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Review

Does naloxone provision lead to increased substance use? A systematic review to assess if there is evidence of a 'moral hazard' associated with naloxone supply

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ABSTRACT

Background: Take home naloxone (THN) programs have been rapidly upscaled in response to increasing opioid-related mortality. One often cited concern is that naloxone provision could be associated with increased opioid use, due to the availability of naloxone to reverse opioid overdose. We conducted a systematic review to determine whether THN provision is associated with changes in substance use by participants enrolled in THN programs.

Methods: We conducted a systematic review of the literature to assess changes in heroin or other substance use by people who use opioids following THN provision.

Results: Seven studies with 2578 participants were included. Of the seven studies, there were two quasi-experimental studies and five cohort studies. Based on the Joanna Briggs Institute quality assessment, four studies were of moderate quality and three studies were of high quality. Of the five studies that reported on the primary outcome of heroin use, no study found evidence of increased heroin use across the study population. Five studies reported on other substance use (benzodiazepines, alcohol, cocaine, amphetamine, cannabis, prescription opioids), none of which found evidence of an increase in other substance use associated with THN provision. Four studies reported on changes in overdose frequency following THN provision: three studies reporting no change, and one study of people prescribed opioids finding a reduction in opioid-related emergency department attendances for participants who received naloxone.

Conclusion: We found no evidence that THN provision was associated with increased opioid use or overdose. Concerns that THN supply may lead to increased substance use were not supported by data from reviewed studies.

Introduction

Over the past two decades, an increased emphasis has been placed on harm reduction in response to the growing rate of opioid-related harms across a range of high-income countries (Seth, Scholl, Rudd, & Bacon, 2018), with overdose deaths almost doubling in United States over the past decade (National Institute on Drug Abuse, 2021). Take home naloxone (THN) programs, where laypeople are educated about overdose prevention and provided with naloxone, have been implemented in many countries in an effort to increase naloxone coverage within the community. Support and uptake of THN by health services remains inconsistent (Strang et al., 2019) despite there being good evidence that laypeople can be trained to effectively reverse opioid overdose and correlational evidence demonstrating that THN programs can reduce overdose mortality at the population level (Bird & McAuley, 2019; Clark, Wilder, & Winstanley, 2014; McDonald & Strang, 2016; Walley et al., 2013).

A common objection to THN programs is that they could result in increased risk-taking behaviours in people who use opioids by providing a perceived 'safety net' (Green, Bowman et al., 2013; Rudski, 2016).

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Multiple studies describe how health professionals perceive that the provision of THN may serve to increase opioid use (Bailey & Wermeling, 2014; Nielsen & Van Hout, 2016; Olsen et al., 2019). Similarly, law enforcement officials and policy makers may also hold perceptions of a 'moral hazard' and thus object to increasing naloxone coverage (Banta-Green, et al., 2013; Formica et al., 2018; Green, Zaller et al., 2013; Reichert, Lurigio, & Weisner, 2019; Winograd et al., 2020). A 'moral hazard' is defined as risk taking which may be increased because of a perceived reduced risk of experiencing negative consequences (Rattinger, Jain, Ju, & Mullins, 2008). The 'moral hazard' argument gained momentum with the release of an economic study in the United States about the population level association between THN provision and emergency room visits, crime, and opioid-related mortality (Doleac & Mukherjee, 2018, 2021). Authors found that with increased access to naloxone, opioid-related emergency room visits, and crime increased while opioid mortality remained the same or increased in some states. While the study data were limited to de-contextualised secondary data and have been criticised for incorrect use of causal inferences (Greene, 2018; Khazan, 2018; Stevens, 2020), the concept of 'moral hazard' persists in THN policy and practice.

Within this domain, conflicting perceptions on the impact of THN on substance use have been reported. For example, reports from a qualitative study in the US described some participants stating that no one would intentionally want to have naloxone administered. This conflicted with reports from other participants in the same study who described a scenario when fentanyl of an unknown strength was knowingly used with naloxone present, despite the knowledge of the overdose risk (Heavey et al., 2018). These findings highlight a range of perceptions that warrant exploration in quantitative studies to better understand the expected outcomes of THN provision on substance use.

