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Review

The incidence and outcomes of out-of-hospital cardiac arrest precipitated by drug overdose: A systematic review and meta-analysis

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Abstract

Background: Out-of-hospital cardiac arrests (OHCA) precipitated by drug overdose (OD) are becoming an increasing public health problem in developed countries. Empirical data on the global incidence and outcomes are needed to guide preventive and treatment strategies.

Methods: We conducted a systematic review using MEDLINE, Embase, Emcare, All EBM Reviews and CINAHL to identify observational or interventional studies reporting the incidence or outcomes of adult OHCA precipitated by drug OD between 1990 and 2018. Pooled incidence rates per 100,000 person-years and survival outcomes were summarised using random-effects models.

Results: Twelve articles met the eligibility criteria, of which six were from North America, four from Europe and two from Asia. Only two studies reported the incidence of EMS-attended cases. The pooled incidence of EMS-treated OHCA was 1.4 cases per 100,000 person-years. The pooled rate of survival to hospital discharge and survival with favourable neurological outcome was 9% (95% CI: 6%, 12%; $I^2 = 90\%$; $p < 0.001$) and 6% (95% CI: 2%, 13%; $I^2 = 81\%$; $p < 0.001$), respectively. The pooled rate of return of spontaneous circulation was 25% (95% CI: 11%, 41%; $I^2 = 97\%$; $p < 0.001$). Drug OD OHCA was associated with an improvement in the odds of survival to hospital discharge (pooled odds ratio 2.2, 95% CI: 1.7, 2.7; $I^2 = 0\%$; $p = 0.45$).

Conclusion: The incidence and survival outcomes of drug OD OHCA varies substantially across regions. Effective strategies designed to reduce incidence and improve survival outcomes are needed.

Keywords: Out-of-hospital cardiac arrest, Drug overdose, Emergency medical services, Cardiopulmonary resuscitation

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Introduction

Drug overdose (OD) poses a significant public health problem worldwide and accounts for thousands of deaths each year.[1,2] In 2016, as many as 100,000 adults died from drug OD globally,[1] and opioid OD alone was responsible for about 70% of these deaths.[2] A leading mechanism of death in drug OD is cardiopulmonary arrest occurring before arrival at hospital,[3] which has been estimated to affect as many as 500,000 people in the USA between 2004 and 2014.[2] Out-of-hospital cardiac arrest (OHCA) precipitated by drug OD accounts for as many as one third of all OHCA events, and is particularly prevalent among young adults.[4,5]

Emergency medical services (EMS) are often the first point of contact for most drug OD-related events, and can contribute to reducing the burden of disease from OHCA.[3,6–8] Unfortunately, much of the improvement in survival following OHCA has occurred in populations with presumed cardiac aetiology or initial shockable arrests, who benefit from the early application of life-saving interventions such as cardiopulmonary resuscitation (CPR) and defibrillation.[9–14] In comparison, drug-related OHCA are usually unwitnessed and often present in asystole.[3,7,15] As such, it is unclear if community-based initiatives to increase rates of bystander CPR and defibrillation can help yield additional survivors.

Unlike OHCA precipitated by presumed cardiac aetiology, comparatively little is known about the global incidence and outcomes of drug-related OHCA. The lack of synthesised data on the problem can contribute to delays in the development of novel treatment interventions or preventive strategies which can help minimise the burden of these events in the community. In this study, we aimed to systematically review the literature on the incidence and outcomes of adult OHCA precipitated by drug OD.

Materials and methods

This systematic review was conducted in accordance with the Joanna Briggs Institute (JBI) methodology for systematic reviews of prevalence and incidence.[16] The systematic review protocol was registered prior to commencement of the study (reference number: JBISRIR-2017-003738).

