



An Agenda for Naloxone Distribution Research and Practice: Meeting Report of the Surviving Opioid Overdose with Naloxone (SOON) International Working Group

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Abstract

Opioid-related mortality is a serious and growing issue in North America. Naloxone distribution and basic life support training for people at risk of overdose is a promising opportunity to improve access to potentially lifesaving bystander interventions and essential healthcare. We convened a unique international working group of experts in public health, resuscitation science, and health research methodology, along with clinical, community, policy, industry stakeholders and members of the lay public to explore and address key challenges and opportunities for rigorous research on this intervention.

The findings from the Surviving Opioid Overdose with Naloxone (SOON) International Working Group explored potential research opportunities and identified barriers in four priority areas: research methods, resuscitation guidelines, naloxone delivery device development, and knowledge translation. This novel collaborative effort:

- Identified key steps and challenges for developing an appropriate, feasible and rigorous pragmatic trial of naloxone distribution in various clinical settings;
- Identified emerging naloxone delivery devices and technologies, and described how these devices may alter standards of care for overdose prevention research and practice;
- Engaged resuscitation experts in the development of bystander resuscitation protocols for opioid-associated resuscitative emergencies; and,
- Identified strategies to overcome knowledge translation barriers for patients and providers, as well as characteristics for effective educational tools and program implementation.

The SOON Working Group aims to advance the investigation, implementation, and practice of overdose education and naloxone distribution. Through diverse collaborations, we can use best science to improve practice for individuals at risk of opioid overdose.

Background

Opioid-related mortality is a serious and growing issue in North America [1,2]. In the United States, drug overdose accounted for over 16,000 deaths in 2010, and now exceeds motor vehicle collisions as the leading cause of death due to injury [1,3]. Premature opioid-related mortality in Ontario, Canada, rose from 12.2 deaths per million in 1991 (127 deaths annually) to 41.6 deaths per million in 2010 (560 deaths annually) [2]. The World Health Organization estimates that opioid overdose accounts for between 70,000 and 100,000 annual deaths worldwide [4]. This public health epidemic is largely driven, by

opioid prescriptions [5], and is pervasive across a wide diversity of socio-demographic strata [6,7].

Addressing this complex public health crisis requires comprehensive and multi-sectorial strategies [8]. Naloxone distribution and basic life support training for people at risk of overdose is a promising opportunity to improve access to potentially lifesaving bystander interventions and essential healthcare [9]. This approach has now received the attention of the World Health Organization, and national governments of Canada, the United States (U.S.), and the United Kingdom (U.K.) [4,8-11]. In the U.S., nearly 200 local programs distributed naloxone to more than 53,000

individuals between 1996 and 2010 [9]. Additionally, over 25 states have adopted or are considering policies permitting first responders and public safety professionals such as police officers and fire-fighters, to carry and administer naloxone [12]. In Canada, several such programs have been identified, with published reports and evaluations emerging from British Columbia, Edmonton, and Toronto [13,14,15]. The Scottish Government has established and evaluated a national naloxone distribution program, while local pilot or experimental projects have been reported and celebrated in Russia, Ukraine, Georgia, Kazakhstan, Tajikistan, Afghanistan, China, Vietnam and Thailand [4,16,17]. The biomedical industry's interest in naloxone has grown substantially, resulting in the development of a new range of commercial naloxone formulations and purpose-engineered naloxone delivery devices.

Naloxone distribution programs center around teaching the lay public to activate emergency medical services and deliver potentially lifesaving opioid antagonists and resuscitative maneuvers to critically ill overdose patients. Building and optimizing these programs therefore requires the integration of addictions medicine, drug policy and harm reduction, with bystander resuscitation, prehospital medicine and emergency toxicological expertise and systems.

In March 2014, we convened the Surviving Opioid Overdose with Naloxone (SOON) International Working Group, a meeting of experts and key stakeholders to consider challenges and opportunities to advance naloxone distribution implementation and research in Canada. The meeting was held in Toronto, Ontario, and co-hosted by the University of Toronto Dalla Lana School of Public Health and St. Michael's Hospital Li Ka Shing Knowledge Institute.

