotland and England/Wales. In addition, non-peer-reviewed reports on nationwide statistical data were retrieved via Google and Google Scholar and analysed to quantify differences in ORD drivers between Scotland and England/Wales. **Results:** The systematic review identified some important drivers of ORD, but none of these studies provided direct or indirect comparisons of ORD drivers in Scotland and England/Wales. However, the reports with nationwide statistical data showed important differences in ORD drivers between Scotland and England/Wales, including a higher prevalence of people using opioids in a prob-

lematic way (PUOP), more polydrug use in people using drugs in a problematic way (PUDP), a higher age of PUDP, and lower treatment coverage and efficacy of PUDP in Scotland compared to England/Wales, but no regional differences in injecting drug use, incarceration/prison release without treatment, and social deprivation in PUDP. **Conclusion:** It is concluded that the opioid crisis in Scotland is best explained by a combination of drivers, consisting of a higher population involvement in (problematic) opioid use (notably methadone), relatively more polydrug use (notably benzodiazepines and gabapentinoids), a steeper ageing of the PUOP population in the past 2 decades, and lower treatment coverage and efficacy in Scotland compared to England/Wales. The findings have important consequences for strategies to handle the opioid crisis in Scotland.

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Introduction

In a recent review, trends in opioid prescription rates, prevalence rates of non-fatal and fatal opioid-related incidents, and opioid use disorder treatment in Germany, France, the UK, the Netherlands, and the USA were reported [1]. It was concluded that there is no threat of an opioid crisis in Europe similar in nature and/or magnitude to the current opioid crisis in the USA where high

Fig. 1. PRISMA flow diagram. Retrieval of eligible reports via the checking of reference list of the selected 14 studies was unsuccessful.

numbers of opioid-related deaths (ORDs) and increasing numbers of treatment-seeking opioid use disorder patients are observed [1]. In this review [1], we also noted, however, that Scotland is an exception with an ORD rate even higher than that in the USA. Furthermore, it became apparent that in Scotland, between 2009 and 2018, the number of drug-related deaths (DRDs), including ORDs, more than doubled resulting in the largest number ever recorded, whereas in England and Wales, a much smaller increase in DRDs were seen. A number of people and several agencies from the UK have urged their government to declare a public health crisis in response to the record number of drug-related poisonings in Scotland [2–6].

In a recent inquiry, the Scottish Affairs Committee, appointed by the House of Commons in Scotland, identified several key drivers of DRDs in Scotland, including polydrug use in people using drugs in a problematic way (PUDP; previously described as “problem drug users” or PDU), ageing of PUDP, low addiction treatment coverage and efficacy, high levels of injecting drug use, infrequent treatment during incarceration, and social deprivation [7]. However, no quantification of the differences in DRD/ORD drivers between Scotland and England/Wales was provided. In this study, we aimed to compare the prevalence of these drivers in Scotland and England/Wales to explain the observed ORD differences between these British regions.

Methods

Systematic Review Peer-Reviewed Studies

A systematic literature review was performed on 16 October 2020 using the PRISMA protocol to retrieve studies from Medline (PubMed) and PsycINFO (articles published or ahead of print from September 2010 to October 2020) on the following topics of interest: potential drivers of DRDs, ORDs, PUDP, people using opioids in a problematic way (PUOP), polydrug use in PUDP and PUOP, ageing of PUDP/PUOP, treatment coverage and treatment efficacy for patients with problematic opioid use, injecting drug use, treatment during incarceration, and social deprivation. Studies describing quantitative data about the topics of interest observed in Scotland and/or England/Wales were considered for inclusion if they were reported full text in Dutch, English, German, or French. The exclusion criteria were reviews, commentaries, and – as we aimed to collect population-based data – reports with a small sample size (<100 subjects). Two researchers (J.v.A. and M.P.) were involved in the selection of appropriate studies, which was executed in 2 rounds. Initially, 348 studies were retrieved of which 234 unique studies remained after removal of duplicates. These 234 studies were further processed, that is, the title and abstract were screened to determine eligibility applying the inclusion and exclusion criteria mentioned above. In a second round, the reference list of the selected 14 studies was checked for eligible studies. In total, 14 papers were finally included. Figure 1 shows the PRISMA diagram of the identification, screening, and inclusion of the reports. (See Figure 1 for flow diagram of the systematic search and “see online suppl. material; for all online suppl. material, see www.karger.com/doi/10.1159/000516165” for the PRISMA checklist.)

