

The impact of opioid agonist treatment delivered in different settings on all-cause mortality and specific causes of death:

A systematic review and meta-analysis

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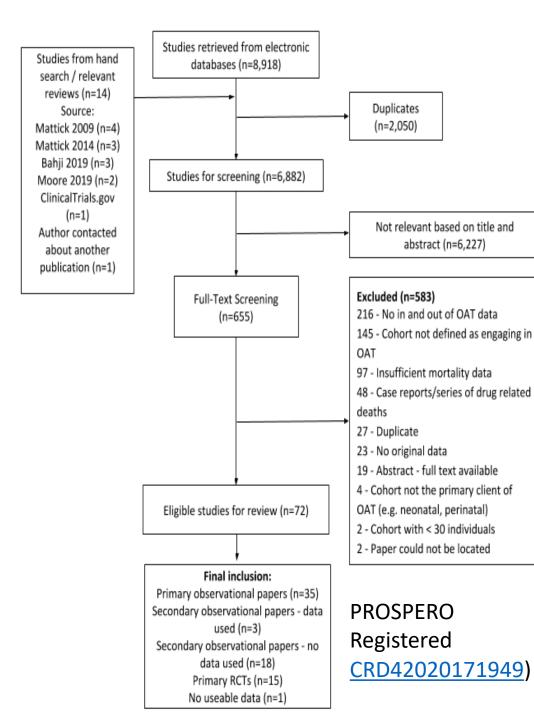
## Summary

- Strong consistent evidence that Opioid Agonist Treatment (OAT) halves mortality risk in people with opioid use disorder
  - Risk of overdose and suicide substantially reduced.
  - Weak evidence that other causes also lower (liver, cancer, CVD)
- Little or no evidence from RCT on mortality.
- Mortality risk elevated in first 4 weeks leaving OAT. And elevated in 1<sup>st</sup> 4 weeks on OAT with methadone but not for buprenorphine.
- OAT reduces mortality risk during and in critical period after prison
- Evaluate OAT delivery and impact on population health in the UK



University of BRISTOL	NCD: 24.1% (95%	Cl, 17.1%-31.2%	)	Trauma: 18.1% (95% Cl, 12.6%-23.7%)
		Cancer: 6.5% (95% Cl, 3.6	752	
				Other trauma: 9.7% (95% Cl, 3.2%-16.2%)
	Other NCD: 12.6% (95% CI, 7.8%-14.5%)	Liver: 5.0% (95% Cl, 2.8	%-7.3%)	
	ID: 19.7% (95%	Cl, 11.7%-27.8%	5)	
				Suicide: 8.4% (95% Cl, 4.4%-12.5%)
Poisoning or drug-dependence:			Other ID: 4.4% (95% CI,	Unknown: 6.5%
31.5% (95% CI, 25.1%-37.8%)	AIDS: 15.3% (95% CI, 6.7		0%-15.8%)	(95% Cl, 2.8%-10.3%)

Larney et al JAMA Psychiatry. 2020; 77(5):493-502.



Identification

Screening

Eligibility

Included

## Prisma Flow Diagram

- Multiple Databases and Trial Registries to January 2020
- P Opioid Use Disorder
- I Opioid Agonist Treatment (OAT)
- C not on OAT
- O mortality risk (All cause, Overdose and other causes)
- 22 eligible RCTs (15 reported on mortality outcomes)
- 36 observational cohort studies
- 2\* no. of cohorts, 6\* no. patients, 3\* PY follow-up than last review (Sordo BMJ 2017)