This report summarizes our proceedings and proposes future directions for research and practice related to the distribution of naloxone to people at risk of overdose. Our goal was to convene the international and inter-professional expertise necessary to advance the practice, investigation, and implementation of bystander naloxone administration for opioid-associated resuscitative emergencies. Working Group members included clinicians and researchers in resuscitation science, emergency medicine, primary care, addictions, prehospital care, public health, and harm reduction, as well as decision-makers, educators, and community members. Working Group members also included representatives from local and regional naloxone distribution programs in Canada and the United States, leadership in mental health and addictions from the World Health Organization, and representatives from biomedical technology firms engaged in the development of naloxone delivery devices. Prior to the

meeting, the planning committee identified four priority objectives related to naloxone distribution programs: [1] advance research strategies and methods, [2] identify and develop appropriate technologies for the user-friendly and safe administration of bystander naloxone, [3] identify and synthesize consistent bystander basic life support and resuscitation practices, and [4] develop widely available and broadly applicable knowledge translation strategies for this intervention. Based on their expertise and perspectives, participants were divided into four meeting streams, each corresponding with each of the four priority objectives.

Research Strategies and Methods

Although naloxone distribution is expanding rapidly, there are no completed experimental studies on this intervention that examine mortality as an outcome. Most of the existing literature describes self-reporting of naloxone administration from participants returning for naloxone kit refills, with limited active follow-up of participants [18]. For nearly 15 years, practitioners and scientists have identified that the evidence to support a decrease in mortality from naloxone distribution remains thin, and called for higher quality research [18,19]. Clark et al. 2014 systematic review on community naloxone distribution programs identified 19 published studies, including 14 uncontrolled longitudinal studies, three descriptive papers with limited summary statistics, and two qualitative studies. All relied on participant self-reports and most suffered from elevated attrition rates. No randomized studies or controlled cohort studies were identified, and the authors were unable to draw a summary conclusion regarding the overall effectiveness of naloxone distribution to prevent opioid-related deaths [18]. A 2013 time series analysis by Walley et al. found that areas in Massachusetts with greater enrolment in naloxone distribution programs had lower rates of opioid-related overdose death than comparators lower enrolment [20]. We are aware of two prospective randomized trials, both in the recruitment phase, that are designed to test the effects of this intervention on opioid-related morbidity and mortality. The Seattle-based "Project OOPEN" is designed to test the effects of emergency department-based naloxone distribution and overdose prevention education on rates of fatal and non-fatal overdose and drug use behaviours [21]. The U.K.-based "NALIVE" trial focuses on mortality following release from prison in people with a history of opioid use [22].

People at risk of dying from opioid overdose deserve high quality, evidence-based care. We proposed a working definition of people at risk of opioid overdose based on the available literature (Table 1).

People at Risk of Opioid Overdose may be defined as people who use opioids and also meet one or more of the following criteria:
• Known or suspected prescription opioid dependence or heroin use [30]
• History of emergency care for opioid overdose [31]
• Opioid use with known or suspected use of alcohol or benzodiazepines, or other drugs known to increase overdose risk [30,31]
• Release from prison with a history of opioid dependence [34]
• Discharge from a treatment program for opioid dependence [35]
• Enrollment in opioid dependence treatment with methadone during specific times such as induction or discharge [34,35]
• High doses of prescribed opioids [36]

Table 1: A Working Definition of People at Risk of Opioid Overdose

As naloxone distribution to opioid users is rolled out in harm reduction settings, the window of opportunity closes for prospective trials or observational studies comparing overdose prevention interventions with and without naloxone. Participants identified methodological and design challenges to researching the effectiveness of bystander administered naloxone for opioid-associated resuscitative emergencies, and outlined opportunities for future intervention research.

Most existing overdose prevention and naloxone distribution programs enroll individuals who use opioids and access harm reduction services [18]. Harm reduction programs may have limited interaction with the full diversity of people at risk of opioid overdose, and especially limited interaction with those who use primarily oral opioid formulations or prescribed medications. There remains significant uncertainty about whether harm reduction literature can be generalized to other populations at risk of overdose, such as chronic pain patients, prison populations, or non-injection opioid users. There is a lack of data on fatal or non-fatal overdose event rates in many of the potential populations that could be used in planning future research.

Participants in the research methods stream did not generally think that there is clinical equipoise to support an effectiveness trial in all settings, and advocated for future research to focus on implementation trials [21]. There was support for high quality ecological studies and for research designs involving staggered introduction of overdose prevention training and naloxone distribution, such as a stepped wedge design [22]. Other SOON participants thought that the effectiveness of naloxone distribution to people at risk of overdose had not yet been established in all relevant clinical settings, such as emergency departments, and may present new opportunities for a pragmatic randomized controlled trial.

