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ARTICLE

Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis

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Abstract

Opioid use disorder (OUD) is associated with a high risk of premature death. Medication-assisted treatment (MAT) is the primary treatment for opioid dependence. We comprehensively assessed the effects of different MAT-related characteristics on mortality among those with OUD by a systematic review and meta-analysis. The all-cause and overdose crude mortality rates (CMRs) and relative risks (RRs) by treatment status, different type, period, and dose of medication, and retention time were pooled using random effects, subgroup analysis, and meta-regression. Thirty cohort studies involving 370,611 participants (1,378,815 person-years) were eligible in the meta-analysis. From 21 studies, the pooled all-cause CMRs were 0.92 per 100 person-years (95% CI: 0.79–1.04) while receiving MAT, 1.69 (1.47–1.91) after cessation, and 4.89 (3.54–6.23) for untreated period. Based on 16 studies, the pooled overdose CMRs were 0.24 (0.20–0.28) while receiving MAT, 0.68 (0.55–0.80) after cessation of MAT, and 2.43 (1.72–3.15) for untreated period. Compared with patients receiving MAT, untreated participants had higher risk of all-cause mortality (RR 2.56 [95% CI: 1.72–3.80]) and overdose mortality (8.10 [4.48–14.66]), and discharged participants had higher risk of all-cause death (2.33 [2.02–2.67]) and overdose death (3.09 [2.37–4.01]). The all-cause CMRs during and after opioid substitution treatment with methadone or buprenorphine were 0.93 (0.76–1.10) and 1.79 (1.47–2.10), and corresponding estimate for antagonist naltrexone treatment were 0.26 (0–0.59) and 1.97 (0–5.18), respectively. Retention in MAT of over 1-year was associated with a lower mortality rate than that with retention ≤1 year (1.62, 1.31–1.93 vs. 5.31, −0.09–10.71). Improved coverage and adherence to MAT and post-treatment follow-up are crucial to reduce the mortality. Long-acting naltrexone showed positive advantage on prevention of premature death among persons with OUD.

Introduction

Globally, the use of opioids, including the use of heroin, opium and the non-medical use of pharmaceutical opioids,

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has stabilized at high levels, affecting 0.7% of the world's adult population aged 15–64 [1]. With an estimated 33 million affected individuals in the world in 2014, the use of opiates and prescription opioids continues to produce severe health and social problems [2]. Opioid use disorder (OUD) is associated with high risk of premature death. Worldwide, illicit opioid dependence was the largest contributor to the direct burden of DALYs (disability-adjusted life years, 9.2 million; 95% confidence interval (CI): 7.1–11.4), accounting for 45.8% among the 20 million DALYs caused by illicit drugs [3]. In addition, the epidemic of prescription opioids overdose in recent years has underscored the importance of addressing OUD as a worldwide public health challenge [4]. The estimated all-cause mortality rate among those with regular or dependent heroin and other opioids use was 2.09 per 100 person-years (PY), which was almost 15 times that of the general population [5]. Specifically death from drug overdose is the primary cause of drug-related deaths worldwide and opioids are the main drug type implicated in these deaths [1]. In Europe, opioids were found in 82% of fatal overdoses, of which heroin or its metabolites was detected in the majority of overdose deaths; other opioids including methadone, buprenorphine, fentanyl, and tramadol were also regularly found in toxicological reports [6].

Medication-assisted treatment (MAT) including the agonists, methadone and buprenorphine, and opioid antagonist, naltrexone is the primary evidence-based treatment for OUD [7]. Opioid agonist therapy with methadone and buprenorphine, mainly known as opioid substitution treatment (OST), is the main form of care for OUD, which has showed effectiveness in reducing both illicit opioids and prescription opioids use [8, 9], and risk of HIV infection [10], as well as improving physical and mental health [11]. Recently, extended-release naltrexone also represented a promising treatment to maintain abstinence, reduce relapse, and retain patients in treatment, which was crucial for reducing the risk of death from overdose [12, 13]. Studies have shown that MAT is effective in reducing mortality in patients with OUD [14, 15]. Research on mortality estimates has been carried out in those with OUDs [5, 16], those who inject drugs [17], and alcohol use disorder patients [18].

Mortality risk varies before entering, during and after MAT, and also varies with different medicine types among individual with OUD_S [19, 20]. A recent meta-analysis estimated mortality rate of periods during and after OST, and found that receiving methadone and buprenorphine treatment was associated with substantial reductions in the mortality of those with OUDs [21]. The risk of death of individuals with OUDs reduced largely after entry into MAT [22], but the pooled level of net mortality reduction due to MAT was still uncertain compared to untreated individuals with OUDs. Another previous meta-analysis also failed to determine the risk of death in untreated individuals with OUDs, as it combined those discharged from treatment with untreated individuals as a comparison group [5]. A clear distinction between the discharged group and the untreated group could help for assessing the effect of MAT on mortality more objectively and exactly among those with OUDs. Previous meta-analysis mainly focused on the opioid agonist treatment with methadone and buprenorphine, and no estimate of the overall mortality rate related to naltrexone antagonist treatment has been made to date.

Other characteristics such as retention time, medication dose, sex, and geographical region are also important factors that influence the estimates of mortality rate and risk. In previous systematic reviews, there were no comprehensive assessments of the effects of different MAT characteristics on mortality rates and risks among those with OUDs [5, 16, 23]. In recent years, more large-scale longitudinal cohort studies and cumulative evidence examined the association of MAT with mortality by different characteristics of treatment (including different treatment status, medication type, retention duration, periods of treatment transition, and drug dose) [14, 15, 19, 20, 24, 25]. This made it possible to quantitatively evaluate the specific mortality rate and risk in those with OUDs based on different MAT-related characteristics. These data are essential for understanding the scope of problems related to OUDs as well as the impact of MAT as a strategy to combat opioid-related problems. Hence, the present study reviewed and quantitatively integrated existing data on mortality associated with MAT characteristics from longitudinal cohort studies by meta-analysis.

Methods

Data sources and search strategy

We performed a systematic review and meta-analysis in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [26]. We searched PubMed and Embase (through the Ovid platform) from inception through 15 August 2017 using both MESH terms and text words with a limitation of English language. Briefly, our search strings included terms relating to substitution, maintenance, methadone, buprenorphine, naltrexone, mortality, and cohort studies. The search was restricted to human studies. In addition, full texts of systematic reviews on the topic of MAT for OUDs under study during the titles and abstracts screening stage were read to identify all potentially relevant studies. All studies included in the earlier reviews [5, 16, 21, 23] were assessed for inclusion in the present study. Additionally, reference lists of included studies were screened to detect complementary articles which met the inclusion criteria. The

detailed search strategy for PubMed was shown in eAppendix 1 in the Supplement.

Eligibility criteria

All studies were eligible in this meta-analysis for the following inclusion criteria: (a) study design: longitudinal cohort study; (b) participants: patients with OUD; (c) treatment: MAT involving either methadone, LAAM (levo-alpha-acetylmethadol), buprenorphine, naltrexone, or heroin; (d) comparison group: those with OUDs either discharged from MAT or not treated in MAT; (e) outcome measures: all-cause or overdose mortality rate (crude mortality rate [CMR] and standardized mortality ratio [SMR]), mortality rate ratio (RR), or hazard ratio (HR); (f) duration of follow-up: at least one year. We included studies that directly examined the effects of MAT on mortality among those with OUDs. Studies that assessed the mortality risk of different medication types or dosage levels were also included.

We excluded cross-sectional or serial cross-sectional studies and comparative analysis of autopsy records or medical records to identify death relating to MAT, as well as studies in prison and recently-release settings. Letters, reviews and comments were also excluded. We excluded studies which did not specify the drug of use and studies focusing on only HIV-positive individuals [27, 28]. Studies regarding other types of treatment but not MAT (e.g., detoxification treatment, therapeutic community, or psychological treatment alone) or unknown treatment modality were not included. We also excluded studies if mortality rate was not calculated by dividing the number of deaths by the total person-time in the corresponding treatment status. Studies with no comparison group or reporting mortality not separated by treatment status were also excluded. For duplicate studies from the same cohort, studies with detailed mortality data by treatment status or longer follow-up duration were included.

Study selection and data extraction

After removal of duplicates, titles and abstracts of retrieved articles were screened and clearly irrelevant articles were excluded. Full texts of the remaining studies were read to determine whether they met eligibility criteria for inclusion in the meta-analysis. Data were extracted from the eligible articles by two independent authors. The extracted data included study characteristics (country, study design, follow-up period); sample characteristics (sample source, sample size, age, and percent male); comparison modalities (treatment status, different periods in or out of treatment, medication type, treatment duration, or different dosage levels); and mortality estimates (such as all-cause CMRs and SMRs, overdose CMRs, RRs and HRs). Discrepancies were resolved by discussion or through consultation with a third author. For studies providing separate mortality rate and risk estimates by different medicines without a summary estimate [20, 29, 30], data were extracted separately and divided into different medication groups.

Quality assessment

The methodological quality of the studies was independently assessed using the nine-star Newcastle–Ottawa scale (NOS) [31] by two authors. Each study was evaluated based on eight items with a total score of 9, containing some perspectives about sample selection, comparability of cohorts, and outcome assessment for cohort studies. Studies with a score of 7 or greater were defined as high quality [32].

