AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 14: Substance Abuse

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. HHSA290201000006C

Prepared by:
ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

June 2014

Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Suggested citation: ECRI Institute. AHRQ Healthcare Horizon Scanning System Potential High-Impact Interventions: Priority Area 14: Substance Abuse. (Prepared by ECRI Institute under Contract No. HHSA290201000006C.) Rockville, MD: Agency for Healthcare Research and Quality. June 2014. http://effectivehealthcare.ahrq.gov/index.cfm/

Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

Richard Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Yen-pin Chiang, Ph.D.
Acting Director
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 150 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists three topics for which preliminary phase III or U.S. Food and Drug Administration (FDA) bioequivalence study data were available for a drug or a pilot was under way for a program; information was compiled and sent for expert comment by May 15, 2014, in this priority area; and for which we received five to eight sets of comments from experts between July 1, 2013, and May 23, 2014. Fourteen topics in this priority area were being tracked in the system as of May 15, 2014, three of which were eligible for high-impact consideration at this time. Two topics were designated as having high-impact potential (indicated below with an asterisk) based on experts' comments and their assessment of potential impact. Readers are encouraged to read the detailed information on these interventions that follows the Executive Summary.

Priority Area 14: Substance Abuse

Topic	High-Impact Potential
1. * Community-based opioid overdose prevention program (Project Lazarus)	Moderately high
2. * Evzio for emergency treatment of opioid overdose by nonclinicians	High
3. Off-label baclofen for treatment of alcohol use disorder	No high-impact potential at this time

Discussion

In this priority area, relatively few topics have met criteria for tracking in the horizon scanning system, relative to other, broader priority areas such as cancer or cardiovascular areas. We are tracking topics that span a variety of aspects of substance abuse, with an emphasis on alcohol, cocaine, and opioid abuse interventions, including novel technologies for detecting substance abuse. However, during the current reporting period, no topics targeting alcohol or cocaine dependency or abuse detection emerged as having high-impact potential.

The two topics that emerged as having high-impact potential address opioid overdose (both prescription and illicit opioids such as heroin), a growing public health concern at local, state, and national levels. Along with access to relatively inexpensive illicit opioid drugs, such as heroin, and increased use of prescription opioids to treat chronic pain, opioid dependence, abuse, and overdose has risen markedly. According to 2010 Centers for Disease Control and Prevention (CDC) reports,

prescription opioid overdose was a significant cause in about 17,000 deaths nationwide. Although opioid overdose is prevalent in metropolitan areas, including Baltimore, MD, and Staten Island, NY, higher overdose rates are often reported in more rural areas, such as Rio Arriba, NM, and Central Appalachia (a region that encompasses rural counties across Kentucky, North Carolina, Tennessee, Virginia, and West Virginia).

Eligible Topics Not Deemed High Impact

- One topic, an off-label use of baclofen, a gamma aminobutyric acid (GABA) B-receptor agonist, for treating alcohol use disorder, was considered, but deemed by experts to have no high-impact potential at this time. Experts commented that available clinical trial data thus far show little-to-no superiority over competing approved and off-label medications for treating alcohol use disorder. Experts wanted to see additional clinical trial data assessing baclofen's long-term safety and efficacy, optimal dosage, and evidence of treatment superiority in general or specific patient populations to consider upgrading this intervention's impact potential. Trials are ongoing, and we are continuing to track this topic until the results are reported.

Community-Based Opioid Overdose Prevention Program (Project Lazarus)

- **Key Facts:** Increased reliance on prescription opioids for treating chronic pain is a key contributor to rising rates of opioid overdose; additionally, epidemiologists have noted that opioid overdose rates have risen most rapidly in rural regions. Although prevention and treatment programs have been initiated throughout the country, these efforts have seen limited success, partially due to the isolated nature of individual efforts. Responding to above-average overdose fatalities rates in Wilkes County, NC, community leaders partnered with the Community Care of North Carolina (CCNC, the State's nonprofit Medicaid management entity) to design and implement a coordinated, community-based, integrative opioid-overdose prevention program and care model. This program, Project Lazarus, is a secular, nonprofit public health organization with the following central tenets: activating the community and building coalitions, monitoring and analyzing epidemiologic health data, preventing overdose through medical education and other means, providing community members with naloxone to reverse overdoses, and regularly evaluating and adjusting project components.

