

‘What is known about community pharmacy supply of naloxone’: A scoping review.

Highlights :

- Take-home naloxone may be expanded through community pharmacy
- Early work indicates pharmacists are willing to supply naloxone
- Existing models for community pharmacy of naloxone supply exist
- Supply models have important cost implications for consumers
- Larger implementation studies are needed to determine effectiveness

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Abstract

Background

There is growing evidence that expanded supply of take-home naloxone to prevent opioid overdose deaths is needed. Potential routes for expansion of naloxone provision include through community pharmacies. The aim of this scoping review is to establish what is known about community pharmacy supply of naloxone, in light of unique challenges and opportunities present in pharmacy settings.

Methods

A scoping review methodology was employed using the six stage iterative process advocated by Arksey and O’ Malley (2005) and Levac et al., (2010). Searches used key words and terms such as ‘naloxone’; ‘overdose prevention/drug overdose/opiate overdose’; ‘community/retail pharmacy’; ‘pharmacist/pharmacy/community pharmacy/pharmaceutical services’; ‘professional practice/role’; ‘community care’; attitude of health personnel’; ‘training/supply/cost’). Appropriate search terms were selected for each database. After initial exploratory searches, comprehensive searches were conducted with Cochrane Database of Systematic Reviews, Medline, Medline in Process, Embase, PsycINFO and CINAHL. Eligibility criteria centered on whether studies broadly described supply of naloxone in community pharmacy or had content relating to community pharmacy supply.

Results

The search identified 95 articles, of which 16 were related to pharmacy supply of naloxone. Five themes were presented after initial review of the data and consultation with the project Expert Group, and are; ‘Pharmacists Perceptions of Naloxone: Facilitators and Barriers’, ‘Patient

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Populations: Identification and Recruitment’, ‘Supply Systems and Cost’, ‘Legal Issues’, and ‘Training of Pharmacists and Community Pharmacy Naloxone Recipients’.

Conclusion

The community pharmacy based route for distribution of take home naloxone provision warrants further consideration and development. Existing strengths include a range of established supply models, and training curricula, few direct concerns regarding legal liability of pharmacists in the supply of naloxone (once legal supply systems have been established) and the wide range of potential identifiable patient populations, which include pain patients that may not be in contact with existing naloxone supply programmes.

Key words

Pharmacy, Naloxone, Supply systems, Community Pharmacy, Overdose, Opioid

Introduction

With the rising rates of opioid overdose deaths, naloxone has become one of a range of important strategies to address overdose (Straus, Ghitza, & Tai, 2013). Naloxone has been used for more than 40 years to reverse the effects of opioids in clinical and medical settings. Supply of naloxone for bystander administration is more recently becoming a well-established practice in the United States, Canada and the United Kingdom, with numerous studies and reviews confirming the feasibility, efficacy and cost-effectiveness of such programmes (Bennett, Bell, Tomedi, Hulsey, & Kral, 2011; Clark, Wilder, & Winstanley, 2014; Coffin & Sullivan, 2013; Giglio, Li, & DiMaggio, 2015; Walley, et al., 2013).

Community based naloxone for overdose reversal was first implemented through community based initiatives established through peer-led advocacy work, with the Chicago Recovery Alliance prescribing and dispensing naloxone in an outreach model in 1998 (S. Maxwell, Bigg, Stanczykiewicz, & Carlberg-Racich, 2006). Initial models of supply were based in systems that had a strong harm reduction focus and included peer-training through a developed training curriculum, and supply through peer-outreach services (S. Maxwell, et al., 2006). These early programmes, developed through advocacy from organisations oriented towards the needs of people who inject drugs (PWID), described hundreds of reports of successful reversals of opioid overdose in the first published programme descriptions (S. Maxwell, et al., 2006).

In the past 15 years momentum has gathered to expand the reach take-home naloxone programs for opioid reversal within communities and in order to reach the diverse profile of potential

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recipients. A shift in the nature of opioid dependence and mortality has been observed in some geographic regions over the same time period, from illicit opioids such as heroin to prescription opioids (J. Maxwell, 2011; Roxburgh & Burns, 2014). The increased role of prescription opioid medication in overdose fatalities, combined with the desire to expand the geographic reach of take-home naloxone initiatives has brought into sharp focus the opportunity for community pharmacy to become an important outlet and harm reduction partner in responding to concerns around opioid-related mortality.

Although benefits of existing models of naloxone supply are clear, with the involvement of peers and programs embedded in services targeted to reach people who use and inject drugs, there may be a number of advantages to expanding the capacity of community pharmacy as a distribution point for take-home naloxone. Community pharmacies already supply medications to the general public and represent widely accessible health care sites in terms of geographic locations and opening hours. Many patients with an overdose risk may not be in contact with existing providers of take-home naloxone. Those not accessing naloxone through existing services may include pain patients using prescription opioids, in addition to those that choose to avoid services identified for people who use drugs due to concerns such as anonymity. In Scotland and England community pharmacy is already well integrated into the harm reduction provider network, with increasing engagement demonstrated over time (Matheson, Bond, & Tinelli, 2007; Sheridan, Manning, Ridge, Mayet, & Strang, 2007).