Statistical analysis

Meta-analyses were performed to generate pooled estimates of CMRs for corresponding treatment status across studies, and SMRs, if data permitted. The CMR was expressed as the number of deaths per 100 PY. In some cases, mortality rates were not reported but could be estimated using reported raw data with the method described by Degenhardt [5]. CMRs were both pooled for all-cause and overdose death among opioids users by three treatment-related status (i.e. while receiving MAT, after medication treatment cessation, and not treated in MAT), as well as medication type (agonist [methadone or buprenorphine], antagonist [naltrexone], and unspecified).

We also performed meta-analyses to compare the relative risks (RRs) of mortality based on treatment status and medication type. Within studies, RRs were calculated by the following comparative groups: untreated versus in MAT, discharged from MAT versus in MAT. When the number of deaths within a subgroup was zero, we dealt with this problem by setting the number of deaths at 0.5 to allow inclusion in comparative analyses [33]. All statistical analyses were performed by using STATA, version 12.1. Heterogeneity between and within studies was estimated using the Cochran Q-statistic and the I^2 statistic. Random effects models were used for all analyses in current study due to the expected large between-study heterogeneity.

To explore heterogeneity, cohorts were divided into subgroups according to sex (male or female), geographical region (Europe, North America, Australasia, or Asia), follow-up duration (<8 years or ≥8 years), study design (data linkage or follow-up investigation), cohort size (<2500 or ≥2500), and year of publication (before 2010 or in the year of 2010 and later). Differences by these characteristics were estimated using meta-regression analysis. We also performed meta-analyses based on different periods on or off MAT (first two weeks following treatment

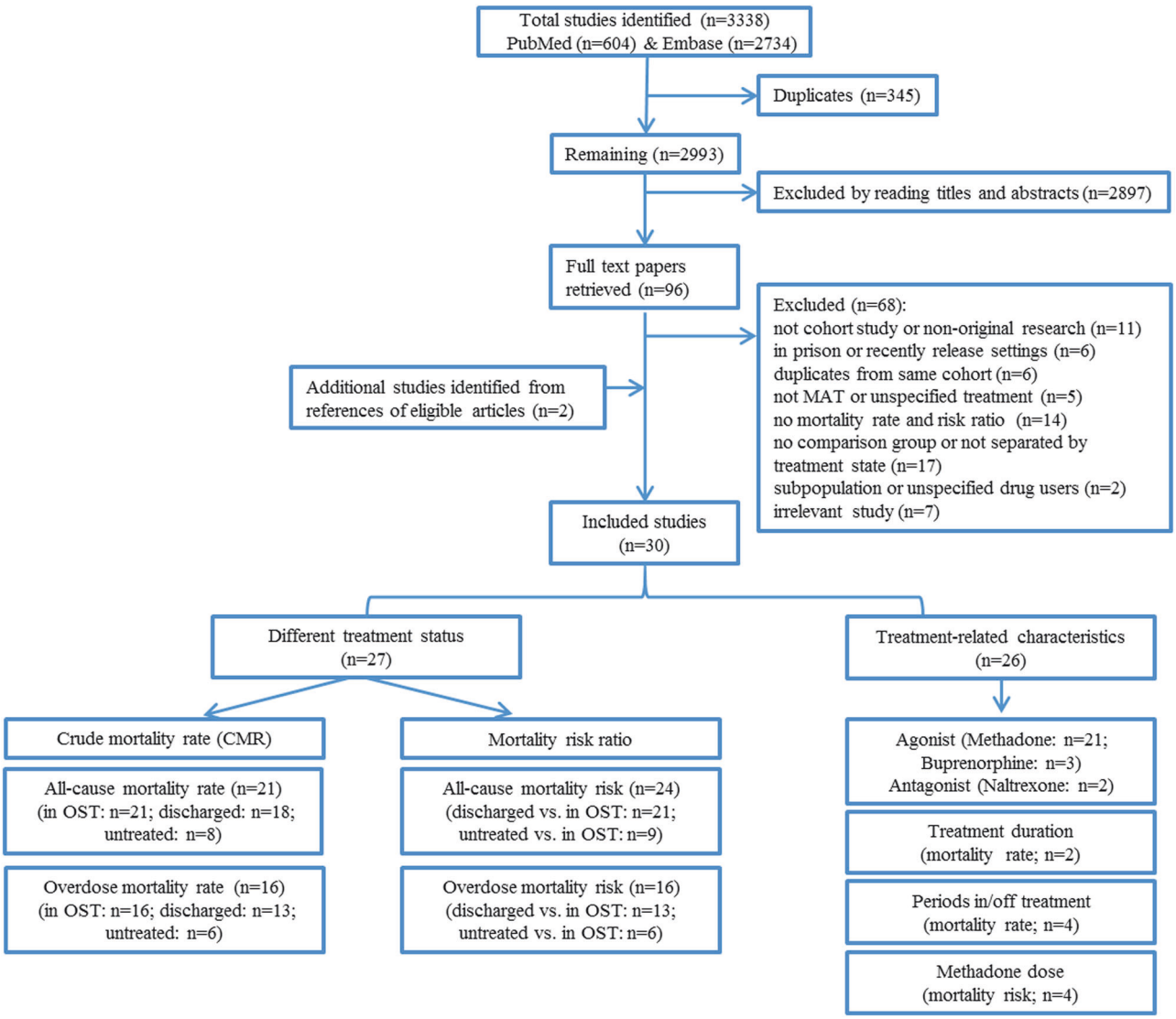

Fig. 1 Flow chart of identification of eligible studies

initiation, maintenance period during treatment, first 2 weeks after terminating MAT, or remaining period after terminating MAT), treatment duration (≤1 year or >1 year) and methadone dose (<60 mg/day or ≥60 mg/day). Finally, the potential for publication bias was examined using funnel plot and Begg's test [34]. Sensitivity analyses were conducted to examine the influence of individual study on pooled estimates, as well as the impact of quality of the included studies.

Results

Studies included

The flow chart summarizing the process of study selection was shown in Fig. 1. Among 2993 articles, 30 studies involving 370,611 participants (1,378,815 PY) were eligible for the meta-analysis. Twenty-four studies (165,732 participants, 883,821.6 PY) reported all-cause mortality rate or risk ratio pertaining to different treatment status [14, 15, 19, 20, 29, 30, 35–52], of which three studies only provided mortality risk ratio [45, 47, 52]. Sixteen studies involving 272,210 participants (1,183,985 PY) reported overdose mortality rate or risk ratio [14, 20, 35–38, 41–44, 46, 50, 51, 53–55].

Table 1 showed the characteristics of the included studies. Twenty-one studies provided all-cause mortality rate during in treatment [14, 15, 19, 20, 29, 30, 35–44, 46, 48–51]; eighteen studies provided all-cause mortality rate after terminating MAT [14, 15, 19, 20, 29, 30, 35–37, 39–41, 43, 44, 48–51]; and eight studies provided all-cause mortality rate for an untreated period [36, 38, 40–42, 46, 48, 50]. Twenty-one studies compared all-cause mortality risk during in treatment with that after terminating MAT [14, 15,

Table 1 Characteristics of included studies

Study (country)	Study design	Population	Participants (*N*/type of MAT)	Baseline age, *Y* mean (SD)	Total PY (in/discharged/untreated)	Follow-up period	CMR_{AL} (/100 PY)	CMR_{OD} (/100 PY)	In/off[a] (cut-off)	Other outcomes[b]	NOS score
Abrahamsson, (Sweden) [51]	Data linkage	O	4501/unspecified OST	Median: 34.4	21,438 (14,550/6888/—)	2005–2012 (7.5 Y)	In: 1.33; Discharged: 2.37	In: 0.57; Discharged: 1.60	90-day	RR_{AL}, RR_{OD}	8
Appel, (USA) [49]	Data linkage	O	1544/MMT	—	8484 (6129/2355/—)	1966–1976 (10 Y)	In: 1.52; Discharged: 3.52	—	—	RR_{AL}; CMR_{SEX}	5
Brugal, (Spain) [38]	Follow-up	H	5049/MMT	29.3 (6)	23,048.2 (5399.5/—/17,648.6)	1992–1999 (7 Y)	In: 2.20[c]; Untreated: 5.03[c]	In: 0.20; Untreated: 1.90	—	RR_{AL}, RR_{OD}	7
Buster, (Netherlands) [53]	Data linkage	O	5200/MMT	—	29,729 (18,747/10,983/—)	1986–1998 (13 Y)	—	In: 0.22; Discharged: 0.24	3-day	RR_{OD}	7
Cao, (China) [24]	Follow-up	O	1511/MMT	—	5391 (—/—/—)	2004–2010 (6 Y)	—	—	30-day	CMR_{MD}, CMR_{TD}	7
Caplehorn, (Australia) [35]	Data linkage	H	296/MMT	23.5 (3.2)	3796 (1792/2004/—)	1970–1991 (20 Y)	In: 0.50; Discharged: 1.65	In: 0.22[c] Discharged: 0.95[c]	—	RR_{AL}, RR_{OD}	6
Chang, (China, Taiwan) [42]	Follow-up	H[d]	1283/unspecified OST	37.5 (8.8)	5819 (4394/—/ 1 425)	2006–2011 (6 Y)	In: 1.55; Untreated: 2.39	In: 0.21[c]; Untreated: 0.77[c]	—	RR_{AL}, RR_{OD}	6
Clausen, (Norway) [36]	Data linkage	O	3789/unspecified OST	41.6 (7.1)	10,934 (6450/1303/3181)	1997–2003 (7 Y)	In: 1.40; Discharged: 3.53; Untreated: 2.40	In: 0.37; Discharged: 2.15; Untreated: 1.90	—	RR_{AL}, RR_{OD}; CMR_{SEX}	7
Cornish, (UK) [19]	Data linkage	O	5577/unspecified OST	<40: 89.5%	17,732 (8940/8792/—)	1990–2005 (16 Y)	In: 0.69; Discharged: 1.32	—	28-day	RR_{AL}; CMR_{TP}; CMR_{MB}	8
Cousins, (Ireland) [14]	Data linkage	O	6983/MMT	<40: 89.7%	28,895.3 (22,647.9/6247.4/—)	2004–2010 (6 Y)	In: 0.51; Discharged: 1.57	In: 0.24; Discharged: 0.39	3-day	RR_{AL}, RR_{OD}; CMR_{TP}; CMR_{MD}	9
Cushman, (USA) [44]	Follow-up	O	547/MMT	—	1952 (1655/ 297/ —)	1966–1976 (10 Y)	In: 1.51; Discharged: 4.70	In: 0.24[c] Discharged: 2.36[c]	—	RR_{AL}, RR_{OD}; CMR_{SEX}	4
Davoli, (Italy) [54]	Follow-up	H	10,258/MMT	Mean: 31.5	6749.0 (5751.3/997.7/—)	1998–2001 (2.5 Y)	—	In: 0.12; Discharged: 0.90	1-day	RR_{OD}	9
Degenhardt, (Australia) [37]	Data linkage	O	42,676/unspecified OST	—	425,998 (202,337/223,661/—)	1985–2006 (20 Y)	In: 0.60; Discharged: 1.15	In: 0.21; Discharged: 0.64	7-day	RR_{AL}, RR_{OD}; CMR_{TP}	8