### A. All cause mortality in RCTs of OAT and a comparator by setting

	Deaths/N	Deaths/N					%
Study	OAT	Comparator		Favours OAT	Favours Comparato	RR (95% CI) r	Weight
Community							
Kakko, 2003 - B	0/20	4/20		•		0.20 (0.01, 2.8	2) 11.82
Gunne, 1981 - M	0/17	2/17	_	•		0.33 (0.03, 4.2	8)7.33
Yancovitz, 1991 - M	0/149	2/152	_	•		0.34 (0.03, 4.2	4)7.80
Metzger, 2015 - B	8/623	9/627				0.94 (0.57, 1.5	7) 44.36
Lee, 2018 - B	4/287	3/283			<b>←</b>	1.13 (0.59, 2.1	7) 18.48
Newman, 1979 - M	3/50	1/50		-	_ <b></b>	1.50 (0.82, 2.7	3) 10.21
Krook, 2002 - B	0/55	0/51				(Excluded)	0.00
Schottenfeld, 2008 -	B0/44	0/82				(Excluded)	0.00
Gruber, 2008 - M	0/72	0/39				(Excluded)	0.00
Strain, 1993 - M	0/166	0/81				(Excluded)	0.00
Tanum, 2017 - B	0/79	0/80				(Excluded)	0.00
Ling, 2010 - B	0/108	0/55				(Excluded)	0.00
Subtotal (I-squared	= 22.5%, p	= 0.265)		$\langle$	>	0.86 (0.59, 1.2	3) 100.00
				-			
Prison							
Rich, 2015 - M	0/114	0/109				(Excluded)	0.00
Kinlock, 2009 - M	0/71	0/140				(Excluded)	0.00
Gordon, 2014 - B	0/104	0/107				(Excluded)	0.00
Subtotal (I-squared	= .%, p = .)					. (., .)	0.00
		.01		1	8		

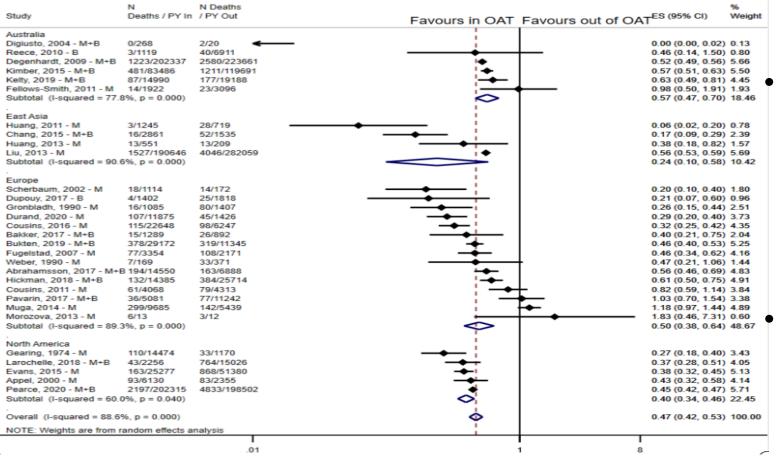
- 15 RCTs (N=3,852 participants).
  - 8 North America; 8 at single clinics; 80% commenced prior to 2010; 60% lasted six months or fewer
- 40 deaths reported
  - 7/15 RCTs with 0 deaths
  - Weak evidence that Mortality lower on those allocated to OAT (RR 0.86; 95%Cl 0.59-1.23)
  - No evidence from prison RCT
- Completely underpowered
  - None of the RCTs had survival as the primary outcome; most counted mortality as an adverse event

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Santo et al JAMA Psychiatry. 2021;78(9):979-993. 2021;

# BRISTOI Observational Studies – All Cause Mortality





36 studies (N~750K (110-300K, 1.9M PY; >20,000 deaths)

### Strong evidence of protective effect of OAT globally

- pooled all-cause CMR on OAT 1.0 per 100PY vs 2.4 per 100PY
- pooled RR 0.47; 95%CI 0.42-0.53)
- Meta-regressions no evidence of differential effect
- by study year, sample size, follow-up, age, gender, comorbidity

## University of BRISTOL

### All-cause mortality rates

## Lower risk of mortality during OAT across participant, treatment, & study characteristics

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Participant characteristics	Rate Ratios (95% Cls)
Women	↓ <b>44 %</b> *
Men	↓ 55 %*
Age	
<35 years	↓ <b>52 %</b> *
>=35 years	↓ <b>52 %</b> *
People who inject drugs	↓ 48 %*
HIV+	↓ 44 %*
HCV+	↓ 47 %*
Treatment provider	
Specialist	↓ <b>69 %</b> *
GP/mixed/other	↓ 53 %*

