DEPARTMENT OF EPIDEMIOLOGY & PUBLIC HEALTH
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Opioid agonist treatment and risk of death or rehospitalization following injection drug use-associated bacterial and fungal infections: a cohort study in New South Wales, Australia

Thomas D. Brothers, Dan Lewer, Nicola Jones, Samantha Colledge-Frisby, Michael Farrell, Matthew Hickman, Duncan Webster, Andrew Hayward, Louisa Degenhardt

Brothers TD, et al. PLOS Medicine. 2022.

Disclosures

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  - Dalhousie University Faculty of Medicine
  - Canadian Society of Internal Medicine

- No relationships with industry

Injecting-related bacterial & fungal infections

- Injecting-related infections are an increasingly common cause of pain, disability, and death[1]
- Treatment has tended to focus on antimicrobial therapy and/or surgery, without addressing underlying substance use
- For example, use of medications for opioid use disorder:
  - 6% within 30 days after hospital discharge[2,3]
  - 24% within 3 months after hospital discharge[4]

[1]Brothers TD, BMJ Open, 2021; [2]Barocas J, CID, 2021; [3]Barocas J, DAD, 2020; [4]Kimmel S, JAMA Netw Open, 2020

Opioid agonist treatment may reduce recurrence

- After an injecting-related infection, use of opioid agonist treatment (OAT; e.g. methadone, buprenorphine) reduces mortality[1] and might reduce recurrence
- OAT allows people to inject less frequently (or not at all), to reduce reliance on illegal drug market, and to better engage in health care[2]
- Limited evidence in preventing infection recurrence:
  - Small sample sizes and wide confidence intervals[1,3,4];
  - Lack of information on methadone in U.S. insurance databases[3;4]

[1]Kimmel S, JAMA Netw Open, 2020; [2]Brothers TD, BMJ Open, 2021; [3]Barocas J, CID, 2021; [4]Barocas J, DAD, 2020

Research question

- Among a cohort of people with opioid use disorder who have been hospitalized with injecting-related bacterial or fungal infections…

Is use of OAT associated with decreased risk of death and of re-hospitalization with injecting-related infections?

Methods: Design & setting

- Opioid Agonist Treatment Safety (OATS) study[1]
- Population-wide cohort; reliable data on methadone and buprenorphine

- All OAT permits in NSW, Australia
- August 2001 – June 2018
- OAT permits linked to hospital, incarceration, and mortality records
- Estimated to include >75% of people who inject opioids in NSW[2]

1. Larney S, Int J Epidemiol, 2020
2. Horyniak D, Harm Reduct J, 2013

Methods: Participants

- People with opioid use disorder (OATS study participants)
- Unplanned hospitalization with injecting-related infections:
  - Skin and soft-tissue infection
  - Sepsis or bacteremia
  - Endocarditis
  - Osteomyelitis
  - Septic arthritis
  - Brain or epidural abscess
- Survived hospitalization and discharged to the community

Methods: Measures

Outcomes

1. All-cause death
2. First rehospitalization with injecting-related bacterial or fungal infection

Primary exposure

- OAT use (methadone or buprenorphine) after hospital discharge, defined as time-varying by day of receipt
- Each participant's follow-up time divided up into treated and untreated time periods

Methods: Covariates

Participant characteristics
1. Age
2. Sex/gender
3. Indigenous status
4. Comorbidity
Prior hospitalizations for poisoning or toxicity from:
5. Opioids
6. Stimulants
7. Alcohol
8. Prior incarceration

Index hospitalization characteristics
9. Calendar year
10. Length of stay (days)
11. Premature discharge against medical advice

Methods: Analysis

1. Extended Kaplan-Meier curves for time-varying exposures, to describe cumulative hazard of each outcome[1]

- Interpreted as the estimated survival for patients who did not change their OAT status during follow-up

2. Cox proportional hazards models to estimate associations between OAT and each outcome

- Adjusted hazard ratios with 95% confidence intervals

1. Snapinn SM, et al. American Statistician. 2005.

Results: Descriptive statistics

Participant characteristics	N (%)
Total sample	8,943 (100%)
Age, mean ± SD	39 ± 11
Women	3,080 (34%)
Indigenous	1,321 (15%)
Comorbidity, median [IQR]	3 [2 – 5]
Prior hospitalizations for:	
Opioids	749 (8%)
Stimulants	205 (2%)
Alcohol	929 (10%)
Prior incarceration	3,845 (43%)

Index hospitalization characteristics	N (%)
Type of infection:	
Skin & soft tissue	7021 (79%)
Sepsis/Bacteraemia	1207 (14%)
Endocarditis	431 (5%)
Osteomyelitis	375 (4%)
Septic arthritis	323 (4%)
Brain or epidural abscess	69 (1%)
Length of stay (days), median [IQR]	4 [2 – 8]
Premature discharge against medical advice	1,246 (14%)

