AHRQ Healthcare Horizon Scanning System – Potential High Impact Interventions Report

Priority Area 14: Substance Abuse

Potential High Impact Interventions Report

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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. HHSA29020100006C). 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 closer to diffusion into practice in the United States. Drafts of 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 those interventions that experts deem, 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 six 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 the horizon scanning, assessing the leads for topics, or provide 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 target technologies and innovations in health care and to create an inventory of target technologies 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 the analysis of 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 utilization 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 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 e-mail to effectivehealthcare@ahrq.hhs.gov.

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Table of Contents

Figures

Executive Summary

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 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, more than 7,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas.

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 annually. Topics eligible for inclusion are those interventions expected to be within 0 to 4 years of potential diffusion (e.g., in phase III trials for pharmaceuticals or biotechnologies or in phase II or a trial with some preliminary efficacy data on the target population for devices and programs) 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 a profile on topics and issuing topic profile 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 350 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 (COI).

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 seven or 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 high impact potential designation. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the potential high impact 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 potential 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 material on interventions in this Executive Summary and report is organized alphabetically by disease state. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary. The table below lists the eight topics for which (1) preliminary phase III data were available for drugs, or preliminary data were available for off-label use, or a pilot was underway for a program; (2) information was compiled by November 2011 in this priority area; *and* (3) we received six to eight sets of comments from experts between February 2011 and November 1, 2011. (A total of 18 topics in this priority area were being tracked in the system as of November 2011.) For purposes of the Potential High Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present one summary on two topics (indicated below by an asterisk) that emerged as potential high impact on the basis of experts' comments and their assessment of potential impact.

Priority Area 14: Substance Abuse
1. *Buprenorphine implant for treatment of opioid dependence
2. Carvedilol for treatment of cocaine addiction
3. *Extended-release naltrexone (Vivitrol) for treatment of opioid dependence
4. Gabapentin for treatment of alcohol dependence
5. Interactive text message program (Text2Quit) for smoking cessation
6. Mecamylamine for treatment of depression and alcohol dependence
7. Off-label use of dronabinol for treatment of cannabis dependence
8. Pentoxifylline for treatment of alcohol-related hepatitis

Discussion

In this priority area, relatively few topics have met criteria for tracking in the horizon scanning system, relative to other broader priority areas. For this report, topics that emerged as higher impact focused on extended-release treatment for opioid dependence. No topics on cocaine, nicotine, cannabis, or alcohol dependence emerged as having potential for high impact for this report.

Opioid Addiction

Opioid abuse is one of the most common forms of prescription drug abuse. Opioid dependency management includes medically supervised detoxification and opiate replacement therapy. For this condition, pharmacotherapy (buprenorphine or naltrexone) is already available in oral, injectable, and skin-patch forms. Currently available, short-acting treatments for opioid dependence (e.g., naltrexone, methadone, buprenorphine) are associated with limitations, including low patient adherence and medication diversion, each of which can lead to cravings, withdrawal symptoms, and drug-use relapse. Therefore, an unmet need exists for therapies to address these limitations. Long-acting formulations of these pharmacotherapies might address the problems of low adherence and medication diversion, because the drugs' effects may last for several weeks.

Long-Acting Pharmacotherapy for Opioid Dependency

- **Key Facts**: Two long-acting versions of currently used pharmacotherapies (buprenorphine and naltrexone) have been developed for treatment of opioid dependence.

  Implanted buprenorphine (Probuphine™, Titan Pharmaceuticals, Inc. , South San Francisco, CA) is under study to address the unmet need of low adherence to therapy to treat opioid addiction., has developed a new delivery system for the drug composed of a sublingual buprenorphine-naloxone tablet induction followed by a buprenorphine implant placed under the skin in a physician's office and removed after 6 months. The buprenorphine implant is currently in two phase III trials, one of which is funded by the National Institute on Drug Abuse. The company completed a meeting with U.S. Food and Drug Administration (FDA) in October 2011 about preparing its new drug application and the company announced that FDA supported submission of a New Drug Application (NDA) via the 505(b)(2) pathway. The company plans to complete its submission by mid-2012.

  Alkermes, plc (Dublin, Ireland), has developed an injectable, extended-release formulation of naltrexone (Vivitrol®), an opioid antagonist that was recently approved by FDA for treatment of opioid dependence. Oral (tablet) once-daily naltrexone was approved in 1984 for the treatment of opioid dependence, but this new injectable, long-acting formulation, intended for once-monthly dosing, is the first of its kind to reach market. This drug was approved for opioid dependence in September 2010, and had been approved for treatment of alcohol dependence in 2006. The cost of Vivitrol was reported to be about $1,000 per injection (per month) when first approved for opioid addiction treatment, but reports of slow adoption for this indication have purportedly increased the cost to about $1,300 per month, or more than $15,000 for a year of treatment. The optimal duration of treatment varies, but is typically in the range of 6 months to a year.

