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Opioid Agonist Treatment and Mortality Among People With Opioid Dependence

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Disclosure of interests

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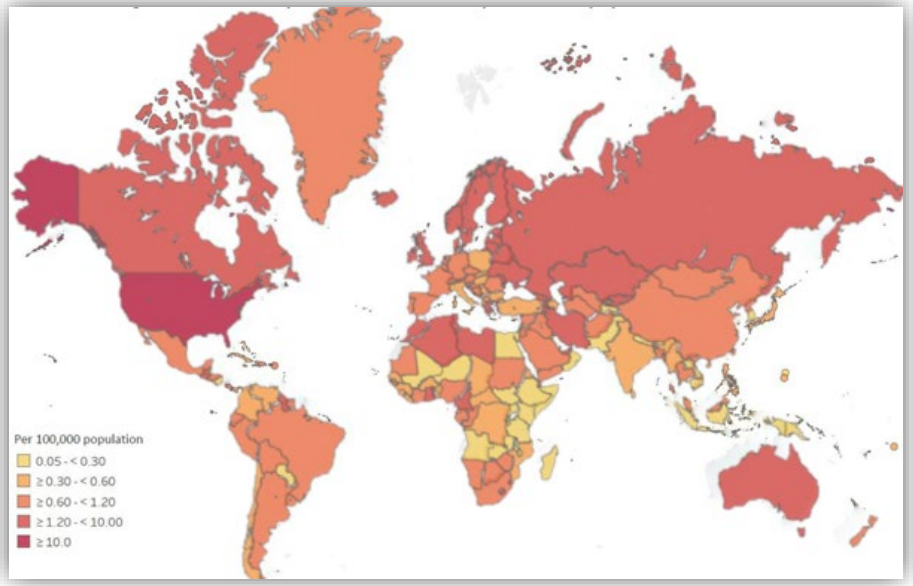
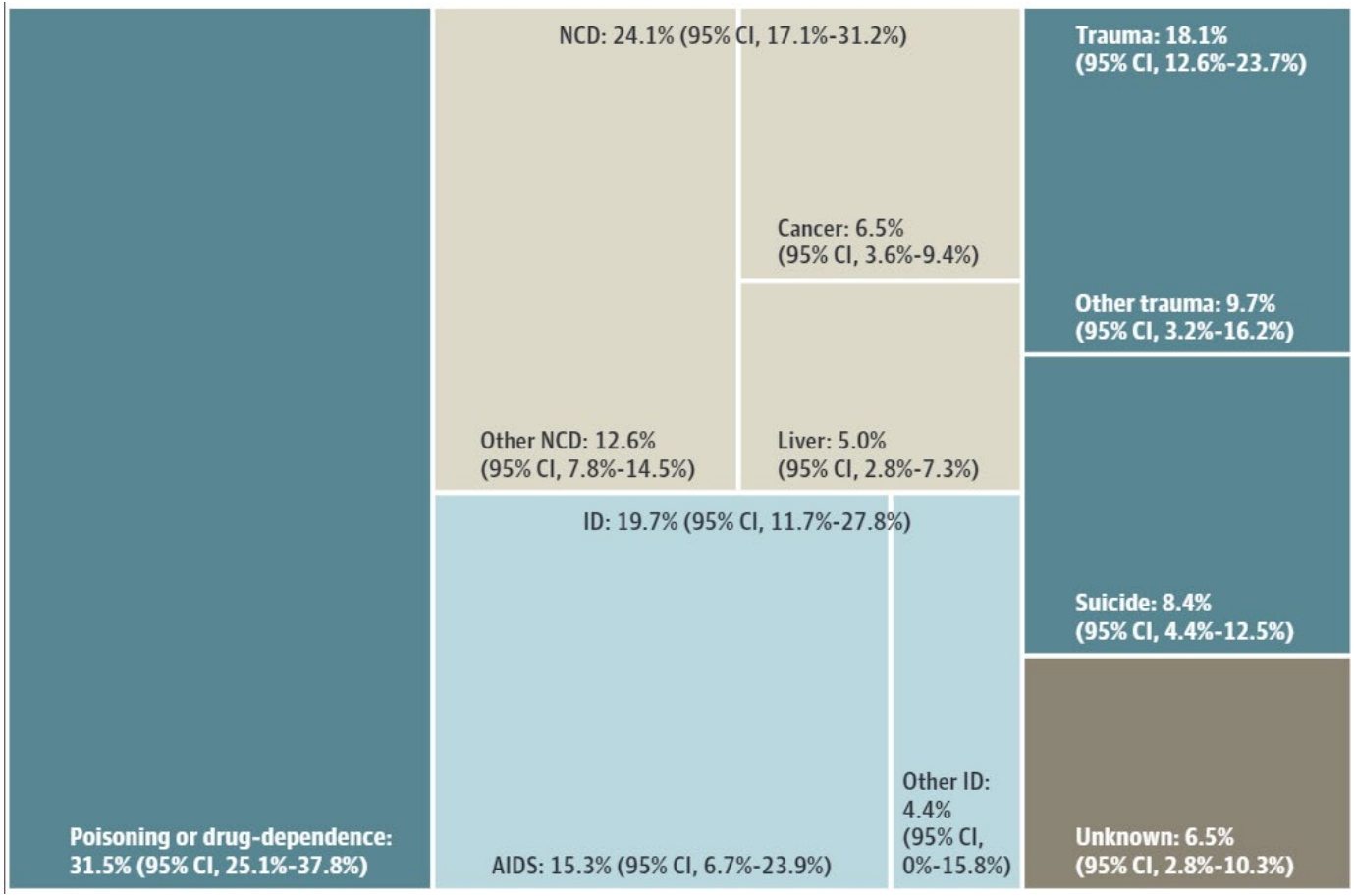
Group or Project Logos

