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

Priority Area 14: Substance Abuse

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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. HHSA290-2010-00006-C). 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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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.

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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 the three topics for which (1) preliminary phase III or bioequivalence study data for drugs were available; (2) information was compiled and sent for expert comment before November 4, 2014, in this priority area; and (3) we received five to seven sets of comments from experts between January 1, 2014, and November 13, 2014. (Twelve topics in this priority area were being tracked in the system as of November 4, 2014.) One topic was 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. * Evzio for emergency treatment of opioid overdose by nonclinicians	High
2. Off-label baclofen for treatment of alcohol use disorder	No high-impact potential at this time
3. Off-label topiramate for treatment of cocaine dependence	No high-impact potential at this time

Discussion

Relatively few topics in this priority area have met criteria for tracking in the horizon scanning system, compared with other priority areas such as cancer or cardiovascular medicine. Currently tracked topics span many aspects of substance abuse and pertain to alcohol, cocaine, and opioid abuse interventions, including technologies for detecting and preventing substance abuse.

One topic emerged as having high-impact potential in this report period; it addresses an opioid overdose treatment intended for use by lay persons. Inexpensive and readily available illicit opioid drugs, such as heroin, and increased use of prescription opioids to treat chronic pain have led to rising opioid dependence, abuse, and overdose rates resulting in death. Opioid misuse has been recognized as a significant public health issue. In 2014, the U.S. Centers for Disease Control and Prevention reported that of 22,114 deaths related to pharmaceutical overdose in 2012, 16,007 (72%) involved opioid pain relievers. Additionally, opioid overdose broadly affects American communities, with high prevalence rates reported in major metropolitan, suburban, and rural areas.

Prior High-Impact Topics Archived Since June 2014 Report

The following topic from the June 2014 Potential High-Impact Interventions report has been archived because the program has diffused, spreading to other geographic areas and being proposed as a national model:

- **Community-based opioid overdose prevention program (Project Lazarus):** Project Lazarus is a multifaceted opioid overdose prevention program, first initiated in Wilkes County, NC. The program focuses on harm reduction through community education; epidemiological surveillance; and distribution of naloxone, a U.S. Food and Drug Administration (FDA)-approved medication for reversing opioid overdose. Since we first identified this intervention, Project Lazarus was expanded statewide and is supported by multiple State-level organizations, including Community Care of North Carolina. The program's founders also report diffusion occurring in Maine, New Mexico, Ohio, and Virginia; the Office of the National Drug Control Policy has also cited Project Lazarus as an innovative example of programs supported as part of a nationwide National Drug Control Strategy.

Eligible Topics Not Deemed High Impact

- **Off-label baclofen for treatment of alcohol use disorder:** 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, pending further development of clinical data. 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 protocols, and evidence of treatment superiority in general or specific patient populations to consider upgrading this intervention's impact potential. Trials are ongoing, and we continue to track this topic, awaiting further data.
- **Off-label topiramate for treatment of cocaine dependence:** An off-label use of the anticonvulsant topiramate for treating cocaine dependence was also considered; however, experts deemed it to have no high-impact potential at this time. Experts commented that available clinical trial data thus far showed inconsistent efficacy, and little-to-no superiority over competing off-label medications for this indication. Experts wanted to see more convincing clinical trial data demonstrating topiramate's efficacy and optimal dosage regimens, either as a monotherapy or adjunct, to consider upgrading this intervention's impact potential. Two late-phase multicenter trials are ongoing, and we continue to track this topic.

Evzio for Emergency Treatment of Opioid Overdose by Nonclinicians

- **Key Facts:** Fatal opioid overdoses of both prescription and illicit opioids are a mounting public health concern nationwide. Although naloxone has been a proven treatment for reversing opioid overdose, used for more than 40 years, opioid overdose mortality rates continue to rise. Clinicians and emergency medical technicians use naloxone to reverse overdose, injecting it intravenously in patients who have overdosed. It can reverse opioid overdose events within 3 minutes of administration. However, nonclinicians, who are often first to identify and respond to an opioid overdose, do not have access to using intravenous naloxone injections, limiting their ability to provide life-saving interventions.

Evzio is a naloxone auto-injector intended for emergency treatment of individuals with a known or suspected opioid overdose. It is designed for use by lay persons, with an included electronic voice instruction system and written instructions printed on the device. Each auto-injector delivers a single 0.4 mg naloxone dose, equal to a typical dose administered by medical professionals to treat opioid overdoses.