# All Cause Mortality – Buprenorphine and BRISTOL Methadone

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### C. All cause mortality in OAT compared to out of OAT by medication type Deaths/P) ES (95% CI) Deaths/PY in OAT out of OAT Weight Study Favours in OAT Favours out of OAT Buprenorphine 0/240 7/131 0.04 (0.00, 0.64) 0.94 Chang, 2015 Digiusto, 2004 0/88 1/13 0.05 (0.00, 1.41) 0.67 Dupouy, 2017 4/1402 25/1818 0.21 (0.07, 0.60) 5.85 Pearce, 2020 87/13190 570/23712 0.27 (0.22, 0.34) 27.01 68/22110 324/31817 0.30 (0.23, 0.39) 25.49 Kimber, 2015 40/6911 Reece, 2010 3/1119 0.46 (0.14, 1.50) 4.90 Kelty, 2019 28/6097 78/8619 0.51 (0.33, 0.78) 18.48 Hickman, 2018 20/2877 94/7024 0.52 (0.32, 0.84) 16.67 Subtotal (I-squared = 52.3%, p = 0.040) 0.34 (0.26, 0.45) 100.00 Methadone Huang, 2011 3/1245 28/719 0.06 (0.02, 0.20) 1.15 16/2621 45/1404 0.19 (0.11, 0.34) 3.28 Chang, 2015 18/1114 14/172 0.20 (0.10, 0.40) 2.58 Scherbaum 2002 80/1407 Gronbladh, 1990 16/1085 0.26 (0.15, 0.44) 3.51 ++++++ Gearing, 1974 110/14474 33/1170 0.27 (0.18, 0.40) 4 66 Durand, 2020 107/11875 45/1426 0.29 (0.20, 0.40) 5.02 Cousins, 2016 115/22648 98/6247 0.32 (0.25, 0.42) 5.75 13/551 13/209 0.38 (0.18, 0.82) 2.27 Huang, 2013 Evans, 2015 163/25277 868/51380 0.38 (0.32, 0.45) 6.62 Appel, 2000 93/6130 83/2355 0.43 (0.32, 0.58) 5.50 Pearce, 2020 2085/188113 4237/174431 0.46 (0.43, 0.48) 7.24 77/3354 108/2171 0.46 (0.34, 0.62) 5.53 Fugelstad, 2007 Weber, 1990 7/169 33/371 0.47 (0.21, 1.06) 2.08 36/1493 31/662 0.51 (0.32, 0.83) 3.91 Ledberg, 2017 Liu, 2013 1527/190646 4046/282059 0.56 (0.53, 0.59) 7.23 Kimber, 2015 750/136200 1777/183696 0.57 (0.52, 0.62) 7.12 Hickman, 2018 106/9926 266/17517 0.70 (0.56, 0.88) 6.14 Kelty, 2019 59/8893 99/10569 0.71 (0.51, 0.98) 5.26 Cousins, 2011 61/4068 79/4313 0.82 (0.59, 1.14) 5.15 Fellows-Smith, 2011 14/1922 23/3096 0.98 (0.50, 1.91) 2.74 Muga, 2014 299/9685 142/5439 1.18 (0.97, 1.44) 6.36 Morozova, 2013 6/13 3/12 1.83 (0.46, 7.31) 0.89 0 Subtotal (I-squared = 90.0%, p = 0.000) 0.47 (0.41, 0.54) 100.00 NOTE: Weights are from random effects analysis

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 Stratified by methadone treatment (22 studies) and buprenorphine (8 studies)

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- Both OAT treatments showed strong protective effect
- methadone (RR 0.47 95%CI 0.41-0.54)
- buprenorphine (RR 0.34 95%CI 0.26-0.45)

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### University of OAT Impact on Other Causes of Death BRISTOL