Table 1. Description of included studies on DRD, PUDP, PUDP, polydrug use, age of PUDP, and treatment coverage and efficacy, injecting drug use, treatment during incarceration, and social deprivation

No.	Sample	Time frame	Data source	Main results	Ref.
1	150,517	1996–2007	All people released from all Scottish prisons	Opioid substitution therapy in Scottish prisons decreased the rate of DRD by 40%	[19]
2	3,182	2006–2013	NRS	Scotland's National Naloxone Programme was associated with a 36% reduction in the proportion of ORDs	[18]
3	33,128	2009–2013	Scotland's Prescribing Information System and NRS	Higher methadone-specific DRD rates in older clients	[13]
4	3,262	2009–2015	NRS	Circulatory disease as comorbidity most likely implicated in the 4-fold increase of methadone-specific DRD risk at 45+ yrs	[14]
5	2,418	2007–2012	National databases for England and Wales	Buprenorphine is 6 times safer than methadone with regard to overdose risk	[20]
6	69,456	1996–2006	SDMD	Drug users, especially those HCV-diagnosed showed an increased mortality risk	[10]
7	69,457	1996–2006	Registration of drug treatment in Scotland	Discharge of people in treatment for drug dependence from hospitalization were at increased risk of DRD	[16]
8	3,850	2013–2014	PWID survey	15% of drug injectors reported overdosing during the preceding year	[15]
9	Not specified	1979–2013	NRS	Age-standardized rates for DRDs among young adults rose during the 1990s in Scotland, especially for males living in the most deprived areas	[11]
10	198,247	2005–2009	Drug treatment and criminal justice sources in England	Opioid users' excess mortality persists into old age	[8]
11	151,983	2005–2009	NDTMS and ONS	Patients receiving only psychological support for opioid dependence in England were at greater risk of DRD	[9]
12	1,266 DRDs	2005–2009	NDTMS	Sharp age-related increase in the risk of methadone-specific death in the UK	[12]
13	>98,000	1996–2010	SDMD	Hospital-discharge gives increased DRD vulnerability, especially for drug injectors	[17]
14	3,731	2008–2011	NDTMS and ONS	The English public treatment system for opioid use disorder prevented 880 deaths yearly from opioid-related poisoning	[21]

NRS, National Records of Scotland; SDMD, Scottish Drug Misuse Database; NDTMS, National Drug Treatment Monitoring System in England; ONS, Office for National Statistics in England; ORD, opioid-related death; PUDP, people using drugs in a problematic way; PWID, persons who inject drugs.

Review Non-Peer-Reviewed Studies

In addition, information from non-peer-reviewed sources (grey literature) reported in the last 10 years was retrieved via searches in Google and Google Scholar (J.v.A. and M.P.) using appropriate combinations of key words and Boolean operators, including “file:pdf.” Examples of key words that were used are Scotland, England, DRD, mortality, “drug mortality,” “opioid-related overdos*,” opioid, heroin, methadone, incarceration, persons who inject drugs (PWID), PDU, Opioid Substitution Treatment (OST),

National Drug-Related Deaths Database (NDRDD), English' National Drug Treatment Monitoring System (NDTMS), Scottish Drugs Misuse Database (SDMD), National Health Service (NHS), England/Wales' Office for National Statistics (ONS), Public Health England (PHE), Scottish' Information Services Division (ISD), Needle Exchange Surveillance Initiative (NESI), National Records of Scotland (NRS) and the Scottish Prison Service (SPS). This search resulted in several hundreds of potential useful hits/reports, the abstracts were screened, and reports were included if eligible.

Table 2. DRD and ORD per 100,000 adults aged 18 years and older in the USA, EU+ (data extracted from our previous review [1]), as well as in England/Wales and Scotland [22–24]

	USA	EU+	England/Wales	Scotland
DRD	20.6 ¹	2.3	11.2	33.6
ORD	14.3 ¹	1.2 ²	5.7	28.9

ORD, opioid-related death; DRD, drug-related death; EU+, European Union plus Turkey and Norway. ¹ 2018 [23]. ² 78% related to all opioids, but primarily heroin [24].

The inclusion and exclusion criteria were the same as described above for peer-reviewed studies. Note that the direct comparisons made in this review and their interpretations should be interpreted with caution due to small differences in definitions of DRD/ORD that were used in these reports. As such searches are not fully reproducible, the eligible non-peer-reviewed reports are not specified in Figure 1.

