

WEB APPENDIX

METHODS - Calculation of Average Mortality Rate Ratio

The mortality rates and adjusted rate ratios from different time periods during and after treatment (Figure 1) were used to estimate the average mortality rate ratio and probability that OST reduces average mortality for patients exposed to different durations on OST compared to if they had been unexposed. For this analysis we assumed that the death rate in the period greater than four weeks after treatment represented the ongoing “out of treatment” death rate. The average mortality rate ratio (RR_{OST}) indicates whether OST increases or decreases mortality compared to no treatment. This is estimated as follows:

$$RR_{OST} = [4 \times RR_{ostA} + (D - 4) \times RR_{ostB} + 2 \times RR_{ostC} + 2 \times RR_{ostD}] / (D + 4),$$

where RR_{ostA} , RR_{ostB} , RR_{ostC} and RR_{ostD} are the adjusted mortality rate ratios for the first four weeks on OST, remaining weeks on OST, and weeks 1-2 and 3-4 after leaving OST respectively, compared to the IDU mortality rate when not on OST (greater than four weeks after treatment has ceased); and D is the duration on OST in weeks. We randomly sampled 1,000 different parameter sets from the uncertainty distributions for each rate ratio (assuming lognormal distributions and the same 95% CI as estimated for each rate ratio) in order to generate median and 2.5%/25%/75%/97.5% percentiles for the average mortality rate ratio RR_{OST} for a specific duration on OST (Figure 2). We also estimated the probability that $RR_{OST} < 1$, i.e. the chance that OST results in a reduction in mortality, by calculating the percentage of RR_{OST} estimates that were less than one for each duration of OST modelled (Figure 3).

Figure A. Flow Chart – Cohort inclusion and exclusion

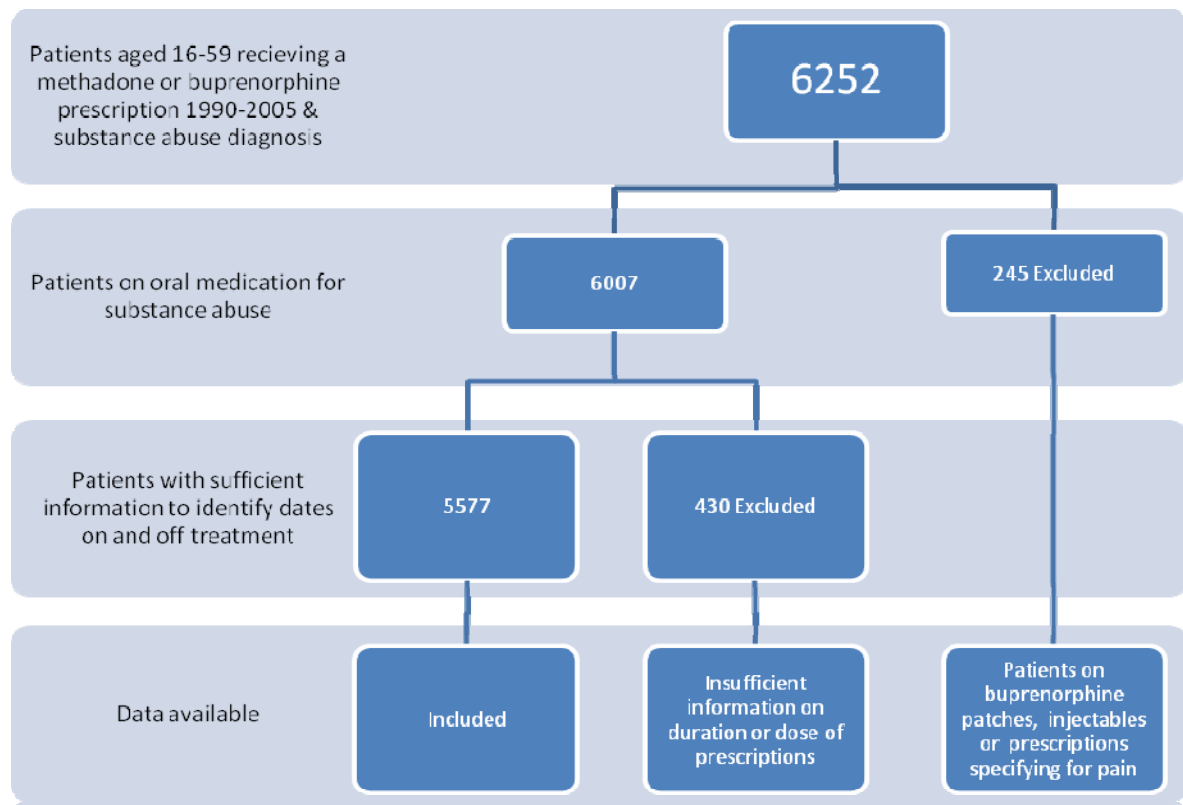


Table A:- Analysis of mortality during and after OST – based on last treatment episode only

Treatment period	Crude RR (95% CI)	Adjusted ¹ IRR (95% CI)
First 14 days on treatment	3.74 (1.96, 7.13)	3.79 (1.98, 7.27)
Days 15-28 on treatment	4.25 (2.13, 8.51)	4.28 (2.13, 8.58)
Remainder on treatment	1.00	1.00
First 14 days off treatment	8.63 (5.13, 14.52)	9.03 (5.29, 15.39)
Days 15-28 off treatment	8.06 (4.67, 13.91)	8.59 (4.91, 15.03)
Remainder off	1.81 (1.23, 2.66)	2.07 (1.38, 3.09)
	p<0.001	p<0.001
Overall on	1.00	1.00
Overall off	1.84 (1.35, 2.51)	2.04 (1.47, 2.84)
	p<0.001	p<0.001

1. Adjusted for age, sex, calendar year, comorbidity

Table B: Analysis of mortality during and after OST - excluding patients who EVER had a prescription for dihydrocodeine

Treatment period	Adjusted ¹ IRR (95% CI)
First 14 days on treatment	3.91 (1.61, 9.48)
Days 15-28 on treatment	1.58 (0.37, 6.63)
Remainder on treatment	1.00
First 14 days off treatment	10.56 (5.61, 19.87)
Days 15-28 off treatment	8.77 (4.44, 17.33)
Remainder off	2.48 (1.54, 3.98)

1. Adjusted for age, sex, calendar period, comorbidity