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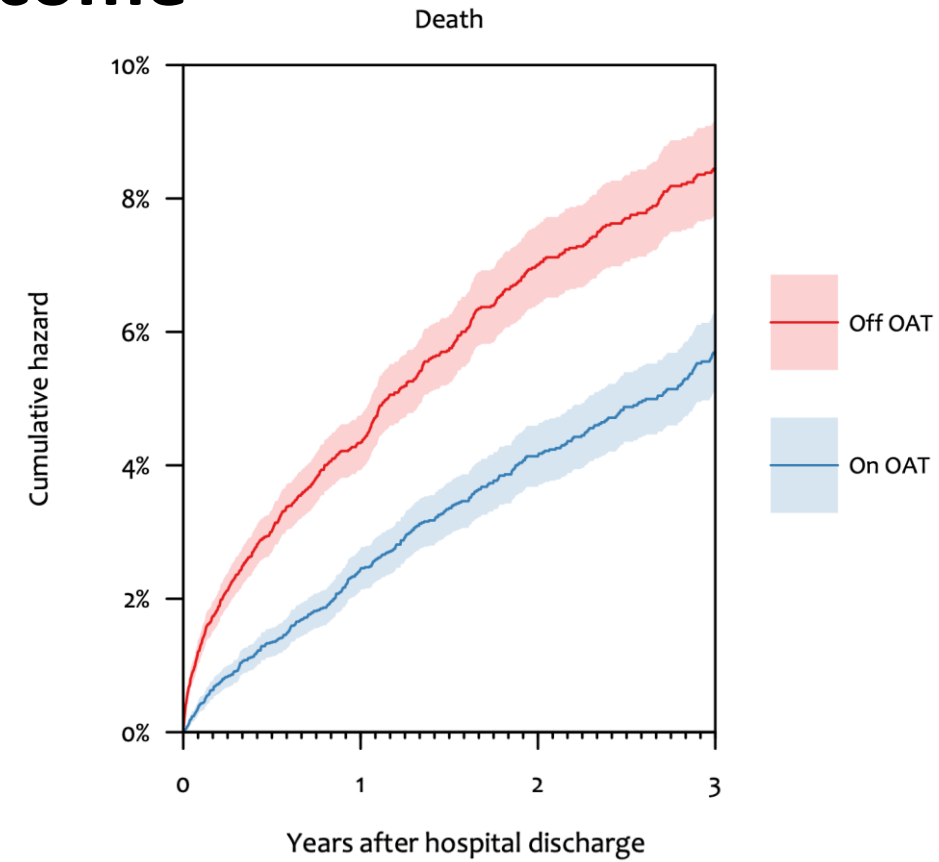
Results: Mortality outcome

- 1,481 (17%) participants died over median 6.56 years follow-up

- OAT associated with reduced hazard of all-cause death (adjusted HR = 0.63, 95% CI 0.57 – 0.70)



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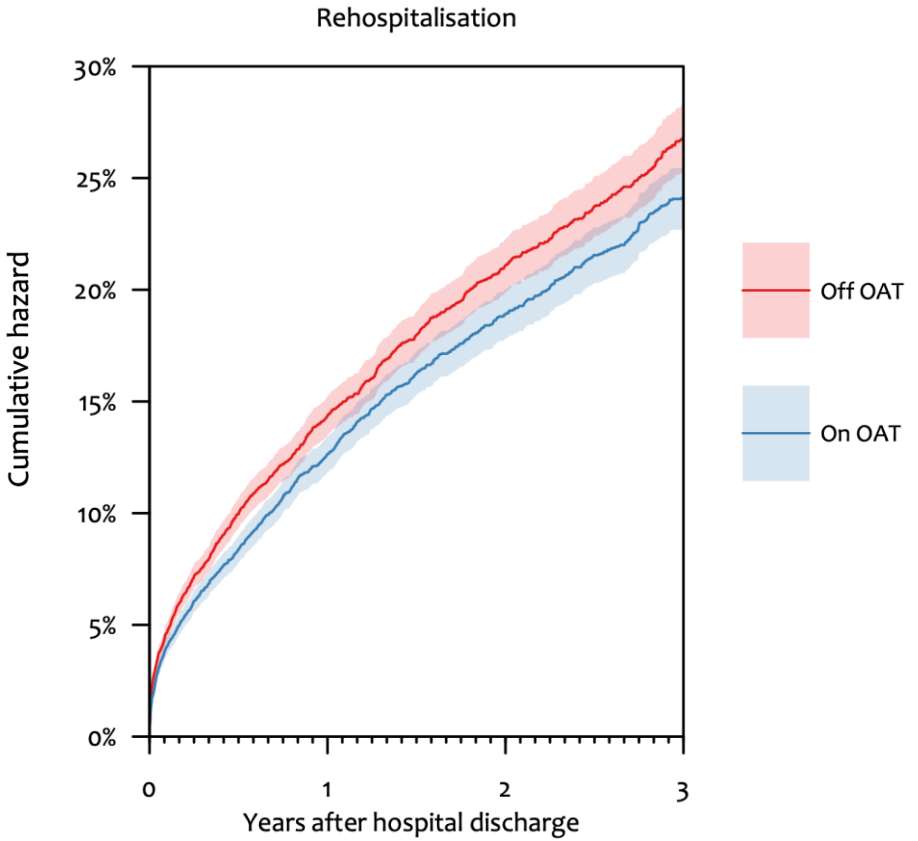
Results: Rehospitalization outcome