A previous review conducted by McDonald and Strang (2016) assessed the effectiveness of THN to establish the impact of naloxone on overdose-related mortality and the safety of naloxone. Their review examined the relationship between THN provision and overdose-related mortality, but did not specifically examine the effect of THN provision on substance use (McDonald & Strang, 2016). Therefore, to date, no systematic review has evaluated individual-level data to answer the question of whether THN provision is associated with changes in substance use or overdose risk.

Given the persistence of the 'moral hazard' argument and some contested findings, the aim of this review is to provide clarity around whether THN provision is associated with increased risk behaviours reflected by changes in substance use or overdose among people who use opioids.

Methods

A systematic literature search was performed and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009) (Fig. 1). The protocol for the review was prospectively registered on PROSPERO (Tse, Lam, Olsen, Dietze, & Nielsen, 2020).

The search aimed to identify randomised controlled trials (RCTs), controlled clinical trials (CCTs), controlled cohort studies, interrupted time-series analyses, case series, and population-based results of THN program implementation. The search was conducted in August 2020 within the following databases: Ovid MEDLINE, Ovid Embase, Classic+Embase, Ovid APA PsycINFO, and Ovid Cochrane Central Register of Controlled Trials. No restrictions were placed on date or language. The detailed search strategy and related terms are reported in Supplementary Material 1. Duplicate articles were removed after exporting records into Covidence, a systematic review software (Kellermeyer, Harnke, & Knight, 2018). The reference lists from reviews that were identified via our search were examined to ensure all relevant studies had been captured by our search strategy.

Study selection

Studies were included if the study population were people who use opioids, and the intervention was THN provision. This is defined as the provision of naloxone for use by lay people, combined with information on naloxone and overdose prevention. We also included studies that provided individual-level data on substance use and other risk-behaviours prior to, and following naloxone supply. Exclusion criteria were:

1. THN was not the primary intervention;
2. THN could not be distinguished from other interventions;
3. Cross-sectional studies;
4. Commentary articles, editorials, clinical overviews of THN and other article types that do not contain empirical data; and
5. Unable to contact study authors to confirm eligibility, or access data to enable inclusion in the review.

Covidence, was used for all article screening. Two authors from the study team (WCT, SN, FD, VB) independently reviewed the titles and abstracts of all identified studies. Articles identified as relevant during title and abstract screening then underwent full text review. Relevant full texts were located and independently assessed for inclusion by two authors with a third author used to assess for disputes in inclusion. The primary reason for exclusion was documented for all articles excluded after full text review (*Table S1*). Corresponding authors of included studies were contacted to supply additional information where information on study main outcomes was not included in the published studies. This included heroin and other substance use pre- and post- THN provision, and overdose rates pre- and post- THN provision.

Outcome measures

The primary outcome was change in heroin use associated with THN provision. Secondary outcomes included changes in other substance use (benzodiazepines, alcohol, cocaine, cannabis, or opioids other than heroin). Data on overdose were also extracted, with overdose frequency considered a proxy for risky behaviour.

Data extraction and quality assessment

A Microsoft Excel data extraction template was used to systematically extract data on sample characteristics and outcomes from eligible studies. Methodological and evidence quality was assessed using the Joanna Briggs Institute (JBI) and National Health and Medical Research Council (NHMRC) assessment tools respectively (Munn, Moola, Riitano, & Lisy, 2014; NHMRC, 2009).

A modified JBI (mJBI) quality assessment was adopted for the methodological assessment of comparative studies without concurrent controls (cohort) using a point scale, with each question worth one point. We excluded Question 6 of the JBI checklist "Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?", because the nature of exposure to overdose and substance use in people who use opioids renders this field irrelevant. The resultant mJBI was scored out of 10 instead of 11. The published version of the JBI quality assessment was used for comparative studies with concurrent controls (quasi-experimental) and scored out of 9 as per JBI guidelines. Quality assessment was independently conducted by two authors (LP, WCT), with differences in scores resolved through discussion and referral to a third author (SN) where necessary. mJBI and JBI assessment scores of 0–3 were considered low quality, 4–6 medium quality, and ≥7 high quality.

The NHMRC assessment of evidence quality was adopted to assess levels of evidence within the hierarchy for non-interventional and interventional studies. The type of research question and design methodology was assessed to assign a grade ranging from level I (systematic review) to level V (non-analytic studies).

