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Rapid widespread distribution of intranasal naloxone for overdose prevention

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ABSTRACT

Background: Take home naloxone programs have been successful internationally in training bystanders to reverse an opioid overdose with naloxone, an opioid antagonist. A multi-site naloxone distribution program began in Norway in 2014 as part of a national overdose prevention strategy. The aim of this study was to a) describe the program, and b) present findings from the government-supported intervention.
Methods: From July 2014 to December 2015, staff from multiple low-threshold facilities trained clients on how to use intranasal naloxone. Distribution occurred without an individual prescription or physician present. Questionnaires from initial and refill trainings were obtained, and distribution rates were monitored.
Results: There were 2056 naloxone sprays distributed from one of the 20 participating facilities, with 277 reports of successful reversals. Participants exhibited known risks for overdosing, with injecting ($p = 0.02$, OR = 2.4, 95% CI = 1.14, 5.00) and concomitant benzodiazepine use ($p = 0.01$, OR = 2.6, 95% CI = 1.31, 5.23) being significant predictors for having had high rates of previous overdoses. Suggested target coverage for large-scale programs was met, with an annual naloxone distribution rate of 144 per 100,000 population, as well as 12 times the cities mean annual number of opioid-related deaths.
Conclusion: A government-supported multisite naloxone initiative appears to achieve rapid, high volume distribution of naloxone to an at-risk population.

1. Introduction

Take home naloxone (THN) programs were first described in the 1990s as a method to prevent overdose fatalities (Darke and Hall, 1997; Strang et al., 1996). These programs train bystanders to respond to an overdose with naloxone, an opioid antagonist. Over the past 20 years, over 200 programs have been implemented worldwide (Clark et al., 2014; Dettmer et al., 2001; Kan et al., 2014; Leece et al., 2013; Lenton et al., 2014), with over 26,000 reported overdose reversals in the United States alone (Wheeler et al., 2015). The majority of these programs have adopted injectable naloxone developed for use by health care staff, yet interest in a more user-friendly intranasal option has emerged. Some programs in the United States (Evans et al., 2012; Maxwell et al., 2006; Walley et al., 2013) and Scotland (Bird et al., 2015a) have experienced decreases in overdose mortality with the implementation of large-scale naloxone programs. Collectively, THN has been found to be effective (McDonald and Strang, 2016), and has demonstrated that in order to have a substantial impact on overdose mortality, widespread and often population-based interventions are necessary (Heller and Stancliff, 2007; Walley et al., 2013).

In 2011, Scotland became one of the first countries to implement a nationally-supported THN program (McAuley et al., 2012), and in its first two years distributed 7300 naloxone rescue kits, mainly injectable (Bird et al., 2015b). They subsequently found a 36% reduction in the proportion of overdose fatalities following prison release during this period (Bird et al., 2015a). Wales also implemented a national program with over 7300 naloxone kits distributed to nearly 3800 individuals since their pilot in July 2009 (Morgan and Smith, 2015). A study from Massachusetts demonstrated that by partnering public health policy with community organizations, high volume intranasal naloxone distribution was possible (Walley et al., 2013). Furthermore, they found an almost 50% reduction in overdose deaths in areas where distribution rates exceeded 100 per 100,000 population (Walley et al., 2013). Governments in Wales (Bennett and Holloway, 2011), Estonia, Norway (National Overdose Strategy, 2014; Lobmaier and Clausen, 2016), and certain health departments in the United States (Seal et al.,

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2005; Tobin et al., 2009; Walley et al., 2013; Winstanley et al., 2015) have also adopted policies that support peer-administered naloxone as part of a large-scale, multi-faceted public health intervention.

Despite the merits of large-scale THN programs, barriers to increased naloxone access have been identified, primarily in regards to financial and legal issues (Coffin et al., 2010; Heller and Stancliff, 2007; Piper et al., 2008). First, financial restraints may severely limit the scope in which THN programs can distribute. Many rely on independent funding to purchase naloxone and a dedicated clinician available to prescribe (Bennett et al., 2011; Heller and Stancliff, 2007; Tobin et al., 2009; Wagner et al., 2010; Winstanley et al., 2015). Second, legal concerns for the prescribers and responders exist. Prescribers have had concerns over liability while prescribing a drug not knowing whom the actual recipient of the drug will be. Responders risk liability in intervening in a medical emergency, and the possibility of arrest at the scene. However, in recent years improvements in third party prescribing, standing orders, and Good Samaritan laws have increased access to naloxone in many US states (Davis and Carr, 2015). Additionally, in 2015 legislation in the UK changed to allow naloxone to be distributed without a prescription (The Human Medicines Amendment, 2015). Lastly, issues with needle-based naloxone have been a barrier for central Asia and Sweden. Although, an intranasal preparation may be a relevant option for countries facing this type of barrier, issues with off-label intranasal use (Strang et al., 2016), ideal concentration (Strang et al., 2016), and complicated assembly (Edwards et al., 2015) continue to exist.