- All injury: (17S, 563,000PY, 2,014D)
- Overdose: (22S, 910,000PY 2,351D)
- Suicide: (14S, 542,000PY 293D)
- Liver Disease: (14S, 520,000PY 597D)
- Cancer: (14S 524,000PY, 522D)
- CVD: (14S 524,000PY, 429D)
- HIV-related (15S 493,493PY, 383D)
- Bacterial/SSTI (13S 500,000PY, 144D)

- RR 0.34 (95%CI 0.27-0.42)
- RR 0.41 (95%CI 0.33- 0.52)
- RR 0.48 (95%CI 0.37- 0.61)
- RR 0.89 (95%CI 0.67- 1.19)
- RR 0.72 (95%CI 0.54-0.98)
- RR 0.69 (95%CI 0.60- 0.79)
- RR 1.14 (95%CI 0.75- 1.74)
- RR 0.90 (95%CI 0.72- 1.12)

## University of Critical Periods in and out of OAT BRISTOL

### All cause mortality by time period on or off methadone or buprenorphine

Study	Deaths/PY	Deaths/PY Remainder In OAT	Favours Other Time Period	Favours Remainder In OAT	ES (95% CI)	% Weight
Methadone - Firs	st Four Weeks	In / Remainder In				
Cousins, 2016	15/3371	100/19277			0.86 (0.50, 1.48)	9.31
Hickman, 2018	13/984	93/8942		•	1.27 (0.71, 2.27)	9.21
Cousins, 2011	28/1623	33/2445	_	• · · · · · · · · · · · · · · · · · · ·	1.28 (0.77, 2.12)	9.41
Pearce, 2020	201/14390	1884/173723			1.29 (1.11, 1.49)	10.03
Kimber, 2015	31/3067	719/133132			1.87 (1.31, 2.68)	9.73
Appel, 2000	7/171	86/5959			2.83 (1.31, 6.11)	8.63
Chang, 2015	2/85	14/2535			4.26 (0.97, 18.75)	6.20
Durand, 2020	15/397	92/11478			4.72 (2.73, 8.14)	9.30
Degenhardt, 200		554/109033			7.39 (5.93, 9.19)	9.96
Ledberg, 2017	8/52	28/1441			7.92 (3.61, 17.37)	8.58
Muga, 2014	26/97	272/9586			9.47 (6.33, 14.16)	9.65
Subtotal (I-squa					2.81 (1.55, 5.09)	100.00
Methadone - Firs	st Four Weeks	Out / Remainder In				
Cousins, 2011	30/1236	33/2445			1.80 (1.10, 2.95)	9.09
Ledberg, 2017	2/36	28/1441			2.86 (0.68, 12.00)	3.06
Degenhardt, 200		554/109033			3.94 (2.84, 5.47)	10.67
Hickman, 2018	45/780	93/8942			5.54 (3.88, 7.92)	10.43
Appel, 2000	9/100	86/5959			6.24 (3.14, 12.39)	7.29
Muga, 2014	29/146	272/9586			7.01 (4.78, 10.29)	10.17
Cousins, 2016	44/1181	100/19277			7.18 (5.04, 10.24)	10.44
Pearce, 2020		1884/173723		•	7.77 (7.17, 8.41)	12.27
Durand, 2020	29/311	92/11478			11.63 (7.66, 17.66)	
Kimber, 2015	167/2416	719/133132		Š	12.80 (10.82, 15.15	
Chang, 2015	5/50	14/2535		<u> </u>	18.11 (6.52, 50.27)	
Subtotal (I-squa					6.58 (4.93, 8.79)	100.00
Buprenorphine	First Four W	eeks In / Remainder In				
Dupouy, 2017	0/44	4/1358	-	L	0.00 (0.00, 0.05)	10.80
Hickman, 2018	3/452	17/2426			0.95 (0.28, 3.23)	25.35
Kimber, 2015	7/2138	61/19973		•	1.07 (0.49, 2.34)	30.50
Pearce, 2020	22/2756	65/10435		•	1.28 (0.79, 2.08)	33.36
Subtotal (I-squa	red = 81.5%,	p = 0.001)			0.58 (0.18, 1.85)	100.00
Buprenorphine -	First Four We	eeks Out / Remainder In				
Dupouy, 2017	0/10	4/1358			0.01 (0.00, 0.23)	5.12
Pearce, 2020	109/2790	65/10435		↓ <b>→</b>	6.27 (4.61, 8.53)	34.55
Hickman, 2018	15/316	17/2426			6.78 (3.39, 13.58)	27.40
Kimber, 2015	37/1698	61/19973		<b>→</b>	7.13 (4.74, 10.73)	32.94
Subtotal (I-squa	red = 83.2%,	p = 0.000)			4.85 (2.37, 9.94)	100.00
NOTE: Weights	are from rand	om effects analysis				
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		.01		1 10		