Table 1 (continued)

Study (country)	Study design	Population	Participants (*N*/type of MAT)	Baseline age, *Y* mean (SD)	Total PY (in/discharged/untreated)	Follow-up period	CMR_{AL} (/100 PY)	CMR_{OD} (/100 PY)	In/off[a] (cut-off)	Other outcomes[b]	NOS score
Degenhardt, (Australia) [39]	Data linkage	O	11,174/MMT	—	19,008 (8071/10,937/—)	1998–2000 (2 Y)	In: 0.35; Discharged: 1.06	—	7-day	RR_{AL}	7
Dupouy, (France) [47]	Data linkage	OUD	713/BMT[e]	32.9 (9.0)	3219.4 (—/—/—)	2007–2013 (7 Y)	—	—	35-day	HR_{AL}	8
Evans, (USA) [15]	Data linkage	O	32,322/MMT	35.3 (12.4)	73,399 (25,277/48,122/—)	2006–2010 (5 Y)	In: 0.64; Discharged: 1.76	—	14-day	RR_{AL}; CMR_{TP}	9
Fellows-Smith, 2011 (Australia) [29]	Data linkage	O	1097/oral NTX; 2520/MMT	NTX: 27.7 (7.0) MMT: 31.1 (7.0)	NTX: 1446 (490/956/—); MMT: 5019 (1922/3096/—)	1998–2000 (2 Y)	NTX: In: 0.61; Discharged: 3.66 MMT: In: 0.73; Discharged: 0.74	—	—	RR_{AL}	6
Fugelstad, (Sweden) [52]	Follow-up	H	678/MMT	Mean: 28.0	—	1985–1992 (8 Y)	—	—	—	HR_{AL}	6
Fugelstad, (Sweden) [48]	Data linkage	H	101/MMT	Mean: 29.2	505.3 (177.3/57.2/270.8)	1986–1993 (8 Y)	In: 3.95; Discharged: 6.99; Untreated: 10.71	—	—	RR_{AL}; CMR_{SEX}	7
Fugelstad, (Sweden) [40]	Data linkage	H	848/MMT	—	5524.5 (3353.9/1310.6/860)	1988–2000 (13 Y)	In: 2.30; Discharged: 5.65; Untreated: 3.95[c]	—	—	RR_{AL}	6
Gearing, (USA) [50]	Data linkage	H	3959/MMT	—	15,765.2 (14,474/1170/121.2)	1965–1972 (8 Y)	In: 0.76; Discharged: 2.82; Untreated: 8.25	In: 0.23[c]; Discharged: 1.79[c]; Untreated: 5.78[c]	—	RR_{AL}, RR_{OD}	5
Gronbladh, (Sweden) [41]	Data linkage	H	281/MMT	—	2550.1 (1143/740.1/667)	1967–1988 (20 Y)	In: 1.40[c]; Discharged: 4.32[c]; Untreated: 7.20[c]	In: 0.61[c]; Discharged: 3.65[c]; Untreated: 6.45[c]	1-day	RR_{AL}, RR_{OD}; CMR_{SEX}	7
Huang, (China, Taiwan) [45]	Follow-up	H[d]	1616/MMT	35.8 (7.9)	759.5 (—/—/—)	2006–2008 (2 Y)	—	—	14-day	HR_{AL}	8
Kimber, (Australia) [20]	Data linkage	O	32,033/MMT; BMT	—	MMT: 137,057.5 (91,792.4/45265.1/—) BMT: 53,175.1 (21,936.2/31,238.9/—)	2001–2010 (10 Y)	MMT: In: 0.69[c]; Discharged: 1.24[c]; BMT: In: 0.40[c]; Discharged: 1.01[c]	MMT: In: 0.18[c]; Discharged: 0.48[c]; BMT: In: 0.14[c]; Discharged: 0.46[c]	7-day	RR_{AL}, RR_{OD}; CMR_{MB}	7
Liao, (China, Taiwan) [25]	Data linkage	O[d]	33549/MMT	37.7 (8.1)	32,943.4 (—/—/—)	2006–2008 (3 Y)	—	—	14-day	CMR_{MD}	9

Table 1 (continued)

Study (country)	Study design	Population	Participants (*N*/type of MAT)	Baseline age, *Y* mean (SD)	Total PY (in/discharged/untreated)	Follow-up period	CMR_{AL} (/100 PY)	CMR_{OD} (/100 PY)	In/off[a] (cut-off)	Other outcomes[b]	NOS score
McCowan, (UK) [56]	Data linkage	O	2378/MMT	<40: 90.0%	12,037 (—/—/—)	1993–2004 (12 Y)	—	—	90-day	HR_{MD}	9
Peles, (Israel) [43]	Follow-up	O[d]	613/MMT	37.6 (8.9)	4711.6 (1891.2/2820.5/—)	1993–2008 (15 Y)	In: 2.20; Discharged: 1.80	In: 0.30; Discharged: 0.50	—	RR_{AL}, RR_{OD}, CMR_{TD}	5
Pierce, (England) [55]	Data linkage	O	151,983/unspecified OST	Median: 32.6	408,144 (272,280/135,864/—)	2005–2009 (4 Y)	—	In: 0.26; Discharged: 0.45	1-day	HR_{OD}	9
Reece, (Australia) [30]	Data linkage	O	255/NTX implants; 2518/ BMT[e]	NTX: 32.5 (7.4); BMT: 33.7 (7.9)	NTX: 1332.2 (259.0/1073.3/—); BMT: 8030.0 (1 118.5/6 911.5/—)	2000–2007 (8 Y)	NTX: In: 0[f]; Discharged: 0.39[f]; BMT: In: 0.27; Discharged: 0.58	—	1-day	RR_{AL}	6
Risser, (Austria) [46]	Data linkage	O	2759/unspecified OST	—	4222.7 (2468.3/—/1754.4)	1995–1997 (3 Y)	In: 1.05; Untreated: 5.26	In: 0.69[c]; Untreated: 3.48[c]	—	RR_{AL}, RR_{OD}	6

BMT buprenorphine maintenance treatment, CMR_{AL} all-cause crude mortality rate, CMR_{OD} overdose crude mortality rate, *H* heroin-dependent, *MAT* medication-assisted treatment, *MMT* methadone maintenance treatment, *NOS* Newcastle–Ottawa scale, *NTX* naltrexone, *O* opioid-dependent, *OST* opioid substitution treatment, *OUD* opioid use disorder, *PY* person-years, *SD* standard deviation, *Y* years

[a]The column refers to how to define a patient as "discharged from treatment", which is based on number of days continuously not receiving a prescription

[b]CMR_{MB} crude all-cause mortality rate by medication, CMR_{MD} crude all-cause mortality rate by methadone dosage, CMR_{SEX} sex-specific crude all-cause mortality rate by treatment status, *CMRTD* crude all-cause mortality rate by treatment duration, *CMRTP* crude all-cause mortality rate by periods in/off treatment, HR_{AL} hazard ration for all-cause mortality, HR_{OD} hazard ration for overdose mortality, RR_{AL} rate ratio for all-cause mortality, RR_{OD} rate ratio for overdose mortality

[c]Mortality rate was calculated by dividing the number of deaths by the total person-years in the corresponding treatment status

[d]Meeting the DSM-IV criteria for opioid dependence

[e]Treatment with buprenorphine or buprenorphine–naloxone (Suboxone)