Via Google and Google Scholar, forty non-peer-reviewed reports from the SDMD, NRS, NDTMS, ISD, PHE, NESI, SPS, and ONS were retrieved (cf. reference list). These reports were crucial sources of national statistical data which allowed quantitative comparisons between Scotland and England/Wales regarding ORD and its presumed key drivers. Data from N-Ireland were not included because of the low availability of the relevant data.

Results

Below, we first describe the findings from the peer-reviewed studies, and then, we separately describe the findings from the non-peer-reviewed studies (grey literature).

Peer-Reviewed Studies

Table 1 summarizes the findings of the eligible peer-reviewed studies. These findings confirmed and underlined that at a population level the ageing of PUDP, injecting drug use, treatment during incarceration, and social deprivation were important risk factors of ORD. For instance, it was shown that in England, opioid users' excess mortality persisted into old age [8] and in patients receiving only psychological support for opioid dependence [9], whereas in Scotland, excess mortality was shown in HCV-diagnosed drug users [10]. Age-standardized rates for DRDs among young adults rose during the 1990s in Scotland, especially for males living in the most deprived areas [11], and a sharp age-related increase in the risk of methadone-specific death in the UK was noted between 2005 and 2009 [12]. Furthermore, in

Scotland, older patients showed higher methadone-specific DRD rates [13], which was partly explained by the higher comorbidity of cardiovascular disease [14]. In England/Wales, drug injectors were at increased risk of DRD, considering that 15% of drug injectors reported overdosing during the preceding year [15]. In Scotland, patients discharged from inpatient drug dependence treatment [16], especially drug injectors [17], were at increased risk of DRD. On the other hand, both Scotland's National Naloxone Programme [18] and the introduction of OST in Scottish prisons [19] have reduced the number of DRDs by 35–40%. In England/Wales, buprenorphine as OST appeared to be 6 times safer than methadone with regard to overdose risk [20]. Finally, the English public treatment system for opioid use disorder annually prevented 880 ORDs [21]. It should be noted, however, that in none of these studies, a direct or indirect (quantitative) comparison was made between Scotland and England/Wales on the role of the different ORD drivers.

PUDP and DRD/ORD in Scotland and England/Wales

To illustrate the unique position of Scotland and England/Wales within Europe and to provide a comparison with the situation in the USA, Table 2 shows DRD/ORD rates in the USA, Europe as a whole, and separate estimates for Scotland and England/Wales using numbers per 100,000 population to allow cross-country comparisons. DRDs are predominantly the consequence of risky drug consumption by people who use drugs in a problematic way (PUDP) and, therefore, the differences in the prevalence of PUDP should be considered when comparing DRD/ORD between certain countries or regions.

Scotland

The prevalence of PUDP in Scotland in 2015/2016 was 1,620 per 100,000 population [25] (see Table 3). In 2018, 1,187 DRDs were registered in Scotland (DRD = 33.6 per 100,000 population), and in 86%, one or more opioids, including heroin, morphine, and/or methadone, were implicated in or seen as potentially contributing to the death (ORD = 28.9 per 100,000) [26]. Methadone was implicated in about 47% of all DRDs (15.9 per 100,000) and heroin/morphine in 45% of all DRDs (15.2 per 100,000) (with some overlap) [26].

England/Wales

The prevalence of PUDP in England in 2018/2019 was 890 per 100,000 population [27]. In England/Wales, in

Table 3. Comparison of the involvement of drugs in DRD in England/Wales versus Scotland in 2018

	England/Wales			Scotland			Ratio ¹
	N	%	rate	N	%	rate	
Total DRD ²	4,359	100	11.2	1,187	100	33.6	3.0
Any opioid	2,208	50.7	5.7	1,021	86.0	28.9	5.1
Heroin/morphine	1,336	30.6	3.4	537	45.2	15.2	4.4
Methadone	419	9.6	1.1	560	47.2	15.9	14.7
Cocaine	637	14.6	1.6	273	23.0	7.7	4.7
Any benzodiazepine	420	9.6	1.1	792	66.7	22.4	20.8
Z-drugs	143	3.3	0.4	24	2.0	0.7	1.8
Gabapentinoids	280	6.4	0.7	367	30.9	10.4	14.4

Rates are given per 100,000 adults aged 18 years and older. DRD, drug-related death. ¹ Scotland versus England/Wales, as calculated by the authors. ² 4,359 DRDs in England/Wales and 1,187 DRDs in Scotland equals 7.4 and 21.8 DRDs per 100,000 population, respectively.