Search strategy

A systematic review of the literature was conducted to identify published and unpublished studies written in English. Two reviewers independently (SA and ZN) performed a three-step search strategy to capture published studies. First, an initial MEDLINE and Embase search using topic-related keywords (e.g. cardiac arrest/CPR and drug overdose/substance abuse) was conducted to analyse text words and index terms contained within the titles and abstracts. Second, an optimised search strategy containing the index terms and relevant keywords identified in step one was applied to a broader database search using MEDLINE, Embase, Emcare, All EBM Reviews (ACP Journal Club, Cochrane Central Register of Controlled Trial, Cochrane Database of Systematic Reviews, Cochrane Methodology Register, Database of Abstracts of Reviews of Effects, Health Technology Assessment, and National Health Service Economic Evaluation), and CINAHL (Table S1 in the supplementary appendix). Third, the reference lists of the eligible articles were reviewed for potential studies that may have been missed. All studies published on or after January 1990 and May 2018 were considered for the review. We chose 1990 as the start of our inclusion period, aligned to the publication of the original Utstein template which sought to reduce variability in the reporting of OHCA definitions.[17] In addition, we searched CORE, MedNar, Trove and Resuscitation Outcomes Consortium for possible grey literature meeting eligibility criteria.

Study selection and eligibility

The titles and abstracts of relevant studies were appraised for eligibility by two authors (SA and ZN) independently. Studies were eligible for inclusion if they reported adults aged greater than 15 years who were attended by EMS for an OHCA precipitated by a drug OD. Cardiac arrest was defined as "the absence of signs of circulation irrespective of whether the assessment was made by a bystander or EMS personnel".[18] Cardiac arrests precipitated by drug OD were defined as "evidence that cardiac arrest was caused by deliberate or accidental overdose of prescribed medications, recreational drugs, or ethanol".[18] Cohort observational studies and interventional studies were included. As the main outcome of this review is to pool the global incidence and outcomes of undifferentiated population of drug-related OHCA, we excluded studies of OHCA caused by isolated drug OD (e.g. tricyclic antidepressants or opioids) or chemical poisoning (e.g. organophosphate or carbon monoxide) which could introduce heterogeneity. Studies describing other populations of sudden cardiac arrest patients were also excluded (e.g. in-hospital cardiac arrests). Finally, studies where incidence could not be derived such as case control, cross sectional studies, case series, case reports, editorials, letters, comments, news, notes and reviews were also excluded. Discrepancies were resolved through discussion between the two authors.

Outcomes

The main outcomes of the review were the pooled incidence of EMS-attended and EMS-treated drug OD OHCA per 100,000 person-years and the pooled proportion of survivors to hospital discharge or 30 days. Secondary outcomes included the pooled proportion of patients who survived with intact neurological function at hospital discharge, achieved prehospital return of spontaneous circulation (ROSC), survived to hospital, and survived to 12 months. In a subgroup of included studies, we also pooled the adjusted odds ratios (AOR) of the effect of drug OD on survival to hospital discharge.

Data extraction

A data extraction form was developed and modified from the JBI.[19] Main components of the form included author(s) name, year of publication, aims, settings, study design and duration, EMS serviceable population, drug OD OHCA definition, mean age, sex, witness status, bystander CPR, arrest location, initial shockable rhythm, naloxone administration, the number of EMS-attended and EMS-treated cases, and survival outcomes. Survival outcomes were extracted as the proportion of EMS treated patients. If odds ratios for the effect of drug OD on survival were reported, we extracted the odds ratio which adjusted for the largest number of confounders. Two reviewers extracted data independently (SA and ZN). Differences in data extraction were resolved through discussion. The authors of two studies were also contacted to confirm the

definition of drug OD OHCA,[20,21] and obtain information relating to the study setting and serviceable population.[20]

Quality assessment

The Joanna Briggs Institute critical appraisal tool for studies reporting prevalence and incidence data were used to assess the quality of the included studies.[19] Each reviewer (SA and ZN) critically appraised study quality independently by answering yes, no, unclear or not applicable to nine questions. Discrepancies were resolved through consensus.

Data synthesis and meta-analysis

The population published in the articles was corrected for the mid-point census population at the time of study (for North American areas, https://factfinder.census.gov/ and http://www12.statcan.gc.ca/; for European areas, http://epp.eurostat.ec.europa.eu/; for Asian areas, http://www.e-stat.go.jp/). Incidence rates of EMS-attended and EMS-treated drug OD OHCA were calculated as the number of cases during a study period divided by the total population at-risk during the same period, per 100,000 person-years. Ninety five percent confidence intervals (95% CI) were calculated assuming a Poisson distribution.[22] The DerSimonian and Laird method was used to pool incidence rates, with the estimates of heterogeneity taken from the inverse variance fixed-effect model. Since the proportions of survival outcomes were below 0.5 and close to 0, the Freeman-Tuckey double arcsine transformation was computed to estimate the proportions and the Wald 95% CI.[23] The AOR for the effect of drug OD on survival to hospital discharge in OHCA cases was computed using the DerSimonian and Laird random-effects model, as above.