  Initiated in 2008, Project Lazarus works towards its goals through collaboration with CCNC, the North Carolina Hospital Association, local hospitals and health departments, primary care providers, law enforcement, and faith-based programs. Pilot program data demonstrated decreased opioid overdose mortality rates in Wilkes County between 2009 and 2011, as well as fewer prescription opioid overdose fatalities among patients who received their prescriptions from a Wilkes County prescriber. Through the CCNC-sponsored Chronic Pain Initiative, Project Lazarus is the basis for a statewide opioid overdose prevention program; statewide expansion has been supported by matching grants from the Kate B. Reynolds Charitable Trust and the North Carolina Office of Rural Health and Community Care. Program evaluation is ongoing at local and statewide levels; positive results from Project Lazarus have been cited favorably for modeling successful prevention programs nationwide.

The start-up and ongoing costs of the program are not totally clear. Funding was needed to coordinate services and recurring Project Lazarus expenditures, including naloxone purchase and distribution, data evaluation, educational initiatives, travel, administrative overhead, and employee salaries. A statewide program expansion was supported by a $2.6 million grant from the Kate B. Reynolds Charitable Trust and the North Carolina Office of Rural Health and Community Care. Other organizations and individuals also have contributed material resources, staff time, and in-kind donations on an ongoing basis, but the exact monetary value of these contributions is unknown.

- **Key Expert Comments:** Experts commenting on this intervention saw significant potential for the program to improve health outcomes for individuals at risk for opioid overdose. They anticipated widespread adoption and acceptance among both clinicians and patients, but noted the substantial collaboration and resource cost necessary to establish, and replicate, a fully integrated, community-based program. Overall, experts provided a positive assessment of this program, but they expressed a need for additional outcomes data to accurately determine its full potential impact on patient health.
- **Potential for High Impact**: Moderately high

Evzio for Emergency Treatment of Opioid Overdose by Nonclinicians

- **Key Facts:** Despite the availability of naloxone, a long-approved treatment for reversing opioid overdose, fatal opioid overdoses—especially heroin and illicit prescription opioids—have been a growing national public health concern. Naloxone is most commonly delivered as an injectable solution to treat opioid overdoses and can reverse opioid overdose events within 3 minutes of administration. However, nonclinicians, who are often first to identify and respond to an opioid overdose such as heroin, may find the injection delivery method difficult to use, limiting their ability provide life-saving emergency interventions.

    Evzio is a naloxone auto-injector intended for emergency treatment of known or suspected opioid overdose. It is designed for use by nonclinicians, with a built-in electronic voice instruction system and written instructions printed on the device. Each auto-injector delivers a single 0.4 mg dose of naloxone, an amount equivalent to that typically administered by medical professionals treating opioid overdoses.

    Evzio was reviewed under FDA's priority review program, based on evaluation of a series of bioequivalence studies conducted by Center for Drug Evaluation and Research (CDER) staff scientists. In their summary review, CDER scientists noted that in user-experience tests, adult and juvenile volunteers were able to successfully use the device to deliver naloxone. A pharmacology study demonstrated that the naloxone dose delivered by Evzio was equivalent to the standard dose recommended for reversing fatal opioid overdoses, with a peak plasma concentration 15% greater than a comparable reference product. Additionally, safety reporting from a bioavailability study in healthy volunteers noted similar adverse event profiles to previous clinical trials using intravenous naloxone.

    In April 2014, FDA granted marketing approval for Evzio for emergency treatment of known or suspected opioid overdose, characterized by respiratory system depression, central nervous system depression, or both. As of June 2014, the product was not yet available in retail pharmacies, so costs are not yet available. An April 2014 article in *The New York Times* reported that some industry experts anticipate that Evzio will retail for approximately $500 per kit. The manufacturer and retail pharmacies indicate the kit will contain two auto-injectors, each with 0.4 mg of naloxone, and one trainer device.