- 3,653 (41%) participants rehospitalised, over median 3.41 years follow-up

- OAT associated with reduced hazard of rehospitalization with injecting-related infection (aHR = 0.89, 95% CI 0.84 – 0.96)



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Supplementary analysis: Period-specific survival analysis

Time since hospital discharge	Mortality outcome	Rehospitalization outcome
Within first year	0.47 (0.40 – 0.55)	0.83 (0.77 – 0.91)
Year 2-3	0.66 (0.54 – 0.81)	0.87 (0.76 – 0.99)
Year 4-6	0.76 (0.58 – 0.98)	1.10 (0.91 – 1.33)

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Strengths & Limitations

Strengths

- Well-established administrative cohort
- Large sample size
- Well-defined exposure (OAT prescription by day); population-wide data

Limitations

- No info on injecting practices, housing status, stimulant use
- Unique risk environment in Australia: powder heroin & good OAT access

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Interpretation

- Among people with opioid use disorder hospitalized with injecting-related bacterial and fungal infections, OAT is associated with decreased risk of death and infection-related rehospitalizations.
- Rates of death and rehospitalization remained high for this young cohort of patients, even among those exposed to OAT.
- The absolute benefit of OAT on rehospitalization risk was modest.

- Clinicians, hospitals, and health systems should offer OAT as part of multi-component treatment planning for patients with bacterial or fungal infections from injection opioid use.

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RESEARCH ARTICLE

Opioid agonist treatment and risk of death or rehospitalization following injection drug use–associated bacterial and fungal infections: A cohort study in New South Wales, Australia

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CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

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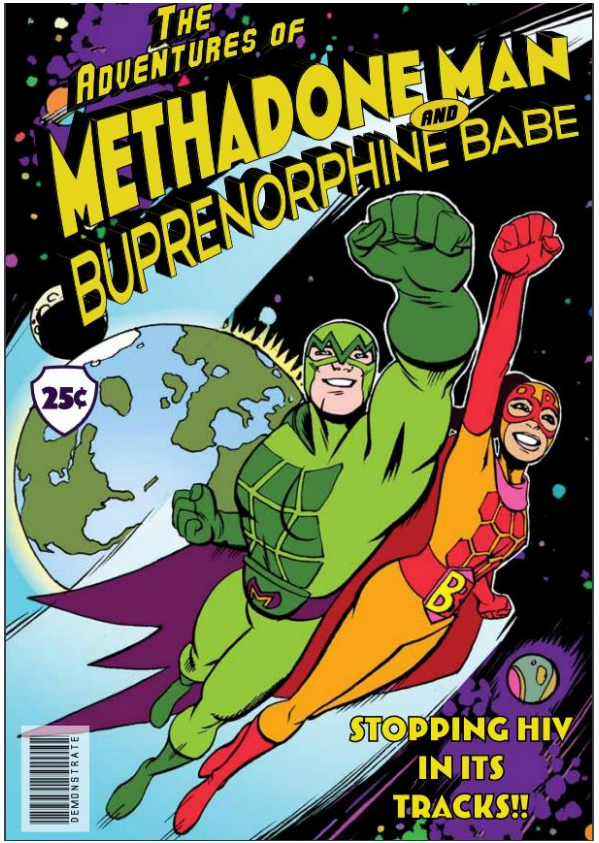
Collaborative Centre for Inclusion Health

Questions?


THE ADVENTURES OF
METHADONE MAN
AND
BUPRENORPHINE BABE
25¢
STOPPING HIV
IN ITS
TRACKS!!
DEMONSTRATE

Appendix slides

OATS Study linkage

- The primary database for this linkage is the Electronic Reporting and Recording of Controlled Drugs (ERRCD) system.
- The ERRCD (formerly Pharmaceutical Drugs of Addiction System) contains records of all OAT prescribed in NSW, in any setting.
- As people seeking OAT must provide identification documents to obtain a prescription, personal identifiers in the ERRCD are considered reliable for probabilistic linkage to other routinely collected data.