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Community pharmacy also has some unique challenges when it comes to the supply of naloxone, in contrast with other existing programmes designed to meet the needs of people who use and inject drugs. Attitudes and knowledge in community pharmacy with respect to harm reduction measures vary greatly, with confidence and attitudes being potential barriers to access as seen in other aspects of substance use treatment (Butler & Sheridan, 2010; Hagemeyer, Alamian, Murawski, & Pack, 2015). In a study from Scotland it was highlighted that some members of the public may not perceive pharmacies as a suitable location for harm reduction services (Gidman & Coomber, 2014). A study conducted in Tijuana, Mexico found that people who use and/or inject drugs may also show reluctance towards accessing harm reduction services in community pharmacies (Davidson, et al., 2012). Preliminary work in Indiana, USA, suggests that pharmacists appear interested in further training in the area of substance use and addiction treatment (Wenthur, et al., 2013). A further study of pharmacists in Estonia identified that not all pharmacists understand or support the provision of harm reduction (Vorobjov, Uusküla, Abel-Ollo, Talu, & Jarlais, 2009). There is great variation in different countries with the involvement of community pharmacy in different aspects of harm reduction (Hammett, et al., 2014). Levels of engagement with harm reduction more broadly vary between the US, Australia, Europe and the United Kingdom (UK), with supervised dosing of opioid substitution treatments for example not being common practice in the US, in contrast with being an accepted practice model in Australia (Green, Dauria, Bratberg, Davis, & Walley, 2015; Watson & Hughes, 2012). Analyses of changing attitudes over time demonstrate that in Scotland, pharmacists have demonstrated a willingness to receive further training, which in turn appears to increase their participation in harm reduction activities (Matheson, Thiruvethiyur, Robertson, & Bond, 2015).

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Given the potential to expand the provision of naloxone initiatives for bystander administration through community pharmacy, the aim of this scoping review was to understand what is currently known about community pharmacy supply of naloxone, with a particular focus on understanding current practice and supply models, and barriers that may need to be addressed in order to embed and optimize the expansion of naloxone supply through this community route.

Methods

Scoping review methodologies have become an increasingly popular and adopted approach across a variety of disciplines in recent years (Anderson, Allen, Peckham, & Goodwin, 2008; Arksey & O'Malley, 2005; Daudt, van Mossel, & Scott, 2013; Levac, Colquhoun, & O'Brien, 2010; Pham, et al., 2014). For the purposes of this study, the definition of a scoping review as a type of research synthesis that aims to *‘map the literature on a particular topic or research area and provide an opportunity to identify key concepts; gaps in the research; and types and sources of evidence to inform practice, policymaking, and research’* (Daudt, et al., 2013) was employed. We chose to undertake a scoping review as such reviews are particularly useful when a topic has not been extensively reviewed (Hidalgo Landa, Szabo, Le Brun, Owen, & Fletcher, 2011). Scoping reviews are additionally used as standalone project to provide a comprehensive descriptive overview of literature of a wide range of study designs and methodologies and do not engage in critical quality appraisal of individual studies or synthesise multiple study outcomes (Arksey and O'Malley, 2005; Brien et al., 2010).

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Scoping reviews utilise a rigorous and transparent method to identify and analyse all relevant literature on a particular topic (Arksey & O'Malley, 2005; Rumrill, Fitzgerald, & Merchant, 2010). An iterative six stage process developed by Arksey and O' Malley (2005) with later recommendations by Levac et al., (2010) was adhered to, and which consisted of (1) identifying the research question, (2) identifying relevant studies, (3) study selection, (4) charting the data, (5) collating, summarizing and reporting the results, and (6) an international expert advisory consultation exercise. The scoping review commenced with the establishment of a research team with addiction, harm reduction, pharmacy with scoping and systematic review expertise (Levac, et al., 2010), who advised on the underpinning research question; *'What is known in the literature about community pharmacy supply of naloxone?'*. The review concerned extant knowledge and gaps around supply of naloxone through community pharmacy. We defined community pharmacy supply of naloxone as programmes where pharmacists were directly supplying naloxone to people accessing retail or 'community' pharmacy settings.

Search terms were agreed by the team, and the general search strategy is illustrated in Figure 1. The search terms for each group in the search strategy were chosen to be specific for each database. The initial search was implemented in July 2015 in National Drug and Alcohol Research Centre (NDARC) Library catalogue (which includes grey literature including policy documents and online reports), Project Cork, PubMed Clinical Queries, Scopus, (exploratory search with selected references downloaded for the purpose of clarifying search terms). Following exploratory searches, comprehensive searches were conducted in the Cochrane Database of Systematic Reviews, Medline, Medline in Process, Embase, PsycINFO and

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CINAHL. The searches on all databases were limited to ‘Humans’, no limitations on language were applied.

Insert Figure 1 about here

Reference lists in articles retrieved were also manually searched by the team to identify any relevant studies, including grey literature, not captured. Members from the Expert group were also asked to identify key studies, including referral to extant grey literature. Citations were managed using the bibliographic software manager EndNote (Thomson Reuters, 2012) with duplicates removed manually. Eligibility criteria centered on whether studies broadly described supply of naloxone in community pharmacy or contained content directly relating to community pharmacy supply of naloxone. To enable the broadest picture of current knowledge and perceptions relating to naloxone in pharmacy settings we included commentary pieces and editorials, in addition to empirical data (See Table 1 for summary). The title and abstract of each citation were screened by the lead author, where any doubt remained in terms of inclusion both authors reviewed the article (Levac et al., 2010). All citations deemed relevant following this screening, were procured for review of the full text version. Studies were excluded at this stage if found not to meet the eligibility criteria. See Figure 2.