- **Key Expert Comments:** Experts commenting on this intervention saw significant potential for Evzio to reduce mortality among individuals experiencing an opioid overdose. They anticipated widespread adoption and acceptance among both clinicians and patients but noted potential concerns from clinicians regarding possible device misuse and abuse and from patients, who may feel stigmatized by the visible presence of emergency naloxone, which indirectly implies that the individual is susceptible to opioid overdose. Overall, the experts provided a positive assessment of this intervention and its high potential to address a critical public health issue.
- **Potential for High Impact**: High

Substance Abuse

Community-Based Opioid Overdose Prevention Program (Project Lazarus)

Unmet need: Increased prescribing of opioids for pain management and illegal use of prescription opioids have contributed to nationwide increases in opioid-associated overdoses and deaths.[1,2] Opioid overdose represents a significant national public health issue, with opioid overdose–related hospital admittances and overdose-attributable deaths steadily increasing year to year since 1991.[2] Existing opioid overdose prevention programs, including treatment facilities and law enforcement initiatives, often operate independently of one another; the lack of collaboration is one factor limiting these efforts' effectiveness. Project Lazarus attempts to address these shortcomings through a community-based opioid overdose prevention model, improving intervention efficacy by coordinating collaborative efforts among existing resources.

Intervention: Project Lazarus was established in 2008, in response to high drug overdose and overdose-related mortality in Wilkes County, NC; at the program's inception, the county's per-capita overdose rate was third highest in the nation.[3,4] Project Lazarus aims to address this issue by coordinating overdose-prevention efforts, building community partnerships, developing and implementing strategic action plans, training community organizers, and raising awareness of opioid overdose as a public health concern.[3]

Project Lazarus is a community-based program based on the idea that the collaborative efforts of multiple organizations (e.g., health departments, universities, government agencies, hospitals, primary care practices) are key to a successful public health intervention. The program aims to boost efficacy through coordinating and integrating existing community efforts, under the premises that overdose-related deaths are preventable, and that communities are responsible for the health of their members.[3,5] Project Lazarus encompasses the following five components:[6]

- Community activation and coalition building. Central community organizers are responsible for coordinating and streamlining prevention efforts and disseminating information to collaborating organizations. All major community-wide decisions are brought to advisory boards; these boards are continuously involved in reevaluating and adjusting program efforts, as needed.[3]
- Promoting rescue medication for overdose reduction. Project Lazarus makes kits containing naloxone—a medication approved by the U.S. Food and Drug Administration (FDA) for reversing opioid overdoses—available for free to patients;[7] the program also promotes naloxone awareness in the community.[3] The naloxone distribution process begins with Project Lazarus–trained physicians using provided risk-assessment tools to identify naloxone priority patients during routine medical care sessions. After patients consent to participating, they watch a 20-minute DVD in the physician's office, covering patient's pain management responsibilities, proper opioid medication storage and disposal, how to recognize and respond to opioid overdoses, and options for opioid abuse treatment. Participants can then receive a free naloxone kit from a predetermined Project Lazarus-affiliated pharmacy.[3]
- Overdose prevention. A primary program component, in conjunction with the Community Care of North Carolina (CCNC) Chronic Pain Initiative (CPI), is teaching primary care providers on outpatient chronic pain management and safe opioid prescribing. Physician education is achieved primarily through meetings and distributing physician chronic pain management toolkits. Toolkits are available in hard copy or online on the CPI Web site, and contain pain management guidelines, opioid risk-assessment tools, information on safe opioid prescribing and defensive prescription-writing, sample patient-prescriber agreements,

and patient education materials; they also contain educational modules on screening, brief intervention, and treatment referral.[3,8] Besides collaborating with primary care physicians, the program also effects changes in first-responder areas, including assigning case managers to hospital emergency departments to coordinate chronic pain care for patients with Medicaid or no health insurance, dedicating specially trained law enforcement officers to cases involving the criminal diversion of prescription drugs, and expanding use of patient-prescriber agreements, which lock the patient into using a single pharmacy and single prescriber for all opioid treatment.[3]

- Monitoring and conducting epidemiologic surveillance. The program primarily draws information from four statewide organizations: data on emergency department visits for substance abuse and accidental poisonings via the North Carolina Disease Event Tracking and Epidemiologic Collection Tool (NC DETECT); reports on outpatient-dispensed controlled substances via the Controlled-Substances Reporting System; fatal accidental poisoning data from the North Carolina Office of the Chief Medical Examiner; and vital statistics from the North Carolina State Center for Health Statistics (NCSCHS).[3,9]