- For this study, the ERRCD is probabilistically linked to five state-wide databases.
- Data were linked probabilistically, based on full name and any recorded aliases, date of birth, sex, and date of last known contact.

- The linkage process is managed by the Centre for Health Record Linkage in collaboration with data custodians.
- Researchers do not receive identifying data for any individual in the cohort at any time.

Table 1 Databases linked in the Opioid Agonist Treatment and Safety Study

Database name	Database description	Linked variables*
Electronic Reporting and Recording of Controlled Drugs	Authorisation for dispensing methadone or buprenorphine for the treatment of opioid dependence.	Dates of OAT entry and cessation. Primary opioid of concern. Start and final dose. Prescriber identification number. Dosing point. Date of provider accreditation. Date of provider's first OAT authority. Statistical area of OAT recipient's address. Statistical area of OAT provider's practice. Reason for OAT cessation.
Admitted Patients Data Collection	All hospitalisations in all public, private, psychiatric and repatriation hospitals in NSW.	Dates of admission and separation. Planned or unplanned admission. Diagnoses (underlying and contributing). Procedures. Mode of separation.
Emergency Department Data Collection	Presentations to emergency departments in NSW.	Date of presentation and separation. Triage category. Diagnosis (underlying only). Planned or unplanned presentation. Mode of separation.
Mental Health Ambulatory Data Collection	Mental healthcare for non-admitted patients, including day programmes, psychiatric outpatients and outreach services.	Mental health diagnoses (primary and additional).
Re-offending Database	Court appearances, juvenile detention and adult incarceration in NSW.	Dates of prison reception and release. Level of Service Inventory-Revised risk category.
Registry of Births, Deaths and Marriages and Cause of Death Unit Record File	Deaths registered in NSW.	Date of death. Cause of death (underlying and contributing).

*All linked databases include sex, month and year of birth, and Indigenous status.
NSW, New South Wales; OAT, opioid agonist treatment.

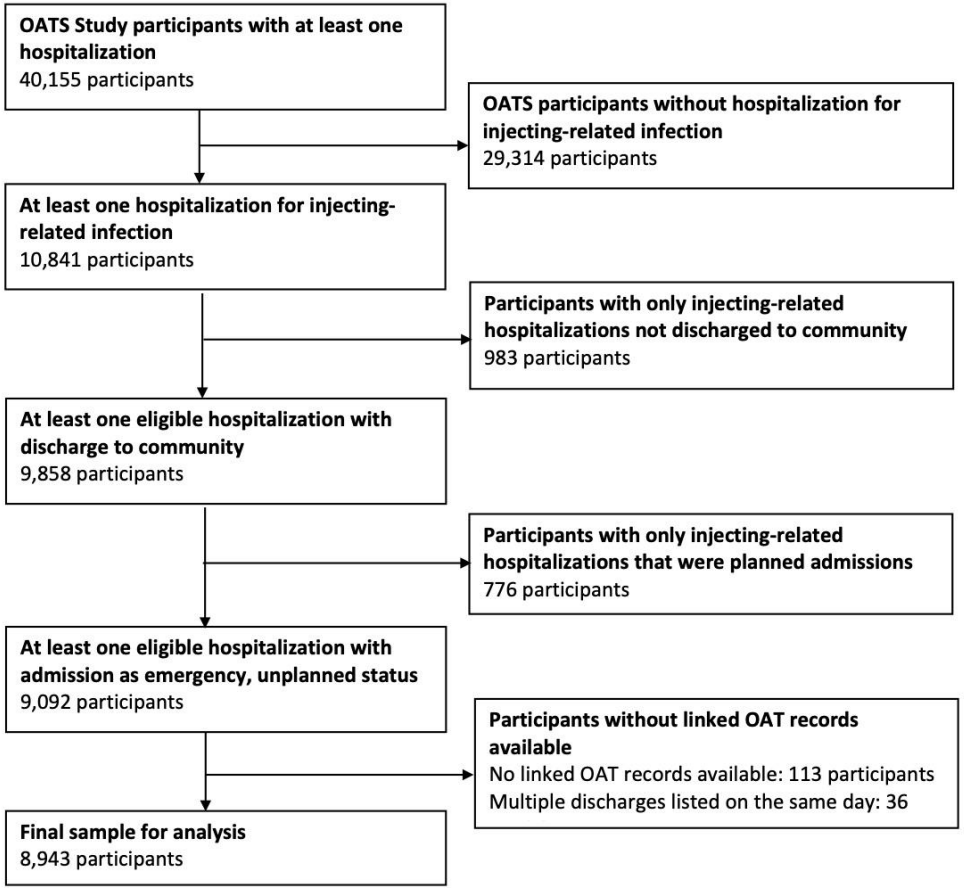


Figure 1. Study flow diagram. OATS Study: Opioid Agonist Treatment Safety Study. OAT: Opioid Agonist Treatment.