- **Key Expert Comments**: Overall, experts commenting on these topics viewed the unmet need for opioid addiction treatment as moderately important citing that some medications are available for this purpose, although adherence is an important issue. They viewed these interventions as having some ability to meet the need for improved patient compliance. However, they believe that questions remain about how much additional benefit this intervention would offer over currently approved therapies, especially because the newer interventions require a shift from at-home oral medication to the clinical treatment setting, and might have higher upfront costs.

- **Potential for High Impact**: Moderately high

Opioid Dependence Interventions

Intervention

Long-acting pharmacotherapy for opioid dependence

Currently available, short-acting treatments for opioid dependence (e.g., naltrexone, methadone, buprenorphine) are associated with limitations, including low patient adherence and medication diversion, each of which can lead to cravings, withdrawal symptoms, and drug-use relapse.[4] Therefore, an unmet need exists for therapies to address these limitations. Long-acting formulations of these pharmacotherapies might address the problems of low adherence and medication diversion, because the drugs' effects may last for several weeks. Two novel, long-acting versions of currently used pharmacotherapies (buprenorphine and naltrexone) have been developed for treatment of opioid dependence

Buprenorphine is a partial opioid agonist that is known to reduce opioid cravings and is approved for the treatment of opioid dependence.[4,5] Buprenorphine falls into the Schedule III class of drugs under the Controlled Substances Act of 1970.[6] For years, buprenorphine has been available primarily in the form of sublingual tablet and film formulations.[5] Titan Pharmaceuticals, Inc., (South San Francisco, CA) has recently developed a new implanted delivery system (Probuphine™) for buprenorphine.[5] According to the manufacturer, the subcutaneous implant system consists a polymer rod that releases a sustained level of buprenorphine for up to 6 months.[7] The rod is placed under the patient's skin, normally in the upper arm, in a procedure performed at a physician's office and is removed at the end of the 6-month period.[5,8]

The buprenorphine implant recently completed a phase III trial program, one of which the National Institute on Drug Abuse is funding. In a July 2011 press release, the manufacturer stated that data from a phase III placebo- and active-drug-controlled confirmatory trial of 287 patients with opioid addiction demonstrated superiority of the implant over placebo in opioid-negative urine screens over the 24-week treatment period.[9] In an August 2011 press release, the company stated that additional results from the phase III confirmatory study suggested that treatment with the implant significantly improved the global severity of opioid dependence ($p = 0.0003$) and overall patient improvement ($p = 0.0002$) versus placebo, as assessed by clinicians. The company further asserted that additional data analyses confirmed the implant's noninferiority to the approved drug Suboxone® (buprenorphine and naloxone).[10] In an October 2011 press release, the company stated that it had completed its pre-NDA (new drug application) meeting with FDA for the implant, and that FDA will not require additional clinical efficacy or safety studies to support the company's NDA submission package.[11] The company announced December 1, 2011, that FDA supported a submission of a New Drug Application (NDA) via the 505(b)(2) pathway. The company stated plans to complete its submission by mid-2012.

Naltrexone exerts its effects on mu, delta, and kappa opioid receptors, each of which is thought to play a role in opioid dependence.[2] Blockade of the mu-opioid receptor in particular appears to be linked with diminished opioid dependence.[2] Vivitrol® (Alkermes, plc, Dublin, Ireland) is a novel, injectable extended-release formulation of naltrexone, an opioid antagonist, that was recently (October 2010) approved by FDA for the treatment of opioid dependence.[1] Oral (tablet) once-daily naltrexone was approved in 1984 for the treatment of opioid dependence. The new injectable, long-acting formulation, intended for once-monthly dosing, is the first of its kind to reach market.[2] Because patient adherence to daily naltrexone dosing is a major limitation in the treatment of opioid dependence, the once-monthly injectable formulation has the potential to meet an unmet need.[2] According to the drug's prescribing information, extended-release naltrexone for opioid dependence is intended to be dosed at 380 mg intramuscularly every 4 weeks, or once per month. It is intended that a health care professional gives the injection as an intramuscular gluteal injection, alternating buttocks for each injection.[12] This