- Overall Mortality Risk
  - 6 times higher in 1<sup>st</sup> month out of OAT (95%CI 4.3-8.4)
  - 1.9 times higher in 1<sup>st</sup> month in OAT (95%CI 1.10, 3.35)
  - compared to rest of time on OAT
- Mortality risk similar leaving OAT for patients on buprenorphine or methadone
- But big difference in mortality risk in 1<sup>st</sup> month of OAT for methadone and buprenorphine

University of OAT in Prison on Mortality in Prison and in 1<sup>st</sup> 4 BRISTOL weeks after release

Mortality in Prison (1 Study)

- On OAT (11D 16,440PY) 0.67 per 100PY vs
- Not on OAT (40D 14,548PY) 2.75 per 100PY
- RR OAT impact 0.24 (95%Cl 0.12, 0.47)
- Drug-related Deaths First 4 weeks post-release (2 Studies)
  - Release on OAT (10D 2,856PY) 3.5 per 100PY
  - No OAT prior to release (47D 2,578PY) 21.1 per 100Py
  - RR OAT impact 0.19 (95%Cl 0.10, 0.37)

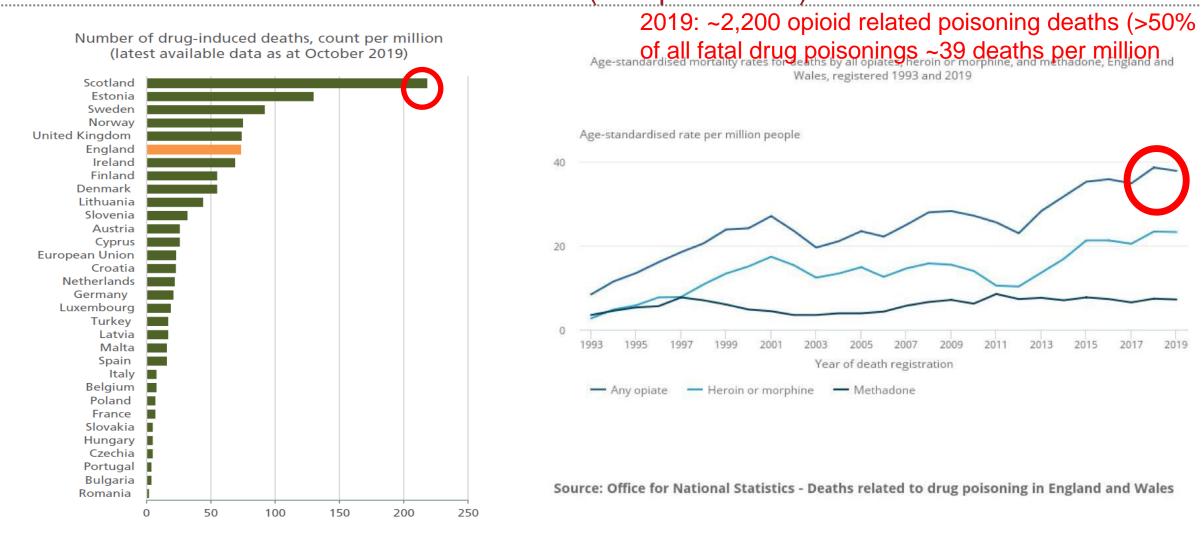




- OAT strongly associated with lower risk of mortality ( $\downarrow$  51%)
- **Lower** risk of multiple causes of mortality in OAT...
  - Suicide (52%), cancer (28%), alcohol-related (41%), cardiovascular-related (31%), and drug-related mortality (59%)
- ↓ Mortality risk in OAT during and after release from incarceration
- Retention critical to achieve population benefits of OAT
  - Evaluate OAT in UK on averting OD and ACM
- Strengthen evidence on OAT in prison on mortality risk in and out of prison