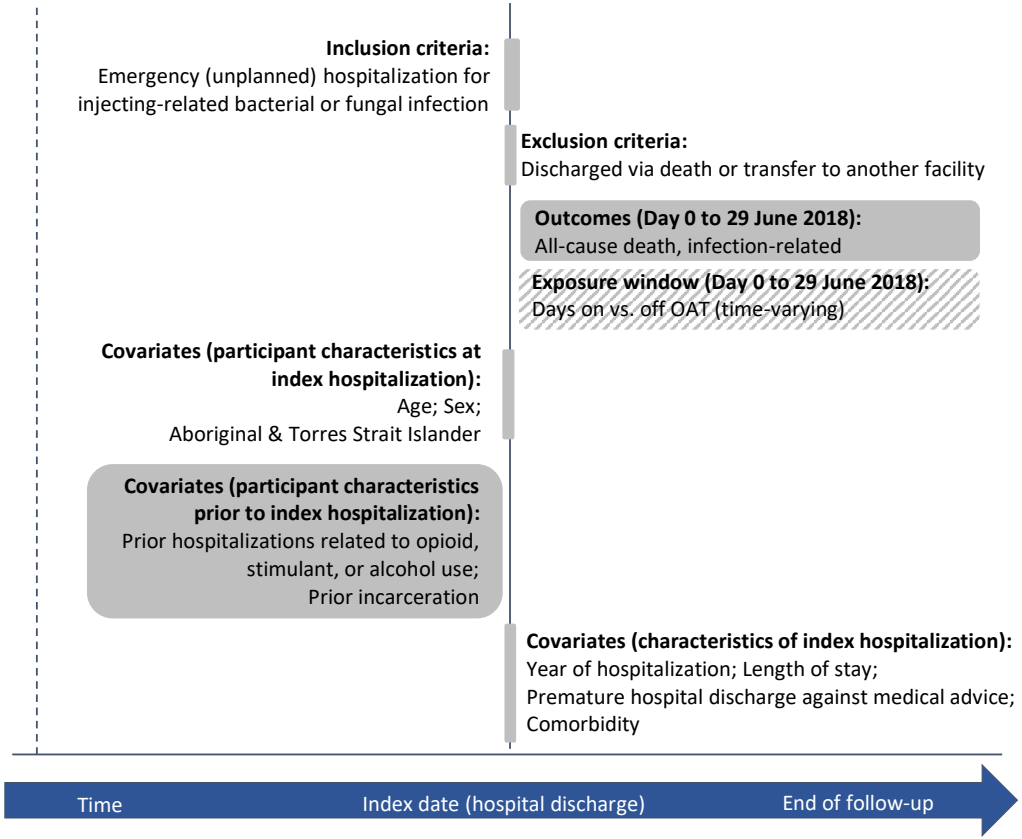


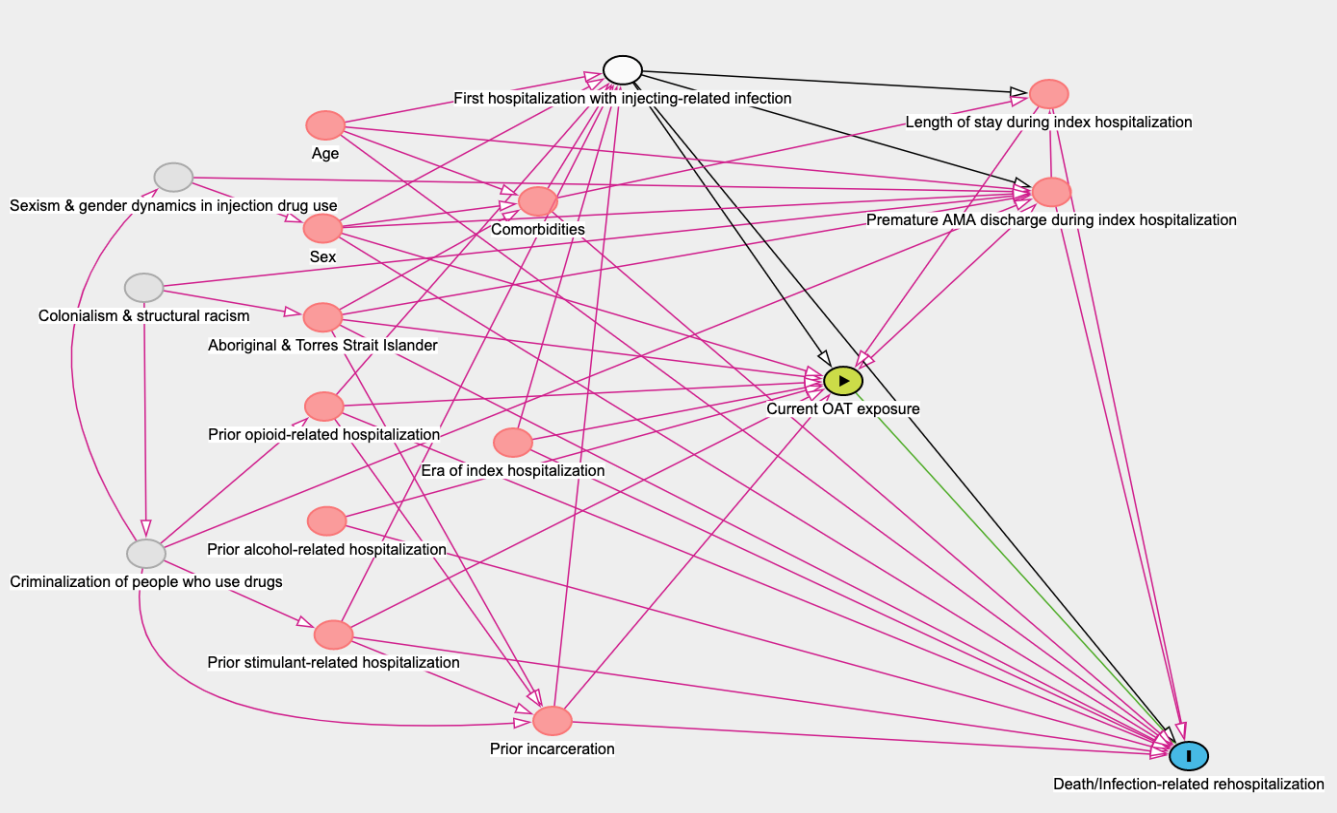
Figure 2. Study design.

Supplementary Table 1. ICD-10 codes to define infections of interest.

Variable name	Codes	Diagnosis
Skin and soft tissue infections	A48.0	Gas gangrene
	L02.X	Cutaneous abscess, furnuncle and carbuncle
	L03.X	Cellulitis
	L08.8	Other specified local infections of skin and subcutaneous tissue
	L08.9	Local infection of skin and subcutaneous tissue, unspecified
	L97	Ulcer of lower limb, NEC
	L98.4	Chronic ulcer of skin, NEC
	L98.8	Other specified disorders of skin and subcutaneous tissue
	L98.9	Disorder of skin and subcutaneous tissue, unspecified
	M72.6	Necrotizing fasciitis
	R02	Gangrene, NEC
Sepsis and bacteraemia	A40.X	Streptococcal sepsis
	A41.X	Other sepsis
	R57.2	Septic shock
	B37.7	Candidal sepsis

Supplementary Table 1. ICD-10 codes to define infections of interest.

Variable name	Codes	Diagnosis
Endocarditis	B37.6	Candidal endocarditis
	I33.0	Acute and subacute infective endocarditis
	I33.9	Acute endocarditis, unspecified
	I34.0	Mitral (valve) insufficiency
	I34.2	Nonrheumatic mitral (valve) stenosis
	I34.8	Other nonrheumatic mitral valve disorders
	I34.9	Nonrheumatic mitral valve disorder, unspecified
	I35.X	Nonrheumatic aortic valve disorders
	I36.X	Nonrheumatic tricuspid valve disorders
	I37.X	Pulmonary valve disorders
	I38	Endocarditis, valve unspecified
	I39.X	Endocarditis and heart valve disorders in diseases classified elsewhere
	T82.6	Infection and inflammatory reaction due to cardiac valve prosthesis
Septic arthritis	M00.X	Pyogenic arthritis
Osteomyelitis & vertebral discitis	M86.X	Osteomyelitis
	M46.2	Osteomyelitis of vertebra
	M46.3	Infection of intervertebral disc (pyogenic)
	M46.4	Discitis, unspecified
	M89.9	Disorder of bone, unspecified
Central nervous system infections	G06.0	Intracranial abscess and granuloma
	G06.1	Intraspinal abscess and granuloma
	G06.2	Extradural and subdural abscess, unspecified



Supplementary Figure 1. Directed Acyclic Graph (DAG) describing hypothesized relationships between primary exposure, covariates, and outcomes.