[f]When the number of deaths within a subgroup was zero, we dealt with this problem by setting the number of deaths at 0.5

19, 20, 29, 30, 35–37, 39–41, 43–45, 47–52], and nine compared all-cause mortality risk while receiving MAT with untreated period [36, 38, 40–42, 46, 48, 50, 52]. For patients treated in MAT, methadone was the main drug of maintenance treatment ($n = 21$), with other medicines including buprenorphine ($n = 3$) [20, 30, 47], naltrexone ($n = 2$) [29, 30], and unspecified drugs ($n = 7$) [19, 36, 37, 42, 46, 51, 55]. Of the seven studies with unspecified drug types, six studies combined patients treated with methadone or buprenorphine as a whole [19, 36, 37, 42, 46, 51], and one study did not report the type of medicine prescribed for MAT [55]. Studies were mainly from Europe ($n = 15$) and Australasia ($n = 6$), mostly using linked registers ($n = 22$) to identify treatment-related information and mortality data. The population of the 30 studies consisted of opioid-dependent individuals ($n = 19$) [14, 15, 19, 20, 24, 25, 29, 30, 36, 37, 39, 43, 44, 46, 49, 51, 53, 55, 56], heroin-dependent individuals ($n = 10$) [35, 38, 40–42, 45, 48, 50, 52, 54], and outpatients with opioid use disorder ($n = 1$) [47]. Of the 30 studies, 4 studies reported that the participants were diagnosed according to the DSM-IV criteria for dependence [25, 42, 43, 45]. Follow-up duration ranged from 2 to 20 years, with a mean of 8.7 years. Newcastle–Ottawa scale for quality assessment showed that the overall score ranged from 4 to 9 and there were 19 studies with a score of 7 or more.

Estimates of mortality rate and risk in different treatment status

Table 2 showed the all-cause and overdose mortality rates. Random effects models suggested pooled all-cause CMRs of individuals with OUDs while receiving MAT, after terminating MAT and for an untreated period were 0.92 per 100 PY (95% CI: 0.79–1.04; Fig. 2a), 1.69 (1.47–1.91; Fig. 2b), and 4.89 (3.54–6.23; Fig. 2c), respectively. The pooled overdose mortality rates were 0.24 (0.20–0.28) during in-treatment period, 0.68 (0.55–0.80) after treatment discharge, and 2.43 (1.72–3.15) for an untreated period (Table 2; Supplementary Figure S1). Individuals with OUDs had higher risks of all-cause death (2.33, 95% CI: 2.02–2.67; Fig. 3a1) and overdose death (3.09, 2.37–4.01; Fig. 3a2) after terminating MAT than that while receiving MAT. Meanwhile, compared with patients receiving MAT, both higher all-cause mortality risk (RR 2.56, 1.72–3.80; Fig. 3b1) and overdose mortality risk (8.10, 4.48–14.66; Fig. 3b2) were presented in untreated individuals with OUDs.

Estimates of mortality rate and risk by different medicines

As can be seen in Table 2, the all-cause CMRs during and after agonist therapy were 0.93 (0.76–1.10), and 1.79 (1.47–2.10), respectively. The all-cause CMRs while in active antagonist treatment and after discontinuation of antagonist treatment were 0.26 (0–0.59), and 1.97 (0–5.18), respectively. Figure 2 showed the all-cause mortality rate stratified by different medicines. During the periods of receiving MAT, all-cause mortality rate for naltrexone treatment was the lowest (0.26, 0–0.59), followed by buprenorphine treatment (0.38, 0.31–0.46), and methadone treatment (1.05, 0.86–1.25; Fig. 2a). After terminating MAT, all-cause mortality rates for patients exiting from methadone treatment and naltrexone treatment were 2.03 (1.67–2.39) and 1.97 (0–5.18), respectively. Compared to these two medicines, patients exiting from buprenorphine treatment had a lower all-cause mortality rate (0.80, 0.38–1.22; Fig. 2b). Further analysis showed that buprenorphine groups had lower mortality risk than methadone groups after treatment discharge (RR 0.81, 0.70–0.93; Fig. 2d).

Effects of retention time, treatment transition, and drug dose on mortality

Longer retention duration was associated with a lower all-cause mortality rate (>1 year vs. ≤1 year: 1.62 per 100 PY, 1.31–1.93 vs. 5.31, −0.09–10.71; Fig. 4a). The all-cause mortality rate also varied during different stages on or off treatment. During periods of MAT initiation, the all-cause mortality rate decreased from 4.89 (3.54–6.23; Fig. 2c) in untreated periods to 1.44 (0.20–2.69; Fig. 4b) in the first two weeks following treatment onset. Then the all-cause mortality rate decreased continuously and the lowest all-cause mortality rate was observed in MAT maintenance period (0.57, 0.52–0.62). Subsequently, the mortality rate increased sharply in the first two weeks after discharging from medication treatment (4.71, 1.69–7.73), and then gradually decreased at the remaining period after exiting from MAT (1.28, 1.03–1.53; Fig. 4b).

The pooled all-cause CMR of low-methadone dosage group (1.66, 0.78–2.53) was higher than that of high-dosage group (1.14, 0.72–1.57; Supplementary Figure S2A); however, the mortality risk was not statistically significant between different methadone dose groups (RR 1.02, 0.71–1.46; Supplementary Figure S2B).

Pooled estimates of mortality rates stratified by other characteristics

Subgroup analyses and meta-regression were conducted to explore differences in study-level characteristics. Males had higher CMRs than females while receiving MAT (1.46 [1.25–1.67] vs. 1.28 [1.00–1.57]), after exiting from MAT (3.92 [3.40–4.44] vs. 3.23 [1.52–4.94]), and for an untreated period (7.55 [1.39–13.72] vs. 4.20 [1.37–7.03];

Table 2 Pooled estimates and subgroup analyses of crude all-cause mortality rates (CMRs)

Characteristics	In MAT				Discharged from MAT				Untreated			
	N	PY	CMR (95% CI)	I^2, %	*N*	PY	CMR (95% CI)	I^2, %	*N*	PY	CMR (95% CI)	I^2, %
All-cause ($n = 21$)	21	448,667.9	0.92 (0.79–1.04)	93.6	18	405,245.4	1.69 (1.47–1.91)	94.9	8	25,928.0	4.89 (3.54–6.23)	93.7
Sex[b]												
Male	5	11,637.9	1.46 (1.25–1.67)	7.2	4	3451.7	3.92 (3.40–4.44)	27.3	3	2818.8	7.55 (1.39–13.72)	93.5
Female	5	3916.4	1.28 (1.00–1.57)	0.0	4	1003.6	3.23 (1.52–4.94)	53.9	3	1300.0	4.20 (1.37–7.03)	76.8
Medication type												
OST	15	208,779.9	0.93 (0.76–1.10)	93.8	14	162,572.3	1.79 (1.47–2.10)	95.1	—	—	—	—
Methadone	14	185,725.2	1.05 (0.86–1.25)	93.4	13	124,421.9	2.03 (1.67–2.39)	93.4	—	—	—	—
Buprenorphine	2	23,054.7	0.38 (0.31–0.46)	0.0	2	38,150.4	0.80 (0.38–1.22)	93.6	—	—	—	—
Antagonist (naltrexone)	2	749.0	0.26 (−0.06–0.59)	0.0	2	2029.3	1.97 (−1.23–5.18)	96.1	—	—	—	—
Unspecified	6	239,139.0	1.09 (0.74–1.43)	95.4	4	240,643.8	1.90 (1.30–2.51)	95.4	—	—	—	—
Geographical region[a]												
Europe	9	65,129.6	1.38 (0.96–1.79)	95.4	7	25,338.1	2.91 (2.11–3.71)	93.0	6	24,381.8	5.17 (3.66–6.69)	94.2
North America	4	47,535.0	1.03 (0.69–1.37)	91.4	4	51,944.0	2.94 (1.73–4.15)	89.9	1	121.2	8.25 (3.14–13.36)	—
Australasia	6	329,718.1	0.49 (0.38–0.60)	86.4	6	325,142.8	1.02 (0.84–1.20)	90.7	—	—	—	—
Asia	2	6285.2	1.81 (1.19–2.44)	63.9	1	2820.5	1.80 (1.31–2.29)	—	1	1425.0	2.39 (1.59–3.19)	—
Follow-up duration												
<8 years	9	87,647.7	0.78 (0.55–1.01)	93.0	7	85,534.2	1.57 (1.09–2.04)	96.6	3	6360.4	3.24 (1.82–4.67)	89.0
≥8 years	12	361,020.2	1.05 (0.88–1.21)	94.4	11	319,711.2	1.80 (1.54–2.06)	92.3	5	19,567.6	6.06 (4.49–7.63)	75.7
Study design[a]												
Data linkage	17	435,328.2	0.77 (0.66–0.88)	92.2	16	402,127.9	1.66 (1.43–1.88)	95.2	6	6854.4	5.67 (3.63–7.71)	90.5
Follow-up	4	13,339.7	1.85 (1.46–2.25)	61.5	2	3117.5	2.99 (0.19–5.78)	80.5	2	19,073.6	3.74 (1.15–6.32)	97.2
Cohort size[a]												
<2500	10	21,284.4	1.36 (0.88–1.86)	89.9	9	11,613.7	3.14 (2.00–4.28)	94.0	4	3222.8	5.55 (2.88–8.22)	91.0
≥2500	13	427,383.5	0.76 (0.64–0.86)	93.9	11	393,631.7	1.38 (1.17–1.60)	95.4	4	22,705.2	4.59 (2.70–6.47)	95.8
Year of publication[a]												
2010 and later	10	203,288.9	0.70 (0.55–0.86)	92.9	9	172,347.5	1.33 (1.05–1.60)	95.4	1	1425.0	2.39 (1.59–3.19)	—
Before 2010	11	245,379.0	1.32 (0.99–1.64)	94.6	9	232,897.9	3.36 (2.26–4.45)	94.5	7	24,503.0	5.35 (3.88–6.83)	93.2
Cause-specific												
Overdose ($n = 16$)	16	673,613.5	0.24 (0.20–0.28)	82.0	13	446,839.5	0.68 (0.55–0.80)	93.7	6	24,797.2	2.43 (1.72–3.15)	91.7

