

# Impact of supervision of methadone consumption on deaths related to methadone overdose (1993-2008): analyses using OD4 index in England and Scotland

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## ABSTRACT

**Objective** To evaluate the impact of introduction of supervision of methadone dosing on deaths related to overdose of methadone in Scotland and England between 1993 and 2008 while controlling for increased prescribing of methadone.

**Design** Analysis of annual trends in deaths related to overdose of methadone in relation to defined daily doses of methadone prescribed.

**Setting** Scotland and England.

**Population** Deaths in which methadone was coded as the only drug involved or as one of the drugs implicated.

**Main outcome measure** Annual OD4-methadone index (number of deaths with methadone implicated per million defined daily doses of methadone prescribed in that year).

**Results** OD4-methadone declined substantially over the four epochs of four years between 1993 and 2008. It decreased significantly ( $P<0.05$ ) in 10 of 12 epoch changes: in Scotland from 19.3 (95% confidence interval 15 to 24) to 4.1 (2.8 to 5.4) and finally to 3.0 (2.4 to 3.5) for methadone only deaths (and from 58 to 29 to 14 for deaths with any mention of methadone); in England from 27.1 (25 to 29) to 24.8 (23 to 27) and finally to 5.8 (5.3 to 6.3) for methadone only deaths (and from 46 to 42 to 12 for deaths with any mention of methadone). The decreases in OD4-methadone were closely related to the introduction of supervised dosing of methadone in both countries, first in Scotland (1995-2000) and later in England (1999-2005). These declines occurred over periods of substantial increases in prescribing of methadone (18-fold increase in defined daily doses per million population annually in Scotland and sevenfold increase in England).

**Conclusions** Introduction of supervised methadone dosing was followed by substantial declines in deaths related to overdose of methadone in both Scotland and England. OD4-methadone index analyses, controlled for substantial increases in methadone prescribing in both countries, identified at least a fourfold reduction in deaths due to methadone related overdose per defined daily dose (OD4-methadone) over this period.

## INTRODUCTION

Heroin and other opiates contribute disproportionately to deaths from drug overdoses, compared with their low prevalence of use in many developed countries.<sup>1-3</sup> Deaths due to overdose of opiates, for example, accounted for 9% of deaths in young Australian adults under the age of 50 in 1998 and for more than 10% in several European cities despite the fact that they were used by less than 1% of adults in any year.<sup>4,5</sup> We need to understand better the factors driving these deaths if they are to be reduced. Opioids are implicated in more than three quarters of all illicit drug related deaths in the United Kingdom.<sup>2-7</sup>

The prescribed opioid methadone is used as maintenance treatment for opioid dependence, leading to a major reduction in deaths from overdose.<sup>8-14</sup> Almost all methadone is prescribed for treatment of opioid addiction; for example, 99.5% of all methadone prescriptions in Scotland in 2008-9 were for "treatment of substance dependence."<sup>6</sup> The vast majority of this is prescribed as oral liquid/linctus: 100% in Scotland and 96% in England.<sup>6,15</sup>

Careless or unsanctioned use of methadone contributes to deaths due to overdose.<sup>2</sup> During the 1990s, for example, methadone was implicated in as many drug related deaths in the UK as was heroin.<sup>16,17</sup> Recommendations were made for UK clinical practice to align with other countries, with the introduction of new arrangements for supervised consumption of methadone,<sup>18,19</sup> and major change occurred over the past decade.<sup>15</sup>

Methadone prescribing practice in the UK was changed in the mid-late 1990s, with the aim of reducing deaths related to overdose of methadone; daily dispensing and supervision of methadone dosing were introduced or increased to reduce diversion.<sup>2,18,19</sup> These changes occurred first in Scotland, from 1992 onwards,<sup>20-29</sup> and only later in England (fig 1).<sup>30-37</sup>

We examined the impact of these changes on deaths related to overdose of methadone per million defined daily doses (see later for definition) of prescribed methadone: the OD4-methadone index. We

