

Research paper

A systematic review and meta-analysis of the prevalence of take-home naloxone (THN) ownership and carriage



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ABSTRACT

Background: Drug-related deaths globally are increasing year on year, with the largest proportion of these being opioid-related. The opioid antagonist naloxone distributed for take-home use ("Take-Home Naloxone (THN)") has been championed as one method of tackling this public health crisis, however to be effective it must be available at an opioid overdose. Ownership and carriage are therefore fundamental to THN success. This study aimed to assess the prevalence of ownership and carriage of THN internationally among people who use drugs (PWUD).

Methods: NHS Scotland Journals, AMED, EMBASE, HMIC, MEDLINE, PsycINFO, CINAHL Complete, PubMed, Cochrane Library, PROSPERO and grey literature were searched for articles which measured prevalence of THN ownership or carriage between 1996 and 2020. Ownership was defined as report of a personal supply of THN. Carriage was defined as the participant carrying THN on their person at time of data collection or reporting a frequency of how often they carry THN. Risk of bias was evaluated using the Joanna Briggs Checklist for Prevalence Studies.

Results: Systematic search yielded 6363 papers, with ten eligible papers identified. Eight articles were included in ownership prevalence and five articles included for carriage prevalence, with an overlap of three studies between both measures. Pooled prevalence indicated moderate ownership levels (57%, CI 47–67%) but lower carriage levels (20%, CI 12–31%). Analysis was complicated by the limited number of available studies and lack of standardised terminology and measurement.

Conclusion: Understanding naloxone ownership and carriage globally is hampered by limited evidence and heterogeneity across studies. From the available data, prevalence of THN carriage overall appears low, despite moderate ownership. Given the variation across studies, future research should seek to utilise more standardised terminology and methods of measurement. Furthermore, services distributing THN must ensure the importance of regular carriage of naloxone is consistently emphasised.

Introduction

Across the globe, the impact of problematic opioid use is increasing. Rising drug-related death rates are being seen in the UK, USA, parts of Africa, and South-East Asia, the majority of which are attributed to opioids due to overdose (UNODC, 2020). According to the United Nations World Drug Report (2020), 66% of an estimated 167,000 deaths related to drug use disorders worldwide were due to opioids, using most recent available data. Given these premature, highly preventable deaths, there is a growing need to identify and implement effective interventions. Consequently, the opioid antagonist naloxone, distributed for take-home use, has been progressively championed as one method of

tackling drug-related deaths (DRD) (Strang et al., 2014). Distribution of naloxone for use at home by lay people or people who use drugs (PWUD) through peer administration ("Take-Home Naloxone (THN)") has significantly strengthened internationally since early initiatives in the 1990s (McDonald and Strang, 2016).

The majority of THN studies to date have assessed distribution or effectiveness of THN programmes and have indicated significant impact on rates of opioid overdose deaths (McDonald and Strang, 2016; Walley et al., 2013). Despite findings which indicate the potential of THN in preventing fatalities, overdose remains a major cause of premature mortality in the developed world (EMCDDA, 2020). It is important to assess what may facilitate or prevent the optimal use of naloxone. Tobin et al. (2018) refer to the naloxone 'cascade of care' which outlines the five phases they suggest are required for optimal THN use:

1. awareness of THN;
2. access to a supply;

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3. training in use;
4. use in an overdose situation;
5. possession meaning carriage on the person and the frequency of this.

There has been a significant research focus on awareness, supply, and training in THN use, with increasing interest in its use in an overdose situation (Bennett & Holloway, 2012; Giglio et al., 2015; McAuley et al., 2015; Nolan et al., 2017). Whilst naloxone awareness, access, and training are essential, they are insufficient in themselves to ensure optimal overdose prevention outcomes: there is the additional need for availability during overdose situations (Tobin et al., 2018). As a result, the aim of this study was to assess the prevalence levels of ownership and carriage of THN internationally among people who use drugs. In order to achieve this a systematic review of the literature was conducted and the results were subjected to meta-analysis.

Methods

We have used the term ‘carriage’ within this paper, rather than Tobin’s term of ‘possession’, because there is ambiguous use of “possession” within the literature. Historically possession has been used within different studies to signify both carrying naloxone on one’s person, as well as simply owning or receiving naloxone. This imprecision can lead to ambiguity in measuring these different constructs. Someone may have ‘received’ naloxone but no longer own or carry it, and they may ‘own’ naloxone but never carry it, yet, because of this ambiguity, they may all be deemed to ‘possess’ it. For this study, the terms of interest were *ownership* and *carriage* of naloxone which were defined as follows:

- ownership: the participant reported a personal supply of THN (e.g. at home or other easily accessible place);
- carriage: the participant carried THN on their person at time of data collection OR reported a frequency of how often they carry THN on their person.