Subgroup analysis by study regions and case definition (i.e. aligned with Utstein definition and not aligned with Utstein definition) was used to explore potential sources of heterogeneity. Where appropriate, we also conducted sensitivity analyses by excluding outlying observations which differed significantly in population characteristics. Heterogeneity was assessed statistically using I^2 tests. The I^2 values of 25%, 50%, and 75% indicate low, moderate and high heterogeneity, respectively.[24] All statistical analyses were undertaken using STATA 15.0 (Statacorp, College Station, Texas, USA).

Results

Study selection

Our search for published studies yielded 5575 citations. After removing duplicates (n = 1894), irrelevant study designs (n = 744) and those that did not meet our eligibility criteria (n = 2914), 23 articles underwent full text review. Eight articles met the inclusion criteria, and an additional four articles were identified from reference lists. The total studies included in the quantitative data synthesis was 12 (Fig. 1).

Study characteristics

Study characteristics are presented in Table 1. Fifty percent of the pooled population were from North America, 33% from Europe, and 17% from Asia. The total serviceable population was 102.6 million. All studies were of retrospective cohort design. Two studies reported the incidence of EMS-attended cases and all studies reported the incidence of EMS-treated cases. Age was reported in seven studies, with a mean age ranging between 36 and 50 years. Sex was reported in seven studies, with a percentage of males varying between 63% and 73%. The study by Kitamura et al. from Osaka, Japan had the lowest rates of witnessed arrest, bystander CPR and initial shockable rhythms with a rate of 5%, 18% and 1%, respectively. Eleven studies reported the percentage of patients who survived to hospital discharge with the highest observed in Pittsburgh, USA (19%) and the lowest in Korea (3%).

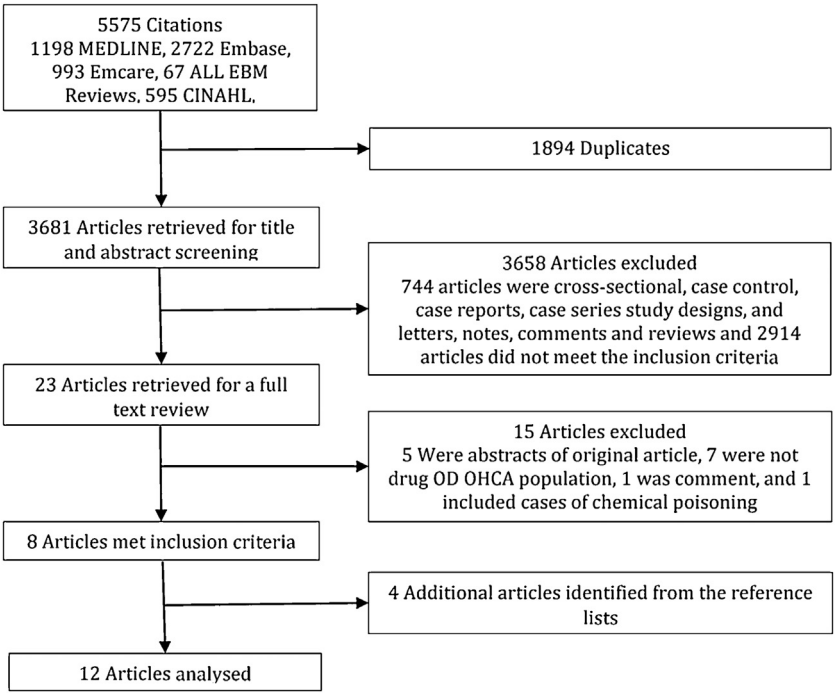

Fig. 1 – Literature search results.

Table 1 – Demographics and clinical characteristics.