Insert Figure 2 about here

Results

The initial search identified 93 articles, of which 12 were identified to directly relate to community pharmacy supply of naloxone. A further four references were identified through the review process, including conference presentations and articles identified by the project Expert Group. Five themes were explored after initial review of the data and consultation with the scoping review Expert Group. The themes of (1) Pharmacists’ Perceptions of Naloxone: Facilitators and Barriers, (2) Patient Populations: Identification and Recruitment, (3) Supply Systems and Cost, (4) Legal Issues, (5) Training of Pharmacists and Community Pharmacy Naloxone Recipients.

Pharmacist Perceptions of Naloxone: Facilitators and Barriers

Three studies presented detail on perceptions of pharmacists on the supply of naloxone. One US study with in-depth interviews of community based pharmacy practitioners (n = 6) (Bailey & Wermeling, 2014) identified the potential for pharmacists to play a role in providing naloxone, educating patients and disseminating education within the community. Pharmacists indicated high levels of acceptance and support, with provider support viewed as instrumental in dispensing naloxone for overdose prevention. Where ethical considerations were raised (e.g. perceptions that naloxone supply may condone or support ongoing substances use) the pharmacists interviewed indicated that though it was conceivable that a pharmacist may refuse supply on ethical grounds, none of the pharmacists involved would do so once they understood the rationale for naloxone supply. Bailey and Wermeling (Bailey & Wermeling, 2014) also

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reported that pharmacists described difficulties in financial and reimbursement issues despite gaining support from prescribers.

Focus groups held with multidisciplinary members of the health care team (including 10 physicians, nine nurses and four pharmacists) described a lack of consensus about who should be prescribed naloxone, with fear around offending patients and potential for increased risk behaviours in patients prescribed naloxone raised as potential barriers (Binswanger, et al., 2014). They described some level of discomfort with prescribing naloxone in contrast with other emergency outpatient medicines. This discomfort centered on fears of offending patients, patients potentially engaging in increased risk behaviours, complexities around naloxone and opioid prescribing decisions, treatment of a symptom rather than the problem of over prescribing and inadequate pain management, patient safety, overdoses and diversion of naloxone and the potential for seizures and cardiac arrests. The medico-legal risks raised by Binswanger et al (2014) around the decision to supply naloxone as potentially identifying patients as ‘at risk’ may represent a barrier to supply, and may support the use of universal supply approaches for all patients exposed to opioids.

Zaller et al., (Zaller, Yokell, Green, Gaggin, & Case, 2013) conducted in depth interviews with PWID (n = 21) and pharmacy staff (15 pharmacists and six technicians/interns) in Rhode Island, USA. This study highlighted overall that there was support for pharmacy based naloxone interventions. Some barriers were identified, such as misinformation, mismatch in perceived willingness to partake, interpersonal relationships between PWID and pharmacy staff, physical

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restrictions in pharmacy settings, and concerns around staffing, time, space, reimbursement of time and cost. Study findings suggested that the misconceptions about willingness of both pharmacists and PWID to participate in pharmacy-based naloxone supply appeared unfounded, as both groups were willing to be involved in naloxone supply programs in pharmacy settings.

Patient Populations: Identification of at-risk patient populations

Potential patient populations

Five studies presented detail on potential populations that may be appropriate for community pharmacy based naloxone interventions. An editorial by Wermeling (Wermeling, 2010) identified target patients groups 1) including anyone in receipt of a methadone prescription, 2) those on high doses of opioids (including high potency opioids), 3) patients with a recent opioid poisoning, 4) those with a suspected history of illicit or non-medical use of opioids, 5) those with concurrent use of opioids with antidepressants, benzodiazepines, or alcohol 6) those prescribed opioids with major organ dysfunction (renal, hepatic, cardiac, or pulmonary) and 7) patients released from opioid detoxification programs. This editorial also highlighted the requirement to train bystanders, family members or caregivers as first initial witnesses of overdose and most likely to respond. Green et al (Green, et al., 2015) in their case study described comprehensive eligibility for patient participation in Collaborative Pharmacy Practice Agreements (CPAN) in Figure 3, which were consistent with patient groups described by Wermeling (2010).

Insert Figure 3 about here

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Bailey and Wermeling, 2014 (Bailey & Wermeling, 2014) described interviews with six community based pharmacy providers who had collaborated with physician specialists in opioid abuse and overdose prevention for initiation of outpatient naloxone dispensing. They identified key patient groups in the United States (US) through prescription or medical records, prescription processing or provider screening tools as centering on patient demographics at the practice site and also high risk patient groups, namely (1) patients on high-dose opioids for chronic pain management or (2) patients at high risk of overdose secondary to abusing opioids, whether prescription or illicit. Collaborative care agreement between pharmacists and prescribers were advised to allow for initiation of discussion and prescribing of naloxone to patients without the need to go through another provider. This study highlighted that high-risk patients (those who currently abuse opioids or have a history of abuse) require additional proactive screening efforts and involvement of a drug and alcohol abuse specialists to refer patients best suited to outpatient naloxone.

A separate study focusing on overdose prevention described a focus on pain medication prescribing including mandatory patient-prescriber agreements, use of a ‘pharmacy home’ (a single pharmacy for all dispensing), and supply of naloxone through the pharmacy home (Albert, et al., 2011). Data from Wilkes County (USA), the study location, identified a high frequency of overdose deaths in the home setting from pain medications, where family members could have intervened if they were aware of overdose signs and symptoms. This resulted in a programme of free-naloxone supply for patients receiving pain medications that met criteria for overdose risk

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through community pharmacy. The criteria for eligibility for naloxone described by Albert et al (2011) are similar to those described above by Green et al (2015).