Eligibility criteria

This research focused on PWUD who engage with harm reduction or health services on this basis. This population is used in comparison to those who may be perceived to use substances recreationally, or who engage with statutory services for prescribed medications on a short-term basis for an acute problem. We recognise that there may be some overlap between these groups, as those who receive prescribed medications may augment with illicit substances, however, they would only be included in this study if they engaged with services specifically due to an issue linked to their substance use. The inclusion criteria were as follows:

- study population must include PWUD, or who have formerly used drugs, and who engage with harm reduction or health services on this basis, people deemed to be at risk of opioid overdose, and PWUD who are likely to witness overdose;
- study designs must be observational, but may include cohort studies, cross-sectional studies, case-control studies, surveys;
- studies must include outcome measures of carriage or ownership levels observed.

Exclusion criteria included:

- studies reporting solely qualitative analyses;
- ownership of naloxone by first responders/law enforcement or other professional care providers rather than by PWUD in a ‘take-home’ capacity;
- ownership/carriage by family members of PWUD, who themselves do not use drugs;
- ownership of naloxone by specific population groups (e.g., in pregnancy).

Search strategy and information sources

A comprehensive literature search was conducted through NHS Scotland Journals, AMED, EMBASE, HMIC, MEDLINE, PsycINFO, CINAHL Complete, PubMed, Cochrane Library and PROSPERO. Grey literature searches were undertaken via Google and Ovid (conference proceedings). Hand searches of relevant contents pages within selected journals and the reference sections of relevant articles were also conducted. In addition, authors in the field of harm reduction and take-home naloxone were contacted via email to ascertain whether any further literature existed that reviewers had not gleaned via formal search. Search structure and terms were discussed with an experienced information specialist, then conducted by two investigators (GB, JS). The following search terms were used:

1. (Naloxone OR Narcan OR Prenoxad OR Evzio) AND
2. (‘Take home’ OR ‘Take-home’) AND
3. (Overdose OR ‘Drug-related death’)

under ‘all-text’ searches where applicable. Searches were not combined with ‘AND’ for Cochrane Library or PROSPERO because search returns were too small to ensure adequate coverage when terms were combined. For this reason, three separate searches with the above three groups of terms were conducted for these databases and results pooled. Searches were limited to those articles published between January 1996 and April 2020. This date range was chosen as it best reflects the years during which THN has been most actively implemented within national programmes. The range was set as intentionally wide in order to ensure that relevant information was not missed, for example to identify potential serial analysis which may have initially published early but which may have more up to date data available unpublished (the reference for which might be missed by narrowing the search too early in the process). In the instance of serial analyses, the most recent available data was used. Language was not used as a formal search criterion.

A search report was created with all identified titles captured in RefWorks or Mendeley (Table 1). Reviewers (GB, JS) then removed duplicates and conducted initial screening independently. Abstracts and full text articles were assessed for eligibility then results compared to provide quality assurance. Discussions took place regarding which papers to include within the review and consensus reached between authors (GB, JS, AM) regarding the papers to be included, without the need for arbitration.

Data extraction and analysis

Data extraction was undertaken by two reviewers independently (GB, AY) and results compared, according to the agreed upon definitions. The study aim was to assess regular carriage, therefore, for those papers that did not directly measure or define ‘regular’ carriage, for example those using a frequency breakdown, it was important to define what frequency of carriage was consistent enough to be deemed regular. Where necessary, email contact was made with authors of eligible papers to clarify definitions or information provided, and/or to request raw data. It was agreed that measures of ‘often/always’, ‘regular’, and ‘on the day of interview’, were all measures which were sufficiently regular for the numbers reporting this level of carriage to be used in the pooled analysis. As a result, study respondents who reported ‘rarely’, ‘sometimes’, or other occasional carriage, were not included within the pooled analyses, as these reported levels were classed as too infrequent. The rationale for measuring regular carriage is to measure maximum accessibility, as those who carry THN more regularly have the greatest potential for using it. To explore the effect of “carriage on the day of interview” on carriage prevalence, studies which measured this were excluded in one subgroup analysis for carriage. Ownership data was pooled in three ways according to the time period of ownership specified by each study: 1. ownership of naloxone at any point; 2. current

Table 1

Search strategy: search terms utilised and results.