- Program component evaluation. Project Lazarus attempts to evaluate all components of the program model, to optimize its efforts. Although the comprehensive approach of Project Lazarus confounds these analyses, the program continues to assess and measure various factors at local and statewide levels.[3,5]

The latter four components operate in a cyclical manner, building upon community advisory boards that serve in a central capacity to develop and guide aspects of the intervention as a whole.[6]

Clinical trials: Evaluation and refinement of Project Lazarus is an ongoing process that involves continuous data monitoring from statewide sources including NC DETECT, the North Carolina Controlled Substances Reporting System, NCSCHS, North Carolina's Office of the Chief Medical Examiner, and regular logs and surveys submitted by community coalition leaders, CPI regional directors, and health directors.[9] Statewide data is aggregated by CPI for analysis, with recommendations for program improvements and adjustments administered by the CCNC.

Project Lazarus reported preliminary efficacy data from 2009 and 2010 for Wilkes County, demonstrating a significant reduction in annual drug overdose mortality rates, from 46.6 per 100,000 in 2009, to 29.0 per 100,000 in 2010.[3] Based on unpublished Wilkes County Health Department data, the annual overdose mortality rates subsequently decreased to 14.4 deaths per 100,000 individuals in 2011.[5,10] Additionally, in 2011, no opioid overdose-related deaths were reported in Wilkes County.[9]

Wilkes County hospitals' emergency department visits related to substance abuse and overdose also decreased 15% between 2009 and 2011, despite the State average rising by almost 7%. Project Lazarus' efforts also contributed to these declines, despite opioid prescribing rates remaining steady countywide.[10]

Program developers and funding: Project Lazarus is a secular, nonprofit public health program founded in 2008 by community leaders in Wilkes County, in collaboration with the CPI. The program also collaborates with local and statewide organizations including the CCNC, the North Carolina Hospital Association, primary care doctors, local hospitals and emergency departments, local law enforcement, and regional faith-based programs. Fred Wells Brason II serves as the program's president and chief executive officer; Mr. Brason is also Project Director for the statewide CPI.[5]

Project Lazarus is funded and supported by the CCNC, Northwest Community Care Network, the Drug Policy Alliance, Qualla Boundary Eastern Band of the Cherokee Indians, Smoky Mountain LME (local management entity), Wilkes Healthy Carolinians Council, and The

Governor's Institute.[3] These programs and organizations may have also received material or in-kind support for overdose prevention efforts.[3] Statewide program expansion was supported by a $2.6 million grant from the Kate B. Reynolds Charitable Trust and the North Carolina Office of Rural Health and Community Care.[11] Various organizations and individuals also contribute material resources, staff time, and in-kind donations on an ongoing basis; the exact monetary value of these contributions is unknown.

Recurring Project Lazarus expenditures include naloxone purchase and distribution, data evaluation, educational initiatives, travel, administrative overhead, and employee salaries.[3]
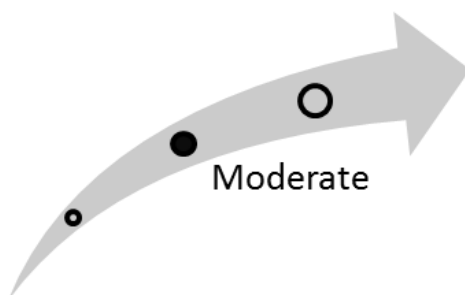
Diffusion: Project Lazarus was initiated in 2008 in Wilkes County, NC.[12] The program reported that by 2010, 70% of Wilkes County prescribers were registered with the State's prescription-drug monitoring program, compared with a 26% statewide average.[12] Project Lazarus has since expanded to all counties in North Carolina, with additional infrastructure and financial support from the North Carolina Medical Board, CCNC, the Kate B. Reynolds Charitable Trust, and the North Carolina Office of Rural Health and Community Care.[5,13] Statewide program resources now include 14 CCNC networks, each acting as a distribution center, with a designated local chronic pain coordinator; 600 statewide care coordinators; and 5,000 participating primary care physicians, who are provided with toolkits and other resources to improve assessment and management of patients who have chronic pain.[14] CCNC has also established a supporting Web site, with links to local and national overdose prevention materials, physician toolkit documents, statewide project event calendars, and other resources.[8]