Risk groups for overdose

In terms of the practical identification of patients, Binswanger et al (Binswanger, et al., 2014) conducted a qualitative study in Colorado (USA) using focus groups to unpack barriers at clinic and provider level (n=10) in the US. Clinical staff described uncertainty around who to prescribe naloxone to, concerns around offending patients and increased risk behaviours in patients prescribed naloxone along with logistical barriers for use in practice. Focus groups identified ‘at least nine risk groups for overdose including patients (1) prescribed high-dose opioids, long-acting opioids, or benzodiazepines; (2) with a history of or predisposition to substance use disorders, or who also use alcohol or marijuana; ... (3) with co-occurring mental health problems ... (4) challenging or unstable social circumstances; (5) no access to ancillary pain services; (6) behavioural characteristics, such as poor coping skills or impulsivity; (7) unrealistic expectations about the efficacy of opioids to control pain; (8) inadequate attention to or understanding of safe use... and finally (9) patients with uncontrolled pain.’ Universal screening of all patients and inclusion of family members were discussed.

Supply Systems and Cost

Supply Systems

Thirteen papers, largely from the US and the UK, describe various aspects of pharmacy supply models for naloxone and associated cost implications. Many of these models have evolved through innovation to enable legal supply while reducing barriers to the expansion of naloxone

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programmes. The main models of naloxone supply relating to community pharmacy are summarized in Table 2, ranging from traditional prescription supply models (i.e. a prescriber writes a prescription to an individual) to pharmacist-led patient screening, training and supply. In many settings multiple models are used, for example, a recent national survey in Scotland (N = 709) found one third of pharmacies were currently willing and able to provide naloxone on prescription, with smaller numbers (n = 34, 4%) supplying naloxone through pharmacist prescribing or through patient group directives (n = 70, 9%) (Matheson, et al., 2015). There have been calls for pharmacists to take the lead in further developing operational models for pharmacies to supply naloxone (Wermeling, 2010), to build on what has been achieved in this area.

Insert Table 1 about here

Community pharmacy supply models were described to meet the needs of existing legal requirements for an individual prescriber to initiate supply to an individual patient, as opposed to necessarily representing ideal or optimized supply systems. Challenges and benefits were described with each of the models, generally with the least restrictive options (e.g. over-the-counter (OTC) supply) allowing for the widest access, but having the greatest complications in terms of reimbursement for supply and need for pharmacist involvement (e.g. to identify and train patients).

In the literature calls have been made for the rescheduling of naloxone to include pharmacy

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(OTC) supply in Australia (Lenton, Dietze, Degenhardt, Darke, & Butler, 2009) and the United States (Beletsky, Rich, & Walley, 2012; Green, et al., 2015). In a commentary discussing how medications are identified to be appropriate for OTC supply, key considerations included whether the patient can accurately diagnose the condition that the medication is for, the possibility of adverse effects (including noting the perception of a moral hazard with naloxone supply), and the need for timeliness in medication supply (Fenichel, 2004). Fenichel also notes that due to complications with reimbursement with non-prescription products that over-the-counter supply may adversely affect the supply through reduced affordability.

Cost

The cost for supplying naloxone through community pharmacist-initiated models, with respect to both the pharmaceutical product and pharmacist time are not well described in the existing literature, with most costs reported in models outside community pharmacy. In a commercial setting such as retail pharmacy, high cost may impact on the feasibility, particularly as it is known that both chronic pain patients and PWID often have limited financial resources.

Many current supply systems involve goodwill and may not represent the true cost. For example, there may not be a mechanism to reimburse pharmacists for time spent delivering overdose prevention training (Zaller, et al., 2013). Some clinics have been reported to be bearing the cost of the drug (naloxone) where funding is not available (Bailey & Wermeling, 2014), and identify that this may be a barrier to larger implementation and sustainability of programmes. Where pharmacies are working with populations covered by some form of health insurance (for example, Medicaid in the US), arrangements have been made for the insurance to cover the cost

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of the medication (Bailey & Wermeling, 2014). In a US study Robinson & Wermeling note that public (e.g. Medicaid) and most private insurance plans cover the supply of the medication (naloxone), but usually do not include the nasal adapter (Robinson & Wermeling, 2014). One option to cover the cost of staff time is through recovering costs through remuneration for as part of delivering a ‘Screening, Brief Intervention, and Referral to Treatment’ (SBIRT) for a patient and a patient’s family on the use of the naloxone rescue kit (Robinson & Wermeling, 2014).

Legal Issues

Four studies discussed legal issues pertaining to pharmacy naloxone supply. Several legal issues were addressed by innovators of naloxone programmes in the implementation of community naloxone supply. Pharmacy groups have identified ways to address the need for naloxone to have a prescription through standing orders and different practice agreements and group directives (see Table 2 for further details). Two studies discussing pharmacy supply of naloxone in the UK described legal changes that preceded the programme establishment that allowed members of the public to administer naloxone, adding naloxone to the list of medications that can be administered by the public for the purposes of saving a life in an emergency (Laird & Hunter, 2014; Yates, 2015).

A concern directly related to community pharmacist practice is medico-legal issues with patient selection. Medico-legal concerns associated with identifying patients receiving opioids as medically ‘at risk’ was raised by a focus group of health care professionals members, suggesting that raising the question of naloxone supply also raises the concern that the patient may be at risk

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if continued on opioids (Binswanger, et al., 2014). Taking a more comprehensive approach to offering naloxone to all patients on opioids was proposed as one way to reduce this legal concern, and also reduce the perception of stigma from the patients’ point of view (Binswanger, et al., 2014). How this may unfold in community pharmacy practice has not yet been explored, but may support the practice of more universal supply of naloxone and within the context of low threshold community supply routes, as was proposed by pharmacists in this study.