Results: OAT exposure

- 4,651 (52%) participants discharged from index hospitalization without an active OAT prescription
  - 706 (15%) initiated OAT within 90 days

- 34,146 (52%) person-years exposed to/receiving OAT
- 31,094 (48%) person-years unexposed to/not receiving OAT

- Median 2 [IQR 0 – 5] treatment switches (on or off OAT) during follow-up

Table 2. Results of Cox regression for survival following discharge from index hospitalization with an injecting-related bacterial or fungal infection.

Variable	Levels	All-cause mortality outcome		Rehospitalization outcome	
		Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)[1]	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)[1]
Primary exposure					
Opioid agonist treatment	Exposed day	**0.72 (0.64 – 0.79)**	**0.63 (0.57 - 0.70)**	0.95 (0.89 – 1.01)	**0.89 (0.84 - 0.96)**
Participant characteristics					
Age	Years (scaled)	2.15 (2.04 – 2.26)	2.04 (1.93 - 2.17)	**1.33 (1.29 – 1.37)**	**1.26 (1.22 - 1.31)**
Sex	Female	**0.83 (0.74 – 0.92)**	0.92 (0.82 - 1.02)	1.05 (0.99 – 1.13)	**1.09 (1.02 – 1.17)**
Aboriginal or Torres Strait Islander	Yes	**0.72 (0.61 – 0.85)**	1.02 (0.86 - 1.20)	0.95 (0.86 – 1.04)	1.00 (0.91 - 1.10)
	Unknown	0.92 (0.52 – 1.62)	0.95 (0.54 - 1.69)	**0.57 (0.37 – 0.88)**	**0.62 (0.41 - 0.96)**
Comorbidities	1	Ref	Ref	Ref	Ref
	2	**1.46 (1.14 - 1.89)**	**1.39 (1.09 - 1.78)**	**1.14 (1.01 – 1.28)**	1.09 (0.97 - 1.23)
	3	**1.88 (1.49 - 2.38)**	**1.74 (1.38 - 2.20)**	**1.15 (1.02 – 1.29)**	1.10 (0.98 - 1.24)
	4	**2.19 (1.73 - 2.79)**	**1.98 (1.55 - 2.51)**	**1.29 (1.14 – 1.46)**	**1.20 (1.06 - 1.36)**
	5	**3.18 (2.50 – 4.05)**	**2.58 (2.03 - 3.30)**	**1.54 (1.35 – 1.75)**	**1.34 (1.18 - 1.54)**
	6+	**5.09 (4.09 - 6.34)**	**3.49 (2.79 - 4.36)**	**1.83 (1.63 – 2.06)**	**1.49 (1.32 - 1.68)**

Sensitivity analysis: Changing exposure definition timing

- Changing how many days after OAT end are assigned as “exposed” (vs. unexposed)

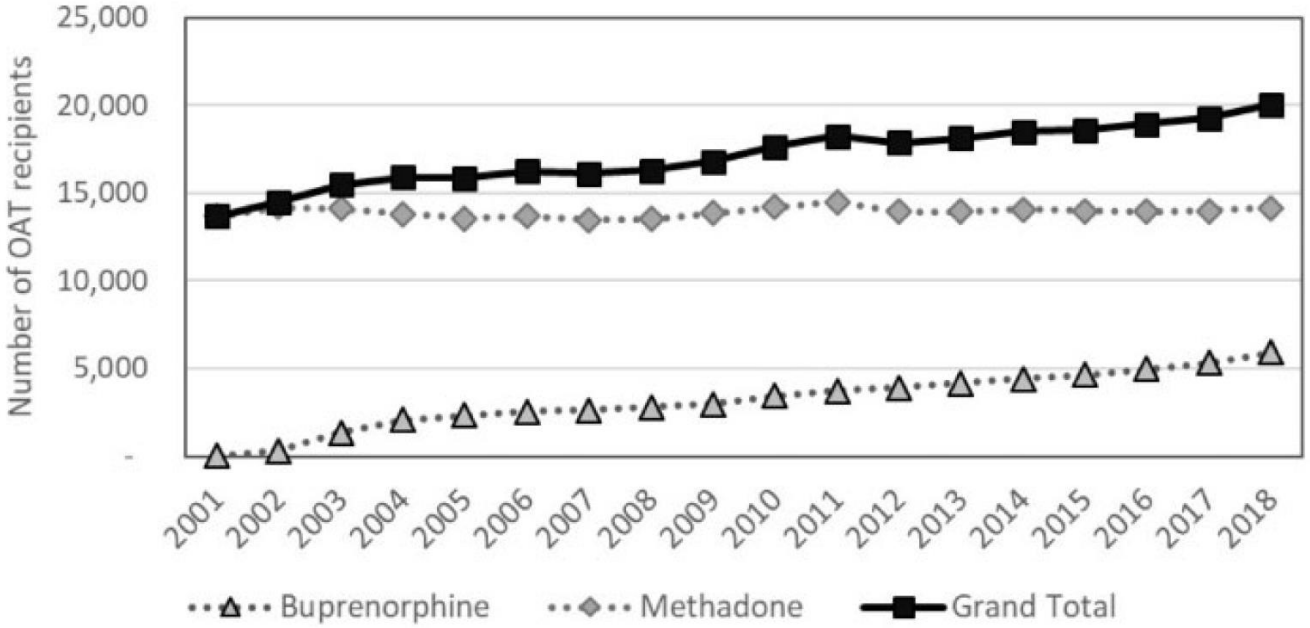
Number of days after OAT end assigned as “exposed”	Mortality outcome	Rehospitalization outcome
Two days	0.51 (0.46 – 0.57)	0.88 (0.83 - 0.95)
Six days (main analysis)	0.63 (0.57 – 0.70)	0.89 (0.84 – 0.96)
10 days	0.72 (0.65 – 0.80)	0.89 (0.84 – 0.95)

