Association of Opioid Agonist Treatment With All-Cause Mortality and Specific Causes of Death Among People With Opioid Dependence: Systematic Review and Meta-analysis

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The Difference is Research

Background & Aims

People with opioid dependence are at 10 times the risk of mortality compared to the general population. Opioid Agonist Treatment (OAT) includes methadone or buprenorphine treatment.

We compared **all-cause & cause-specific mortality rates during and out of OAT** among people with opioid dependence by;

- Study type (RCTs, Observational studies)
- Specific time periods during and out of OAT
- During and after release from incarceration
- Participant, treatment, & study characteristics

Risk of death during OAT is more than half the risk than time out of OAT

- ↓ Risk of suicide (52%), drug-related (59%), cancer (28%), alcohol-related (41%), cardiovascular-related (31%) mortality during OAT vs. time out of OAT
- Mortality 6 times ↑ in 1st month after leaving vs. in OAT > 1 month
- ↓ Mortality risk in OAT after release from incarceration
- ↓ Mortality risk during OAT regardless of participant characteristics

Results (Secondary analyses)

Fifteen RCTs with 3,852 participants (40 total deaths)

- No association between mortality for people allocated to OAT vs. comparison groups (RR, 0.86; 95%CI, 0.59-1.23)

One study **during incarceration** (Larney, 2014)

- People receiving OAT in prison in Australia → significantly lower rates of all-cause and suicide-related mortality

Five studies examined mortality **after release from incarceration**

- Two studies provided OAT upon release (no follow-up), found ↓ all-cause/drug-related mortality in 1st month (~29k ppl.)
- Three studies (~18k ppl.) reported time in/out of OAT post-release from incarceration, ↓ all-cause & drug-related mortality

19 observational studies **controlled for confounding variables**

- 16 of 17 studies found significantly lower rates of all-cause mortality among people in OAT (Subsets of included studies)

Methods

- Searched Embase, MEDLINE, PsycINFO, clinical trial registries, & previous Cochrane reviews in February 2021
- Extracted all-cause deaths, cause-specific deaths (by ICD coding), person-years (PYs; time in/out of OAT), participant/treatment/study characteristics
- Pooled crude mortality rates (CMRs) and rate ratios (RRs) using random-effects meta-analyses

Results (Primary Analyses)

Of 7,980 studies identified, 72 publications included

36 primary cohort studies including 749,634 participants were included in observational analyses.

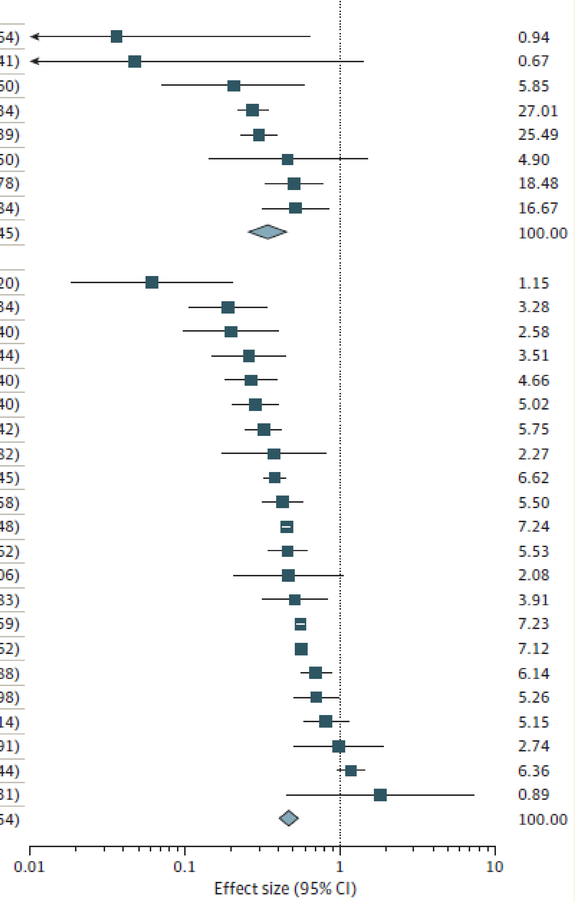
- All-cause mortality in vs. out of OAT (RR, 0.47)
- Not different for methadone (RR 0.47; 95% CI, 0.41-0.54) vs. buprenorphine (RR 0.34; 95% CI, 0.26-0.45)
- Mortality risk during OAT was **lower across participant characteristics** age, sex, location, HIV/HCV status, history of injecting drug use, study methodology, and region
- Lower risk of suicide (RR 0.48;95% CI, 0.37-0.61), cancer (RR 0.72; 95% CI, 0.52-0.98), drug-related (RR 0.41; 95% CI,0.33-0.52), alcohol-related (RR 0.59; 95% CI, 0.49-0.72), and cardiovascular-related (RR 0.69; 95% CI, 0.60-0.79) mortality during OAT

Specific times in treatment

- Receiving OAT > 1 month = lowest mortality risk
- In 1st month receiving OAT, ↑ mortality risk than remainder of **in** treatment time
- 1st month leaving OAT, mortality was 6 times higher in the first 4 weeks after OAT cessation

Association of OAT With All-Cause Mortality From Observational Studies by OAT Type

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
Digiusto 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	87/13190	570/23712	0.27 (0.22-0.34)	27.01
Kimber et al,[58] 2015	68/22110	324/31817	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	110/14474	33/1170	0.27 (0.18-0.40)	4.66
Durand et al,[42] 2020	107/11875	45/1426	0.29 (0.20-0.40)	5.02
Cousins et al,[39] 2016	115/22648	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	163/25277	868/51380	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	2085/188113	4237/174431	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	1527/190646	4046/282059	0.56 (0.53-0.59)	7.23
Kimber et al,[58] 2015	750/136200	1777/183696	0.57 (0.52-0.62)	7.12
Hickman et al,[45] 2018	106/9926	266/17517	0.70 (0.56-0.88)	6.14
Kelty et al,[57] 2019	59/8893	99/10569	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



Conclusions

Risk of all-cause, overdose, suicide, alcohol-related, cancer, and cardiovascular-related mortality was significantly lower for people with opioid dependence during OAT.

Significant association across participant and study characteristics, study power (~750k), consistent findings from studies that adjusted for confounding, & strength of association support results

- ↑ Strategies to increase retention past the first month of OAT
- Reductions in alcohol-related, cardiovascular-related, and cancer-related mortality likely related to ↓ comorbid substance use

Future research & limitations:

- RCTs are underpowered & studies that withhold OAT are unethical, can data linkage studies emulate RCTs?
- Detailed, consistent reporting of results (We were unable to synthesize data from studies that adjusted for confounding)
- Analyses of different types of OAT delivery & adjunct services
- **Few studies examined OAT among people who are incarcerated or who have recently been incarcerated**

Disclosure of interests

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