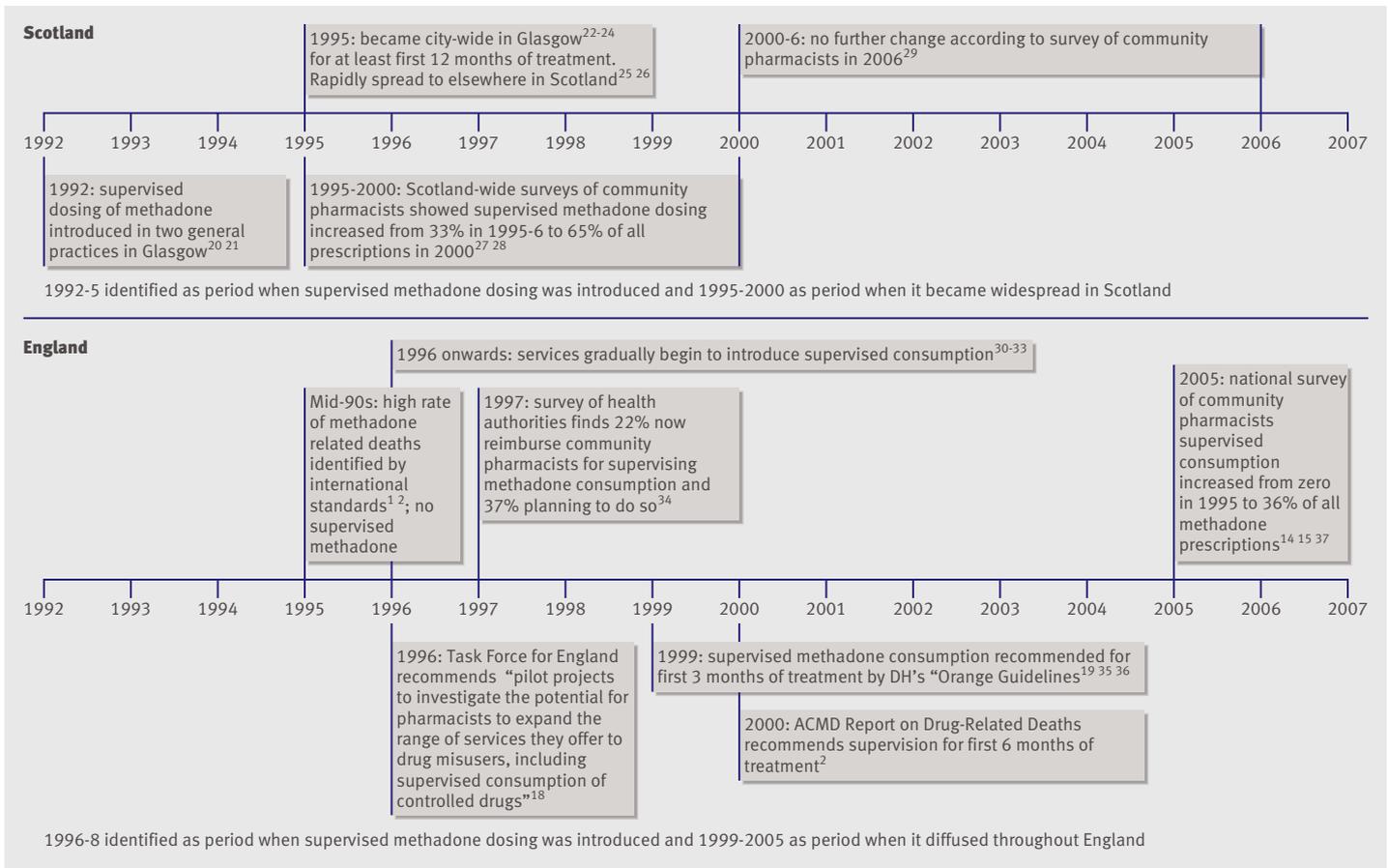


Fig 1 | Timelines of introduction and spread of supervision of methadone consumption in Scotland and England

examined whether reductions in OD4-methadone index (both narrowly and broadly defined) coincided with the period of introduction of supervision of methadone dosing in Scotland and England.

## METHODS

We defined the annual OD4-methadone index as the number of deaths with methadone implicated per million defined daily doses of methadone prescribed in that year. The OD4-methadone index enabled us to examine methadone's contribution to deaths due to opioid overdose while controlling for expansion of methadone treatment during the study period. We defined methadone related deaths in two ways: deaths due to overdose in which methadone was the only drug present and deaths due to overdose in which methadone was one of two or more drugs that were present. These calculations therefore produce two versions of the OD4-methadone index: the OD4-methadone (sole drug) index and the OD4-methadone (any mention) index.

### Statistical methods

We examined annual changes within each country (that is, separately for England and Scotland). We additionally examined the data as four epochs of four years each and did statistical analysis. In deriving 95% confidence intervals for the OD4-methadone index, we

assumed that the number of deaths due to methadone overdose per calendar year and per four year epoch followed a Poisson distribution.