Brothers TD, et al. PLOS Medicine. In press.

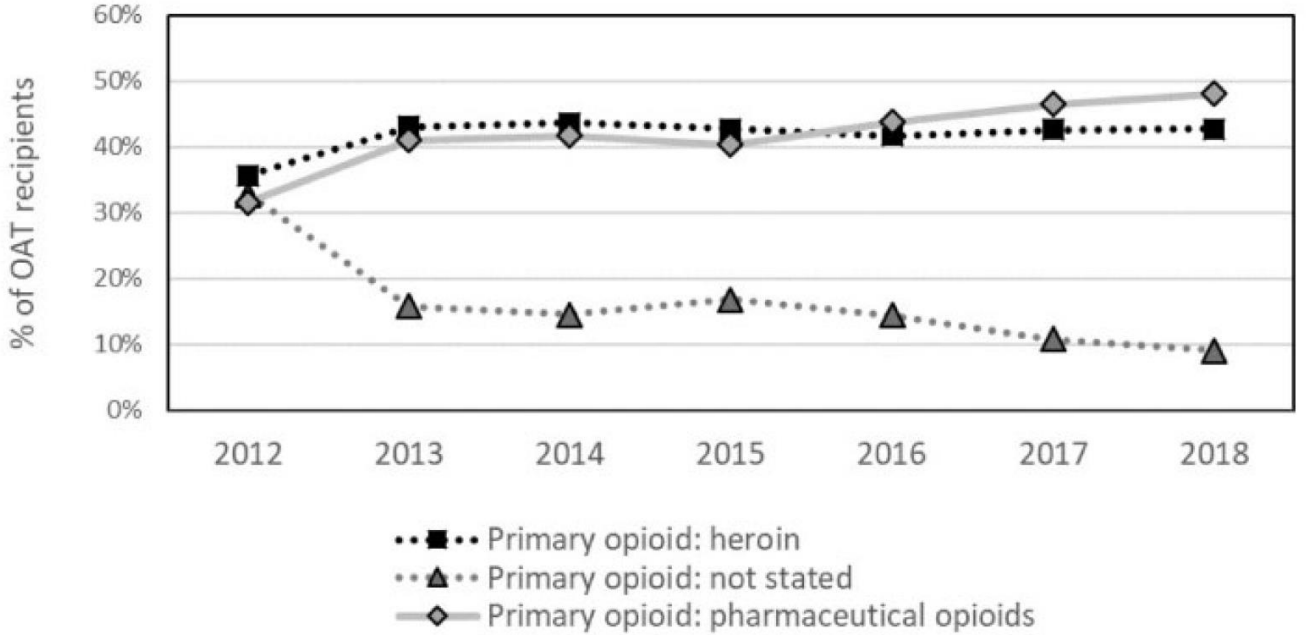
Sensitivity analysis (sample)

- We then conducted a post hoc sensitivity analysis for the mortality outcome, reconstructing the analytic sample only among participants who experienced hospitalization for injecting-related infection at a date following their first record of OAT.
- This sample was slightly smaller (n=7,641).
- Compared to the main analysis, more participants (59%) had an active OAT permit at the time of discharge from their index hospitalization and more follow-up time was exposed to OAT (59%).
- In the fully adjusted model in this smaller sample, OAT was also associated with reduced hazard of all-cause death (aHR 0.56, 95% CI 0.51 – 0.62).

Number of the OATS cohort receiving OAT on 1 January annually, 2001–2018, by medicine prescribed



Proportion of the OATS cohort reporting heroin or pharmaceutical opioids as a primary concern, 2012–2018



Other recorded drugs of concern among OATS cohort participants, by year