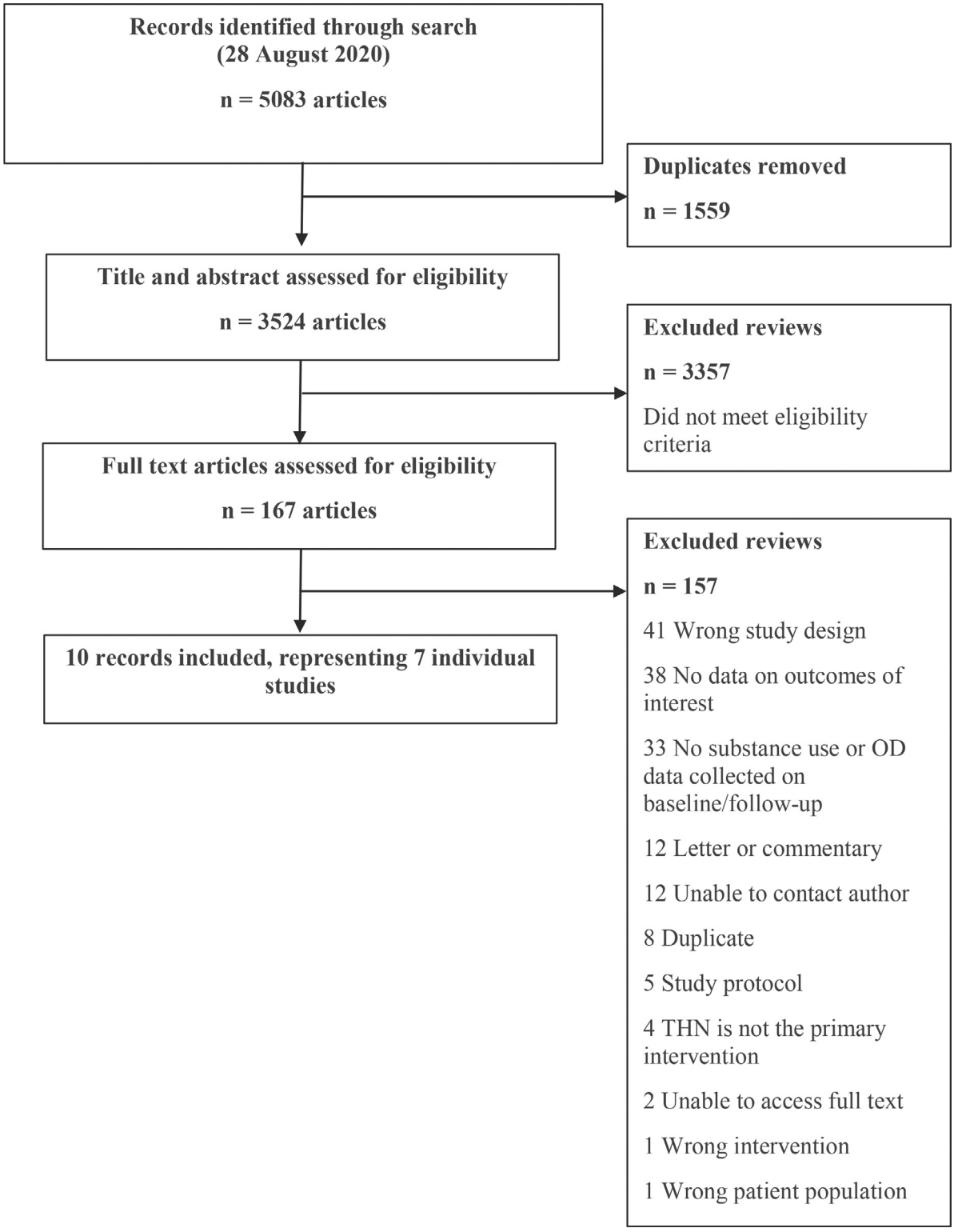

Fig. 1. PRISMA study flow diagram of included studies.

Data synthesis and analysis

Because studies identified were limited to pre- post-study designs without control groups and the outcome measures were heterogenous, a narrative summary of studies was conducted without meta-analysis.