- ~ 40.5 million people with opioid dependence globally (2017)
- People with opioid dependence at **10 times the risk of all-cause mortality** compared to the general population
- COVID and overdose-related death



Degenhardt et al (2019). *The Lancet*



Larney et al (2020). *JAMA Psychiatry*

Evidence for impacts across varied outcomes varies…	Extra-medical use	Injecting risks	Opioid overdose	HIV incidence	HCV incidence	Suicide	Injuries
Individual psychosocial interventions	↓?	↓	--	--	--	--	--
Peer-based self-help groups	↓?	--	--	--	--	--	--
Needle syringe programs (NSP)	✕	↓	--	↓	↓?	--	--
Condom provision	--	--	--	↓	--	--	--
Opioid agonist treatment (OAT)	↓	↓	↓	↓	↓	↓	↓
Naltrexone – Oral	✕	✕	--	--	--	--	--
Naltrexone – Implant	↓	↓	↓?	--	--	--	--
Residential rehabilitation	--	✕	--	--	--	--	--
Detoxification alone	✕	--	--	--	--	--	--
HCV antiviral treatment	↓	↓	--	--	↓	--	--
HIV antiretroviral treatment (ART)	--	✕	--	↓	--	--	--
Safe injecting centres (SICs)	✕	↓	↓?	?	?	--	--
Naloxone provision	--	--	↓?	--	--	--	--
Compulsory detention of drug users	--	↑	--	--	--	--	--
Criminalisation of drug use	--	↑	--	↑	--	--	--

Degenhardt et al (2020). *The Lancet*

Current OAT provision

- Limited availability – 86 countries
- Poor coverage - <20 people per 100 people who inject drugs
- Suboptimal doses
- Limited access to unsupervised dosing
- Urine drug screening, stigma related to OAT

Aims

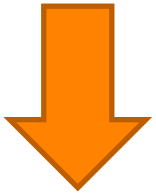
Review studies of all-cause & cause-specific mortality:

- Primary analyses
  - RCTs
  - Observational, cohort studies
- Secondary aims:
  - Specific time periods during and out of OAT
  - Participant, treatment, & study characteristics
  - During and after release from incarceration