Study	Year	Setting	Study time span (years)	Serviceable population[a]	Incidence per 100,000 person-years		Mean age	Male %	Witness %	Bystander CPR%	Initial shockable rhythm%	Discharged alive%
					EMS-attended	EMS-treated						
		Europe										
Kuisma[21]	1997	Helsinki, Finland	2	525,000	–	2.6	–	–	–	–	–	19
Engdahl[51]	2003	Goteborg, Sweden	20	443,000	–	2.0	42	69	24	31	5	3
Jabre[21]	2015	Ile De France, France	3	8,000,000	0.4	0.3	–	–	–	–	–	11
Claesson[15]	2017	Sweden	22	8,941,000	–	0.7	36	67	35	56	17	10
		North America										
Paredes[7]	2004	King County, WA	1	2,000,000	8.5	4.3	40.4	73	14	24	6	13
Hess[52]	2007	Olmsted County, MN	11	124,000	–	0.7	–	–	–	–	–	11
Koller[6]	2014	Pittsburgh, PA	5	935,000	–	3.9	44.8	65	55	48	16	19
Agy[53]	2015	Salt Lake County, UT	6.3	1,017,000	–	1.5	–	–	–	–	9	–
Salcido[8]	2016	Birmingham, AL; Dallas, TX; Milwaukee, WI; Pittsburgh, PA; Portland, OR; San Diego, CA; Seattle, WA; Toronto, ON; Vancouver, BC; Ottawa, ON	4	18,530,000	–	1.8	41	66	31	37	8	13
Orkin[3]	2017	Southern Ontario, ON	7	6,300,000	–	0.9	42.7	66	28	33	8	10
		Asia										
RO[54]	2012	Korea	3	48,600,000	–	0.5	–	–	–	–	–	22
Kitamura[25]	2014	Osaka, Japan	7	7,212,000	–	0.4	49.9	63	5	18	1	4

EMS indicates emergency medical services; CPR indicates cardiopulmonary resuscitation.

[a] Serviceable population is corrected for the mid-point census population at the time of the study.

Quality assessment

Table S2 in the Supplementary Appendix shows the results of the quality assessment for the included studies. The sample frame to address the target population was appropriate in three studies. The study participants were randomly sampled in 10 studies. The majority of studies had adequate sample size. Most studies described the setting where participants were recruited from, but only four studies clearly defined the participants according to Utstein template.[3,7,15,21] Missing data were less than 5% in 10 studies indicating sufficient coverage for data analysis. The methods used to identify the condition was valid in six studies and was not valid or unclear in the remaining studies. The condition was measured in a standard and reliable way for all participants in five studies. The analytical techniques were appropriate in all studies, and the response rates were appropriate in 10 studies. All studies were included in the quantitative synthesis, and subgroup analysis by case definition was considered.

Incidence

The incidence of EMS-attended drug OD OHCA was only reported in two studies which precluded meta-analysis. Fig. 2 shows that the pooled incidence of EMS-treated cases was 1.4 cases per 100,000 person-years (95% CI: 1.1, 1.6; $I^2 = 99\%$; $p < 0.001$). Subgroup analysis was conducted to explore heterogeneity by region. The incidence rate was 2.0 cases per 100,000 person-years (95% CI: 1.4, 2.7) in North America, 1.2 cases per 100,000 person-years (95% CI: 0.7, 1.6) in Europe, and 0.4 cases per 100,000 person-years (95% CI: 0.3, 0.5) in Asia. The test for heterogeneity between the groups was significant ($p < 0.001$).

Survival to hospital discharge

Fig. 3 shows that the pooled rate of survival to hospital discharge was 9% (95% CI: 6%, 12%; $I^2 = 90\%$; $p < 0.001$). In the subgroup analysis, studies that were aligned with the Utstein definition of drug OD had no evidence of heterogeneity and the pooled rate of survival was 10% (95% CI: 8%, 11%, $I^2 = 0.0\%$; $p = 0.39$). In comparison, studies that were not aligned with Utstein definitions had evidence of heterogeneity and the pooled rate was 8% (95% CI: 3%, 13%; $I^2 = 94\%$, $p < 0.001$). Fig. 4 shows that the pooled AOR for the effect of drug OD on survival to hospital discharge was 2.2 (95% CI: 1.7, 2.7; $I^2 = 0\%$; $p = 0.45$).

Secondary outcomes

No study reported on the rate of 12-month survival and only one study reported survival to hospital. The rates of patients who were discharged from the hospital with intact neurological function and who achieved ROSC varied substantially. The pooled rates were 6% (95% CI: 2%, 13%; $I^2 = 81\%$; $p < 0.001$) and 25% (95% CI: 11%, 41%; $I^2 = 97\%$; $p < 0.001$) respectively. In the sensitivity analysis, excluding one study which differed markedly with respect to clinical characteristics,[25] the pooled rate were 9% (95% CI: 6%, 13%; $I^2 = 0.0\%$, $p = 0.52$) and 33% (95% CI: 27%, 38%; $I^2 = 59\%$; $p = 0.06$), respectively.