Changes in substance use and overdose outcomes reported in individual studies were assessed from published data, and statistically significant increases or decreases in substance use were identified. Changes in the proportion reporting substance use from baseline to follow-up were assessed using chi-squared tests and Fisher's exact test was used where the expected value in any cell was < 5. Changes in mean days of substance use or amounts of substances used were assessed using paired t-tests (for comparisons of days of substance use pre- and post-THN provision) or described in Table 2 as they had been reported by the study authors in the original publications. In observational cohort studies where multivariate analysis of outcomes of interest were reported

and key differences in study populations were controlled for, we reported our findings in accordance with the authors' results in the original studies. Where the required data were not available in the published manuscripts, study authors were contacted and, in some cases, they provided data or additional analyses for inclusion in the review.

Results

The search yielded 3524 articles which underwent title and abstract screening. Full texts for 167 articles were screened, resulting in 10 included articles, which represented 7 individual studies with 2578 participants (Table 1). Five of the seven studies were conducted in the United States, one in Australia and one in Canada. We identified two quasi-experimental studies and five cohort studies. Using the NHMRC grading of evidence, two studies were assessed as level III-2 evidence (comparative study with concurrent controls) and five as level III-3 evidence (comparative study without concurrent controls). JBI quality ratings for the quasi-experimental studies ranged from 7/9–9/9 (high quality) and mJBI quality ratings of the cohort studies ranged from 4/10–8/10 (medium to high quality) (Table 1). Follow up durations were three months (Jones, Campbell, Metz, & Comer, 2017; Lintzeris et al., 2020; Wagner et al., 2010), six months (Coffin et al., 2016; Seal et al., 2005), and 1 year (Dong et al., 2012; Samuels et al., 2018). Out of the six studies that assessed substance use, five used self-reporting to assess for substance use changes, none of which reported strategies for addressing social desirability bias. Further information on study locations, interventions, and dates are provided in Table 1.

A summary of the studies identified and reasons for exclusion are provided in the PRISMA diagram in Fig. 1. Ongoing trials identified through the search where results are not yet available are reported in Table S2.

Changes in heroin use

Five studies ($n = 2403$ participants) reported on the primary outcome of heroin use, all of which were self-reported (Table 2) (Dong et al., 2012; Jones, Campbell, Metz, & Comer, 2017; Lintzeris et al., 2020; Seal et al., 2005; Wagner et al., 2010). Based on the mJBI and JBI assessment, four studies were of medium quality (Dong et al., 2012; Lintzeris et al., 2020; Seal et al., 2005; Wagner et al., 2010) and one study was of high quality (Jones et al., 2017). No study provided evidence of an overall increase of heroin use across the study population following THN provision. Jones et al. (2017) reported a statistically significant reduction in average heroin use per day within the past month from 5.6 'bags' per day at baseline to 3.8 'bags' per day at three months follow-up, with 20 bags equating to approximately 1 gram of heroin. Seal et al. (2005) reported a significant reduction in the proportion of participants who used heroin from 89% to 63% at follow-up (Seal et al., 2005). Lintzeris et al. (2020) reported no change in days of heroin use (Lintzeris et al., 2020), and two studies reported no change in the proportion using heroin comparing baseline to follow up (Dong et al., 2012; Wagner et al., 2010).