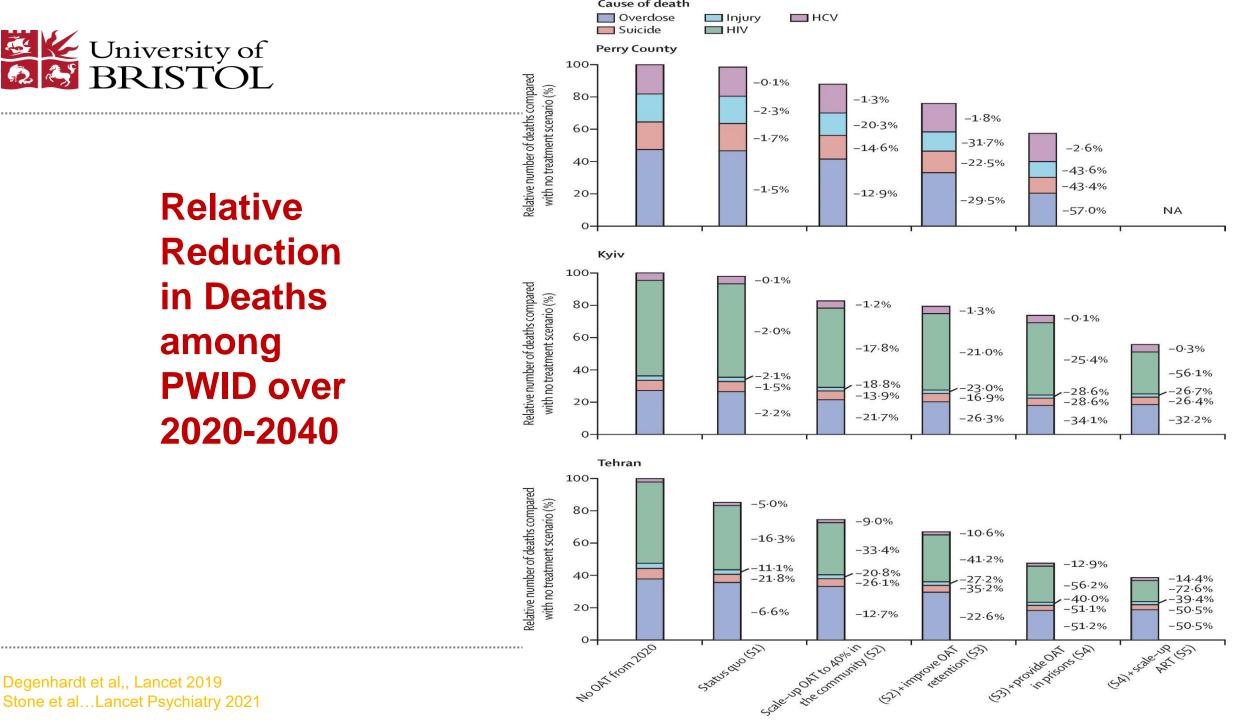
### Opioid overdose deaths increasing in the UK (rate per million)