Methods

- Crude Mortality Rates (CMRs) = # Deaths / # Person-Years
  - Within each study

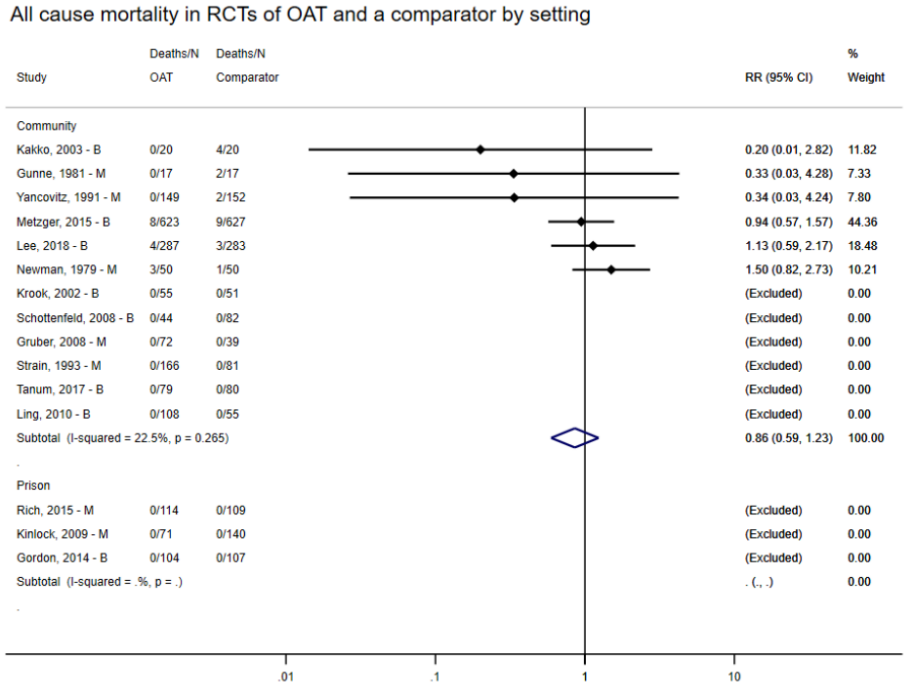
- CMR in OAT versus CMR out of OAT



- Pooled **Rate Ratios** (RRs)
  - Using **Random-effects meta-analyses**

RCTs

- 15 RCTs with 3,582 participants
- 40 total deaths reported, 7 of 15 reported zero deaths



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Description of observational studies

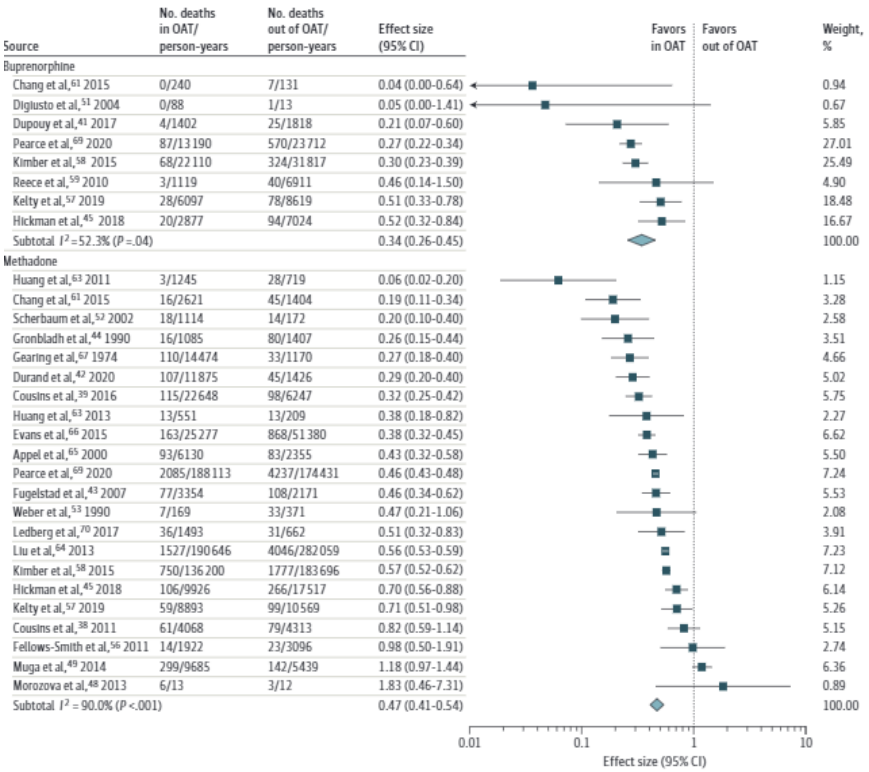
- 36 cohort studies with ~750k participants
  - 110 to 306,786 participants
  - > 20,000 total deaths reported

- 20 studies from Europe, 6 from Australia, 5 from North America

- 28 studies by methadone, 6 by buprenorphine

All-cause mortality rates

- Risk of death during OAT more than half the risk than out of OAT
- All-cause mortality ↓ during methadone & buprenorphine treatment