Table 4. Opioid-related data, including rates of PWID, across PUDP, aged 15–64 years in treatment in England 2018/2019 [27] and Scotland 2015/2016 [25, 31, 32]

PUDP ¹	England (N/rate)	Scotland (N/rate)	Rate ratio ²
PUDP total number ¹	313,971	57,300	–
PUDP rate per 100,000 adult population ¹	890	1,620	1.8
Opioid-related PUDP (mainly heroin) ¹	261,294	57,300	–
Opioid-related PUDP rate per 100,000 population ¹	720	1,620	2.3
Mean age in 2018, yrs	42.9	44.9	
PWID, % of PUDP England 2011; Scotland 2006	43	43	1.0
PWID (rate per 100,000 population) England 2011 Scotland 2006	375	680	1.8
PWID, % of PUDP England 2015; Scotland 2009	40	27	0.7
PWID (rate per 100,000 population) England 2015; Scotland 2009	340	450	1.3
Mean age PUDP (2009–2018), yrs	37.5–42.9	36.6–44.9	
Increase in mean age of PUDP (2009 vs.2018), yrs	5.4	8.3	1.5
Mean age PUDP-entrants (2009–2018), yrs	33.0–31.6	29.7–35.7	
Mean age PUDP-entrants in 2018, yrs	11.3	9.2	0.8
PUDP in treatment: total number	192,696	30,046	
PUDP in treatment: mean age in 2018, yrs	40.0	35.6	0.9
PUDP in treatment: age 35–64 years, %	68	64	0.9
PUDP in treatment: males, %	73	71	1.0
Opioid-related PUDP in treatment: total number ³	139,845	25,569	
Opioid PUDP in treatment: % of total opioid PDU	54 ⁴	45	0.8
Opioid PUDP in treatment: rate per 100,000 adult population	385	724	1.9

PWID, persons who inject drugs; PDU, problem drug users; OST, opioid substitution treatment. ¹ PUDP: people using drugs in a problematic way, previously described as PDU. Users of opiates (heroin, methadone, and other opiate drugs), crack cocaine, or both; does not include the use of powder cocaine. However, Scotland and England adopted different definitions for PDU [32] with PDU defined in Scotland as regular use of illegal opioids, benzodiazepines, or prescribed OST drugs. These data refer to 2016/2017 (England). ² Ratio Scotland versus England. ³ Mentioned as main problematic drug, but more than one drug could be mentioned as primary problematic substance. ⁴ 52% based on 136,701 opioid users receiving in 2016 OST out of 261,294 problem opioid users [33].

2018, the total number of DRD was 4,359 (11.2 per 100,000 population) with one or more opioids involved in 51% of all ORD (ORD = 5.7 per 100,000) [28]. Methadone was implicated in about 10% of all DRDs (1.1 per 100,000) and heroin/morphine in 31% of all DRDs (3.4 per 100,000) (Fig. 2a).

Summary

The rate of PUDP in Scotland is almost 2 times that in England. From Table 2, it can be concluded that DRD/ORD rates in England/Wales are at the high end of the European range and those DRD and ORD rates in Scotland are similar to those in the USA. Importantly, the Scottish rates are much higher than those in England/Wales, notably for the total ORDs (rate ratio 5.1) and methadone-related ORD (rate ratio 14.7) (cf. Table 4). Even if one takes into account the higher rate of PUDP in Scotland than England (rate ratio = $1,620/890 = 1.82$), there is still a much higher rate of ORD in Scotland than

England/Wales (rate ratio = $28.9/5.7 = 5.07$), despite important similarities of these regions in culture, language, and healthcare system (NHS).

Comparison of Risk Factors between Scotland and England/Wales

Here, we present data on some of the known risk factors for ORD separately for Scotland and England/Wales in an attempt to identify potential drivers of the significantly higher ORD rate in Scotland than England/Wales, including potential differences in (a) polydrug use, (b) injecting drug use, (c) addiction treatment, (d) ageing, (e) incarceration, and (f) social deprivation.

Polysubstance Use and ORD

Central nervous system (CNS) depressants (benzodiazepines, Z-drugs, gabapentinoids, and alcohol) boost the

effect of opioids [34] so that a lower opioid dose is required for the intended effect. With regard to benzodiazepines, it is important to note that in the UK, etizolam, which is ten times more potent than diazepam (Valium®), is often sold as “street Valium.” Z-drugs (e.g., zolpidem and zopiclone) are non-benzodiazepines that are used to treat anxiety and insomnia. Although depressants are usually not lethal by themselves, they pose a significant additional risk for ORDs when co-ingested with opioids [35].