Finally, the supply of naloxone to a third party was identified as a potential legal issue for pharmacists. It was identified that although naloxone may be logically supplied to third parties who are trained to administer naloxone, third parties supply is not legal in all US states (Bailey & Wermeling, 2014).

Training of Pharmacists and Community Pharmacy Naloxone Recipients

Three articles described training audiences (pharmacist and naloxone recipients), training processes and curricula directly pertaining to pharmacy practice. Riner et al (Riner & Wermeling, 2014) describe a protocol providing guidance to pharmacists in Kentucky (USA) with regard to education of patients and their families in overdose prevention, recognition and response. Bailey and Wermeling (Bailey & Wermeling, 2014) described training pharmacists and pharmacy staff in administration of naloxone products (intranasal (IN) atomizer or intramuscular (IM) injection and the patient instructions). Both in-house training programs (developed by pharmacies themselves) and formal training (for example www.prescribtoprevent.org) were documented (Bailey & Wermeling, 2014). Educational

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competencies generally center on use of emergency numbers (e.g. 911 in the US) rescue breathing, checking for pulse, preparing the naloxone product for administration, assessing for response and repeating dose if required (Bailey & Wermeling, 2014). This study advocated the training of patients and third parties (i.e. their family members) at time of naloxone dispensing. Additional supports often include video materials which ensure that those with low literacy understood the information around overdose prevention, recognition and response (Bailey & Wermeling, 2014).

In terms of pharmacists training naloxone recipients (lay people), one pilot study of 18 pharmacies in Glasgow, Scotland trained 26 pharmacists and 15 support staff who then provided training and naloxone to people inject drugs through a patient group directive supply model (Laird & Hunter, 2014). This pilot work found that it was feasible and acceptable to staff in community pharmacy settings.

Discussion

The review scoped the extant available literature around what is known about community pharmacy supply of naloxone. We identified a foundation of work which can inform the direction of provision of naloxone to diverse patient groups and their relatives accessing community pharmacy settings. A range of pharmacy specific supply models and logistical barriers were identified. Further work to address these barriers may help harness to capacity of community pharmacy to extend and enhance the reach of take-home naloxone to the diverse patients groups at risk of opioid overdose. The review identified a number of strengths including

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a range of established supply models that may be used depending on the setting, existing training curricula, and identification of patient populations (e.g., people prescribed opioids for chronic pain) that may not access naloxone through programs outside of a pharmacy setting.

Potential challenges to address with health professionals include concerns around a ‘moral hazard’ (Fenichel, 2004), or the risk that the perception of a naloxone as a safety-net might increase substance use or inappropriate self-medication for pain patients. One study conducted in the UK found reductions in heroin use following naloxone training (Gaston, Best, Manning, & Day, 2009). This suggests such concerns may be unfounded, and addressing these unfounded perceptions may be important as part of pharmacist education.

While consistent ‘risk groups’ of people were identified in this review, concerns that identifying ‘at risk’ patients to supply naloxone to may create personal and public stigma, and result in reluctance to supply naloxone and/or opioids due to medico-legal risks must be addressed. Further work may help to resolve these issues and explore the feasibility and cost-effectiveness of proposed universal supply approaches that avoid identifying, and potentially stigmatizing or otherwise identifying specific patient groups who are ‘at risk’. This review identified that pharmacists appeared to support more universal supply strategies. Notwithstanding concerns around targeting specific patient groups, community pharmacists have access to patients’ medication histories, and are optimally positioned to identify those that meet some established risk factors such as poly-pharmacy and higher opioid doses.

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The existing literature on naloxone with respect to legal issues for pharmacists is limited. Few studies directly inform if concerns exist regarding legal liability of community pharmacists in the supply of naloxone. In most countries naloxone is still a prescription only medication, meaning that it can only be administered by a person operating under a legal prescription, and prescribing usually requires that the prescriber has established a relationship with the patient (Burris, Norland, & Edlin, 2001), though other numerous models are described including standing orders and OTC supply were identified through this review.

Challenges identified with supply systems include gaining clarity around payment in different types of health care systems, notably with OTC supply. These issues are particularly timely in Australia where the Therapeutic Goods Administration have announced the decision to reschedule naloxone to an over-the-counter (pharmacist only) medication in February 2016 (Therapeutic Goods Administration, 2015). This will mean for patients receiving subsidies on prescription medications, the cost of OTC supply will almost certainly substantially exceed the cost (currently AUD\$6.10) for a subsidised prescription. This may mean that the impact of greater availability of naloxone through OTC access may not be realized. Reports of medication cost in the US vary with US\$15 per injectable naloxone kit; and around US\$25-\$35 per intranasal naloxone kit (Coffin & Sullivan, 2013; Doe-Simkins, et al., 2014; Robinson & Wermeling, 2014). Some programmes have additionally factored in around US\$10 for staff time per kit (Coffin & Sullivan, 2013). More recently even higher prices have been reported (for example US\$60-\$80 for a 2 dose rescue kit) (Davis, Carr, Southwell, & Beletsky, 2015), though even at much higher prices naloxone supply to heroin users has been demonstrated to be cost

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effective for reversal of heroin overdose (Coffin & Sullivan, 2013). The question remains as to how this cost can be covered, particularly in commercial retail settings such as community pharmacy.