Changes in other substance use

Five studies (Coffin et al., 2016; Dong et al., 2012; Jones et al., 2017; Lintzeris et al., 2020; Wagner et al., 2010) ($n = 2403$ participants), reported on changes in self-reported use of other substances or prescribed opioid dose. Based on the mJBI and JBI quality assessment, three studies were of medium quality (Dong et al., 2012; Lintzeris et al., 2020; Wagner et al., 2010) and two studies were of high quality (Coffin et al., 2016; Jones et al., 2017). Most studies provided data on either the proportion who reported substance use at baseline and follow-up (Dong et al., 2012; Jones et al., 2017; Lintzeris et al., 2020; Wagner et al., 2010), or the days of use at baseline or follow-up (Jones et al., 2017; Lintzeris et al., 2020). Benzodiazepine use was assessed in four studies (Dong et al., 2012; Jones et al., 2017; Lintzeris et al., 2020; Wagner et al., 2010), all of which reported no change in proportion who reported benzodiazepine use. Four studies assessed alcohol use with two finding no change to the proportion who reported alcohol use (Dong et al., 2012; Wagner et al., 2010), and two finding no change in the days of alcohol use from baseline to follow up (Jones et al., 2017; Lintzeris et al., 2020). Cocaine use was assessed in four studies, with all finding no change in proportion of participants reporting cocaine use at follow up compared with baseline (Dong et al., 2012; Jones et al., 2017; Lintzeris et al., 2020; Wagner et al., 2010). Two studies assessed meth/amphetamine use, both finding no change in proportion of the study population reporting use at follow up (Lintzeris et al., 2020; Wagner et al., 2010). Three studies assessed proportion of the sample that had cannabis use, all reporting no change (Dong et al., 2012; Jones et al., 2017; Lintzeris et al., 2020). Five studies reported on use of opioids other than heroin (e.g. prescribed opioids, illicit use of prescription opioids, or methadone/buprenorphine) with three studies finding no change in proportion of participants reporting of any opioid use at follow up (Dong et al., 2012; Lintzeris et al., 2020; Wagner et al., 2010), one study finding no change in days of opioid use at follow up (Jones et al., 2017), and one study reporting no change in the mean dose of prescribed opioids at follow up (Coffin et al., 2016).

Change in overdose

We examined the frequency of overdose as a proxy for increased risky behaviours. Four studies ($n = 1546$ participants) reported on changes in overdose frequency following naloxone provision. Based on the mJBI and JBI assessment, two studies were of medium quality (Lintzeris et al., 2020; Seal et al., 2005) and two studies were of high quality (Coffin et al., 2016; Samuels et al., 2018). Three studies found no change (Lintzeris et al., 2020; Samuels et al., 2018; Seal et al., 2005), while one study among a population prescribed opioids for chronic pain found a greater reduction in opioid-related emergency department attendances (a surrogate measure for overdoses) in the cohort that received THN (Coffin et al., 2016).

Discussion

The evidence base for THN programs is growing, including evidence for overcoming barriers related to costs and logistics (Dietze et al., 2018; Olsen, McDonald, Lenton, & Dietze, 2018). The need for THN is also growing in an era of increased opioid overdose-related harms, in part driven by the prevalence of unknown quantities of fentanyl present in illicit opioids (Belzak & Halverson, 2018; Drug Enforcement Agency, 2016). However, the reach of THN programs is still limited (Strang et al., 2019). One barrier to THN implementation is a perceived 'moral hazard', and connected perceptions that naloxone may provide a 'safety net' for opioid users to engage in riskier behaviour.

To determine if there was evidence indicating that THN provision would increase substance use and overdose risk, we systematically searched the literature for studies that reported on substance use or overdose following provision of THN. Using data from seven studies with over 2500 participants, we found no evidence that THN provision was associated with an overall increase in self-reported heroin use, or other substance use or increases in overdoses measured through emergency department. Instead, some studies showed a mean decrease in the days on which opioids were used, the quantity of opioid use, or the proportion of the population reporting use of opioids or other substances. However, modest sample sizes meant that differences were not always statistically significant. One potential explanation for this finding could be that THN is provided alongside substance use treatment resources and other health information which may in turn support a behavioural change in substance use. Taken together, this represents the most comprehensive analysis to date on the topic of the impacts of THN

Table 1
Study characteristics.