Scotland

As in the rest of the UK, Scottish PUDP mainly purchase their benzodiazepines (“street benzos”), benzodiazepine derivatives (notably etizolam), and gabapentinoids on the black market [35]. Since 2013, co-use of CNS depressants has strongly contributed to DRDs in Scotland (Fig. 2b). In 2018, benzodiazepines and etizolam were implicated in 67% of all DRDs and in 78% of all ORDs, and gabapentinoids in 31% of all DRDs and in 36% in all ORDs (Table 4), while alcohol was – according to the available data – implicated in only 13% of all DRDs [26]. In 2018, only one drug (and sometimes also alcohol) was found in post-mortem toxicology in 6% of all DRDs and was believed to be implicated in or potentially contributed to the cause of death in 15% of all DRDs [26]. The most common combination (69%) of drugs found during post-mortem toxicology in all DRDs in 2016 consisted of an opioid (heroin, morphine, methadone, or buprenorphine) and a benzodiazepine, with heroin combined with benzodiazepines being most prevalent (51%). It is unclear whether the drugs were used in combination simultaneously or taken at different times. The combination of heroin and gabapentinoids has also become increasingly popular (23% in 2016) [36]. Between 2010 and 2018, the number of DRDs involving any opioid correlated positively with that involving benzodiazepines ($r^2 = 0.83$), etizolam ($r^2 = 0.87$), and gabapentinoids ($r^2 = 0.89$), indicating frequent co-ingestion of antidepressants and opioids. Finally, whereas diazepam was present in 70% of Scotland’s DRDs in 2013 or 2014, it was prescribed in the past 30 days in only 15% of DRD victims [37], indicating that the drug was predominately illicitly acquired.

England/Wales

The proportion of deaths involving only heroin/morphine (with or without alcohol) remained relatively stable between 1993 and 2000 (median 75%) but declined to 49% in 2016 [38], indicating an increase in DRDs involving combinations of multiple drugs in England/Wales.

Between 2010 and 2018, the involvement of benzodiazepines in DRDs in England/Wales was stable at around 11% of all DRDs (9.6% in 2018), while that of Z-drugs and gabapentinoids increased to 3.3 and 6.4%, respectively, in 2018 [29, 34, 38] (Table 4). In 2012/2013, 96% of benzodiazepine deaths involved another substance, mainly opiates (87%) [39]. Furthermore, among heroin deaths, there is a clear trend towards increased co-ingestion of other substances, including alcohol, benzodiazepines, and methadone [39].

Summary

In summary, benzodiazepines, benzodiazepine derivatives (notably etizolam), Z-drugs, and gabapentinoids were much more frequently present in DRDs and ORDs in Scotland than in England/Wales, with rate ratios of 20.8, 1.8, and 14.4, respectively (Table 4).

Injecting Drug Use

Injecting drug use (and the related risk of blood-borne infections) is a known risk factor in DRDs and ORDs [40].

Scotland

In 2006, injecting drug use was highly prevalent among Scottish PUDP, where 43% of all PUDP (23,933 out of 55,100; 680 per 100,000 population) injected opioids and/or benzodiazepines [41] (Table 3). In 2016, 56% of all DRDs were PWID [42]. At the time of death, female ORDs were consistently more likely to be PWID than male ORDs, and thus, female users were at a higher risk than male users to die from drug overdose [42]. Interestingly, PWID was much more common in PUDP treatment entrants ≥ 35 years (55%) than in those < 25 years (19%) (ISD, 2020a), which implies a higher risk in the older age group for blood-borne infections and related mortality. Fortunately, the proportion of current PWID among PUDP entrants in Scotland has declined 2-fold since 2006/2007 to 13% in 2018/2019 [43]. On the other hand, the average age of PWID has gradually increased since 2008/2009 with almost three-quarters of PWID aged 35 years or older in 2017/2018, suggesting an ageing cohort of people who inject drugs in Scotland [44].

England/Wales

In 2011 in England, 43% of the 315,000 PUDP ($n = 135,000$; 375 per 100,000 population) were PWID [27, 45] (Table 3). The most commonly injected drugs were heroin (91%) and crack (45%) [15]. Among relatively young drug users injecting drugs became less popular between

2007 and 2017, so the percentage of PWID younger than 25 years decreased from 15% of total PWID in 2007 to 3% in 2017 [46].

Summary

The percentage of PWID in PUDP was similar in Scotland and England/Wales, and fortunately, the percentage of PWID has recently decreased in both constituencies.