### OD4-methadone index

#### *Deaths related to overdose of methadone*

We obtained mortality data for Scotland and England (special retrieval for England only, on request, from the Office for National Statistics).<sup>6 7</sup> We obtained data on the numbers of drug related deaths in which methadone was the "only drug" reported in coroners' reports and the number in which it was "one of more than one drug" reported by coroners.<sup>6</sup> Coronial processes differ in practice and definitions between Scotland and England, so we examined changes over time within each country.

#### *Defined daily dose of prescribed methadone*

We obtained national data separately, by special request, on the total quantity of methadone prescribed annually by the NHS in Scotland and in England (General Register Office Scotland and Department of Health NHS Statistics) for 1993-2008 (tables 1 and 2). We arranged for retrieval of these NHS prescription data for all instances in which the reported indication was "treatment of substance dependence."

We used the World Health Organization's definition of defined daily dose as "the assumed average

**Table 1** | Methadone data—Scotland (population 5.2 million in 2008)

	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
<b>Deaths</b>																
Methadone only	10	21	21	27	20	8	5	5	8	14	12	9	20	35	29	14
Any mention of methadone	25	55	58	99	87	64	62	56	71	99	87	80	72	97	114	181
<b>Quantity prescribed</b>																
Methadone kg (mg × 1 million)	31.0	51.7	72.1	90.8	112.3	127.7	145.5	173.6	210.0	255.0	308.1	363.2	421.9	473.1	520.6	572.5
Year on year increase (%)	–	66.7	39.6	25.9	23.6	13.8	13.9	19.3	21.0	21.4	20.8	17.9	16.2	12.2	10.0	10.0
<b>Defined daily dose (DDD) calculations</b>																
Methadone DDDs—60 mg daily doses (millions)	0.52	0.86	1.20	1.51	1.87	2.13	2.43	2.89	3.50	4.25	5.13	6.05	7.03	7.89	8.68	9.54
<b>OD4 calculations</b>																
OD4 score (methadone only) (per million)	19.4	24.4	17.5	17.8	10.7	3.8	2.1	1.7	2.3	3.3	2.3	1.5	2.8	4.4	3.3	1.5
OD4 score (any mention of methadone) (per million)	48.4	63.9	48.2	65.4	46.5	30.1	25.6	19.4	20.3	23.3	16.9	13.2	10.2	12.3	13.1	19.0

maintenance dose per day for a drug used for its main indication in adults.”<sup>38</sup> This provided an estimate of consumption in a fixed unit of measurement that is independent of price and formulation and so enabled assessment of trends in methadone use. We used a methadone daily dose of 60 mg as the defined daily dose because this was the lower point of the recommended dose range and was close to the average dose prescribed in the UK over the period of study—namely, 47.3 (SD 28.2) mg in 1995 and 56.3 (28.7) mg in 2005.<sup>15 19 37 39</sup>

#### Calculation of the OD4-methadone index

To examine the temporal relation between methadone prescribing and the number of methadone related deaths, we calculated the OD4-methadone index separately for Scotland and England in respect of deaths in which methadone was the sole drug mentioned (OD4-methadone (sole drug)) and deaths in which there was any mention of methadone (OD4-methadone (any mention)).

#### Timing of policy initiative

Supervision of methadone consumption was introduced in Scotland in two general practices in Glasgow in 1992 and subsequently across Glasgow, and then widely throughout Scotland during 1995-2000 (fig 1, top). In England, no supervised consumption existed at the time of a national survey of pharmacists in 1995; it began to appear in 1996 and spread more slowly across England throughout 1999-2005 (fig 1, bottom).

## RESULTS

Over the 16 year period 1993-2008, 1307 deaths related to overdose of methadone occurred in Scotland and 4317 in England. Methadone was the sole reported drug in 258 (20%) of these deaths in Scotland and in 2343 (54%) in England.

#### Methadone prescribing

Over the 16 year study period, 65 million defined daily doses of methadone were prescribed in Scotland (table 1) and 198 million in England (table 2). Rates of prescribing increased dramatically over the study

period (1993-2008) in both countries. In Scotland, it increased from fewer than 0.1 million defined daily doses per million population in the early 1990s to 1.8 million by 2008 (table 1). In England, methadone prescribing increased from approximately 0.1 million defined daily doses per million population in 1993 to just over 0.5 million by 2008 (table 2).