Several studies provided different mortality rates based on medication type, thus the number of studies in some subgroups may be greater than the sum

N number of included studies, *PY* person-years, *OST* opioid substitution treatment

[a] $p < 0.05$

[b] Five studies reporting all-cause CMR during different treatment status separated by male and female opioids users

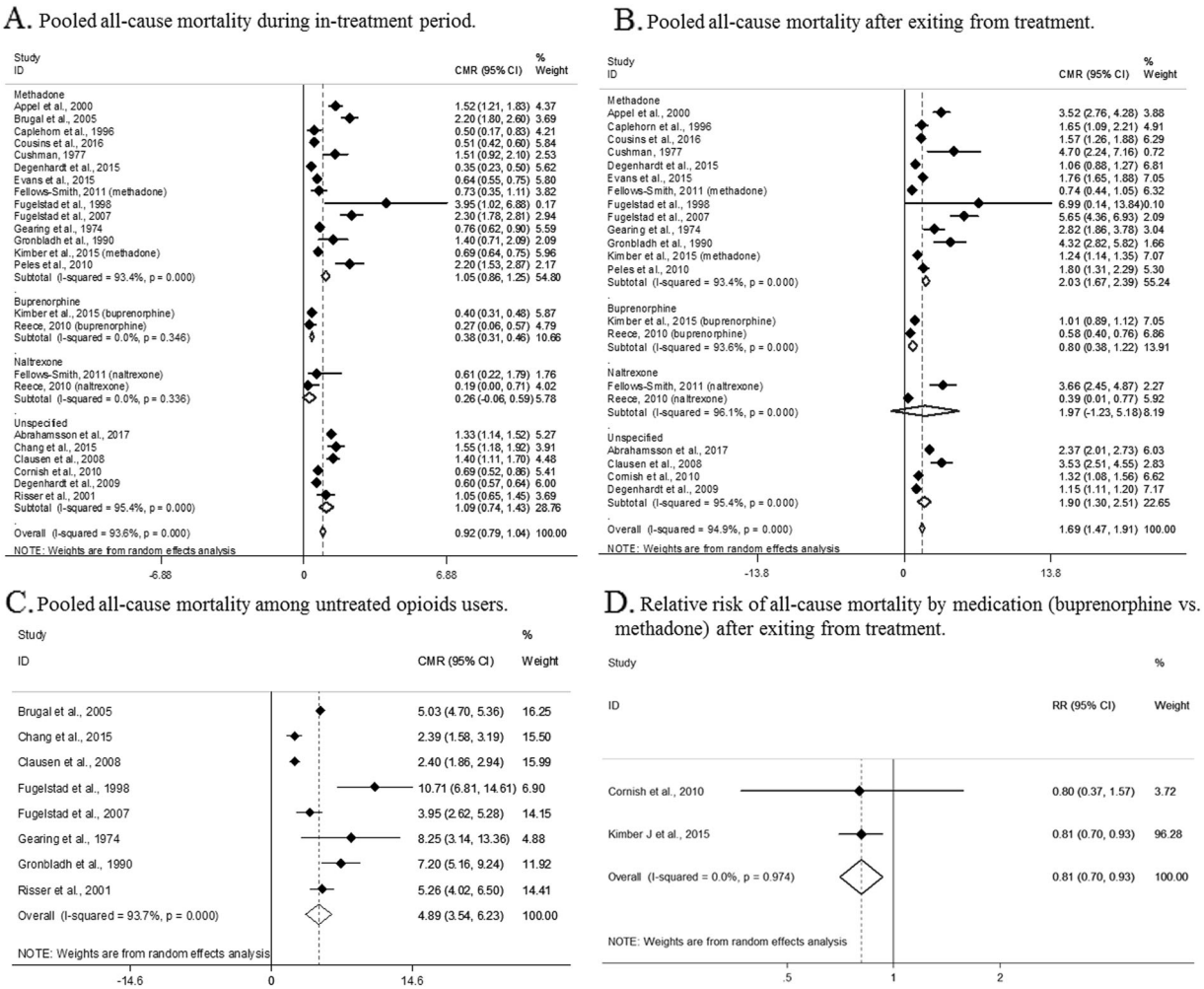

Fig. 2 Pooled estimates of crude all-cause mortality rates and risks by different medicines. (a) Medicine-specific and overall all-cause CMR of individuals with OUD while receiving MAT. (b) Medicine-specific and overall all-cause CMR of individuals with OUD after exiting from MAT. (c) Overall all-cause CMR of individuals with OUD for an untreated period. (d) Risk of all-cause death after exiting from MAT of individuals with OUD treated with buprenorphine compared with those treated with methadone

Table 2). The univariable meta-regression also showed that all-cause mortality rates were significantly different by geographic region, cohort size and year of publication during in medication treatment and after medication treatment cessation. The pooled all-cause CMRs both during and after treatment were lower in studies from Australasia, studies published after 2010 and studies with larger cohort size than the corresponding comparison groups. We found no evidence that the mortality varied by follow-up duration both for treated and discharged groups (Table 2). Full meta-regression models were not conducted because of the limited studies.

Sensitivity analyses and publication bias

From the results of the leave-one-out sensitivity analysis, all the results above in our main analyses were not materially altered. We found no evidence that the results were statistically different stratified by study quality. The funnel plot suggested potential publication bias for mortality estimates. No evidence of publication bias for the analyses of risk estimates was observed based on funnel plots and Begg's tests ($p > 0.1$; Supplementary Figure S3).

Discussion

The present meta-analysis investigated the mortality rates pertaining to three treatment statuses (0.92 per 100 PY during in MAT, 1.69 after cessation and 4.89, for an untreated period) in those with OUDs. In this analysis, we had extended our estimates of mortality rate and risk to untreated individuals with OUDs. The risk of all-cause death and overdose death among untreated patients with