Author (year)	Sample size	Location	Study design	Study population	THN provision characteristics	Reporting on substance use/overdose	Study aim	Main study findings	JBI/mJBI score	NHMRC levels of evidence
Coffin et al. (2016)	759 received naloxone, 1226 (control group^)	San Francisco, USA	Prospective cohort	People prescribed opioids	Providers and clinic staff were trained and supported in naloxone prescribing	Prescribed opioid dose change Emergency department presentation	To evaluate the feasibility and effect of implementing naloxone prescription to patients prescribed opioids for chronic pain.	Naloxone prescribed to the highest risk patients. Mean change in opioid dose (in morphine equivalent) during study period. Mean reduction of 21.6 mg for no-naloxone, mean reduction of 44.9 mg for naloxone group.	7/9	III-2
Dong et al. (2012)	50	Alberta, Canada	Prospective cohort	People attending a needle and syringe program	Overdose education and THN provision	Self-reported	Gather data on the implementation of community-based naloxone delivery for opioid overdose	11 (73%) reported that their drug use had decreased since their naloxone training	4/10	III-3
Jones et al. (2017)#†	130	New York City, USA	Prospective cohort	Current and former people using heroin	Overdose education and THN provision	Self-reported	Examine if participation in THN programs altered drug use frequency, quantity, and severity in heroin users	This analysis found no evidence of compensatory drug use following naloxone/overdose training among two groups of heroin users.	8/10	III-3
Lintzeris et al. (2020)	145	New South Wales, Australia	Prospective cohort	People attending drug treatment	Overdose education and THN provision	Self-reported	Examine effectiveness of THN in enhancing knowledge, attitudes, and behaviors	No significant changes in substance use in period before and after ORTHN	5/10	III-3
Samuels et al. (2018)*	151	Providence, USA	Retrospective cohort, observational	Emergency department patients discharged after a non-fatal opioid overdose	36hr Peer recovery program and THN provision	Emergency department presentation	Examine outcomes of patient outcomes in emergency department THN	Proportions of patients initiating medication for OUD were similar between the usual care and take-home naloxone groups, but there was a non-significant shorter median time to initiation of medication for OUD among those who got a recovery coach and naloxone compared to usual care.	9/9	III-2
Seal et al. (2005)	24	San Francisco, USA	Prospective cohort	People injecting drugs	4 × 2hr overdose education sessions and THN provision	Self-reported	Safety and feasibility of training for people who inject drugs	Knowledge about heroin overdose management increased, whereas heroin use decreased.	5/10	III-3
Wagner et al. (2010)†	93	Los Angeles, USA	Retrospective cohort, observational	People injecting drugs	1hr overdose education and THN provision	Self-reported	Evaluation of overdose prevention training program	At follow-up, participants were asked about changes in their drug use since the training. The majority (53%) reported that their drug use had decreased. In support of this observation, an increased proportion reported enrollment in drug treatment, from 23% to 36% ($p = 0.07$).	5/10	III-3

THN—Take Home Naloxone; NHMRC (National Health and Medical Research Council): I—Systematic review of level II studies, II—Randomized control trial, III-1—Pseudorandomised controlled trial, III-2—Comparative study with concurrent controls, III-3—Comparative study without concurrent controls, IV—Case studies; JBI—Joanna Briggs Institute; JBI/mJBI score: 1–3—Low quality, 4–6 Moderate quality, ≥7—High quality; ^Represented a lower-risk group that did not receive naloxone; #Secondary publications (Jones et al., 2020; Neale et al., 2020); *Secondary publications (Samuels et al., 2019); †Additional analyses provided by study authors (Jones et al., 2017; Wagner et al., 2010).

Table 2
Changes in substance use and overdose after take home naloxone provision.