#### Deaths related to overdose of methadone

In Scotland (table 1), deaths related to overdose of methadone peaked in 1996 and 1997 (and in 1996 for methadone as sole drug); they then declined for the next four years and remained at this lower level for several years. Methadone only deaths began to increase again in the mid-2000s.

In England (table 2), deaths related to overdose of methadone peaked in 1997 and 1998 (and in 1997 for methadone as sole drug) and then declined for six years after 1998. They began to increase again before the final four year epoch (table 3) but had not regained their 1997 level by 2008.

#### OD4-methadone index calculations

The OD4-methadone index for both deaths due to overdose with methadone only and those in which methadone was mentioned declined substantially in both Scotland and England.

In Scotland, the OD4-methadone (sole drug) index declined after 1996; annual deaths due to overdose decreased from around 20 per million defined daily doses to only two by 1999. From 2000 onwards, this OD4 index remained below five (table 1 and fig 2, top). Thus, over a four year period (1997-2000), the deaths with methadone reported as sole drug reduced from 20 to three per million defined daily doses and remained around this lower level thereafter. The reduction in deaths with any mention of methadone was more gradual, from 58 deaths per million defined daily doses in the first four year epoch to 29 in the second and thereafter to 18 and 14 (tables 1 and 3; fig 2, top).

In England, the OD4-methadone (sole drug) index was at a high level until 1998; annual deaths due to overdose in which only methadone was reported

Table 2 | Methadone data—England (population 51.4 million in 2008)

	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
<b>Deaths</b>																
Methadone only	113	144	169	179	268	218	171	144	121	86	71	104	94	121	153	187
Any mention of methadone	195	254	286	300	402	377	323	257	229	191	189	216	209	229	305	355
<b>Quantity prescribed</b>																
Methadone kg (mg × 1 million)	262.6	305.9	360.2	413.2	460.7	472.9	490.1	517.8	557.7	633.6	772.2	931.1	1127.5	1343.0	1530.2	1730.0
Year on year increase (%)	–	16.5	17.7	14.7	11.5	2.6	3.6	5.7	7.7	13.6	21.9	20.6	21.1	19.1	13.9	13.1
<b>Defined daily dose (DDD) calculations</b>																
Methadone DDDs—60 mg daily doses (millions)	4.38	5.10	6.00	6.89	7.68	7.88	8.17	8.63	9.30	10.56	12.87	15.52	18.79	22.38	25.50	28.83
<b>OD4 calculations</b>																
OD4 score (methadone only) (per million)	25.8	28.2	28.2	26.0	34.9	27.7	20.9	16.7	13.0	8.1	5.5	6.7	5.0	5.4	6.0	6.5
OD4 score (any mention of methadone) (per million)	44.6	49.8	47.6	43.6	52.4	47.8	39.5	29.8	24.6	18.1	14.7	13.9	11.1	10.2	12.0	12.3

ranged from 25 to 35 per million defined daily doses. This OD4 decreased thereafter, and deaths steadily declined over the next six years to around six per million defined daily doses and remained at this lower level (table 2 and fig 2, bottom). A similar reduction in deaths with any mention of methadone occurred; the OD4-methadone (any mention) index decreased from 46 and 42 deaths per million defined daily doses in the first and second four year epochs to 17 and 11 thereafter (tables 2 and 3; fig 2, bottom).

#### Relation between changes in OD4 and supervised consumption of methadone

We observed three distinct phases in both of the OD4-methadone index scores (methadone only and any mention) in both Scotland and England: an initial steady state, a rapid decline, and then a new steady state. The initial steady state for the OD4-methadone (sole drug) index in Scotland was around 19 in 1993-6 (table 3 and fig 2, top). This was followed by rapid reduction of OD4-methadone down to four during 1997-2000. The reduction tracks the timing of Scotland's adoption of supervised methadone consumption between 1995 and 2000 (fig 1, top).

The initial steady state for the OD4-methadone (sole drug) index in England exceeded 25 (that is, more than 25 deaths per million defined daily doses) until 1998. This was followed by a decline over a more extended period (1998-2005) to a new lower level of around six deaths per million defined daily doses (tables 2 and 3; fig 2, bottom). The timing of these changes coincided with the later and more gradual implementation of supervised methadone consumption in England between 1999 and 2005 (fig 1, bottom).