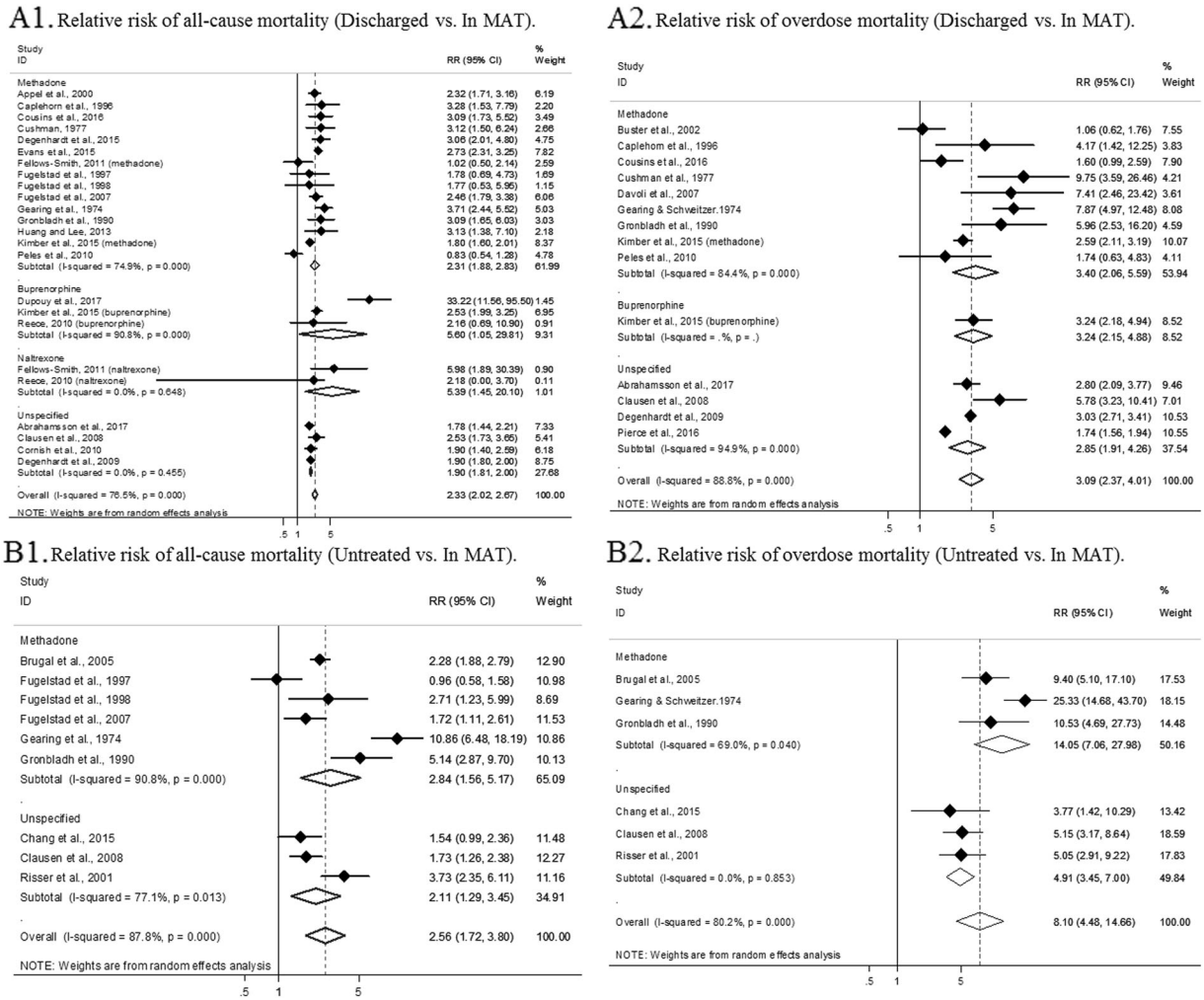

Fig. 3 Pooled estimates of all-cause and overdose mortality rate ratios (RRs) by treatment status. (a1) Risk of all-cause death after exiting from MAT compared with that while receiving MAT in individuals with OUD. (a2) Risk of overdose death after exiting from MAT compared with that while receiving MAT in individuals with OUD. (b1) Risk of all-cause death in untreated individuals with OUD compared with patients treated in MAT. (b2) Risk of overdose death in untreated individuals with OUD compared with patients treated in MAT

OUDs were 2.56 times and 8.10 times that of patients receiving MAT, respectively. The findings verified that longer retention in MAT was associated with a reduction in mortality rate and that discontinuation of MAT increased the risk of death, especially in the first 2 weeks after medication treatment discharge. In addition, this meta-analysis was the first study to assess the mortality rate and risk of three medicines delivered in MAT, agonist (methadone or buprenorphine), and antagonist (naltrexone). The mortality rate was lower while receiving naltrexone treatment than that during buprenorphine and methadone treatment. However, there is still a substantial need for research on the mortality of naltrexone treatment given the limited number of studies, particularly naltrexone delivered in the form of implants and extended-release.

The protective effect of MAT on mortality

These analyses provided pooled evidence that those with OUDs not entering into MAT had the highest level of mortality, especially the risk of overdose death, which was 8.10 times of patients in medication treatment. The present study indicated a markedly net mortality reduction associated with MAT compared to untreated individuals with OUDs. The lowest all-cause and overdose mortality rates were found while receiving MAT, indicating a protective effect of MAT on mortality. Researches showed that MAT was associated with decrease in drug injection [57] and HIV infection [10], which may contribute to the reduction of mortality. Medication treatment cessation was a major risk factor for both all-cause and overdose mortality, and the risk of all-cause death and fatal overdose after terminating MAT

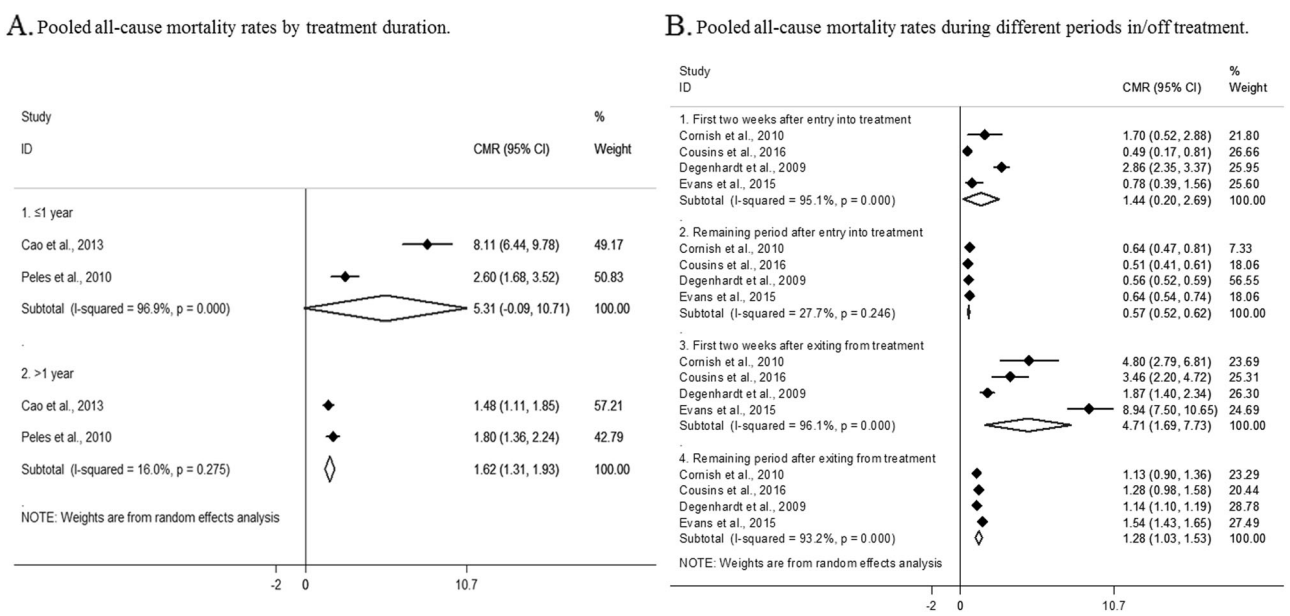

Fig. 4 Pooled estimates of all-cause mortality rate by retention-related characteristics. (a) All-cause CMR of individuals with OUD treated in MAT ≤ 1 year and those treated in MAT > 1 year, respectively. (b) All-cause CMR of individuals with OUD in the first 2 weeks following MAT initiation, during MAT maintenance period, in the first 2 weeks and subsequent period after exiting from MAT, respectively

were 2.33 times and 3.09 times higher than that during in MAT. In contrast, longer retention time was associated with a reduction of mortality rate. These analyses were the first to provide integrated pooled data demonstrating that increased retention of treatment was beneficial for survival during MAT, and we found a lower mortality rate in patients who retained in medication treatment more than 1 year. Studies also showed that the hazard of death fell 5–13% for each additional year of treatment [56, 58].

Mortality risk was higher during the first two weeks following treatment onset than that during the remaining maintenance period. The reason for this may be the use of inappropriate starting dosage prescribed during induction into treatment, without taking into account the patient's tolerance to opioids [59]. A prior study found that patients who enrolled in OST had higher risk of fatal overdose in the initial weeks of treatment [53]. Similarly, the mortality rate was especially high during the first two weeks after discontinuation of MAT, which may contributed to the high level of mortality rate following medication treatment cessation. The findings suggested that maintaining retention in treatment and extending treatment duration could be effective in reducing deaths. In fact, a considerable proportion of patients in this meta-analysis comprised multiple episodes of medication treatment initiation and cessation [14, 19, 37]. This indicated that MAT clients frequently transitioned into and out of treatment, which increased exposure to the known risk periods of drug overdose [60]. It is essential to stringently assess a patient's tolerance prior to treatment initiation and improve retention over the long term. Moreover, a post-treatment follow-up should be considered after medication treatment cessation, particularly in the first few weeks following treatment discharge.

As a supplement of our findings, evidence showed that OST was also an effective strategy to reduce deaths both in prison and the immediate post-release period. Cohort studies found that prison-based OST was associated with a 74% reduction of hazard of death during incarceration, and continuation of OST after release was associated with a substantial reduction in all-cause and overdose mortality in the first month after release [61, 62]. Receiving OST in prison contributed to greater community treatment engagement in the first month of release [63]. This continuation of OST after release could further reduce the risk of death from overdose in the immediate post-release period [64]. These evidence supported the scale-up of MAT provision in both community and prison settings to reduce mortality risk.

The impact of different medicines on mortality estimates and risks

Methadone, buprenorphine, and naltrexone are currently three medications approved for treating OUDs [7]. As a full opioid agonist, methadone is the most frequently used medication in OST for the management of OUDs [65]; however, buprenorphine, a partial agonist, is thought to have a superior safety profile to methadone as it is less likely to induce respiratory depression, posing a lower mortality risk from overdose, especially during treatment

induction [20]. This is consistent with the results of our study which showed a lower all-cause mortality rate during buprenorphine treatment than during methadone treatment. Moreover, we found a significantly lower mortality risk with buprenorphine than methadone after medication treatment cessation.