The program's founders report diffusion is also occurring in New Mexico, Ohio, Virginia, and Maine.[5] Additionally, the Office of the National Drug Control Policy (ONDCP) has cited Project Lazarus as an innovative example of programs that ONDCP supports as part of a nationwide National Drug Control Strategy.[15]

Current Approach to Care

Many existing programs focus on preventing opioid abuse and overdose. The majority of these programs emphasize teaching preventive measures and providing educational materials to medical providers, outreach organizations, patients and community members; a few local organizations (such as the Chicago Recovery Alliance and Massachusetts' Overdose Education and Naloxone Distribution project) augment the approaches by supplying naloxone.[16,17] For patients requiring chronic opioids for pain management or help with treating opioid dependence, interventions include detoxification treatments, opioid replacement therapy (i.e., methadone or buprenorphine maintenance therapy), or other inpatient and outpatient substance-abuse treatment programs.

Figure 1. Overall high-impact potential: community-based opioid overdose prevention program (Project Lazarus)

Most experts commenting on this intervention agreed on the significant unmet need associated with the challenging public health issues of prescription opioid abuse and overdose. The majority of

experts indicated that this program has moderate to significant potential to improve patient health outcomes, but stated that replicating the model in other communities may be difficult, due to the need for coordination among multiple entities and support from external organizations. Although experts overall commented positively on this program, some noted that their enthusiasm for the model was limited because of the lack of long-term efficacy data. Based on this input, our assessment is that this intervention has moderate high-impact potential.

Results and Discussion of Comments

Six experts, with clinical, research, health devices, and health systems backgrounds, offered perspectives on this community-based opioid overdose prevention program.[18-23] We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Overall, opioid dependence, abuse, and overdose represents a moderate to significant unmet need, the experts agreed. Several experts with research or health systems background acknowledged the preliminary nature of the programs' overdose prevention efficacy data, but indicated that the program has a moderate to significant potential to improve patient outcomes. One expert indicated that although preliminary results suggest that the program is effectively addressing an unmet need in North Carolina, it may be difficult to replicate its success when implemented in other locales.[21]

Acceptance and adoption: Most experts anticipated widespread adoption of this program by clinicians and patients, with one expert specifically noting that with over 70% compliance among physicians in 30 counties across North Carolina, the program's preliminary data already demonstrated broad clinician acceptance.[21] One expert with a research perspective noted that additional clinician training could present an initial barrier to adoption and that patients' reluctance to acknowledge substance abuse could also hinder program acceptance.[19] Overall, experts remarked that the program's model and positive data supported strong acceptance and adoption potential.

Health care delivery infrastructure and patient management: Overall, experts indicated that because the program model uses existing health care resources, this intervention would have limited impact on delivery infrastructure and patient management. One clinical expert also noted that this program could decrease infrastructure and management demands by reducing burdens created by emergency department visits and overdose-related hospitalizations.[20]

Health disparities: The majority of experts believe that this intervention is likely to have moderate potential to lessen health disparities by delivering care and support to a typically underserved patient population. One expert with a research background, however, stated that certain underserved patient groups (i.e., poor or illiterate) may be unaware of the program or hesitant to participate, resulting in widening health disparities for these groups.[22]

Evzio for Emergency Treatment of Opioid Overdose by Nonclinicians

Unmet need: Opioid overdoses can be fatal when not treated within 3 hours; however, in a majority of cases, overdose events can be reversed by administering naloxone during this critical care window.[24-26] Unfortunately, most fatal overdose events occur outside of controlled health care environments, in the presence of lay persons who may not have access to or adequate training in using naloxone. Evzio is a naloxone delivery device specifically designed for nonclinician use; by providing a portable emergency source of naloxone, the device purports to contribute to reducing opioid overdose-related deaths.