Author (year)	Heroin use (Days of use, quantity used, proportion used, percent population increased or decreased)	Benzodiazepine use	Alcohol use	Cocaine use	Amphetamine type substances use	Cannabis use	Other opioid use (Illicit and Licit)	Opioid Overdose
Coffin et al. (2016) (n = 759 naloxone n = 1226 control)	NR	NR	NR	NR	NR	NR	Naloxone group: Mean dose change in MEQ (SD), mg: −44.9 (228.2) Control group: Mean dose change in MEQ (SD), mg: −21.6 (197.6)	Patients who received naloxone had 47% fewer opioid-related ED (incidence rate ratio [IRR], 0.53 [95% CI, 0.34 to 0.83]; p = 0.005)
Dong et al. (2012)[1] (Data from n = 15)	B: 20% FU: 20% p = 1.00 (FES) No change	B: 87% FU: 53% p = 0.11 (FES) No change	B: 53% FU: 60% $\chi 2$ = 0.14 p = 0.71 No change	B: 53% FU: 20% p = 0.13 (FES) No change	NR	B: 47% FU: 53% $\chi 2$ = 0.13 p = 0.72 No change	*Morphine*ˆ B: 87% F: 47% p = 0.05 (FES) No change *Oxycodone*ˆ B: 80% F: 47% p = 0.13 (FES) No change	NR
Jones et al. (2017)[#] (n = 130, with two subpopulations: Heroin use n = 61> In treatment N = 69)	B^q: 5.59 (SEM: 0.66) FU^q: 3.8 (SEM: 0.66) Significant reduction from baseline	(n = 130) B: 19% FU: 16% $\chi 2$ = 0.42 p = 0.52 No change (n = 130)	B^d: 3.19 (SEM: 0.89) FU^d: 3.07 (SEM: 0.84) No change	(n = 130) B: 33% FU: 30% $\chi 2$ = 0.29 p = 0.59 No change (n = 130)	NR	(n = 130) B: 37% FU: 22% $\chi 2$ = 6.66 p = 0.10 No change (n = 130)	B^d: 7.6 (SEM: 1.3) FU^d: 5.6 (SEM: 1.7) No change	NR
	B^q: 1.86 (SEM: 0.28) FU^q: 1.3 (SEM: 0.29) No change		B^d: 2.34 (SEM: 0.79) FU^d: 3.18 (SEM: 0.86) No change		NR		B^d: 5.4 (SEM: 1.2) FU^d: 3.1 (SEM: 1.0) No change	NR
Lintzeris et al. (2020) (n = 95)	B^d: 3.2 (SD: 7.3) FU^d: 2.6 (SD: 6.6) No change	B: 47% FU: 43% $\chi 2$ = 0.34 p = 0.56 No change	B^d: 3.9 (SD: 7.2) FU^d: 3.8 (SD: 7.6) No change	B: 3.2% FU: 2.1% p = 1.00 (FES) No change	B: 32% FU: 36% $\chi 2$ = 0.38 p = 0.54 No change	B: 62% FU: 59% $\chi 2$ = 0.20 p = 0.66 No change	B: 11% FU: 13% $\chi 2$ = 0.21 p = 0.65 No change	B: 6.3% FU: 5.3% $\chi 2$ = 0.10 p = 0.76 No change

(*continued on next page*)

Table 2 (*continued*)

Author (year)	Heroin use (Days of use, quantity used, proportion used, percent population increased or decreased)	Benzodiazepine use	Alcohol use	Cocaine use	Amphetamine type substances use	Cannabis use	Other opioid use (Illicit and Licit)	Opioid Overdose
Seal et al. (2005)[2] (n = 24)	B: None:13% 1–90+: 87% FU: None: 37% 1–90+: 63% p = 0.01 (FES) Decreased	NR	NR	NR	NR	NR	NR	B: 17% FU: 13% p = 1.00 (FES) No change
Samuels et al. (2018)[3] (n = 151)	NR	NR	NR	NR	NR	NR	NR	B: 100%* FU: THN: 17.6% Usual care: 23.0% $\chi 2$ = 1.30 p = 0.25 No difference
Wagner et al. (2010)# (Data from n = 60)	B: 97% FU: 91% p = 0.35 (FES) No change	B: 12% FU: 8.8% p = 0.74 (FES) No change	B: 20% FU: 21% $\chi 2$ = 0.05 p = 0.82 No change	B: 38.3% FU: 35.3% $\chi 2$ = 0.14 p = 0.70 No change	Methamphetamine B: 3.3% FU: 5.9% p = 0.62 (FES) No change	NR	Other opioids: B: 10.0% FU: 2.9% p = 0.42 (FES) No change Methadone (non-prescribed) B: 5.0% FU: 8.8% p = 0.66 (FES) No change	NR

NR = Not Reported, B = Baseline, FU = Follow-up FES = Fisher Exact Statistic. Note that follow-up periods were 3 months unless otherwise stated below. d: days used q: quantity used (reported in bags, with 1 bag equating to 1/20th a gram of heroin); Dong 2012[1] 1-year follow-up; Seal et al. (2005)[2] 6-month follow-up; Samuels et al., 2018[3] 1-year follow-up; ˆThe two most commonly used opioids (oxycodone and morphine) are reported in Table 2. Data also reported baseline and follow-up use of codeine, propoxyphene, hydromorphone and methadone, where a significant difference in the proportion reporting use at baseline and follow up did not differ. *Non-fatal opioid overdose in ED one year from index ED visit. #Additional analyses provided by study authors (Jones et al., 2017—Heroin use, Alcohol use, Other opioid use; Wagner 2010—Heroin use, Benzodiazepine use, Alcohol use, Cocaine use, Amphetamine use, Other opioid use).

on substance use outcomes and supports findings from other systematic reviews on net public-health benefits from THN provision (Chimbar & Moleta, 2018).