Discussion

In this meta-analysis of 12 studies, the pooled incidence rate of EMS-treated drug OD OHCA was 1.4 per 100,000 person-years. The

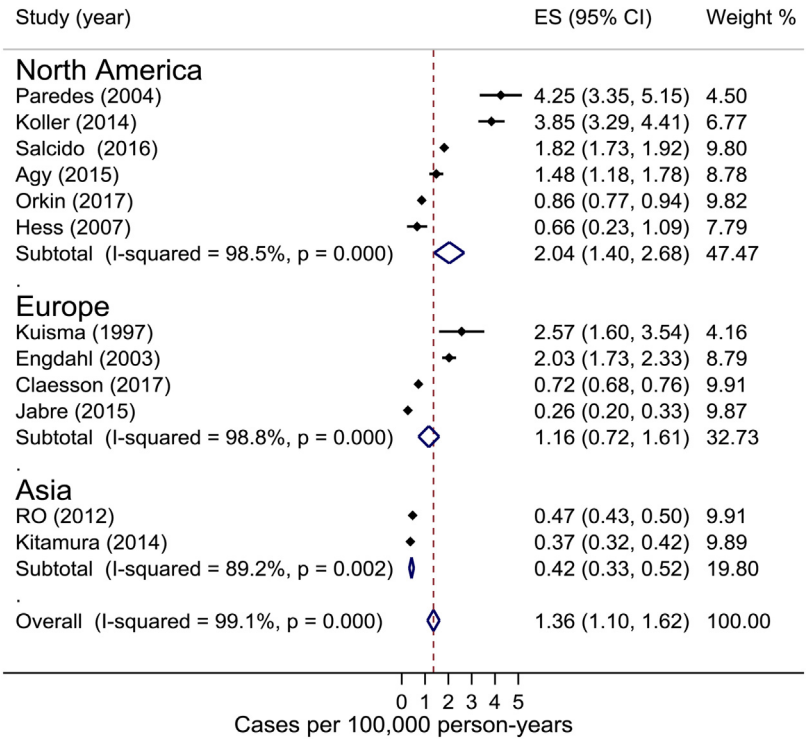

Fig. 2 – Incidence rate of EMS-treated cases per 100,000 person-years.

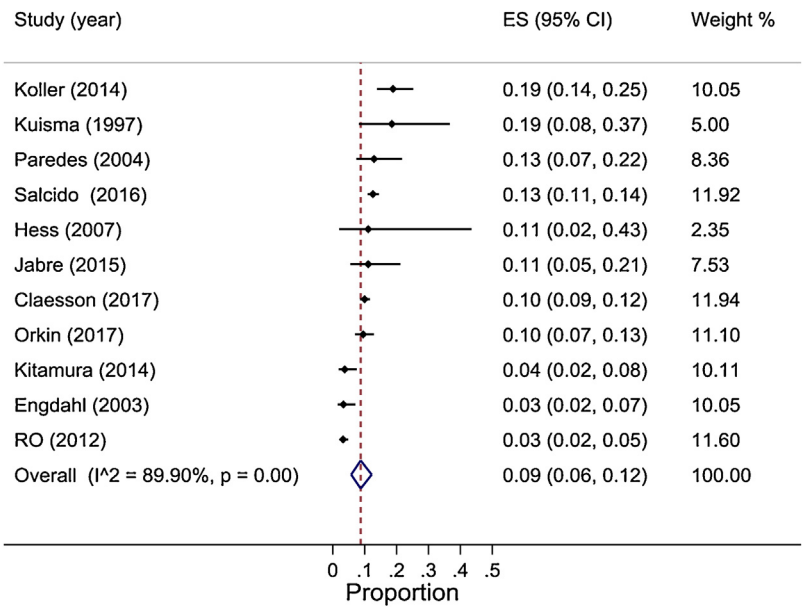

Fig. 3 – Pooled rate of survival to hospital discharge.