Source	No. deaths in OAT/ person-years	No. deaths out of OAT/ person-years	Effect size (95% CI)	Weight, %
Buprenorphine				
Chang et al,[61] 2015	0/240	7/131	0.04 (0.00-0.64)	0.94
Diglusto et al,[51] 2004	0/88	1/13	0.05 (0.00-1.41)	0.67
Dupouy et al,[41] 2017	4/1402	25/1818	0.21 (0.07-0.60)	5.85
Pearce et al,[69] 2020	87/13 190	570/23 712	0.27 (0.22-0.34)	27.01
Kimber et al,[58] 2015	68/22 110	324/31 817	0.30 (0.23-0.39)	25.49
Reece et al,[59] 2010	3/1119	40/6911	0.46 (0.14-1.50)	4.90
Kelty et al,[57] 2019	28/6097	78/8619	0.51 (0.33-0.78)	18.48
Hickman et al,[45] 2018	20/2877	94/7024	0.52 (0.32-0.84)	16.67
Subtotal I^2 = 52.3% (P = .04)			0.34 (0.26-0.45)	100.00
Methadone				
Huang et al,[63] 2011	3/1245	28/719	0.06 (0.02-0.20)	1.15
Chang et al,[61] 2015	16/2621	45/1404	0.19 (0.11-0.34)	3.28
Scherbaum et al,[52] 2002	18/1114	14/172	0.20 (0.10-0.40)	2.58
Gronbladh et al,[44] 1990	16/1085	80/1407	0.26 (0.15-0.44)	3.51
Gearing et al,[67] 1974	110/14 474	33/1170	0.27 (0.18-0.40)	4.66
Durand et al,[42] 2020	107/11 875	45/1426	0.29 (0.20-0.40)	5.02
Cousins et al,[39] 2016	115/22 648	98/6247	0.32 (0.25-0.42)	5.75
Huang et al,[63] 2013	13/551	13/209	0.38 (0.18-0.82)	2.27
Evans et al,[66] 2015	163/25 277	868/51 380	0.38 (0.32-0.45)	6.62
Appel et al,[65] 2000	93/6130	83/2355	0.43 (0.32-0.58)	5.50
Pearce et al,[69] 2020	2085/188 113	4237/174 431	0.46 (0.43-0.48)	7.24
Fugelstad et al,[43] 2007	77/3354	108/2171	0.46 (0.34-0.62)	5.53
Weber et al,[53] 1990	7/169	33/371	0.47 (0.21-1.06)	2.08
Ledberg et al,[70] 2017	36/1493	31/662	0.51 (0.32-0.83)	3.91
Liu et al,[64] 2013	1527/190 646	4046/282 059	0.56 (0.53-0.59)	7.23
Kimber et al,[58] 2015	750/136 200	1777/183 696	0.57 (0.52-0.62)	7.12
Hickman et al,[45] 2018	106/9926	266/17 517	0.70 (0.56-0.88)	6.14
Kelty et al,[57] 2019	59/8893	99/10 569	0.71 (0.51-0.98)	5.26
Cousins et al,[38] 2011	61/4068	79/4313	0.82 (0.59-1.14)	5.15
Fellows-Smith et al,[56] 2011	14/1922	23/3096	0.98 (0.50-1.91)	2.74
Muga et al,[49] 2014	299/9685	142/5439	1.18 (0.97-1.44)	6.36
Morozova et al,[48] 2013	6/13	3/12	1.83 (0.46-7.31)	0.89
Subtotal I^2 = 90.0% (P < .001)			0.47 (0.41-0.54)	100.00