Search Terms Year limits applied from beginning of search	Number of Articles Group One – Ovid NHS Scotland Journals AMED Embase HMIC Medline APA PsycINFO 1996 - 2020	CINAHL Complete Jan 1996 to April 2020 All text	PubMed 1/1/1996 to 12/04/2020	PROSPERO 01/01/2011 to 12/04/2020	Cochrane Library pub date Jan 1996 to April 2020 All text
1 Naloxone OR Narcan OR Prenoxad OR Evzio	Multifield Search, all fields (Naloxone or Narcan or Prenoxad or Evzio).af. 57834	TX Naloxone OR Narcan OR Prenoxad OR Evzio 7828	All fields: ("naloxone"[MeSH Terms] OR "naloxone"[All Fields] OR "naloxone"[MeSH Terms] OR "naloxone"[All Fields] OR "narcan"[All Fields] OR "evzio"[All Fields] OR "naloxone"[MeSH Terms] OR "naloxone"[All Fields]) AND (1996/1/1:2020/4/12[pdat]) 16420	56	Reviews: 71 Protocols: 5 Trials: 2541 Clinical Answers: 10 Total: 2627
2 'Take home' OR 'Take-home'	Multifield Search, all fields: (Take home or Take-home).af. 16246	TX "Take home" OR "Take-home" 11342	All fields: ("take home"[All Fields]) AND (1996/1/1:2020/4/12[pdat]) 2760	15	Reviews: 54 Protocols: 1 Trials: 639 Editorials: 1 Clinical answers: 1 Total: 696
3 Overdose OR 'Drug-related death'	Multifield Search, all fields: (Overdose or "drug-related death").af. 86475	TX Overdose OR "Drug-related death" 22936	All fields: ("drug overdose"[MeSH Terms] OR ("drug"[All Fields] AND "overdose"[All Fields]) OR "drug overdose"[All Fields] OR "overdose"[All Fields] OR "overdoses"[All Fields] OR "overdosed"[All Fields] OR "overdosing"[All Fields] OR "Drug-related death"[All Fields]) AND (1996/1/1:2020/4/12[pdat]) 19929	136	Reviews: 187 Protocols: 17 Trials: 1426 Special collections: 1 Clinical answers: 8 Total: 1639
1 + 2 + 3 all fields OR Total of 3 searches (PROSPERO + Cochrane)	732	298	164	Overall PROSPERO Total: 207	Overall Cochrane total: 4962
					Total 6363

ownership (defined as currently having a personal supply at time of data collection); 3. ownership within the last 12-month period.

Study quality assessment

The JBI critical appraisal instrument for studies reporting prevalence data tool was utilised by one reviewer (GB) (Munn et al., 2015). This provides an overall analysis of quality and an insight into risk of bias within the context of studies specifically focusing on prevalence data, given that the context and bias profiles of these are unlike those of other non-randomised research designs (Joanna Briggs Institute, 2014). Where no response rate or sample size calculation was given, a standard sample size calculation was used for comparison, using the following formula by Naing et al. (2006) and the conventions of 95% confidence interval, 20% expected prevalence, and 5% precision: $n = \frac{Z^2 P(1-P)}{d^2}$. Considering that much of the data for this research was found in peer-reviewed journals, there is a high potential for publication bias. We attempted to minimise this by making direct contact with authors and professionals in the harm reduction field, and by performing grey literature searches, to glean evidence which may exist outside formal publication. An overall quality assessment and risk of bias was made for each paper which can be seen in Supplementary Table 1. Funnel plots were also created to assess risk of reporting bias (Supplementary Figs. 1 and 2).

Statistical analysis

When combining results from observational studies, heterogeneity of design, population and outcome is generally anticipated (Stroup et al., 2000). We assessed heterogeneity using both descriptive

analysis and the I^2 statistic to quantify the extent that variability across studies was due to heterogeneity and not due to random sampling. The convention of I^2 over 75% indicating high heterogeneity was utilised. Data was presented graphically using forest plots. Meta-analysis was undertaken using a random-effects (DerSimonian and Laird) model to account for heterogeneity and was performed using the MetaXL add-on for Microsoft Excel (www.epigear.com). Pooled prevalence figures were calculated with 95% confidence intervals, and appropriate subgroup analyses conducted to explore possible causes of heterogeneity and robustness of results. To address variance instability, the Freeman-Tukey double arcsine transformation was applied to pooled prevalence estimates (Barendregt et al., 2013). Statistical analyses were undertaken by two authors (GB, AY) to ensure accuracy of results.

Results

Search results

Database searches resulted in a total of 6363 papers being identified. A further 17 papers or reports were identified via grey literature search, hand search, or direct author contact, and included one paper submitted for publication. Following removal of duplicates, 4469 papers remained. Whilst language was not used as a formal search criterion, the authors did not find any papers which contained relevant data that had not been published in the English language. To minimise overlap of sampling populations, or due to study design or quality, nine studies were discounted from the ownership analysis (Buresh et al., 2020; Davis et al., 2016; Glick et al., 2017; Lopez Gaston et al., 2009; Marco et al., 2018; Nolan et al., 2017; Schneider et al., 2019; Tobin et al., 2018). Five