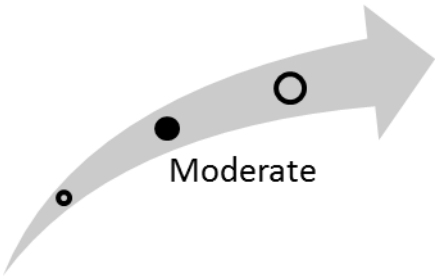
drug was approved for opioid dependence in October 2010, and had been approved for treatment of alcohol dependence in 2006.[3]

Clinical Pathway at Point of This Intervention

Treatment for opioid dependence typically begins with medically supervised detoxification and includes a combination of medical and behavior therapy and/or counseling.[13] Opiate substitution therapy is intended to transition the patient to treatment with methadone or buprenorphine. Of these, buprenorphine is becoming the preferred target because it is less active than methadone. However, buprenorphine may not be sufficient for patients who were taking very high quantities of opiates. Naltrexone therapy is also available, although used less often than either methadone or buprenorphine.

These long-acting pharmacotherapy formulations would compete with shorter-acting oral, sublingual, injectable, or patch-delivered therapies. Nonpharmacologic interventions, such as behavior therapy and counseling, are expected to remain as complementary interventions.

Figure 1. Overall High Impact Potential: Long-acting pharmacotherapy for opioid dependence



Overall, experts commenting on these topics viewed the unmet need for opioid addiction treatment as moderate because some medications are available, although adherence is an important issue. They viewed these interventions as having a moderate ability to meet the need for improved patient compliance. However, they believe that questions remain about how much additional benefit this intervention would offer over currently approved therapies, especially because the newer interventions require a shift from at-home oral medication to the clinical treatment setting, and might have higher upfront costs. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Six experts, with clinical, research, or health systems backgrounds, offered their perspectives on the buprenorphine implant. Seven experts with similar backgrounds offered perspectives on the extended-release naltrexone injection.[14-26] One expert who offered perspectives on the naltrexone injection disclosed a potential conflict of interest because he is principal investigator on a project with the manufacturer of the injection.[25] This perspective is balanced by the perspectives of other experts who did not report a potential conflict of interest.

Experts generally agreed that opioid dependence therapies that offer improved patient adherence represent a moderately important unmet need, especially in light of low treatment adherence in this population, and the devastating effects that opioid dependence has on the patient, his or her family, and employers. However, this view was tempered by the understanding that other treatments for opioid addiction are already available.

Most of these experts agreed that the theories underlying the proposed interventions are sound, based on the historical success of other buprenorphine and naltrexone formulations in treating opioid addiction. Most also expressed confidence in this intervention's potential to improve health outcomes, in terms of opioid and methadone addiction, medication diversion, and adherence. However, experts shared the belief that these drugs' benefits would prove to be only incremental over available treatments, especially considering that newer interventions are likely to be more expensive than current treatments.

Experts were divided about how this intervention would affect patient management and treatment models. For those experts who compared the buprenorphine implant delivery system to other buprenorphine formulations, consensus was that this would not dramatically change current treatment models. For those who compared this formulation to inpatient methadone treatment, a large shift in care was predicted from rehabilitation clinics to physicians' offices, a reduction in the number of followup visits, and reduced use of complementary behavioral interventions. For the naltrexone injection, experts noted that the intervention still requires an inpatient detoxification period, with ongoing cognitive therapy, as current therapies do, but that the monthly visit to a provider for the injection represents a small shift in the way patients would be managed.

Experts offered different perspectives about potential patient and clinical acceptance. Regarding the buprenorphine implant, experts thought that clinicians would be more accepting than patients, predicting only a small amount of provider reluctance because of the intervention's "invasive" nature and the possible side effects of an implant. In terms of patient acceptance, some experts predicted that patients would appreciate the convenience of an implant, but most experts expected that patients would resist an implant because it is technically a "surgical" intervention. One expert noted that this intervention might be more readily accepted by rural patients because of access barriers to health care. Experts predicted that this intervention would have higher upfront costs compared with currently available therapies, but some experts stated that if adherence is improved and the need for daily medication is obviated, that some of these costs might be offset over the long term.

Experts were similarly divided regarding potential acceptance of the naltrexone injection. Some experts suggested that the cost of the injection might be prohibitively high for many members of this population, especially considering that less expensive products are available for this condition. One expert, speaking from a health systems perspective, noted that the injection, which has been on the market for several years for the treatment of alcohol dependence, was associated with serious injection site reactions, prompting FDA to issue a warning letter in 2008 regarding the improper administration of the product. According to this expert, "Since then, there has been improved administration techniques; however, the medical community is very apprehensive of using this product."[21] On the other hand, several experts predicted that patients and clinicians might be willing to adopt this intervention if it is proven to be more convenient for patients and reduces the need for daily medication use.

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