Evzio was reviewed under FDA's priority review program, based on evaluation of a series of bioequivalence studies conducted by staff scientists at the FDA's Center for Drug Evaluation and Research (CDER). In the summary review, CDER scientists noted that in user-experience tests, adult and juvenile volunteers successfully used 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. Additionally, a bioavailability study in healthy volunteers noted similar adverse event profiles between Evzio and previous clinical trials using intravenous naloxone.

In April 2014, FDA approved Evzio for emergency treatment of known or suspected opioid overdose, characterized by respiratory system depression, central nervous system depression, or both. Evzio first went on sale in August 2014, with cartons initially priced between $588 and $636 per carton; each carton contains two single-use auto-injectors and one trainer device.

- **Key Expert Comments:** Experts commenting on this intervention thought that Evzio has significant potential to reduce fatal opioid overdose events. They also anticipated widespread adoption and acceptance among both clinicians and opioid users and their families. However, experts noted potential concerns among clinicians, who may be concerned about possible device misuse and abuse; and among patients, who may fear social stigma associated with naloxone use, which implies that the individual is at risk for opioid overdose. Overall, the experts delivered a positive assessment of this intervention's potential to make a high impact by saving lives, reducing costs of emergency care for overdose, and addressing a critical public health issue.
- **High-Impact Potential**: High

Substance Abuse

Evzio for Emergency Treatment of Opioid Overdose by Nonclinicians

Unmet need: Opioid overdoses can be fatal when not treated within 3 hours; however, in most cases, overdose events can be reversed by administering naloxone during this critical care window.[1-3] Unfortunately, most fatal overdoses 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 designed for use by people other than clinicians; by providing a portable emergency source of naloxone, the device purportedly contributes to reducing opioid overdose–related deaths.

Intervention: Evzio is a single-use, pocket-sized naloxone auto-injector, intended for emergency treatment of known or suspected opioid overdose. Each auto-injector has a built-in electronic voice instruction system and written instructions, to aid nonclinician use. Evzio delivers one 0.4 mg naloxone dose, the minimum recommended dose for treating opioid overdose.[4,5]

Each device has 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.[6,7] The electronic voice instruction system activates when the outer case is removed.[4,6] Evzio also incorporates red and green light-emitting diodes (LEDs), providing an alternate visual indication of device status; before use, the green LED is active, switching to a red blinking LED after use.[6]

Evzio is intended for intramuscular or subcutaneous administration at a patient's outer thigh; for infants, Evzio should be administered while pinching the middle of the outer thigh.[6] If required, additional Evzio doses may be administered at 2–3 minute intervals until professional responders intervene.[4,6]

Evzio retail cartons contain 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. Trainer devices are distinguishable by their color branding (auto-injectors are yellow and purple, trainer devices are black and white), and are rated for 1,000 simulated uses.[8]

Clinical trials: U.S. Food and Drug Administration (FDA) priority review for Evzio was based on evaluation of a series of bioequivalence studies conducted by FDA's Center for Drug Evaluation and Research (CDER).[7] CDER scientists reported results from three bioequivalence studies: a clinical pharmacology study, comparing Evzio's naloxone hydrochloride solution to a reference product; a user experience study with adult and juvenile volunteers; and a safety study, evaluating the effects of Evzio administered to healthy volunteers.

In clinical pharmacology testing, Evzio's pharmacological profile was comparable to a reference naloxone product. Measures were similar to an approved reference for median peak plasma concentration time (T_{max}; 0.25 hours vs. 0.33 hours), half-life (1.28 hours vs. 1.36 hours), and area under the concentration curve (AUC; 90% confidence intervals of AUC were within established CDER bioequivalence limits of 80% to 125%). Naloxone peak plasma concentration (C_{max}) was also reported as 15% greater after Evzio administration than after reference product administration.[7]

CDER's user experience study enrolled adult (n=21) and adolescent (n=19) untrained volunteers testing simulated Evzio administration. All adult volunteers, and 15 of 19 adolescent volunteers, successfully used Evzio, removing the safety guard and engaging the auto-injector. However, of these 36 successful attempts, 3 attempts (2 adult volunteers and 1 adolescent volunteer) failed to depress the device with adequate force to activate the auto-injector. Among the remaining 33 attempts, 4 adult and 2 adolescent volunteers administered Evzio to the inner thigh; noting this,