Finally, in terms of the last theme of training, numerous studies have demonstrated that laypersons can be effectively trained in a range of settings [see (Clark, et al., 2014) for review], though we only identified pilot studies examining feasibility and not effectiveness of naloxone training delivered by pharmacists. Research is needed to confirm the efficacy of a pharmacy-led brief intervention for naloxone and overdose prevention, given pharmacists are generally not experts training in how to respond to drug overdoses. Numerous studies also advocate the importance of naloxone prescribing within an overall overdose management programme which includes resuscitation training and cardiopulmonary resuscitation (CPR), though the feasibility of overall overdose management programs with CPR in community pharmacy programs may be questioned (Dong, et al., 2012; George & Moreira, 2008; Leece, et al., 2013; Piper, et al., 2007).

While earlier versions of recipient training programs were up to eight hours in duration (Doe-Simkins, Walley, Epstein, & Moyer, 2009; Seal, et al., 2005), more recently brief training (5-10 minutes) appeared sufficient to improve comfort and ability in responding to overdose (Behar, Santos, Wheeler, Rowe, & Coffin, 2015; Liu, Mazur-Routsolias, Lu, & Aks, 2013). Five to ten minute training would be ideally suited to community pharmacy settings where time is an often cited barrier when implementing new services (Firth, Todd, & Bambra, 2015; Mansoor, Krass, Costa, & Aslani, 2015; Watson & Hughes, 2012). Further work may address the feasibility of

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training in a community pharmacy setting, including address previously identified concerns around privacy in these settings (Saramunee, et al., 2014). One study among substance using participants found few behavioral differences between trained and untrained overdose rescuers, possibly due to high levels of baseline knowledge due to informal training and information sharing among untrained participants (Doe-Simkins, et al., 2014). This finding may suggest for some patient groups training is less critical.

As naloxone supply in pharmacy expands it remains to be established as to the most effective way to upskill the diverse workforce of pharmacy settings. Mayet et al., (Mayet, Manning, Williams, Loaring, & Strang, 2011) examined training drug and alcohol clinicians and found modest success of the ‘cascade method’ in training activity aimed at large clinician workforces. This method utilises trained clinicians to then train other clinicians and drug users and requires further refinement for applicability in naloxone programming. Challenges in using this method centered on knowledge gaps, lack of confidence, formulation of naloxone, and requirement for local leads. Training modalities such as online training www.getnaloxonenow.org ("Site Offers Free Online Naloxone Training," 2015) for emergency practitioners and laypeople significantly increased knowledge around opioid overdose and confidence in appropriate responses with naloxone, and online training may represent a practical mode of training for pharmacists.

Some gaps in the literature were identified. Although studies have captured pharmacists’ perceptions, the studies only represent a small number of pharmacists (25 pharmacists in total, all from the United States). Further work may help understand how well the support and concerns

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expressed in these studies relating to naloxone are echoed by other pharmacists, particularly pharmacists from different countries or different practice settings. Understanding the range of potential issues and barriers may facilitate implementation, in addition to fostering ongoing training opportunities, which appears to be related to increased involvement with other harm reduction programs (Matheson, et al., 2015). Given the relatively early stage of research in terms of pharmacy naloxone supply, the literature reviewed included editorials and commentaries, which add to the understanding of attitudes and perceptions around naloxone, but are limited in their scientific rigor. Large empirical studies demonstrating effectiveness of community pharmacy training of recipients (given that research on efficacy of naloxone training has largely examined training by peers or drug and alcohol experts) and of pharmacy naloxone supply more broadly were not identified. Further, the acceptability and affordability of pharmacy supply for people who inject drugs should be explored. Finally, it should be acknowledged with the proposal to supply naloxone to chronic pain patients that gaps also exist in the both the acceptability of naloxone supply for pain patients, and the cost effectiveness of take-home naloxone for patients receiving opioids for pain given the large population and relatively lower overdose frequency.

It should be acknowledged that limitations may also exist resulting from the scoping review methodology itself. While we aimed to be comprehensive in our approach, there is the possibility that not all relevant work was identified by the searches or databases used. In addition, scoping reviews do not include an assessment of study quality as the focus is on covering the range of work that informs the topic rather than limiting the work to studies that meet particular standards of scientific rigour.

Conclusion

Provision of naloxone for bystander administration to prevent opioid overdose deaths appears increasingly feasible and warranted given the rise in rates of overdose deaths. Community pharmacy supply of take home naloxone warrants further development and consideration, in light of general support from the small number of pharmacists included in research so far. Barriers including cost and remuneration for community pharmacists’ time, and how pharmacists may effectively identify and train naloxone recipients were identified in this review. In summary, some work has been done to lay the groundwork for larger scale implementation of naloxone supply in pharmacy. Future studies may help to understand and resolve barriers to support expansion of pharmacy supply models in different geographical regions.