Naloxone Administration Devices

Existing naloxone kits are cumbersome and inconsistent, involving a collection of glass ampoules, syringes, needles or atomizers, printed instructions, and personal protective equipment, usually designed and packaged by individual programs. Rescue medications for other conditions have received comparatively more investment from both clinical and biomedical engineering communities, for example epinephrine auto-injectors (e.g.: Epi-Pen®) for the treatment of anaphylaxis. Technological innovations in naloxone distribution and delivery may have profound effects on both the scientific and evidentiary landscape to support this intervention, and on the socio-political will to support research, implementation, and investment in this area [25].

We aimed to build the collaborations necessary to advance user-friendly and purpose-made naloxone delivery for research and practice, and to integrate them with appropriate knowledge translation and educational tools. We reached out to biomedical firms with active naloxone related projects, to gather information about emerging products, and understand how technological innovations in this field may alter naloxone distribution practices and administration by bystanders.

Naloxone delivery devices and kits entered a period of fast-paced transformation in 2013 and 2014, driven largely by three key biopharmaceutical players:

1. Lightlake Therapeutics, a U.K.-based biopharmaceutical company, participated in the SOON Working Group and provided information about their intranasal naloxone delivery device. In December 2013, Lightlake announced the initial findings of its clinical trial with the U.S. National Institute on Drug Abuse, showing that its nasal spray may deliver circulating naloxone doses equivalent to parenteral formulations [26]. Lightlake has since filed an investigational new drug application in the U.S. (July 2014).

2. Kaléo Pharma is a U.S.-based pharmaceutical firm with experience in epinephrine autoinjector devices. In April 2014, Kaléo announced U.S. Food and Drug Administration approval for its naloxone autoinjector, called Evzio®, as well as financing plans for its commercialization.

3. Anti-OP, a U.S.-based pharmaceutical company with expertise in intranasal delivery systems, announced its plans to develop a naloxone nasal spray in partnership with Reckitt Benckiser pharmaceutical group in May 2014.

These and other new products have the potential to transform the future of naloxone distribution, delivery, research and practice by providing mainstream commercial alternatives to ad hoc naloxone kits. Uncertainty remains about how these new devices will alter educational practices, basic life support standards, and associated program and end-user costs. The introduction of these devices may also challenge the external validity of existing studies on the effectiveness of naloxone distribution programs using soon-to-be obsolete kits.

Basic Life Support and Bystander Resuscitation Guidelines

Limited evidence and inadequate collaboration with resuscitation experts has hampered the development of consistent and effective bystander overdose resuscitation techniques. In 2010, the American Heart Association (AHA) had insufficient data to support the use of specific antidotes in a cardiac arrest due to opioid overdose [26]. The AHA recommendations state that “Naloxone has no role in the management of cardiac arrest” [28]. Existing basic life (BLS) support guidelines provide little specific guidance regarding bystander or layperson best practices in the management of suspected opioid-related emergencies. In the absence of expert or evidence-based guidelines, individual programs have developed or adopted a variety of resuscitation protocols (Table 2).

Since our meeting, the World Health Organization released guidelines on community management of opioid overdose, with some instructions on resuscitation practices [29]. These are not aligned or coordinated with international resuscitation science and basic life support groups like the AHA and European Resuscitation Council, leaving room for further cooperation in this area. The current lack of coordination creates challenges for programs and groups that are

seeking to deliver recommendations or basic life support training to people at risk of opioid overdose. We aim to conduct a systematic

review of the literature on best basic life support practice for opioid-associated emergencies when naloxone is used in the community.