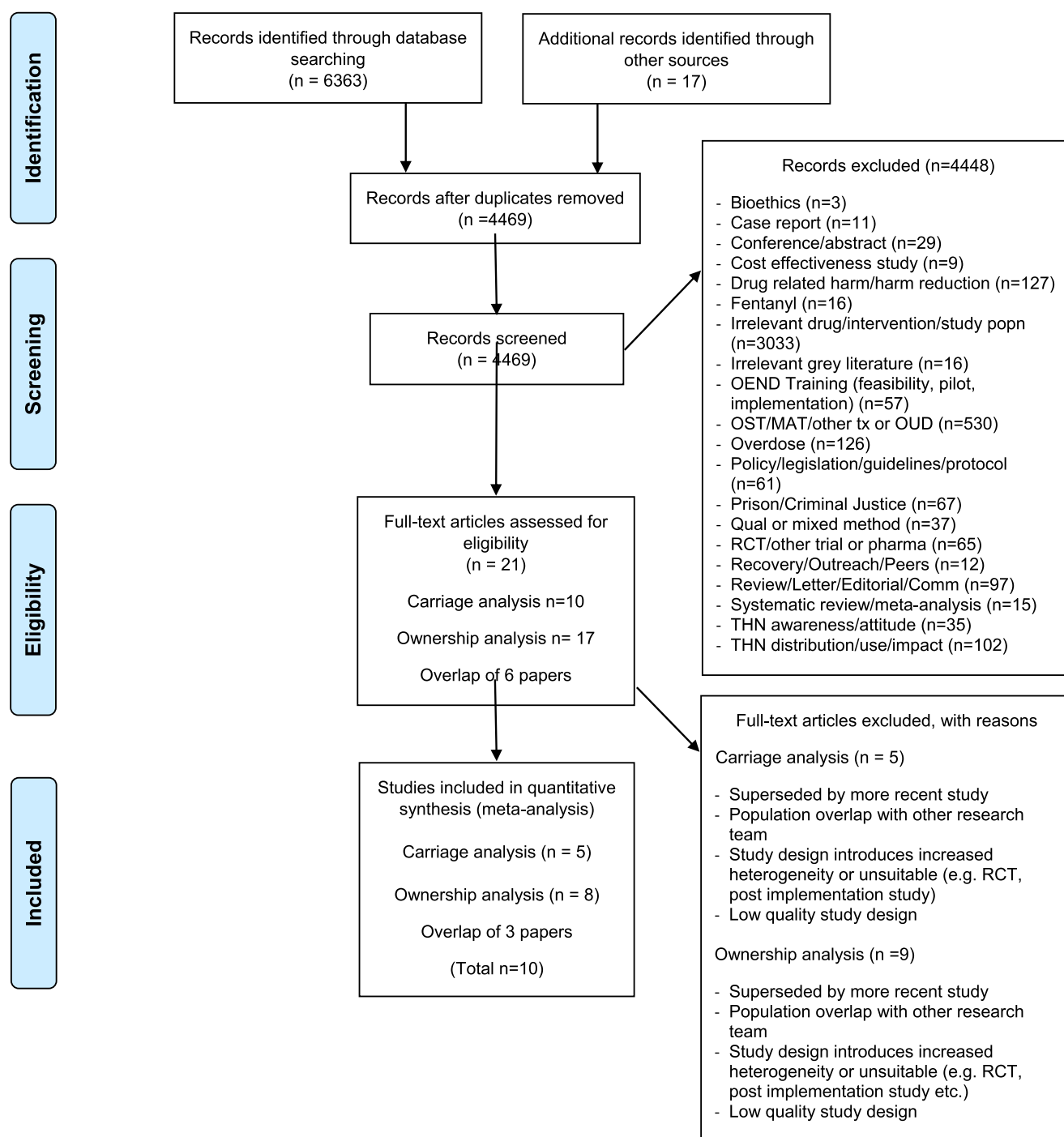


Fig. 1. PRISMA Diagram.

studies initially reviewed for carriage analysis were also discounted (Buresh et al., 2020; Lopez Gaston et al., 2009; Parmar et al., 2017; Tobin et al., 2018; UAM 2019), due to study design, quality, or overlap of sample populations. Additional information on the search results are provided within the PRISMA diagram (Fig. 1 and Table 1).

Study characteristics

Whilst the search criteria allowed for several study designs, all eventual eligible studies were cross-sectional analyses with validated measures. These were included if prevalence of ownership or carriage were presented or could be calculated from the data provided. Study popu-

lations ranged from 72-2130 respondents, with countries of origin including the US (five papers), Canada (two papers), the UK (two papers), and Europe (one paper). Drug use status ranged from study populations being asked whether they had used substances within the past 30 days, up to use within the past 12-month period. A fuller summary of study characteristics can be seen in Table 2. Eight papers met the criteria for inclusion within the ownership analysis. For the carriage analysis, four studies met the criteria, with a further study obtained through direct author communication, giving a total of five articles. Three articles are included within both analyses (Dayton et al., 2019; Khatiwoda et al., 2018; Health Protection Scotland, 2019). The 10 included studies measured prevalence of ownership, or prevalence or frequency breakdown of car-

Table 2
Summary of included studies.