Naltrexone is an opioid antagonist that blocks the pleasurable and euphoric effects of heroin and other opiates [7]. Compared to methadone and buprenorphine, the evidence for the efficacy of naltrexone antagonist therapy in mortality remains comparatively weak. The pooled result in our study showed that mortality rate during naltrexone treatment was lower than that during methadone and buprenorphine treatment. This was the first study to integrate data about the effects of naltrexone on mortality rate and risk, which verified naltrexone as an effective medication treatment on prevention of premature mortality, especially extended-release or implant naltrexone treatment. Implant formulations represent a preferable option to deliver naltrexone treatment, since it has been associated with increasing overall time in treatment [12]. Prior research has shown that patients treated with implant naltrexone have significantly lower mortality than patients treated with oral naltrexone [66], and naltrexone implants had a favorable mortality profile both during and after treatment than buprenorphine [30]. A randomized clinical trial also indicated that extended-release naltrexone was as safe and effective as buprenorphine–naloxone in preventing relapse for patients who successfully initiated medication [67]. Additionally, more benefits could be gained by retaining patients in naltrexone and buprenorphine treatment, as the magnitude of RRs for all-cause mortality after treatment versus during treatment were larger for naltrexone and buprenorphine than for methadone. Taken altogether, these results underscore the potential benefits of naltrexone as a treatment of opioid use disorder. More large-scale studies directly comparing the mortality risk of naltrexone, particularly in the form of implants and extended-release, with other medications are warranted in the future.

The impact of other characteristics on mortality estimates

There was significant heterogeneity among the included studies, such as large geographic variation and sex difference. Australasia had lower all-cause CMR estimates both during in-treatment period and after exiting from MAT compared with other regions. This may be explained by the low background mortality among opioids users in Australasia [5]. Moreover, treatment settings (primary care-based or specialized treatment clinics), mode (low-threshold or high-threshold) and quality (supervised or take-home medication dispensation) of treatment delivered in different countries were varied, being the possible reasons of different mortality risk [68, 69]. Notably, no studies from regions such as Africa were identified, and further evidence of the effectiveness of MAT is required in these settings. We found that female opioids users had lower risk of mortality, which may be related to the fact that females seem to have a greater chance of surviving an overdose [53]. Additionally, studies published after 2010 tend to report lower mortality rates either in or off MAT. This may be related to the increasing proportion of opioids users entering buprenorphine therapy over time [70], which is associated with reduction in overdose deaths [71].

Differences were also found in mortality rates according to cohort size and study design. These factors may explain the large heterogeneity among included studies. Related to the dosage of medicine, no significant difference in mortality risk was found between low- and high-methadone dosage groups; however, few studies were available for analysis. Prior evidence has shown that higher methadone dosages were superior in retaining patients [43]. Further research is needed to examine the role that dosage might play in reducing mortality across the available medications.

Strengths and limitations

This meta-analysis was the first study to provide pooled net reduction of all-cause and overdose mortality rate in individuals with OUDs who receiving the MAT, compared with the individuals not getting medication treatment, which was different from the recent meta-analysis mainly focusing on the mortality rate during and after OST [21]. We identified several additional studies that were not included in the above meta-analysis [24, 25, 29, 38, 39, 42, 45–47, 49, 51, 52, 55, 56], and added the estimate of mortality rates and risks among different medication types, treatment retention, and drug doses. In addition to OST including methadone and buprenorphine, we firstly pooled the mortality estimate of antagonist treatment with naltrexone among individual with OUDs. Thus, our findings have extended and added to the current knowledge on the comprehensive effects of MAT on mortality risk among patients with OUDs receiving medicines treatment. In addition, we provided the pooled evidence that longer retention time of MAT reduced the risk of mortality.

Our review has several limitations. First, most included studies were registry-based studies which were vulnerable to selection bias. Differences between individuals receiving different medications could account for the differing effects that were associated with the medications. Misclassification may have occurred in death and treatment group in studies based on data linkage. Besides, the number of studies regarding to naltrexone treatment was limited. Second, the studies included were still predominantly from Europe and

Australasia. Thus, the results of the present study may not reflect the effectiveness of MAT in worldwide. Studies in low and middle income countries are especially needed. Third, information about ancillary services such as counseling, or psychosocial services was limited. The provision of additional interventions such as psychosocial interventions might additionally reduce the risk of death [54]. Finally, most of individuals included in this meta-analysis were either from drug-free programs or underwent a short duration of detoxification when waiting for entry into MAT [41]. These individuals may differ from the individuals who never received any drug treatment. Notwithstanding these limitations, this analysis has added quantitative evidence on the effectiveness of MAT in reducing mortality among patients with OUDs in community settings.

Implications

This study provided strong quantitative evidence that links mortality rate and mortality risk to different characteristics of MAT, further highlighting the importance of MAT in the prevention of premature death among individuals with OUDs. Opioids-related deaths remain a large burden to public health [4]. Increased efforts and interventions should be focused on lengthening retention time and target patients in their early stage of medication treatment initiation and cessation, and post-treatment follow-up should be emphasized after medication treatment cessation. Despite the protective effect of MAT on mortality, barriers still exist in the access to and utilization of MAT [7]. Facing the situation of limited coverage of OST and other harm reduction interventions in worldwide [72], increased coverage and expanding access to MAT are crucial components of the effort to reduce opioids-related deaths and alleviate disease burden. Naltrexone represents an alternative option to deliver medication treatment for those with OUDs, especially in the form of implants or extended-release, given that it was associated with a lower mortality rate than methadone and buprenorphine treatment. More researches are still needed regarding to the effects of long-acting naltrexone treatment on mortality and other aspects among individuals with OUDs.

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Author contributions YB, JS and LL were responsible for study design. JM and YB were responsible for the literature search and study selection. JM, MS, RW, and ML were responsible for data extraction and quality assessment. JM was responsible for statistical analysis and manuscript drafting. JS, LL, RW, MS, ML, JL, LD, MF, FB, MI, and YB were responsible for critical revision of the manuscript.

Compliance with ethical standards

Conflict of interest In the past three years, LD and MF have received investigator-initiated untied educational grants for studies of opioid medications in Australia from Indivior, Mundipharma and Seqirus. The other authors declare that they have no conflict of interest.

References

1. United Nations Office on Drugs and Crime. World drug report. Vienna: United Nations Office on Drugs and Crime; 2015.
2. United Nations Office on Drugs and Crime. World drug report. Vienna: United Nations Office on Drugs and Crime; 2016.
3. Degenhardt L, Whiteford HA, Ferrari AJ, Baxter AJ, Charlson FJ, Hall WD, et al. Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010. Lancet. 2013;382:1564–74.
4. Gostin LO, Hodge JG Jr., Noe SA. Reframing the opioid epidemic as a national emergency. JAMA. 2017;318:1539–40.
5. Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction. 2011;106:32–51.
6. European Monitoring Centre for Drugs and Drug Addiction. European Drug Report 2016: trends and developments. Publications Office of the European Union, Luxembourg: European Monitoring Centre for Drugs and Drug Addiction; 2016.
7. Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies—tackling the opioid-overdose epidemic. N Engl J Med. 2014;370:2063–6.
8. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev. 2009; 3:CD002209.
9. Nielsen S, Larance B, Lintzeris N. Opioid agonist treatment for patients with dependence on prescription opioids. JAMA. 2017;317:967–8.
10. MacArthur GJ, Minozzi S, Martin N, Vickerman P, Deren S, Bruneau J, et al. Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. BMJ. 2012;345:e5945.
11. Reimer J, Verthein U, Karow A, Schafer I, Naber D, Haasen C. Physical and mental health in severe opioid-dependent patients within a randomized controlled maintenance treatment trial. Addiction. 2011;106:1647–55.
12. Ayanga D, Shorter D, Kosten TR. Update on pharmacotherapy for treatment of opioid use disorder. Expert Opin Pharmacother. 2016;17:2307–18.
13. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet. 2011;377:1506–13.
14. Cousins G, Boland F, Courtney B, Barry J, Lyons S, Fahey T. Risk of mortality on and off methadone substitution treatment in primary care: a national cohort study. Addiction. 2016; 111:73–82.
15. Evans E, Li L, Min J, Huang D, Urada D, Liu L, et al. Mortality among individuals accessing pharmacological treatment for opioid dependence in California, 2006-10. Addiction. 2015; 110:996–1005.
16. Desmond DP, Maddux JF. Deaths among heroin users in and out of methadone treatment. J Maint Addict. 2000;1:45–61.
17. Mathers BM, Degenhardt L, Bucello C, Lemon J, Wiessing L, Hickman M. Mortality among people who inject drugs: a systematic review and meta-analysis. Bull World Health Organ. 2013;91:102–23.