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Figure 1 Search Terms and Strategy

1.	Naloxone	
2.	Overdose prevention or drug overdose or opiate overdose	
3.	community pharmac* or retail pharmac* or pharmacist* or pharmacy or community pharmacy services or pharmaceutical services or professional practice or professional role or community care or attitude of health personnel	
4.	training or supply or cost	
5.	3 or 4	
6.	buprenorphine or buprenorphine-naloxone or buprenorphine adj naloxone	
7.	1 and 2 and 5	
8.	7 not 6	
Databases were searched using the appropriate subject headings in each database and/or keywords or textwords for the above search groups:		
Sample Search (Medline (via Ovid platform) searched on 21/7/15		
#	Searches	Results
1	*Naloxone/	6699
2	exp Drug Overdose/	8002
3	"overdose prevention".tw.	102
4	"opiate overdose".tw.	119
5	or/2-4	8061
6	"community pharmac*".tw.	3144
7	"retail pharmac*".tw.	354
8	exp Pharmaceutical Services/ or exp "Attitude of Health Personnel"/ or exp Pharmacists/ or exp Community Pharmacy Services/ or exp Professional Role/	212463
9	pharmacist*.tw.	18811
10	pharmacy.tw.	25009
11	"community care".tw.	3141
12	or/6-11	234448
13	exp Inservice Training/	25011
14	training.tw.	238913
15	supply.tw.	89976
16	"Costs and Cost Analysis"/	43221
17	or/13-16	386504
18	12 or 17	598633
19	buprenorphine.ti.	2685
20	buprenorphine-naloxone.ti.	184
21	(buprenorphine adj naloxone).ti.	184
22	or/19-21	2685
23	1 and 5 and 18	43
24	23 not 22	42
25	limit 24 to (humans and (evaluation studies or journal article or meta analysis or randomized controlled trial or "review" or systematic reviews))	40

Figure 2 Flowchart for inclusion and exclusion of literature

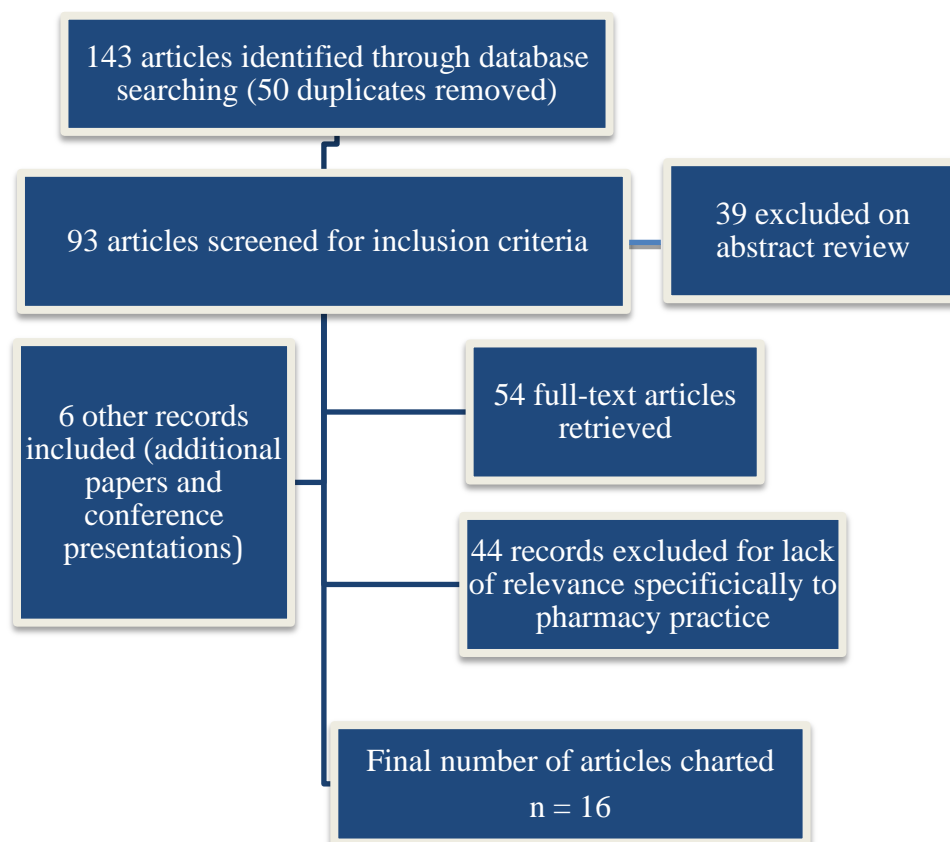


Figure 3 Eligibility for patient participation in Collaborative Pharmacy Practice Agreements (CPAN)

- Voluntarily request;
- Recipient of emergency medical care for acute opioid poisoning;
- Suspected illicit or nonmedical opioid user ;
- High dose opioid prescription (>100 morphine mg equivalents daily);
- Methadone prescription to opioid naïve patient;
- Dispensed an opioid prescription and:
 - History of smoking;
 - COPD;
 - Respiratory illness or obstruction;
 - Renal dysfunction or hepatic disease;
 - Known or suspected concurrent alcohol abuse;
 - Concurrent benzodiazepine prescription;
 - Concurrent SSRI or TCA anti-depressant prescription;
 - Recently released prisoners from a correctional facility;
 - Released from opioid detoxification or mandatory abstinence programme;
 - Patients entering a methadone maintenance treatment programme; and
 - Patients that may have difficulty accessing emergency medical services.