Program	Call EMS	Rescue Breathing	Chest Compressions	Naloxone dose & route
Preventing Overdose in Toronto (POINT) Program Toronto Public Health	✓	✗	✓	0.4mg IM prn x 2
Take Home Naloxone Program, Scottish Drug Forum, Scottish Government	✓	✓	✓	0.4mg IM prn x 2
Community Based Naloxone Overdose Prevention Program, Streetworks, Edmonton	✓	✓	✓ or ✗	0.4mg IM prn x 2
Towards the Heart, British Columbia Centre for Disease Control	✓	✓	✗	0.4mg IM prn x 2
Chicago Recovery Alliance, Chicago, Illinois	✓	✓	✗	0.4mg IM prn x 2
Overdose Education and Naloxone Distribution (OEND), State of Massachusetts Department of Public Health	✓	✓	✗	2mg IN prn x 2
New York State Overdose Prevention Program, NY State Department of Health, AIDS Institute	✓	✓	✗	0.4mg IM prn x 2

Table 2: Program Resuscitation Training Protocols (✓ = included; ✗ = not included); EMS: Emergency Medical Services; IM: Intramuscular; IN: Intranasal; prn: as needed

Participants in the BLS and bystander resuscitation stream clarified the role of bystander naloxone administration, rescue breathing, and chest compressions in the management of unresponsive opioid overdose patients, and developed a strategy for the incorporation of a protocol into future basic life support guidelines. We conducted an expert-facilitated discussion process to arrive at a consensus on appropriate bystander resuscitation practices for opioid-associated emergencies.

The group recommended a standard basic life support algorithm with the integration of naloxone prior to chest compressions. Lay rescuers should presume that cardiac arrest has occurred whenever an unresponsive person is not breathing normally or showing obvious signs of life, even if the etiology is presumed to be opioid toxicity. Bystanders should not perform pulse checks. In all cases of presumed cardiac arrest, bystanders should activate emergency medical services (EMS) promptly, perform chest compressions, and use an automated external defibrillator if available. The group was unable to agree on the role of rescue breathing in opioid-associated resuscitative emergencies. The group concluded that a rigorous guideline based on expert opinion from an internationally recognized organization, such as the AHA, is essential to standardize resuscitation in opioid-associated resuscitative emergencies.

Knowledge Translation

Naloxone distribution programs find their origins in harm reduction programs, but physicians in a variety of clinical settings, first responders, and other community services have contact with people at risk of opioid overdose and may be well situated to translate research on overdose prevention into practice. If, for example, evidence syntheses and ongoing inquiry suggest that naloxone distribution is helpful, it is important to identify and address a range of challenges and barriers to wider implementation of effective therapies. Participants engaged in a facilitated discussion on barriers and opportunities for the development of widely available and broadly applicable clinical and educational tools for a variety of settings beyond addictions services and harm reduction programs.

Participants in the knowledge translation stream referred to a summary of potential barriers to provider and patient participation in naloxone distribution and related research, in the categories of philosophical, logistical, liability and medicolegal, and educational barriers. Philosophical barriers include concerns that the public will “abuse” naloxone by treating it like a safety net to allow riskier use of opioids. Participants identified that these barriers were likely related to stigma about addiction and overdose, and suggested educational and de-stigmatizing approaches for both providers and patients. Logistical barriers relate to accessing training, appropriate naloxone kits, and addressing costs. Barriers related to public liability included fears of being arrested while intervening in an overdose event. Medicolegal concerns include considerations that naloxone may be prescribed to and administered by a third party. The group suggested advocacy for laws to protect bystanders and prescribers. Education with stakeholder groups, along with wider support from professional organizations and government, could also reduce this barrier.

Having considered these barriers and solutions, the group developed a strategy to engage providers and patients in further naloxone-related research and practice. Educational approaches should [1] be tailored to the needs of specific groups (health professional, public, etc.), [2] provide simple instructions for how to use the naloxone device and other basic life support interventions, [3] consider timing and delivery of educational tools (i.e., where and when they are available), and [4] involve educators or “champions” to be a resource within provider or patient subgroups. Participants also identified additional future partners, including government and professional regulatory bodies, correctional facilities, pain medicine practitioners, withdrawal management programs, and First Nations communities.

Conclusion

Advancing research and practice

While naloxone has a history of pharmacological safety and effectiveness for opioid overdose, uncertainties remain regarding its use in the context of bystander intervention in opioid-associated prehospital emergencies.

The findings from the SOON Working Group advance a research and evaluation agenda for naloxone distribution. Advancing naloxone distribution science and practice involves both high quality program evaluations in settings where naloxone distribution is underway, and prospective designs and trials in new settings. The findings of our International Working Group are summarized in Figure 1.