Study	Sample Size	Sample Age	Ethnicity	Gender	% treatment receipt **	% injection drug use ***	Location	Survey item	Ownership or Carriage Prevalence %
Ownership Analysis									
Allen et al., 2019	371	Mean 35.8	White: 83.4%	Female: 40.4% Male: 59.6%	N/A	88.7%	West Virginia, US	In the past 6 months, did you get Narcan or naloxone to carry with you?	179/371 48%
Banta-Green et al., 2020	1264	Mean 36	White: 82%	Female: 43% Male: 57% Transgender/Other: <1%	60%	97%	Washington State, US	At any time in the past 3 months, have you had a naloxone/ Narcan kit?	915/1265 72%
Dayton et al., 2019	577	Mean 47 +/-11	N/A *	Female: 34% Male: 66%	63%	63%	Baltimore, US	Have you ever been prescribed or received a kit containing Narcan?	380/577 66%
Goldman-Hasbun et al., 2017	177	Median 22.2 IQR 20.2, 23.4	White: 54.8%	Female: 38.4% Male: 61.6%	55.9% ^a	38.4% ^b	Vancouver, B.C, Canada	Do you currently own a THN rescue kit?	40/177 23%
Health Protection Scotland, 2019	2130	Mean 40.6 Median 40.2	N/A	Female: 27% Male: 73%	Last 6 months: 56.3%	Last 6 months: 69%	Scotland	Have you been prescribed take-home Naloxone in the past year?	1299/2130 61%
Khatiwoda et al., 2018	100	Inclusion >18 yrs No other ref made	White: 90.8%	Female: 58% Male: 42%	N/A	N/A	North Carolina, US	Have you ever gotten a Kit for yourself?	74/100 74%
Madah-Amiri et al., 2019	497	Mean 44.9	N/A	Female: 24.5% Male: 75.5%	51.1%	72.4%	Norway	Do you have naloxone?	188/497 38%
Moustaqim-Barrette et al., 2019	348	Median 40 IQR 32, 49	First nations: 24.7% (n=86)	Female: 35.6% Male: 62.6% Other: 1.7%	N/A	35.1%	British Columbia, Canada Rural, urban environs	Do you have a Naloxone/ Narcan kit?	246/348 71%
Carriage Analysis									
Dayton et al., 2019	345	Mean 47+/-11	N/A *	Female: 34% Male: 66%	63%	63%	Baltimore, Maryland, US	How often do you carry Narcan with you?	31% often/always
Health Protection Scotland, 2019	1299	Mean 40.6 Median 40.2	N/A	Male: 73% Female: 27%	Last 6 months: 56.3%	Last 6 months: 69%	Scotland	Are you carrying any naloxone with you today?	13% carriage on day of interview
Khatiwoda et al., 2018	72	Inclusion >18 yrs No other ref made	White: 90.8%	Female: 58% Male: 42%	N/A	N/A	North Carolina, US	How often do you carry a Kit with you?	19% always 31% mostly Total: 50%
McDonald et al., 2020	131	Mean range 25-44	N/A	Female: 26.3% Male: 73.7%	N/A	N/A	Results from London/ Birmingham	Are you carrying any naloxone with you today?	8% carriage on day of interview
Reed et al., 2019	571	Median 35 IQR 29, 44	White: 63.9% Black/non-Latino: 11.7% Latino/Hispanic: 21.2%	Female: 21.7% Male: 78.3%	56.3%		Philadelphia, US	Do you carry Narcan?	12% regular carriage

* N/A refers to a study making no reference to the inclusion of this data.

** the widest time periods for measurement of receipt of treatment was in the past 12-month period.

*** the widest time period for measurement of injection drug use was in the past 12-month period.

^a (Goldman-Hasbun et al., 2017) refers more broadly to 'Drug and Alcohol treatment'.

^b (Goldman-Hasbun et al., 2017) refers to public injecting only.

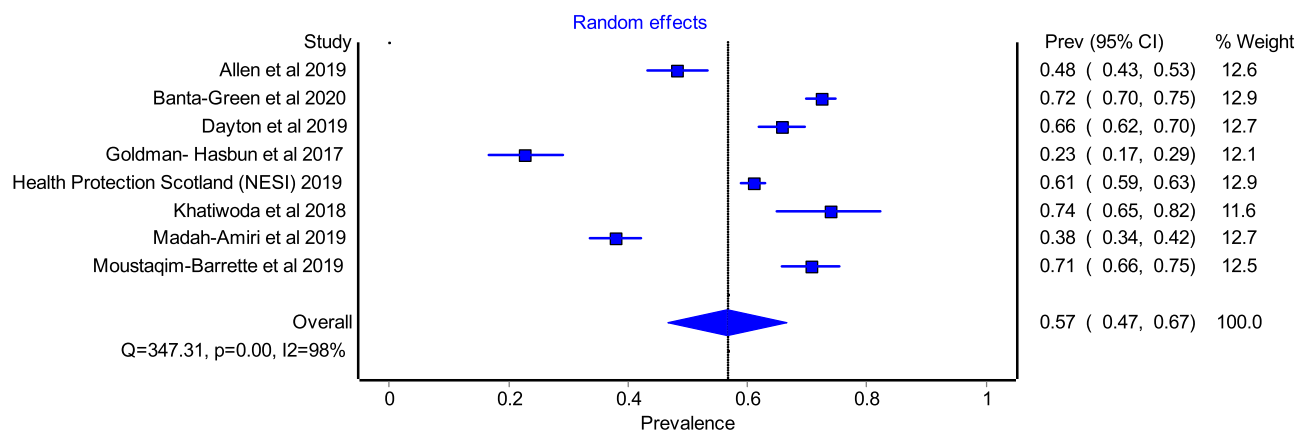


Fig. 2. Forest plot - Ownership pooled prevalence estimate.