Although Norway has a robust social welfare system, including around 60% coverage of opioid maintenance treatment (OMT) and other treatments and services for people who inject drugs (PWID), overdose mortality remains a significant concern. The average overdose mortality rate in Europe is estimated to be 18 per million population, with Scandinavian countries experiencing greater than 40 deaths per million (European Drug Report, 2016). In recent years, advocacy organizations, researchers, and politicians have played an important role in advocating for increased naloxone access for bystanders in Norway. As a response to this persistent public health concern, in 2014 the Norwegian government launched a national overdose strategy, including an intranasal naloxone distribution project (National Overdose Strategy, 2014). Though large-scale naloxone programs have existed in the past, few have done so with the use of intranasal naloxone, and none have previously been implemented in Scandinavia. The aims of this paper are to: 1.) describe characteristics of a multi-site naloxone distribution project in Norway, and 2.) present findings from this government-supported intervention, including: a.) characteristics of the population trained, specifically identifying factors associated with having the highest rates of repeated overdoses, b.) outcomes following the use of naloxone, and c.) distribution rates.

2. Material and methods

2.1. Setting

There are approximately 6200–10,300 high-risk opioid users in Norway, with the majority injecting heroin (The Drug Situation in Norway, 2015). Since 1998, OMT has been available nationwide, and by the end of 2015 nearly 7500 clients were currently enrolled (Waal et al., 2016). The Norwegian health system provides drug treatment, healthcare, shelter, and low-threshold services for PWID at no cost to the client. All costs associated with the project, as well as funding for evaluation, were covered by the Norwegian Directorate of Health.

This project utilized an extensive network of existing facilities as naloxone distribution sites. In the first year of the project, targeted groups were those outside of formal treatment, as they are known to be at highest risk of overdosing (Clausen et al., 2008; Rowe et al., 2015). Therefore sites included: drop-in day centres, medical facilities, overnight shelters, a prison, and a safe injection facility. The majority of the sites are publically funded low-threshold facilities, which require no referral or payment from the clients. All sites were located within Norway's two cities with the highest overdose rates, Oslo and Bergen (Amundsen, 2015).

2.2. Study participants

From June 2014 – December 2015, interested participants from low-threshold facilities volunteered to take part in this study. Naloxone training sessions were available to anyone interested and likely to experience or witness an overdose. Recruitment occurred via posters and brochures, or word-of-mouth by the facility staff. The majority of trainings were targeted towards PWID; however, trainings were also available to those likely to be in contact with someone at risk of overdosing. Therefore, courses for relatives, police, and security staff were also available.

2.3. Opioid overdose prevention training

All trainings were performed by facility employees who had attended the staff trainer course, enabling them to distribute naloxone without the presence of a physician (Madah-Amiri et al., 2016). Sessions were brief, flexible, and offered as individual or group sessions. The curriculum covered in training is comparable to similar THN programs (Clark et al., 2014). Clients were instructed to administer 0.4 mL of naloxone in each nostril (total 0.8 mL) and give rescue breathes while awaiting response. If there was no response after two minutes, the client was instructed to administer another 0.4 mL in each nostril. If still no response and the ambulance had not yet arrived, the client was advised to commence with cardiopulmonary resuscitations. Information on aftercare, side effects, including potential withdrawal symptoms and risk for future overdoses was given. Clients were instructed to practice opening and assembling a sample device and at some locations could practice administering on a doll. Naloxone kits included the prefilled syringe, nasal atomizer, breathing mask, and instructions for use. It was mandatory that clients attend an initial training in order to receive naloxone.

An intranasal device was chosen carefully by the Norwegian Directorate of health, given its demonstrated effectiveness (Barton et al., 2005; Kerr et al., 2009; Lobmaier et al., 2011; Robertson et al., 2009) and user-friendly administration. However, at the time, an ideal pre-assembled registered intranasal preparation was unavailable. The Norwegian Medicines Agency issued a waiver for this project allowing for the assembly and distribution of a novel nasal spray device (Fig. 1). The 2.0 mL pre-filled syringe consisted of five 0.4 mL doses with a concentration of 1 mg/1 mL naloxone (total 2 mg/2 mL). Clients were instructed on how to titrate dosing. A nasal atomizer was added and the needles were removed from the original Prenoxad package. Norwegian instructions and pictorial information was also added to the packaging. The expiration date was written on the outer packaging, with a three-year shelf life.

A key component for accessibility for this project included the approval to distribute intranasal naloxone without need for individual prescription. This was achieved by involvement of a community physician appointed to the project, who could order naloxone in bulk from contracted pharmacies for the facilities involved. This allowed for distribution to occur without a physician present, given that the appropriate rescue training was accompanied.