Finally, we examined these data in four epochs of four years each. In Scotland, the largest decline in OD4-methadone occurred between the first and second epochs (table 3). In England, by contrast, the most pronounced decline occurred between the second and third epochs. All changes were statistically significant ( $P \leq 0.02$ ) for transitions between epochs for OD4 index involving both methadone only and any

mention of methadone, except for the two epoch changes marked with an asterisk in table 3.

#### DISCUSSION

This study shows the value of the OD4-methadone index expressed in terms of defined daily dose in assessing the impact of policy changes on the safety of methadone prescribing. Our findings show a remarkable improvement in the safety of methadone prescribing in both Scotland and England, particularly over the period 1995-2004.

The absence of systematic tracking of deaths has meant that this substantial improvement in the safety of methadone treatment has hitherto been neither detected nor quantified. We found that the timing of these changes was precise and was related to a specific change in clinical practice that occurred at different times in the two countries—namely, the widespread supervision of methadone dosing during the early months of treatment. The previous failure to detect this improved safety may be because the change occurred over a period of very substantial increases in prescribing of methadone.

#### Other possible explanations

Before cautiously accepting this inference that the decline in the rate of deaths due to methadone overdose was the result of this increased supervision of dosing, we need to evaluate and exclude other possible explanations of the decline in OD4-methadone. Firstly, we can exclude the possibility that the decline in OD4-methadone reflects either a reduction in availability of heroin, such as occurred in Australia after 2001,<sup>40</sup> or a decline in the number of people using heroin. No evidence exists of any sustained heroin shortage or reduction in the number of heroin users in the UK over the study period. In fact, all indices of the availability and use of heroin, including deaths due to heroin overdose, rose steadily during the study period,<sup>41</sup> as did the number of heroin dependent people being treated by methadone maintenance.<sup>42</sup>

The same is true for changes in the route of opiate use, such as increased use of non-injecting routes.

**Table 3** | Changes in OD4 score over four epochs of four years

Outcome	1993-6	1997-2000	2001-4	2005-8
<b>Scotland (population 5.2 million in 2008)</b>				
Drug related deaths: methadone as only drug	79	38	43	98
Drug related deaths: any mention of methadone	237	269	337	464
Quantity of methadone prescribed (mg × 1 million)	245.6	559.1	1136.3	1988.1
Implied methadone patient years (DDD (60 mg)/365)	11 215	25 530	51 889	90 781
OD4 score: methadone only (95% CI)	19.3 (15 to 24)	4.1 (2.8 to 5.4)	2.3 (1.6 to 2.9)†	3.0 (2.4 to 3.5)*
OD4 score: any mention of methadone (95% CI)	57.9 (50 to 65)	28.9 (25 to 32)	17.8 (15.9 to 19.7)	14.0 (12.7 to 15.3)‡
<b>England (population 51.4 million in 2008)</b>				
Drug related deaths: methadone as only drug	605	801	382	555
Drug related deaths: any mention of methadone	1035	1359	825	1098
Quantity of methadone prescribed (mg × 1 million)	1341.9	1941.5	2894.6	5730.7
Implied methadone patient years (DDD (60 mg)/365)	61 274	88 653	132 174	261 676
OD4 score: methadone only (95% CI)	27.1 (24.9 to 29.2)	24.8 (23.0 to 26.5)*	7.9 (7.1 to 8.7)	5.8 (5.3 to 6.3)
OD4 score: any mention of methadone (95% CI)	46.3 (43 to 49)	42.0 (40 to 44)§	17.1 (15.9 to 18.3)	11.5 (10.8 to 12.2)

DDD=defined daily dose.

Z scores are provided when 95% confidence intervals overlap.

\*All OD4 changes across epoch were significant, except for those concluding here.

†Z score versus previous epoch=2.42.

‡Z score versus previous epoch=3.25.

§Z score versus previous epoch=2.33.

Heroin “chasers” have fewer fatal overdoses than do heroin injectors,<sup>43</sup> and a considerable proportion of UK heroin users are chasers.<sup>44 45</sup> No evidence exists, however, that the proportion of chasers increased over the study period. Even if this had occurred, it would be more likely to reduce deaths due to heroin than deaths involving methadone. It would also not explain the difference in timing between Scotland and England.