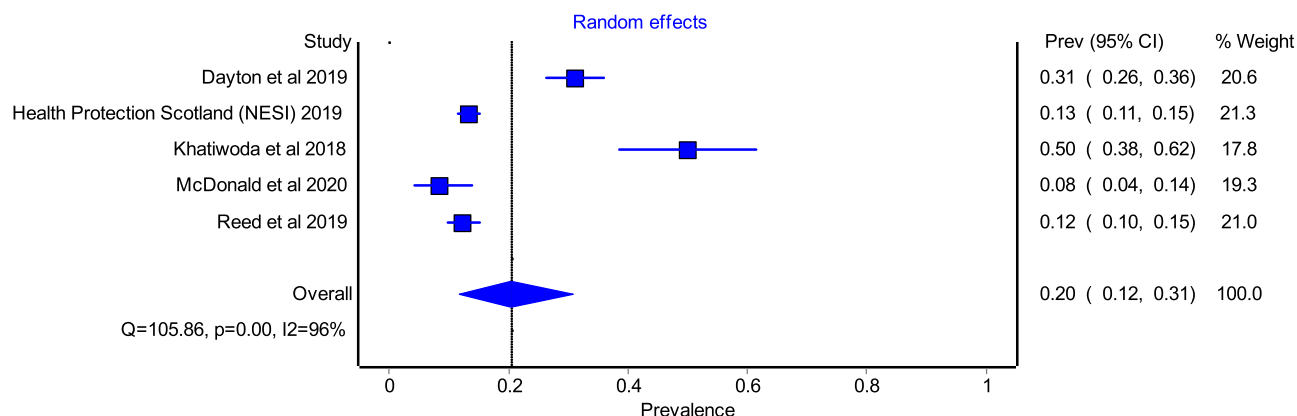


Fig. 3. Forest plot - Carriage pooled prevalence estimate.

riage. Time periods for ownership studies varied from current ownership at time of data collection (three studies), ownership within the previous 3, 6 or 12 months (three studies), or ownership at any time (two studies). Three of the carriage papers measured total regular carriage, either by measuring carriage on the day of data collection, or by asking about regular carriage, and two provided a frequency breakdown of carriage (often/always, sometimes/mostly, never/rarely). All studies used structured questionnaires completed on paper or electronically, with data captured either by a researcher during face-to-face interviews (seven studies), or through participant self-completion (two studies). One further study used mixed data collection methods involving face-to-face interviews for demographic and other information, with computerised self-completion for what was deemed 'sensitive risk behaviour data' (Dayton et al., 2019, p3).

Participants were generally recruited in one of two ways. The first method used harm reduction or medical treatment sites, such as addiction services, injection equipment providers, drug treatment centres, or community pharmacies, which we have termed 'fixed site' sampling. The second approach we have termed 'mobile/outreach' and includes those studies which undertook street-based sampling at known high use areas, or via agencies who work with PWUD on the street, which generally resulted in respondent driven or snowball sampling procedures.

The JBI nine-point critical appraisal tool was used to assess studies in terms of their sampling methods, size, demographics, coverage, validity and standardisation, statistical methods, and response rate. Based on Naing et al's (2006), formula the estimated adequate sample size rate would be 246 responses, therefore any study with a sample over this was deemed to have an adequate response level. The main risks in the included studies were non-random sampling methods (convenience or snowball sampling), recruitment from non-representative samples (e.g. solely from medication-assisted treatment (MAT) clinics), small sample

sizes, and high risk of inherent response/recording bias (mostly due to data collection method). A formal assessment of study quality can be seen in Supplementary Table 1. An assessment of reporting bias can be observed for ownership in Supplementary Fig. 1 and for carriage in Supplementary Fig. 2. Both funnel plots indicate a significant degree of skew and graphic paucity which indicates the potential for a high degree of publication bias.

Pooled prevalence analyses

Ownership

The pooled prevalence for ownership at any time (Fig. 2) indicated a proportion of 57% (CI 47-67%) and a heterogeneity score of 98%. Two additional subgroup analyses were also conducted to provide a more nuanced picture of ownership and investigate possible rationales for observed heterogeneity: ownership at time of interview, termed here 'current ownership', and 'ownership within the past 12 months' were created to compare with overall pooled ownership at any time. A pooled prevalence of 43% (CI 16-72%) was observed for current ownership (three papers, Supplementary Fig. 3), compared to a pooled prevalence of 52% (CI 40-65%) for ownership within the preceding 12 months (six papers, Supplementary Fig. 4).

Carriage

Pooled prevalence observed for those studies within the carriage analysis was 20% (CI 12-31%), with a heterogeneity score of 96% (Fig. 3). To evaluate whether the measure 'carriage on the day of interview' may act as a confounding factor, a subgroup analysis was conducted which excluded those papers using this (McDonald et al., 2020,

Health Protection Scotland, 2019). Results indicated a slightly higher pooled carriage prevalence of 28% (CI 10-50%), with a heterogeneity score of 97% (Supplementary Fig. 5).