University of BRISTOL



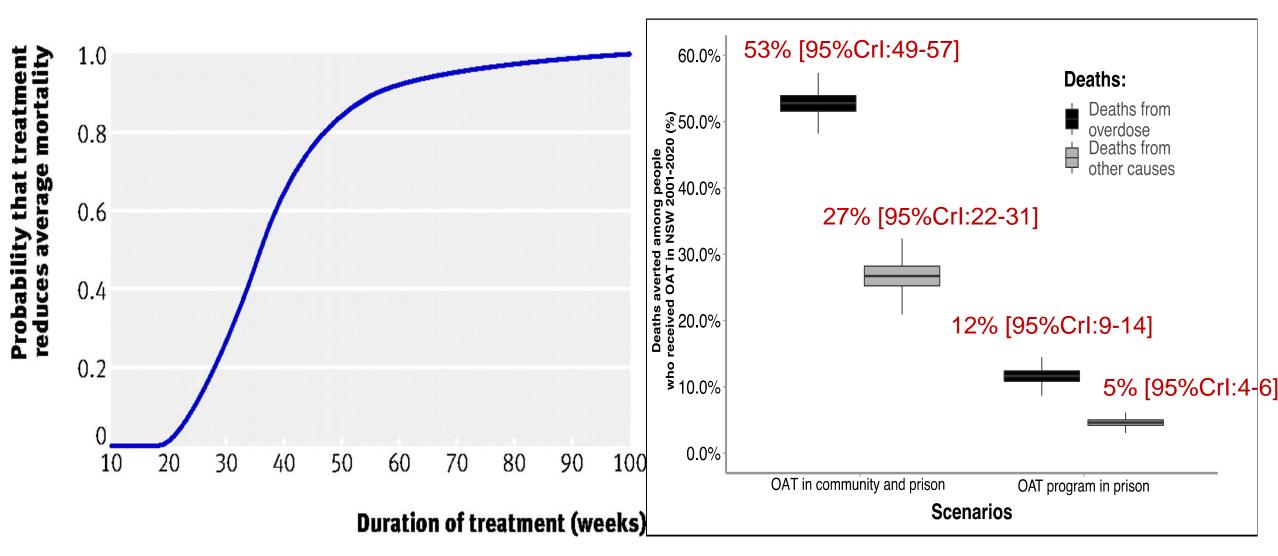
Relative Reduction in Deaths among **PWID** over 2020-2040



Degenhardt et al,, Lancet 2019 Stone et al...Lancet Psychiatry 2021

# Probability that OAT reduces mortality for different durations of treatment

Proportion of deaths averted through OAT program from 2001-2020 NSW



Chaillon... Bórquez et al. Addiction 2021 (in press)



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- NIHR HS&DR Project: 12/136/105 Evaluating the impact of opiate substitution treatment on drug related deaths in the population: a natural experiment using primary care, other drug treatment databases & model projections. ISAC CPRD Protocol 14\_073R2.
- MRC Addiction Research Clinical Training programme (MR/N00616X/1)
- NIHR Health Protection Research Unit (HPRU) in Behavioural Science and Evaluation
- NIHR School of Public Health Research & NIHR BRC at UoB
- The funder had no role in study design, data collection, the analysis and interpretation, or the writing of this report. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health



Evidence for impacts across varied outcomes varies	Extra- medical use	Injecting risks	Opioid overdose	HIV incidence	HCV incidence	Suicide	Injuries
Individual psychosocial interventions		$\checkmark$					
Peer-based self-help groups							
Needle syringe programs (NSP)	×	$\mathbf{+}$		$\checkmark$	<b>↓</b> ?		
Condom provision				$\checkmark$			
Opioid agonist treatment (OAT)	$\checkmark$	$\mathbf{\mathbf{\mathbf{\mathbf{\mathbf{\mathbf{\mathbf{\mathbf{\mathbf{\mathbf{\mathbf{\mathbf{\mathbf{\mathbf{\mathbf{\mathbf{\mathbf{\mathbf{$	$\checkmark$	$\checkmark$	$\checkmark$	$\rightarrow$	$\checkmark$
Naltrexone – Oral	×	×					
Naltrexone – Implant	$\checkmark$	$\checkmark$					
Residential rehabilitation		×					
Detoxification alone	×						
HCV antiviral treatment	$\checkmark$	$\checkmark$			$\checkmark$		
HIV antiretroviral treatment (ART)		×		$\checkmark$			
Safe injecting centres (SICs)	×	$\checkmark$	<b>↓</b> ?	?	?		
Naloxone provision							
Compulsory detention of drug users		↑					
Criminalisation of drug use		ſ		Ť			

Degenhardt et al (2020). The Lancet