Addiction Treatment

There is ample evidence that (stable) OST reduces the risk of ORD, but methadone induction and OST discontinuation may (temporarily) increase the risk of ORD (e.g., [31, 47]).

Scotland

In Scotland, 25,569 of all 57,300 PWOP (45%; 724 per 100,000 population) were in addiction treatment in 2016 (Table 3). In Scotland, methadone is (still) the most (91%) prescribed opioid substitute in OST [48]. In 2018, methadone was involved in 47% of all DRDs in Scotland [49] (Fig. 2b; Table 4). In 2016 in 78% of methadone-related DRDs, the victim was in OST with supervised methadone prescribing for one year or more, and in at least 67%, the prescribed dose was adequate [42]. It should be noted, however, that another illicit drug (notably, heroin/morphine, etizolam, and/or gabapentin) was detected at post-mortem toxicology in all, but 2, of these methadone-related DRDs [42].

In Scotland, about 95% of PUDP entrants were admitted for treatment within 3 weeks or less [50], although in 2019, a quarter of Scottish applicants still had to wait for up to 18 weeks or more before initiating treatment [50]. Additional problems in addiction care were the high rate of people who “did not attend,” the poor compliance among those engaged with OST, the high rate of “cycle in and out,” and the high number of “unplanned discharges” [5, 51]. This is worrisome, since instable OST with repeated methadone initiations and frequent opioid substitution discontinuations are a specific risk for ORDs (e.g., [47]). The supply rate of take-home naloxone (THN kits) in Scotland and England was comparable with 120–137 kits per 1,000 PUDP in 2017/2018 [33, 52, 53].

England/Wales

In England/Wales, 139,845 of all 261,294 PWOP (54%; 385 per 1,000,000 population) were in treatment in 2016 [27] (Table 2) and 52% (136,701 patients) were receiving OST [53]. According to figures of PHE, the proportion of opiate users in treatment in England is 60%, and 98% of

opioid treatment entrants in England had to wait in 2017–2018 three weeks for the first and the subsequent interventions; 94% of opioid only dependent patients in treatment were prescribed OST, typically methadone or buprenorphine [27].

Summary

OST coverage appears rather similar in Scotland (45%) and England/Wales (54%), but caution is needed since there may be methodological differences in the estimation of the denominator, that is, the number of PWOP. The same is true for the similarity in the supply of THN kits.

Ageing

Age is an important risk factor for DRDs and ORDs since the increasing mean age in the 2 groups is associated with a higher rate of PWID [43, 44] and more chronic illnesses [10, 14, 36, 43, 44].

Scotland

Using all available data and after we performed some extrapolations, the mean age(s) of PUDP and their ranges between 2009 and 2018 were determined. Median age of PUDP and PUDP entrants, that is, those entering treatment, increased between 2009 and 2018 from 36.6 to 44.9 years and from 29.7 to 35.7 years, respectively [43]. As such, the Scottish cohort of PUDP is ageing, and the duration of PUDP is getting longer, that is, three-quarters of all DRDs had used drugs for at least 10 years with over half of them for 20 years or more [54]. The median age of all DRDs in Scotland increased between 2009 and 2018 from 37.0 to 42.5 years [26], with the highest mortality rates in the higher age groups (Fig. 3). In 2018, three-quarters of all DRDs were aged 35 or older, whereas in the early 2000s, their proportion was still approximately 35% [26].

Of particular interest is that ORD rates involving methadone increased with age [12, 13], suggesting that older users are more susceptible to methadone overdosing. It is also of interest that methadone and gabapentins were less involved in younger (<35 years) (33 vs. 22%, respectively) than in older DRD victims (≥35 years) (52 and 34%, respectively) [26, 30], whereas the rates were independent of age for other opioids and benzodiazepines, except that opioids were less often involved in those aged younger than 25 years. Finally, the percentage THN recipients aged 45 years or older doubled from 9% in 2015/2016 to 19% in 2017/2018, providing another indication of ageing of the opioid-related PUDP population in Scotland [33].

Fig. 3. DRD in Scotland involving combination of drugs (2010–2016) [26, 42]. Benzodiazepines, like diazepam, etizolam, and diclazepam. No data available for 2017–2019. DRD, drug-related death.