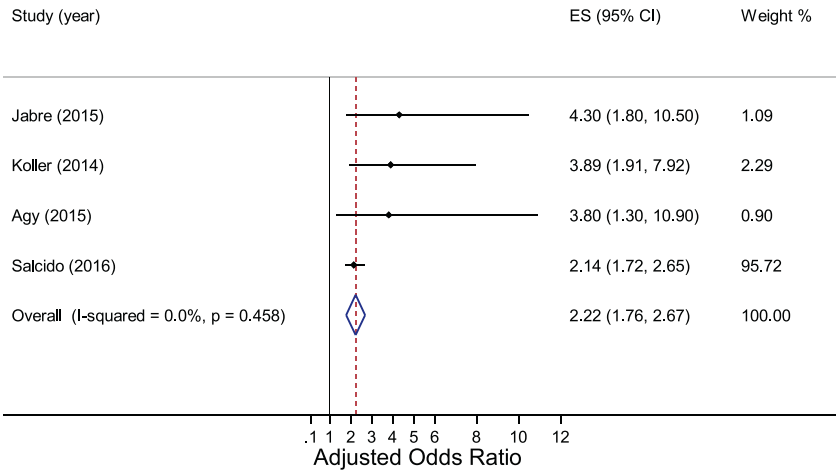

Fig. 4 – Pooled AOR of drug OD OHCA on survival to hospital discharge.

pooled rate of survival to hospital discharge and survival with intact neurological outcomes was 9% and 6%, respectively. Cases of drug OD OHCA were 120% more likely to survive to hospital discharge compared to cases of non-drug OD OHCA. Extrapolating these estimates would suggest that as many as 105,000 adults globally will receive an attempted resuscitation by EMS for a drug-related OHCA annually, of which approximately 9000 survive to hospital discharge.

However, our pooled estimates are derived from studies published across different time periods, and regions, and should therefore be interpreted with some caution. The global epidemic of drug-related OD has increased rapidly over the past decade,[26] and there is also evidence of an increasing temporal trend in the incidence of drug OD OHCA.[3] Therefore, it is possible that our findings may not be representative of the current burden of drug-related mortality in many communities. Although our review identified intercontinental differences in the incidence of drug OD OHCA, incidence also varied significantly within continents. The communities of Pittsburgh[6] and King County[7] reported rates of drug OD OHCA that were three to four times higher than other communities in North America. A myriad of sociological factors, and changes to the access of certain drugs, may be responsible for this variability.

For instance, death from prescription opioid OD is increasing disproportionately to illicit drugs in some communities,[27] and this may be related to local differences in the access to opioid prescriptions. While the rate of opioid prescription is associated with the rate of death from drug OD, these rates vary among communities.[28] For example, between 2013 and 2015, the rate of opioid prescription in Pennsylvania, US was 14% higher than the average national rate.[29] In 2016, the incidence of drug-related deaths was also 39% higher than the national rate.[29] In addition, the 2017 Narcotic Drugs report indicated that the US population had the highest standard daily doses of opioid worldwide, and was four, six, and eighteen times higher than Sweden, France and Korea,

respectively.[30] The standard daily doses of opioid also varied considerably between Canada and US,[30] a finding which could explain the variability across North American sites.

Variation in EMS activation could also influence the incidence and outcomes of drug OD OHCA. Disparities in seeking medical aid by drug users varies between 13% and 68%.[31] The most common reason for this variation is related to fear of legal prosecution perceived by the drug users or witnesses.[32] Although Good Samaritan laws provide immunity from legal prosecution, the dissemination of this law varies across our studied regions. For instance, the law was enacted in 2008 in South Korea, while Washington, US, enacted the law in 1975.[33,34] The degree to which an individual is protected from legal liability in drug related events also varies between communities. For instance, people seeking medical aid in drug-related events are not prosecuted for possession of a controlled substance in Washington, US,[35] but may be charged in Minnesota, US.[36] These differences could result in either a reluctance or delay in accessing EMS for drug-related events.