Intervention: Evzio is a naloxone auto-injector intended for emergency treatment of known or suspected opioid overdose. Each pocket-sized device has a built-in electronic voice instruction system and written instructions, to aid nonclinician use. The device's overall design is modeled on one of its manufacturer's existing products, an epinephrine auto-injector that has been commercially available since 2012. Evzio delivers a single 0.4 mg dose of naloxone, formulated as naloxone hydrochloride solution, equivalent to the minimum recommended dose for treating opioid overdose.[27,28]

Three pieces comprise each device: a protective outer case, with a product indicator window; a removable needle safety guard; and the auto-injector, with a 5/8-inch retractable needle.[29,30] An electronic voice instruction system is activated when the outer case is removed and provides instructions on proper administration.[27,29] Evzio also incorporates red and green light-emitting diodes (LEDs), providing an alternate visual indication of device status; prior to use, the green LED is active, switching to a red blinking LED to indicate that the injector has been used.[29]

Evzio is intended to deliver an emergency dose of naloxone intramuscularly or subcutaneously via administration at a patient's outer thigh; for patients younger than 1 year, Evzio should be administered while pinching the middle of the outer thigh.[29] If required, additional doses may be administered at 2–3 minute intervals until professional responders can provide treatment.[27,29]

Evzio retails in kits containing two single-use auto-injectors and one "trainer" device, which has an identical size, shape, and safety guard as functional auto-injectors but lacks a needle and injectable solution. Auto-injectors and trainer devices are distinguishable by their differing color branding (auto-injectors are yellow and purple, trainer devices are black and white); each trainer device is rated for 1,000 simulated uses.[31]

Clinical trials: Evzio's FDA's priority review was based on evaluation of a series of bioequivalence studies conducted by FDA's Center for Drug Evaluation and Research (CDER).[30] CDER scientists reported results of three bioequivalence studies: a user experience study, with adult and juvenile volunteers; a clinical pharmacology study, comparing Evzio's naloxone hydrochloride solution to a reference product; and a safety study, evaluating Evzio administered to healthy volunteers.

In CDER's user experience study, adult (n=21) and adolescent (n=19) untrained volunteers tested Evzio in a simulated administration task. All adult volunteers, and 15 of 19 adolescent volunteers were able to successfully remove the safety guard to administer naloxone using Evzio; of the 36 successful attempts, 3 volunteers (2 adult and 1 adolescent) failed to adequately depress the device with adequate force to activate the auto-injector. Of the successful administrations, 4 adult and 2 adolescent volunteers administered Evzio to the inner thigh; although Evzio's ideal administration site is the outer thigh, the manufacturer reported, if the drug is administered to the inner thigh, a patient would still receive a sufficient dose of naloxone.[30]

Clinical pharmacology testing demonstrated that Evzio's pharmacologic profile was similar to a reference naloxone product:

- Median peak plasma concentration time: T_{max} 0.25 hours for Evzio versus 0.33 hours reference product
- Half-life was 1.28 hours versus 1.36 hours
- For area under the concentration curve (AUC), 90% confidence intervals (CIs) were within established CDER bioequivalence limits of 80% to 125%

Additionally, naloxone peak plasma concentration (C_{max}) was calculated to be 15% greater after Evzio administration than the reference product (geometric mean 1.15, 90% CI, 0.97 to 1.37).[30]

Dizziness, nausea, anosmia (loss of olfactory function), dysgeusia (altered taste perception), hyperhidrosis (increased perspiration), and hematoma were the only reported adverse events in healthy subjects administered Evzio in a relative bioavailability study. In the study's comparator arm, CDER noted that volunteers reported nausea, headache, injection site pain, and presyncope (i.e., lightheadedness).[30]

Manufacturer and regulatory status: Evzio is manufactured by kaléo, Inc. (Richmond, VA), formerly known as Intelliject, Inc.[32] In April 2014, FDA granted marketing approval for Evzio for emergency treatment of known or suspected opioid overdose, characterized by respiratory system depression, central nervous system depression, or both.[27,33]