These findings are important in terms of providing healthcare professionals, law enforcement, and policy makers with some confidence that the studies reviewed to date have not shown evidence that THN programs increase substance use or overdose among program participants. In particular, the finding of either decreased or stable substance use suggests that the provision of THN—and the accompanying discussions around raising awareness about overdose risk—has no negative effect, and potentially has a net benefit in terms of drug use behaviours (Bird & McAuley, 2019; Walley et al., 2013).

Qualitative studies have reported mixed findings regarding substance use following THN provision (Hanson, Porter, Zold, & Terhorst-Miller, 2020). One study mentioned the use of fentanyl in the context of naloxone availability (Heavey et al., 2018). In contrast, another qualitative study found participants reported reduced substance use and had an increased overdose risk awareness following actual experiences of naloxone administration (McAuley, Munro, & Taylor, 2018). Another qualitative study specifically sought to explore if participants would increase their drug use in the presence of naloxone, finding instead that participants described decreases in substance use and a wish to avoid having naloxone administered (Lai et al., 2021). As naloxone administration is known to precipitate unpleasant withdrawal symptoms, it appears unlikely that naloxone would be routinely and intentionally used as a 'safety net' and descriptions from Lai et al. (2021) are consistent with this.

Resistance to delivering THN has been found among doctors, pharmacists, and other health professionals (Matheson et al., 2014; Olsen et al., 2019), and the concept of 'moral hazard' has persisted in describing people who use opioids as reckless and immoral. Further, it appears that some health professionals believe that THN provision will lead to increased substance use (Bailey & Wermeling, 2014; Nielsen & Van Hout, 2016; Olsen et al., 2019). Such beliefs about people who use drugs are commonly underpinned by stigma and discrimination which can impede on THN implementation (Fomiatti et al., 2020). Indeed, some health professionals may not appreciate that people who use drugs can make rational choices about risk when given access to information and options. Although participants may report variations in substance use over a study period, increasing heroin or other substance use does not appear to be a common outcome of THN provision. This contrasts with individual comments in qualitative studies (Heavey et al., 2018; McAuley et al., 2018).Our findings may therefore be able to help address the misconceptions that present an important barrier to THN provision.

This review consolidates evidence from seven studies to suggest that naloxone provision does not increase drug use. To mitigate ongoing concerns or misconceptions about risky drug use behaviour associated with THN provision, a consistent assessment of substance use and other risk-taking behaviours in high-quality studies on THN may support future meta-analysis and allow stronger conclusions to be made.

Limitations

Our findings must be considered in the context of existing limitations in quality of the studies. The current body of evidence is largely limited to pre-post measures from prospective studies, many without a control group. Most notably, much of the evidence is based on self-reported substance use and overdose frequency with variations in study follow-up times and definitions. The small number of studies and varied reporting metrics in studies with control groups precluded meta-analysis. The absence of a control group may be less concerning given the focus is on understanding behaviours among those who are provided with naloxone; however larger prospective studies with rigorous designs—with an emphasis on clear baseline and follow-up measures and strong measures of potential covariates—would be better placed to address potential confounders. Given the low follow-up rates observed in some of these studies, a focus should be placed on maximising participant retention in longitudinal studies. An additional limitation related to some studies is that their small sample sizes limited statistical power to examine changes in substance use.

Conclusion

This systematic review did not find evidence that THN provision leads to increased substance use or overdose. Notably, it highlighted a gap in current studies involving THN programs, which mostly lacked rigorous longitudinal measures of substance use. Nevertheless, these findings may allay concerns that could otherwise be a barrier to the broader implementation of THN programs.

Declarations of Interest

In the past 5 years, SN and SL have been investigators on untied education grants from Indivior, unrelated to the current work. SN has provided training to health care professionals on identifying and treating codeine dependence for which her institution has received payment from Indivior. SN and TL have been investigators on untied educational grants from Seqirus, unrelated to the current work. PD has received an investigator-driven grant from Gilead Sciences for unrelated work on Hepatitis C and an untied educational grant from Reckitt Benckiser for unrelated work on the introduction of buprenorphine-naloxone into Australia. PD and SN have served as unpaid members of an Advisory Board for an intranasal naloxone product.

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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.2021.103513.

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