Although pooled survival from drug OD OHCA was 9% in our review, there was strong evidence of heterogeneity across regions (ranging from 3% to 19%). This variation could be explained, in part, by differences in case definition and predictors of survival such as the rates of witnessed arrest, bystander CPR, and initial shockable rhythms.[37,38] For instance, the study from Pittsburgh, US,[6] reported high rates of initial shockable rhythms (16%), bystander witness status (55%) and survival to hospital discharge (19%). In addition, our subgroup analysis of studies aligned with the Utstein definition of drug OD showed less evidence of statistical heterogeneity. Importantly, there is evidence that variation in survival outcomes from one community to another is likely despite adjustment for Utstein variables.[39]

Although we observed low rates of bystander CPR and initial shockable rhythms across most studies, our review does suggest that drug OD OHCA is associated with improved odds of survival. The causative pathophysiological mechanisms in many of these arrests includes hypoxia and circulatory collapse.[40] It is therefore plausible that timely EMS treatment including adequate ventilation, chest compressions and inotropic support could help to increase ROSC and survival in these patients. Variation in the quality of CPR and delays in EMS access could therefore explain the variation in survival observed among our included studies,[41,42] and be an important factor in the improvement of outcomes in this population.

The variability in survival across regions offers potential opportunities for public health interventions. While initial shockable rhythm is one of the major determinant of survival, increasing the rate of bystander application of automated external defibrillator could increase survival.[43,44] However, this may appear implausible in population with drug OD OHCA whose arrests are typically unwitnessed and of private arrest location.[45] Alternatively, increasing the rate of bystander CPR could extend time to defibrillation by EMS.[45] Unfortunately, there is evidence that the rate of bystander CPR is significantly lower in drug OD OHCAs compared to non-OD OHCAs.[3,46,47] Evidence suggests that family members and friends are reluctant to perform CPR as a result of panic and fear of causing harm and failure.[26] Focused CPR-training programs for potential rescuers may increase the rate of CPR and subsequently improve survival.

There are opportunities for public health initiatives to prevent death and reduce the incidence of drug OD OHCA. Most drug-related events occur in private residences and many of these are witnessed by individuals who are known to the drug user, such as friends and family members.[2] As opioids are a leading cause of drug-related events,[48] community engagement in naloxone administration may help to prevent cardiorespiratory arrest.[2] However, this relies on witnesses who are not also compromised by drugs to be available and willing to administer naloxone. The Wales government in 2010 has launched take home-naloxone program for opiate users to reduce the annual incidence of drug-related deaths which was 85 in previous years.[49] After one year of program assessment, the annual incidence of drug-related deaths was reduced to 68, a reduction of 18%.[49]

Similarly, there was an 18% reduction of drug-related deaths in communities who had access to naloxone and were trained in naloxone administration compared to those who had not, as demonstrated by a study conducted in Massachusetts, US.[50] Unfortunately, community access to naloxone in many countries is by physician prescription, and some countries also lack the availability of naloxone in medical settings.[2] Broader access to naloxone and targeted training programs for at-risk communities may help reduce the incidence of drug-related deaths.

Limitations

This review has a number of limitations. First, all studies were observational in design which suffer from inherent methodological limitations. Second, although incidence and survival estimates were pooled from a handful of communities, no estimates were found from regions such as Australia, the United Kingdom. Africa and South America. As such, our estimates may not be globally representative. Third, it is difficult to ascertain whether all patients were in cardiac arrest at the time the resuscitation began, and this may lead to differences in case capture across studies. Fourth, many studies did not include patients who did not undergo an EMS attempted resuscitation, and thus we were not able to estimate the incidence of EMS-attended cases. Fifth, few studies reported the clinical predictors of survival such as witnessed status, bystander CPR and initial shockable rhythm, and we were unable to statistically assess their effect on survival outcomes. Finally, the odds ratios for the effect of drug OD OHCA on survival to hospital discharge were taken from different studies, and some of the confounders considered for adjustment in these studies varied.

Conclusion

The findings from this meta-analysis provide a benchmark to evaluate the future preventive and treatment strategies for drug-related OHCA. Globally, as many as 105,000 adults annually will be treated by EMS for drug-related OHCA, of which 9000 survive to hospital discharge. These global estimates should be interpreted with caution, as these pooled estimates are derived from select communities and may not reflect existing temporal trends in drug-related OHCA. Effective strategies designed to reduce the incidence rate and improve survival outcomes are needed. This includes more research with comprehensive data reporting to enable precise measurement of the disease burden and to assess the value of treatment interventions. Broader access to naloxone and CPR training programs for communities at-risk may also be effective in preventing OHCA.

Conflict of interest

None to declare.

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None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2018.12.020.

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