Other changes in methadone prescribing and dispensing are unlikely to explain the decline. Recommendations were made to increase doses and rates of daily dispensing of methadone, but doses increased only slowly and the increase in daily dispensing was modest by comparison with the very substantial expansion of supervised methadone consumption in both countries.<sup>37 46</sup>

#### Data sources and collection

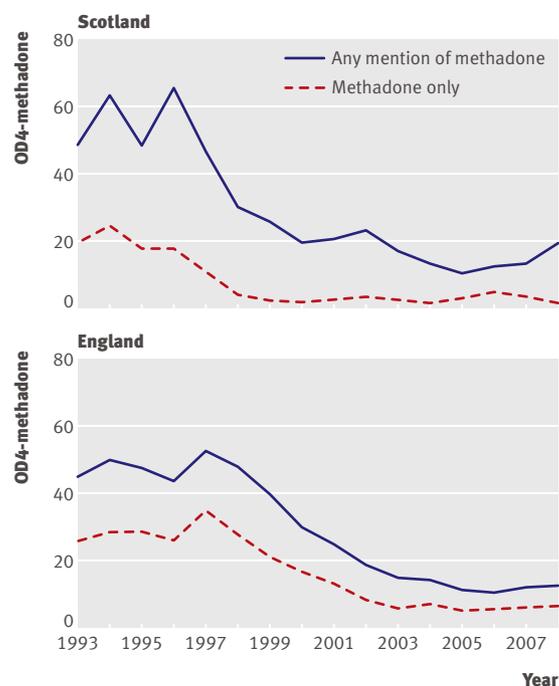
The definition of a death related to overdose of methadone can be restrictive (methadone only) or inclusive (any mention of methadone). Both definitions depend on toxicological assessments and the reporting practices of coroners. We measured deaths in both ways to minimise the impact of these definitions on our findings. The fact that both measures showed parallel changes albeit at different levels over the study period is reassuring. Both also showed the same difference in timing between the two countries. The decline was somewhat faster for methadone only deaths, which one may expect to be more sensitive to any benefits of supervised dosing.

Incompleteness of the data is unlikely to explain the decline. Although dosing data were not available for non-NHS (“private”) practice or for methadone dispensing at on-site hospital pharmacies, these practices relate to only small numbers of prescriptions. Only

1.5% of all methadone prescriptions were from private practice in 1995 and 1.0% in 2005,<sup>15 37</sup> and on-site dispensing in England was rare, accounting for probably less than 1% of dispensing.

#### Conclusions and policy implications

This is the first study to use publicly available mortality data to assess whether increased supervision of methadone has, as intended, reduced deaths due to overdose involving prescribed methadone. The OD4 index can also potentially be used to assess the safety of other



**Fig 2** | OD4-methadone index, Scotland and England, 1993-2008

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Methadone maintenance treatment has repeatedly been shown, across cultures, settings, and epochs, to reduce mortality substantially among heroin addicts entering treatment

Misuse, unsanctioned co-administration, and poorly compliant intake are all associated with risk of death from overdose of methadone

Risk-benefit analysis shows clear advantages of appropriate provision of methadone maintenance treatment

## WHAT THIS STUDY ADDS

Progressive introduction and use of facilities for supervision of methadone consumption during the 1990s was associated with a major reduction in death due to methadone overdose

This reduction occurred over a period of continued growth of the heroin addiction problem and also major expansion of methadone provision

The OD4 index (overdose deaths per daily dispensed dose) decreased approximately fourfold in both Scotland and England coinciding with the period of introduction of supervised consumption

forms of treatment for opioid dependence (such as prescription of buprenorphine): these further analyses should now be done. Our finding of a major reduction in deaths related to overdose of methadone raises the question of whether other changes in treatment practice could achieve even greater reductions in deaths related to overdose of methadone and other opioids.

The General Register Office Scotland (deaths, Scotland), Office for National Statistics (deaths, England), and information services NHS Scotland and England (prescription data) helpfully did special retrievals of national data. We are grateful to John Witton for help with securing these data.

**Contributors:** JS had the idea for the OD4 index and did preliminary investigative analyses; these were refined and improved in discussions with WH, MH, and SMB. JS led on obtaining the data and preparing the first draft of the manuscript, and all authors contributed actively to further development and revision. JS is the guarantor.

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**Competing interests:** All authors have completed the Unified Competing Interest form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare that (1) JS, WH, MH, and SMB have not received any funding support from any company or organisation for the submitted work; (2) JS, WH, MH, and SMB have no relationships with any company that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) JS, WH, MH, and SMB have no non-financial interests that may be relevant to the submitted work.

**Ethical approval:** Not needed (analyses of public data).

**Data sharing:** No additional data available.

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