England/Wales

In England between 2009 and 2018, the median age of PUDP increased from 37.5 to 42.9 years and the median age of PUDP in treatment increased from 37.5 to 40.0 years. Interestingly, 78% of PUDP in treatment for opiates was aged 35 years or older. Together, these data suggest that the group of PUDP in England/Wales is ageing. Indeed, in 2017/2018, 69% of people in treatment for opiates had already used heroin for almost 20 years [27]. In England/Wales, the median age of DRDs increased between 2009 and 2018 from 42.6 to 45.2 years [29]. In 2018, the DRD rate per 100,000 population was highest in the age groups of 30–39 years (9.9) and 40–49 years (12.6), whereas the rate for those younger than 20 years and the group of 20–29 years was 0.4 and 5.0, respectively.

Summary

Both in Scotland and in England/Wales, the median age of PUDP and PWOP, and DRDs is increasing in the last decade; however, a slightly higher speed of change and current median ages are observed in Scotland.

Incarceration

Recent prison release, particularly within the first 4 weeks after release, when individuals are commonly on parole, is another frequently reported risk factors for ORDs [55–61]. Ex-prisoners are in danger, especially on the first day of their release when they want to “celebrate” their regained freedom. Incarcerated people with past opioid use and pre-sentence daily opioid use showed an increased ORD risk ($RR = 3.5$) upon release from prison

[60], and from all deaths after prison release, almost 20% were drug-related [62], suggesting immediate provision of OST or NTH kits could have a substantial effect on reducing ORDs.

Scotland

In 2017/2018, Great Britain had the highest incarceration rate in western Europe with 174 and 166 prisoners per 100,000 population in England/Wales and Scotland, respectively (HoCL, 2019). The prevalence of opioid use in Scottish prisoners is very high with 28% of the prisoners testing positive for illicit opioids on reception [63, 64] and about half with a history of drug dependence [65]. Of all prisoners, 20 and 28% had been prescribed methadone or offered drug treatment, respectively [65], implicating that virtually all opioid-dependent prisoners were in treatment for their addiction. Following the introduction of a prison-based OST policy in Scotland, DRDs in the 12 weeks following release were reduced by 49% [19].

England

The most recent available report on drug use in English/Welsh prisons covers the year 1998 [66, 67]. It showed that 31–43% of male and 39–66% of female (remand and sentenced) prisoners had used opioids in the 12 months before imprisonment and that around half of them was drug-dependent with high rates of ever injecting drugs (23–40%). A more recent study confirmed the high rate of drug dependence (57%) among prisoners in London [65, 68]. In the Surveying Prisoner Crime Reduction study performed in 2005/2006 in England/Wales, 40% of the im-

prisoned responders reported to have ever used heroin [69]. Of around 89,000 people in secure settings in 2016/2017, 59,258 adults (63% of total) were in contact with drug and alcohol treatment services, with half of them (29,626; 33% of total) for problem opioid use, of whom 79% received OST. Only 16% of opioid users leaving prison were discharged as having completed treatment, and 65% of discharged opioid users were referred to treatment services in the community on release (PHE, 2018).

Summary

England/Wales and Scotland have similar (high) rates of imprisonment (about 170 per 100,000 population), and in both prison populations, drug dependence is frequent (about 50%) with similar rates in both countries. There were also similar OST treatment rates in opioid-dependent prisoners (around 80%) in Scotland and England/Wales.

Deprivation

Poverty and PUDP operate synergistically and are – at the extreme end – reinforced by psychiatric disorders and unstable housing or homelessness. There are clear differences in DRD rates by deprivation, with higher rates for those living in more deprived areas [37], and therefore, it seems that deprivation is an important indirect driver of DRDs. DRD mainly occurs in PUDP who live in socio-economically deprived areas characterized by long-term poverty, social isolation, broken families, depression, marginalization, unemployment, and homelessness [6, 7, 70]. However, the question is whether PUDP in Scotland are more socially deprived than those in England/Wales and whether regional differences in social deprivation is a driver of the higher rate of ORDs in Scotland than England/Wales.

Scotland

In general, Scotland belongs to the poorest areas in the UK [71] and has poorer health outcomes than other areas in Britain [72]. For instance, Glasgow in particular fares significantly worse when compared to English cities of similar social and economic history (Manchester and Liverpool). Half of people died from DRDs lived in the 20% most deprived neighbourhoods in Scotland [36]. The large impact of deprivation on DRD is well illustrated by the observation that 53% of 195 homeless deaths in 2018 were drug-related [73]. Furthermore, the Scottish Burden of Disease Study found that the overall burden of drug use disorders is 17 times higher in Scotland's most deprived than its least deprived areas [74].