Evzio's manufacturer reported that inner thigh administrations still provide adequate naloxone to reverse an opioid overdose.[7]

In the relative bioavailability study with healthy subjects, the reported administration-related adverse events were dizziness, nausea, anosmia (loss of olfactory function), dysgeusia (altered taste perception), hyperhidrosis (increased perspiration), and hematoma. In the study's comparator arm, CDER noted that volunteers reported nausea, headache, injection site pain, and presyncope (lightheadedness).[7]

Manufacturer and regulatory status: Evzio is manufactured by kaléo, Inc. (Richmond, VA), formerly known as Intellijject, Inc.[9] FDA approved Evzio in April 2014 for emergency treatment of known or suspected opioid overdose, characterized by respiratory system depression, central nervous system depression, or both.[4,10] The treatment can be administered by a lay person.

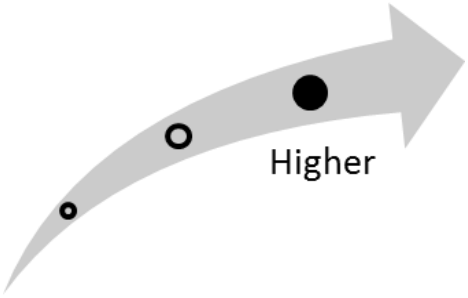
Diffusion: Evzio became available by prescription in August 2014. GoodRx, a U.S.-based online aggregator of prescription-drug prices, lists retail prices for Evzio ranging from $588 to $636 per carton; each carton includes two auto-injectors and one trainer device.[11] kaléo also sponsors a patient savings program, relieving patients of any prescription copayment amount for this product.[12]

National data on diffusion thus far are unavailable for Evzio; as a private company, kaléo has not released actual or projected sales figures for this product. In addition to retail sales, kaléo also sponsors a charitable donation program, providing local law enforcement and first responder applicants with 100 Evzio cartons.[13]

Clinical Pathway at Point of This Intervention

Naloxone is accepted as the standard of care for treating opioid overdoses and is recommended by the U.S. Office of the Attorney General and the World Health Organization for this indication.[14,15] Naloxone can be delivered through intravenous or intramuscular injection or intranasally;[4,16] when administered shortly after the onset of an opioid overdose, naloxone can reverse overdose symptoms in as little as 1–3 minutes.[5,17] Evzio is intended as an emergency first-line option for lay persons treating opioid overdoses in a family member or friend before professional medical care can be obtained.[4]

Figure 1. Overall high-impact potential: Evzio for emergency treatment of opioid overdose by nonclinicians



Most experts commenting on this intervention agreed that this intervention addresses a significant unmet need and might be able to reduce opioid overdose–related mortality without dramatically altering health care infrastructure. The majority of experts expressed concern about a lack of data indicating the specific number of opioid overdose deaths that Evzio could prevent. They also noted Evzio does not address the root causes of opioid overdoses: opioid misuse and dependence. Overall, experts anticipated broad adoption by patients, their families, and clinicians who would recommend to patients' families that it be available for emergency use at home. Based

on this input, our assessment is that this intervention is in the higher 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.[18-23] We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Five experts thought that opioid overdose is a significant public health issue and that Evzio has high potential to address an unmet need for opioid overdose interventions targeted for use by lay persons. The one dissenting expert, a clinical engineer with a background in health devices research, disagreed, noting that the availability of other forms of naloxone limit Evzio's potential to address an unmet need.[19]

Acceptance and adoption: Evzio is likely to be accepted and adopted by clinicians, patients, and patients' families, the experts concluded. One expert noted that patients may be slower to adopt this intervention than families or friends of patients taking opioids, as it could inadvertently expose an individual's use of opioids.[18] Overall, experts commented that Evzio has solid acceptance and adoption potential, based primarily on naloxone's extensive safety and efficacy profile.

Health care delivery infrastructure and patient management: The experts' consensus was that as a portable naloxone delivery device, Evzio is easy to store and use and 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. Medical treatment would be expected to be sought after administration of Evzio.

Health disparities: Experts offered varied opinions on this intervention's potential to address health disparities. Two clinical experts believe it has potential to reduce health disparities, noting that electronic voice instructions and the manufacturer's copayment discount could expand access to patients and families with literacy or financial burdens.[22,23] The remaining four experts were divided in their opinions; they predicted that either Evzio could increase disparities or have no effect, due to concerns regarding product access, cost, and ease of use.

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