18. Roerecke M, Rehm J. Cause-specific mortality risk in alcohol use disorder treatment patients: a systematic review and meta-analysis. Int J Epidemiol. 2014;43:906–19.
19. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ. 2010;341:c5475.
20. Kimber J, Larney S, Hickman M, Randall D, Degenhardt L. Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study. Lancet Psychiatry. 2015;2:901–8.
21. Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ. 2017;357:j1550.
22. Peles E, Schreiber S, Adelson M. Opiate-dependent patients on a waiting list for methadone maintenance treatment are at high risk for mortality until treatment entry. J Addict Med. 2013;7:177–82.
23. Bargagli AM, Davoli M, Minozzi S, Vecchi S, Perucci CA. A systematic review of observational studies on treatment of opioid dependence. Background document prepared for 3rd meeting of Technical Development Group (TDG) for the WHO Guidelines for Psychosocially Assisted Pharmacotherapy of Opiod Dependence. Geneva, Switzerland; 2007.
24. Cao X, Wu Z, Li L, Pang L, Rou K, Wang C, et al. Mortality among methadone maintenance clients in China: a six-year cohort study. PLoS ONE. 2013;8:e82476.
25. Liao DL, Chen PC, Chen CH, Hsieh CJ, Huang YF, Shih WY, et al. Higher methadone doses are associated with lower mortality in patients of opioid dependence in Taiwan. J Psychiatr Res. 2013;47:1530–4.
26. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
27. Nosyk B, Min JE, Evans E, Li L, Liu L, Lima VD, et al. The effects of opioid substitution treatment and highly active antiretroviral therapy on the cause-specific risk of mortality among HIV-positive people who inject drugs. Clin Infect Dis. 2015;61:1157–65.
28. Fugelstad A, Rajs J, Böttiger M, Gerhardsson de Verdier M. Mortality among HIV-infected intravenous drug addicts in Stockholm in relation to methadone treatment. Addiction. 1995;90:711–6.
29. Fellows-Smith J. Opioid-dependent error processing. J Opioid Manag. 2011;7:443–9.
30. Reece AS. Favorable mortality profile of naltrexone implants for opiate addiction. J Addict Dis. 2010;29:30–50.
31. Wells GA, Shea B, O' Connell D, Robertson J, Peterson J, Welch V et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 12 Mar 2016.
32. Zhong S, Zhang X, Chen L, Ma T, Tang J, Zhao J. Statin use and mortality in cancer patients: Systematic review and meta-analysis of observational studies. Cancer Treat Rev. 2015;41:554–67.
33. Mathers BM, Degenhardt L. Examining non-AIDS mortality among people who inject drugs. AIDS. 2014;28:S435–44.
34. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50:1088–101.
35. Caplehorn JR, Dalton MS, Haldar F, Petrenas AM, Nisbet JG. Methadone maintenance and addicts' risk of fatal heroin overdose. Subst Use Misuse. 1996;31:177–96.
36. Clausen T, Anchersen K, Waal H. Mortality prior to, during and after opioid maintenance treatment (OMT): a national prospective cross-registry study. Drug Alcohol Depend. 2008;94:151–7.
37. Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. Drug Alcohol Depend. 2009;105:9–15.
38. Brugal MT, Domingo-Salvany A, Puig R, Barrio G, Garcia de Olalla P, de la Fuente L. Evaluating the impact of methadone maintenance programmes on mortality due to overdose and aids in a cohort of heroin users in Spain. Addiction. 2005;100:981–9.
39. Degenhardt L, Larney S, Kimber J, Farrell M, Hall W. Excess mortality among opioid-using patients treated with oral naltrexone in Australia. Drug Alcohol Rev. 2015;34:90–6.
40. Fugelstad A, Stenbacka M, Leifman A, Nylander M, Thiblin I. Methadone maintenance treatment: the balance between life-saving treatment and fatal poisonings. Addiction. 2007;102:406–12.
41. Gronbladh L, Ohlund LS, Gunne LM. Mortality in heroin addiction: impact of methadone treatment. Acta Psychiatr Scand. 1990;82:223–7.
42. Chang KC, Lu TH, Lee KY, Hwang JS, Cheng CM, Wang JD. Estimation of life expectancy and the expected years of life lost among heroin users in the era of opioid substitution treatment (OST) in Taiwan. Drug Alcohol Depend. 2015;153:152–8.
43. Peles E, Schreiber S, Adelson M. 15-Year survival and retention of patients in a general hospital-affiliated methadone maintenance treatment (MMT) center in Israel. Drug Alcohol Depend. 2010;107:141–8.
44. Cushman P. Ten years of methadone maintenance treatment: some clinical observations. Am J Drug Alcohol Abus. 1977;4:543–53.
45. Huang CL, Lee CW. Factors associated with mortality among heroin users after seeking treatment with methadone: a population-based cohort study in Taiwan. J Subst Abus Treat. 2013;44:295–300.
46. Risser D, Honigschnabl S, Stichenwirth M, Pfudl S, Sebald D, Kaff A, et al. Mortality of opiate users in Vienna, Austria. Drug Alcohol Depend. 2001;64:251–6.
47. Dupouy J, Palmaro A, Fatseas M, Auriacombe M, Micallef J, Oustric S, et al. Mortality associated with time in and out of buprenorphine treatment in french office-based general practice: a 7-year cohort study. Ann Fam Med. 2017;15:355–8.
48. Fugelstad A, Agren G, Romelsjo A. Changes in mortality, arrests, and hospitalizations in nonvoluntarily treated heroin addicts in relation to methadone treatment. Subst Use Misuse. 1998;33:2803–17.
49. Appel PW, Joseph H, Richman BL. Causes and rates of death among methadone maintenance patients before and after the onset of the HIV/AIDS epidemic. Mt Sinai J Med. 2000;67:444–51.
50. Gearing FR, Schweitzer MD. An epidemiologic evaluation of long-term methadone maintenance treatment for heroin addiction. Am J Epidemiol. 1974;100:101–12.
51. Abrahamsson T, Berge J, Ojehagen A, Hakansson A. Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment: a nation-wide register-based open cohort study. Drug Alcohol Depend. 2017;174:58–64.
52. Fugelstad A, Annell A, Rajs J, Agren G. Mortality and causes and manner of death among drug addicts in Stockholm during the period 1981-1992. Acta Psychiatr Scand. 1997;96:169–75.
53. Buster MCA, van Brussel GHA, van den Brink W. An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. Addiction. 2002;97:993–1001.
54. Davoli M, Bargagli AM, Perucci CA, Schifano P, Belleudi V, Hickman M, et al. Risk of fatal overdose during and after specialist drug treatment: the VEdeTTE study, a national multi-site prospective cohort study. Addiction. 2007;102:1954–9.
55. Pierce M, Bird SM, Hickman M, Marsden J, Dunn G, Jones A. Impact of treatment for opioid dependence on fatal drug-related

poisoning: a national cohort study in England. Addiction. 2016;111:298–308.
56. McCowan C, Kidd B, Fahey T. Factors associated with mortality in Scottish patients receiving methadone in primary care: retrospective cohort study. BMJ. 2009;338:b2225.
57. Gowing L, Farrell MF, Bornemann R, Sullivan LE, Ali R. Oral substitution treatment of injecting opioid users for prevention of HIV infection. Cochrane Database Syst Rev. 2011;2:CD004145.
58. Kimber J, Copeland L, Hickman M, Macleod J, McKenzie J, De Angelis D, et al. Survival and cessation in injecting drug users: prospective observational study of outcomes and effect of opiate substitution treatment. BMJ. 2010;341:c3172.
59. Vignali C, Stramesi C, Morini L, Pozzi F, Groppi A. Methadone-related deaths: a ten year overview. Forensic Sci Int. 2015; 257:172–6.
60. Vajdic CM, Marashi Pour S, Olivier J, Swart A, O'Connell DL, Falster MO, et al. The impact of blood-borne viruses on cause-specific mortality among opioid-dependent people: an Australian population-based cohort study. Drug Alcohol Depend. 2015;152:264–71.
61. Larney S, Gisev N, Farrell M, Dobbins T, Burns L, Gibson A, et al. Opioid substitution therapy as a strategy to reduce deaths in prison: retrospective cohort study. BMJ Open. 2014;4:e004666.
62. Marsden J, Stillwell G, Jones H, Cooper A, Eastwood B, Farrell M, et al. Does exposure to opioid substitution treatment in prison reduce the risk of death after release? A national prospective observational study in England. Addiction. 2017; 112:1408–18.
63. Rich JD, McKenzie M, Larney S, Wong JB, Tran L, Clarke J, et al. Methadone continuation versus forced withdrawal on incarceration in a combined US prison and jail: a randomised, open-label trial. Lancet. 2015;386:350–9.
64. Degenhardt L, Larney S, Kimber J, Gisev N, Farrell M, Dobbins T, et al. The impact of opioid substitution therapy on mortality post-release from prison: retrospective data linkage study. Addiction. 2014;109:1306–17.
65. Mathers BM, Degenhardt L, Ali H, Wiessing L, Hickman M, Mattick RP, et al. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. Lancet. 2010;375:1014–28.
66. Kelty E, Hulse G. Examination of mortality rates in a retrospective cohort of patients treated with oral or implant naltrexone for problematic opiate use. Addiction. 2012;107:1817–24.
67. Lee JD, Nunes EV, Novo P, Bachrach K, Bailey GL, Bhatt S, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine–naloxone for opioid relapse prevention (X: BOT): a multicentre, open-label, randomised controlled trial. Lancet. 2017;391:309–18.
68. Bell J, Zador D. A risk-benefit analysis of methadone maintenance treatment. Drug Saf. 2000;22:179–90.
69. Wittchen HU, Apelt SM, Soyka M, Gastpar M, Backmund M, Golz J, et al. Feasibility and outcome of substitution treatment of heroin-dependent patients in specialized substitution centers and primary care facilities in Germany: a naturalistic study in 2694 patients. Drug Alcohol Depend. 2008;95:245–57.
70. Burns L, Gisev N, Larney S, Dobbins T, Gibson A, Kimber J, et al. A longitudinal comparison of retention in buprenorphine and methadone treatment for opioid dependence in New South Wales, Australia. Addiction. 2015;110:646–55.
71. Schwartz RP, Gryczynski J, O'Grady KE, Sharfstein JM, Warren G, Olsen Y, et al. Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995-2009. Am J Public Health. 2013;103:917–22.
72. Larney S, Peacock A, Leung J, Colledge S, Hickman M, Vickerman P, et al. Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: a systematic review. Lancet Glob Health. 2017;5:e1208–20.