England/Wales

Over the last decade, the rate of drug misuse has more than doubled in the north east, one of the most deprived areas of England [28]: DRDs increased from 46.3 per million in 2008 to 96.3 per million population in 2018), a higher rate than that in any other English region or Wales [29].

Summary

Problem drug use and DRD/ORD are more prevalent in socio-economically deprived areas both in Scotland and England/Wales, but no valid data are available to assess the role of social deprivation as a possible driver of the Scottish opioid crisis.

Summary and Conclusion

The explanation for the dramatic 5-fold higher ORD rate in Scotland versus England/Wales appears to be multifactorial. The results of the peer-reviewed studies showed (again) that ageing of PUDP/PUOP, injecting drug use, lack of treatment during incarceration, and social deprivation were important risk factors of DRDs/ORDs. However, in none of these studies, a direct and quantified comparison was made of the key drivers of ORD between Scotland and England/Wales, and therefore, these studies were not able to contribute to a better understanding of the regional differences in ORDs. However, analysis of existing non-peer-reviewed reports showed that the ORD rate in Scotland was indeed much higher than that in England/Wales (RR = 5.1), especially for heroin/morphine-related (RR = 4.4.) and methadone-related (RR = 14.7) deaths, and that this regional difference would remain after controlling for the higher rate of PUOP in Scotland than England/Wales (RR = 2.3), indicating that people in Scotland have a higher risk to become a PUOP, and once PUOP, they have a higher risk to die from an opioid overdose. Possible drivers for this latter risk included (1) higher rates of co-use of other CNS depressants in Scotland (benzodiazepines RR = 20.8, gabapentinoids RR = 14.4, and Z-drugs RR = 1.8); (2) a more limited access to opioid dependence treatment (45 vs. 54%) and a lower efficacy of these treatments in Scotland; and (3) a steeper ageing and a mean higher age of PUOP in Scotland than England/Wales (45 vs. 43 years). There were no clear regional differences in injecting drug use or incarceration and prison OST between Scotland and England/Wales, and therefore, their role as drivers of the Scottish opioid crisis is probably limited. PUDP and

DRD/ORD are more prevalent in socio-economically deprived areas both in Scotland and England/Wales, but no valid data were available to assess the role of social deprivation as a possible driver of the Scottish opioid crisis.

Another point of concern is the high and increasing use of benzodiazepines, gabapentinoids, and especially the benzodiazepine derivative etizolam in opioid users in Scotland compared to England and Wales. There is no explanation for this difference in the literature, and therefore, we advocate to further investigate the possible reasons of this difference and its implication for the prevention of DRD.

To halt the relentless increase in drug deaths in Scotland, it is advocated to develop and apply an evidence-based drugs policy, based on an efficient addiction treatment system that is also able to capture and treat PUDP living in the most deprived areas. To be successful, this treatment should combine OST and psychosocial care, including housing and day activities/work, safe consumption facilities, availability of THN kits, and the introduction of heroin-assisted treatment for therapy-resistant OST patients (e.g., [3, 75, 76]), in addition, awareness-building about the dangers of injection drug use and the combined use of opioids with other depressants (alcohol, benzodiazepines, etizolam, and gabapentinoids). Etizolam is often manufactured domestically, but benzodiazepines and gabapentinoids are often prescribed together with opioids, and vice versa, and partly diverted to the black market. Restricted prescribing of opioids and other depressants (without depriving those in need from their medication) is another important step in the battle against opioid overdose deaths in Scotland. In summary, we need general societal measures to reduce social inequality, poverty and deprivation, awareness programs about the risks of injecting and polydrug use, and an extension and improvement of the addiction treatment services. Only such a concerted action can be successful in solving the opioid crisis in Scotland. The Scottish opioid crisis and the recommendations to escape from it also show us the way to

prevent the development of similar situation in other European countries: take (better) care of the most deprived part of your population, take (better) care of rational medicine prescription programs, and take (better) care of existing addiction treatment services (even in times of economic scarcity).

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Statement of Ethics

An ethics statement was not required for this study type, and no human or animal subjects were used.

Conflict of Interest Statement

Prof. Wim van den Brink is the editor-in-chief of EAR and reports personal fees from Lundbeck, Novartis, D&A Pharma, Take-da, Mundipharma, Angelini, Opiant, and Idivior for services outside the submitted work. Dr. Jan van Amsterdam and Dr. Mimi Pierce report no conflict of interest.

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Author Contributions

Dr. Jan van Amsterdam and Dr. Mimi Pierce performed the systematic search and drafted the paper. Prof. Wim van den Brink critically corrected and completed the final version.

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