Within study comparison – ownership and carriage

A within subject comparison was conducted in order to directly compare the ownership and carriage levels of those studies which report both measures. In studies which reported these, ownership levels were higher than carriage rates, similar to the trend observed in the overall pooled estimates.

Discussion

Meta-analysis of the available literature found that ownership of THN among PWUD was moderate (>50% in all analyses), whilst observed carriage rates were generally low (range 20-28%). This is the first study to attempt a comprehensive review of ownership and carriage rates of THN. The ability to evaluate pooled prevalence for both ownership and carriage of THN is important as this addresses a key component of the naloxone care cascade; that of ensuring the availability and accessibility of naloxone when needed (Tobin et al., 2018).

Ownership as a measure remains important in assessing accessibility, in addition to measuring carriage, because it incorporates those PWUD who have a personal supply of naloxone but who do not report regular carriage. In light of these findings, our recommendation for future research is the standardised use of the measure 'current ownership', by asking the question 'Do you currently own a naloxone kit?'. Using current ownership as a measure gives the most accurate picture of up-to-date personal supply prevalence. Future research should also include serial surveillance studies to allow a better assessment of trends of naloxone ownership in order to influence strategic planning needs and improvement of THN provision.

There are a variety of barriers to carriage which apply, in addition to those for ownership. These include aspects of product design (e.g. bulky packaging) which may impede portability; stigma or identification as a person who uses drugs as a result of THN carriage; and police perceptions or criminal repercussions if THN is perceived to be drug-related paraphernalia. These are all issues which can act as barriers to carriage specifically, on top of ownership (Bessen et al., 2019; Dayton et al., 2019; Lopez Gaston et al., 2009; Khatiwoda et al., 2018; McAuley et al., 2016; Tobin et al., 2018). Primary drug use occurring within the home may also negatively influence carriage of THN, with the perception that it is sufficient to have THN within the home (Strang et al., 1999). However, peer administration for another individual is much more likely to be required in an overdose situation than self-administration, therefore access for one's peers outside the home also needs to be addressed. In addition to this, there is a recognised increased risk of overdose for those PWUD injecting in public spaces, therefore carriage of THN by them, and for use on another's behalf, are important reasons to increase prevalence more widely (Trayner et al., 2020). Moreover, services must ensure that the importance of regular carriage is conveyed when distributing THN to PWUD for these reasons. It is important that these additional barriers to carriage are addressed if rates are to be improved. Future research is therefore needed on issues such as optimised product design in consultation with PWUD, and on factors which PWUD themselves feel would increase engagement and likelihood of carriage.

The rationale for a research focus on ownership and carriage is due to the importance of these in ensuring the presence of THN during overdose. As constructs these are relevant because both ownership and carriage must be adopted in order for THN to become available when needed. If people do not own naloxone they cannot carry it. If people do not carry it they are less likely to have access to it when needed and will not have access to it in all situations. In light of this, and the

results of this analysis, the importance of Tobin et al.'s (2018) naloxone cascade is evident. Of the five pillars proposed, we have focused on what they would term 'access' and 'possession', in order to assess prevalence of ownership and carriage. The rationale for use of the cascade is clear; in order to universally optimise provision and use of naloxone, we must first be able to identify and optimise each pillar. The World Health Organisation and UNODC in 2016 launched the 'Stop Overdose Safely' (SOS) initiative which proposed, as part of a multi-site study, a 90% target for suitable groups to receive overdose risk and management training (WHO, 2016). In turn it was recommended that 90% of those receiving training were supplied with THN, with a further target of ensuring 90% of this group should regularly carry or maintain easy access to THN. Whilst the study is currently conducted in Kazakhstan, Kyrgyzstan, Tajikistan, and Ukraine, there is no reason why these targets should not be applied internationally to optimise THN provision and use, particularly given the current opioid crisis (WHO 2016). These recommendations remain considerably higher than the ownership and carriage prevalence observed within our study. Our analysis has confirmed that prevalence of THN ownership and carriage within the published literature are much lower than might be anticipated after almost 25 years of advocacy and should therefore be addressed as a matter of urgency.

There are clear implications of this work for policy makers and practitioners. Whilst there is sufficient awareness of naloxone to promote ownership, there are still insufficient levels of carriage to promote access when required. As such, the aforementioned barriers towards carriage all require to be addressed. Access to naloxone can and should be widened to include as yet untapped services which are known to be highly utilised by PWUD, including GP or family practitioner services, acute and general medical care and emergency department provision, none of which have so far been optimised. Services external to formal healthcare provision should also be at the forefront of THN provision, such as housing and social care services. In light of the COVID-19 pandemic, widening of access is needed given the relative decrease in face-to-face support and the concurrent increased risk to PWUD. Novel methods of distribution including postal THN distribution and online training, which work around COVID-19 restrictions, should also be used and advertised widely in all forums accessed by PWUD.