(Green, Dauria, Bratberg, Davis, & Walley, 2015, p4)

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Table 1 - Summary of review literature

Authors	Year	Method	Themes
Albert, S., et al.	2011	Preliminary findings from a community based naloxone program	Populations, Supply systems and cost
Bailey, A. & Wermeling, D.	2014	Qualitative interviews with pharmacists	Perceptions, Populations, Supply systems and cost, Legal issues, Training
Beletsky, L. et al..	2012	Commentary on naloxone supply	Supply systems and cost
Binswanger, I. et al	2014	Qualitative interviews with primary care staff (including pharmacists)	Perceptions, Populations, legal issues
Fenichel, R. R.	2004	Commentary on assessing appropriateness of drug for over the counter supply	Supply systems and cost
Green, T. C. et al	2015	Case studies of two supply models from different US jurisdictions	Populations, Supply systems and cost
Hill, D & Mcauley A.	2012	Quantitative survey views on naloxone provision of service providers, service-users and family/friends	Supply systems and cost
Laird, A., & Hunter, C.	2014	Findings from a pilot program of pharmacy naloxone supply	Legal issues, supply systems and cost, training
Lenton, S. et al.	2009	Letter to the editor	Supply systems and cost, legal issues
Matheson, C. et al.	2015	National survey of pharmacists (repeated 4 times over 2 decades). More recent survey included questions on naloxone	Supply systems and cost
Riner, E., & Wermeling, D.	2014	Describes protocol in development for pharmacists naloxone supply	Training
Robinson, A. & Wermeling, D.	2014	Review of information about naloxone focusing on intranasal route	Supply systems and cost
Traynor, K.	2014	Program description in news section of journal	Supply systems
Wermeling, D. P.	2010	Editorial	Populations, Supply systems and cost
Yates, J.	2015	Program description and interim report of pilot study with pharmacy supply	Legal issues,
Zaller, N. et al.	2013	Semi-structured interviews with individuals who inject drugs and pharmacy staff	Perceptions, supply systems and cost

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Table 2 - Pharmacy models of naloxone supply

Supply model	Benefits	Disadvantages	Examples described in the literature
Traditional supply model (i.e. one prescriber supplies for an individual patients though a standard consultation, with subsequent and pharmacy supply)	Doctors can identify appropriate patients in medical settings. The use of usual supply mechanisms allows use of reimbursement models (eg government subsidized prescriptions or health insurance coverage). Training may occur off-site, being provided in the medical setting.	Relies on access to prescriber, limits opportunities for other parties to initiate supply. Not all people who many benefit from naloxone are in contact with prescribers.	Large US metropolitan cities including Boston, Seattle and Pittsburgh, examples of programmes where prescriptions are included on Medicaid Formulary (Bailey & Wermeling, 2014) Wilkes county ‘Project Lazarus’, prescriber of pain medications shows a video to train patient and patient is able access free naloxone at designated pharmacy. (Albert, et al., 2011)
Pharmacists initiated (e.g. pharmacist has prescriptive authority)	Easier to initiate in pharmacy setting, pharmacist can identify and proactively discuss with patients.	May be challenges in pharmacists identifying appropriate patients. Less clear how pharmacists may be reimbursed. Not all pharmacists may have prescribing rights. Training may need to be provided in pharmacy.	One of six pharmacists interviewed by Bailey and Wermeling (2014) had pharmacist prescriptive authority and was able to proactively seek out patients (Bailey & Wermeling, 2014). A national survey identified 4% of pharmacist can prescribe naloxone (Matheson, et al., 2015).
Over the counter pharmacy supply	The least restrictive model of pharmacy supply. Takes advantage of the accessibility of community pharmacy as a primary health care setting. Enables other non-medical services (e.g. support services for people who use drugs) to directly refer patients with no administrative barriers to supply.	May limit ability for reimbursement of medication costs. Requires legal changes in many locations. Training may need to be provided in pharmacy setting if patients have not already received training.	Numerous papers called for over-the-counter supply of naloxone (eg (Lenton, et al., 2009)), though no descriptions of an OTC supply model were found in the literature.

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Supply model	Benefits	Disadvantages	Examples described in the literature
Standing order – naloxone is prescribed using a prewritten medication order so a health care professional (or class of healthcare professionals) can supply naloxone in clearly defined circumstances	Removes barrier for individual prescription. Usually does not require legislative change. May assist implementation of programmes where collaborative practice agreements only permit pharmacists to dispense medication to individuals that are established patients of the prescriber.(Green, et al., 2015)	Still requires a system to be established and administratively may be burdensome. Training may need to be provided in pharmacy.	In a programme description from Massachusetts the medical director serves as the single prescriber to all community-based naloxone recipients (Green, et al., 2015)
Collaborative practice agreement (CPA). Single prescriber authorizes multiple pharmacies to supply naloxone. CPAs permit a pharmacist to work in collaboration with a prescriber for the purpose of drug therapy management within an agreed protocol.	Removes need for individual prescription being required, allowing access to a broader number of people. In some jurisdictions pharmacists can initiate supply under a CPA.	In some jurisdictions it is required that the prescriber has a relationship with the patient. Training may need to be provided in pharmacy.	48 states permit pharmacists to enter into CPAs with prescribers to manage patient pharmaceutical care, and at least 21 states permit pharmacists to initiate medication under a CPA (Green, et al., 2015; Traynor, 2014)
<u>Patient Group Directions</u> (PGDs) are written instructions for the supply or administration of medicines to groups of patients who may not be individually identified before presentation for treatment.	Removes need for individual prescription	Training may need to be provided in pharmacy. Method for payment unclear, and may not translate to community pharmacy setting	Examples of patient group directions exist in the NHS in the UK (Hill & McAuley, 2012; Laird & Hunter, 2014; Matheson, et al., 2015). These models involve pharmacist supply, though they are usually operating within health services as opposed to community pharmacy.

Disclosure statement

By submitting this article we declare that:

- this is our own original work and that it has not been published in whole or in part elsewhere and is not under consideration by any other journal.
- that all persons named as authors have made a major contribution to the work reported, and are prepared to take public responsibility for its contents.

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