All-cause mortality rates

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

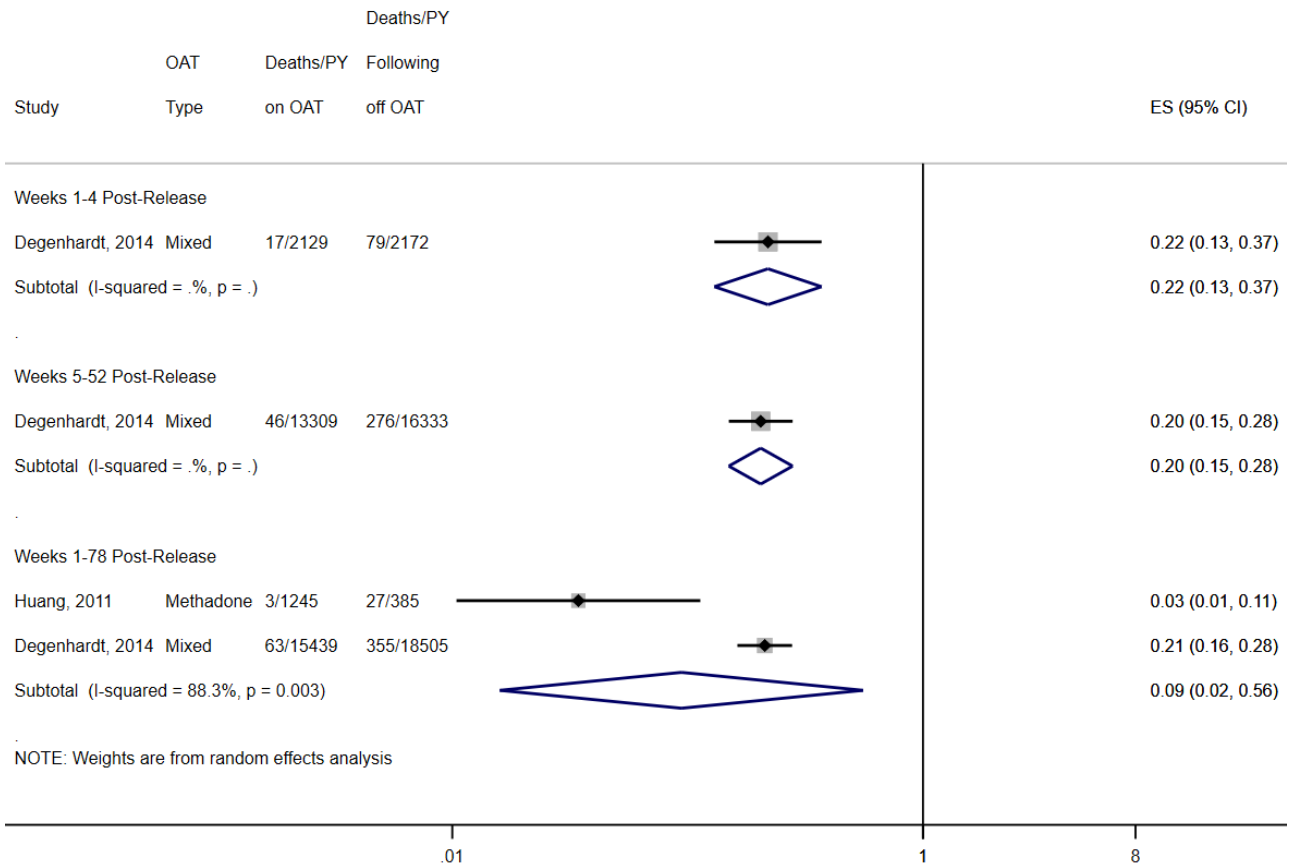
Participant characteristics	Rate Ratios (95% CIs)
Women	**↓ 44 %***
Men	**↓ 55 %***
Age	
<35 years	**↓ 52 %***
>=35 years	**↓ 52 %***
People who inject drugs	**↓ 48 %***
HIV+	**↓ 44 %***
HCV+	**↓ 47 %***
Treatment provider	
Specialist	**↓ 69 %***
GP/mixed/other	**↓ 53 %***

Cause of Death (ICD Coding)	# Studies	Association
Drug-related	22	↓ **58 %***
Unintentional opioid deaths	13	↓ 71 %*
Suicide	14	↓ **52 %***
Alcohol-related	15	↓ **41 %***
Cancer	14	↓ **28 %***
Cardiovascular disease	14	↓ **31 %***

Other causes of death

- No association with Injection Related Injuries and Diseases
- No association with liver-related, respiratory disease, digestive disorders, influenza, HIV-related deaths
  - However - strong association among people with HIV
- Increased association with hepatitis-related death likely due to misclassification
  - Sensitivity analyses
  - Strong association among people with HCV
  - OAT associated with uptake in HCV testing & treatment (Grebely et al, 2021)

After release from incarceration (follow-up in/out of OAT)



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Risk of bias

- Most studies at moderate risk of bias – largely due to confounding

- 19 studies adjusted for confounding in their analyses
  - 17 of 19 found reductions in all-cause / overdose-related mortality after adjusting for confounders

Conclusions

- OAT strongly associated with lower risk of mortality (↓ 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 6 times ↑ leaving OAT in first month vs. in OAT more than 1 month
- ↓ Mortality risk in OAT during and after release from incarceration

Conclusions

- Study **power** (Data from ~750k participants, ~ 2 million PYs)
- **Strength of association**
  - All-cause mortality in vs. out of OAT (RR, 0.47; 95% CI,0.42-0.53)
- 19 studies adjusted for confounding → similar results

Conclusions

- Reduced risk of alcohol-, cancer- & cardio-vascular related death
  - Related to reduced alcohol / stimulant use during OAT?

- More access to screening, early intervention, and treatment engagement while receiving OAT

Conclusions

- Increase access & coverage of OAT for people with opioid dependence
- Improve retention & support for those who leave OAT
- Reduced risk of mortality during induction to treatment
  - Particularly for methadone

Future research & limitations

- Data linkage studies
  - Adjustment for confounding
- Studies that analyse type of OAT delivery
  - Adjunct services
- Few studies among people with opioid dependence **during and after incarceration**

Thank you

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Participants and health providers that shared their data

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