Diffusion: In a press release, the manufacturer stated intentions to have Evzio available by summer 2014 through major retail pharmacies and via mail order, with valid prescriptions.[34] As of June 2014, the manufacturer had not announced a firm availability date; the product Web site notes that Evzio is "FDA approved and available soon."[35]
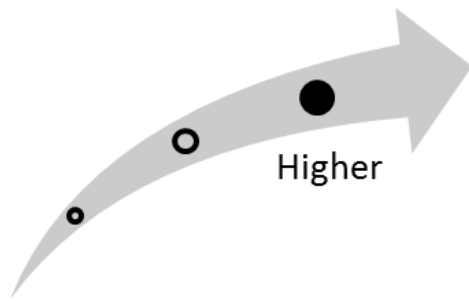
An April 2014 article reported that some industry experts anticipate that Evzio will retail for approximately $500 per kit, with each kit containing two auto-injectors and one trainer device.[36] The manufacturer has indicated plans for a discount program for Evzio prescriptions, but has not publicized detailed information; under one proposed program, insured patients would have no co-payment for Evzio.[36]

Similar but simpler products are used by police or fire departments in a handful of U.S. cities.[16,17,26,37,38] The devices are not intended for laypersons and do not appear to have the audible instructions, LED indicators, or auto-injectors of Evzio. For instance, in May 2014, the New York State Attorney General's office said it would provide funds for the New York City Police Department to purchase naloxone kits for use by police officers who, encountering residents experiencing opioid overdoses, will administer the naloxone intranasally.[39] The New York Times reported that, for the New York Police Department, "a single kit — two prefilled syringes of the drug, a pair of atomizers that allow it to be given through the nose, sterile gloves and instructions — costs roughly $60."[40]

Clinical Pathway at Point of This Intervention

Naloxone is accepted as the standard of care for treating opioid overdoses and is recommended by the Office of the U.S. Attorney General and the World Health Organization for this indication;[41,42] Naloxone can be delivered through intravenous or intramuscular injection, or intranasally;[27,43] when administered shortly after the onset of an opioid overdose, naloxone can reverse overdose symptoms in as little as 1–3 minutes.[28,44] Evzio is intended as an emergency first-line naloxone delivery option for nonclinicians treating opioid overdoses, providing emergency symptom relief prior to professional medical care.[27]

Figure 2. Overall high-impact potential: Evzio for emergency treatment of opioid overdose by nonclinicians

Higher

Most experts commenting on this intervention agreed that this intervention addresses a significant unmet need, potentially positively affecting opioid overdose-related mortality without dramatically altering health care infrastructure. Although the majority of experts noted that this intervention has significant potential to improve patient health outcomes, they expressed concern about a lack of data indicating the specific number of opioid overdose deaths that Evzio could prevent and that Evzio does not address the two primary causes of opioid overdoses: opioid misuse and dependence. Overall, experts were positive about the potential benefits of Evzio, anticipating broad adoption by patients and clinicians. Based on this input, our assessment is that this intervention is in the high end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health devices backgrounds, offered perspectives on this emergency opioid overdose treatment.[45-50] We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Most experts we consulted noted that opioid overdoses represent a moderate to significant unmet need, and interventions preventing overdose-related deaths favorably affect patient health outcomes. Five of six experts opined that Evzio has high potential to address this need. One expert with a clinical engineering/health devices background expressed a differing opinion, that Evzio has little potential to address an unmet need, due to the availability of other forms of naloxone.[46]

Acceptance and adoption: Although this intervention is intended primarily for use by a layperson, the majority of experts predicted that Evzio would be accepted and adopted by clinicians, patients, and their families. One expert expressed concern that patients may be slow to adopt this intervention because it would indirectly broadcast their use of opioids or increased risk of opioid overdose.[45] Overall, experts noted that because of Evzio's extensive safety and efficacy profile of naloxone, it has solid acceptance and adoption potential.

Health care delivery infrastructure and patient management: All experts agreed that, as a portable naloxone delivery device, this intervention would have a negligible impact on health care delivery infrastructure. Multiple experts commented that opioid overdose patient management is unlikely to be affected, because Evzio is an emergency intervention that may extend patient care windows, but does not replace professional medical treatment.

Health disparities: This interventions' potential to address health disparities was a matter of varying opinion. Two clinical experts favorably considered Evzio's potential to reduce health disparities, noting that the electronic voice instructions and proposed co-payment discount would expand access to patients with literacy or financial burdens.[49,50] The remaining experts were divided, predicting that Evzio could either increase or have no effect on health disparities, because of concerns about the product's cost, ease of use, access, or availability.

8

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