The current evidence on prevalence of naloxone ownership and carriage is negatively affected by underpowered studies and a lack of consistency in definitions and measurements. The authors recommend the use of the term 'carriage' when referring to keeping THN on one's person, in contrast to other terms such as possession, because it directly refers to 'carrying' naloxone, rather than allowing inadvertent overlap with ownership of a personal supply. The authors also recommend the use of frequency breakdowns as opposed to other terms such as 'regular' carriage which are vague and open to interpretation. Frequency breakdowns of carriage were only undertaken by two relevant studies in this analysis (Dayton et al., 2019; Khatiwoda et al., 2018). Breakdowns allow more detailed information to be extrapolated, including total carriage prevalence, carriage frequency, and total ownership (as long as the question posed ensures that 'never' carry solely includes those who do currently own naloxone). This study has shown that more clarity in definition and use of terms is needed to ensure that adequately homogeneous, and therefore increasingly meaningful comparisons, can be made between research studies. Ensuring this clarity would require wider international communication and recognition of the importance of adherence to standardised methods and measures in quantitative social research. By doing so it would be possible to extrapolate wider outcomes more easily from research and allow a greater definitive impact.

More broadly, the limitations in the wider availability of data meant that further detailed subgroup analyses were not possible with too few papers available for a sufficiently powered analysis (i.e. <3 papers). Additionally, given the limited number of studies available outside of the US and UK, there is a concern that the pooled findings here may lack generalisability to other countries. Despite the lack of data, our

pooled estimates provide the first insights of the differences which exist in naloxone ownership and carriage across studies. These highlight that there may be sub-optimal THN ownership and carriage across all countries surveyed which potentially indicates the need for a more urgent and focused international response to optimise overdose prevention through THN. Future research in this area should ultimately facilitate meta-analysis which allows for sufficiently powered regional analyses e.g. by country/continent.

Specific limitations of this review and meta-analysis include a high degree of heterogeneity (>95%) which is likely to be linked to the variation in measures utilised by papers, as well as differing sampling populations (e.g. MAT clinics versus street-based outreach). The high heterogeneity seen in the pooled estimates, and the reduced number of appropriate studies, meant that, at times, wide confidence intervals. This limits the utility of pooled prevalence in our analyses. In addition, the skew of sampling in some studies towards treatment facilities (e.g. MAT clinics) may also increase the likelihood that higher numbers of respondents are well engaged in treatment or harm reduction and therefore are more likely to own naloxone. This is a potential confounding factor. Despite our attempts to access grey literature, there is a degree of reporting bias present which is likely to skew overall prevalence estimates. This may be compounded by the fact that all studies found and included were English language studies.

Difficulties lay in deducing exact sampling methods or populations of some studies. It is therefore impossible to say that there was no overlap between community-based harm reduction agencies and street-based outreach sampling. Additionally, where respondent driven sampling is used, it is challenging to identify the population characteristics/demographics this may have incorporated. Use of respondent driven sampling also has the potential to skew towards groups of individuals who share common characteristics, although statistical analyses were undertaken to address this within some studies (Dayton et al., 2019). Certain studies (e.g. Banta-Green et al., 2020) undertook convenience sampling within Injection Equipment Provision (IEP) services which is likely to have oversampled people who inject, as opposed to those who use substances through other routes. The variability of time period in relation to drug use status is also a factor to consider. Some studies stipulated more recent drug use (30 days, four weeks, three months, six months), whereas others may have included those who have formerly used (e.g. 'ever injectors', use in the past 12 months, or not inquiring as to current drug taking status). In light of this, most study populations were therefore mixed between both current and former PWUD. It is possible that ownership/carriage rates may vary between current and former PWUD, however, we were unable to assess this based on the available data.

Conclusions

Understanding naloxone ownership and carriage globally is hampered by limited evidence and heterogeneity across studies. The available data suggests that ownership and carriage of naloxone remains far short of optimal levels, with moderate levels of ownership but low levels of carriage. Standardised classification of measurement in future research would enable more effective monitoring and comparison of the impact of initiatives to expand ownership and carriage globally. Our recommendations include use of 'current ownership' as a measure of ownership, and carriage frequencies in measurement of carriage prevalence. Furthermore, services must ensure going forward that the importance of regular carriage of naloxone is always emphasised.

Registration and protocol

This review was not registered, and a protocol was not prepared.

Availability of data and other materials

Data and materials are available within the supplementary materials and further information can be made available by request to first author.

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Ethical approval

No ethical approval has been required or obtained for this study.

Contributors

GB, AM and TP designed, planned and led the study. GB and JS undertook the literature search and, with AM, applied eligibility criteria. GB and AM applied quality assessment and critical appraisal of papers. GB and AY undertook data extraction. GB, AM and AY designed and applied the statistical methods utilised. GB, AM and TP wrote the original draft of the paper. All authors participated in the preparation, review, and editing process of this paper, and have approved the final article.

Declarations of Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.drugpo.2021.103298](https://doi.org/10.1016/j.drugpo.2021.103298).

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