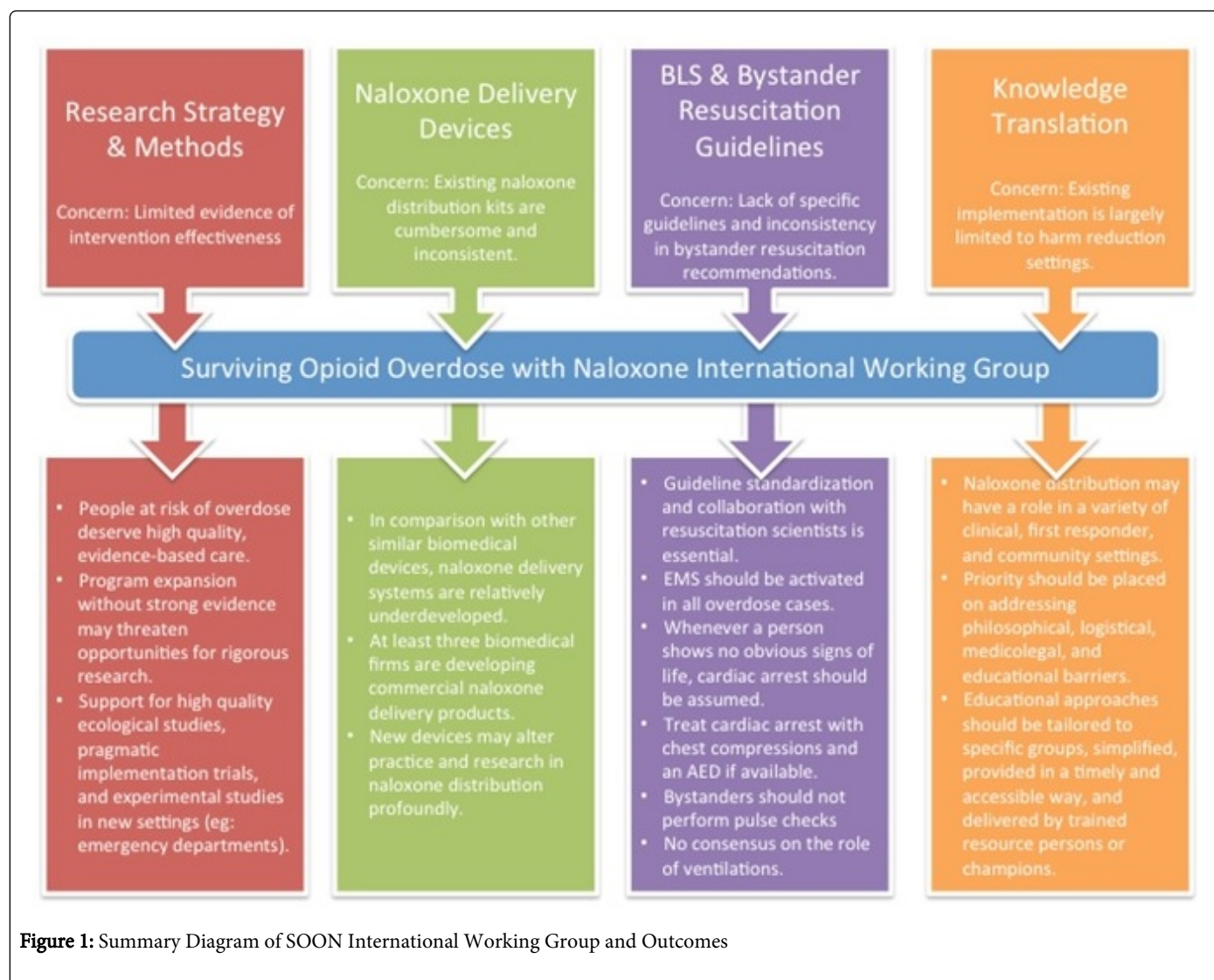


Figure 1: Summary Diagram of SOON International Working Group and Outcomes

The following essential elements should form the basis of efforts to continue building our knowledge:

1. High quality research and evaluation methods;
2. Ongoing appraisal of emerging technologies and their impacts on scientific knowledge, practice, and markets;
3. Appropriate resuscitation guidelines and related science; and
4. Knowledge translation approaches that consider barriers to implementation and educational needs.

Through diverse collaborations, we can address critical scientific uncertainties, synthesize and translate existing knowledge, and use

best science to improve practice in many settings that serve individuals at risk of opioid overdose.

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