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

Priority Area 04: Dementia (Including Alzheimer's Disease)

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

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

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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. 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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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 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

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

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

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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 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 16,200 leads about potential topics has resulted in identification and tracking of about 1,900 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 500 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 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

(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 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 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 data for drugs were available; (2) information was compiled and sent for expert comment before October 27, 2013, in this priority area; and (3) we received six to eight sets of comments from experts between April 9, 2012, and October 29, 2013. (Thirteen topics in this priority area were being tracked in the system as of October 29, 2013.) We present a summary on one topic (noted below with an asterisk) that emerged as having higher-impact potential on the basis of expert comments and assessment of potential impact.

Priority Area 04: Dementia (Including Alzheimer's Disease)

Topic	High-Impact Potential
1. Florbetapir F18 (Amyvid)-enhanced positron emission tomography (PET) for detection of beta-amyloid plaques	No high-impact potential at this time
2. Flutemetamol-enhanced PET for detection of beta-amyloid plaques	No high-impact potential at this time
3. * Off-label intranasal insulin for treatment of Alzheimer's disease	Moderately high

Discussion

Most of the research activity in the dementia priority area focuses on Alzheimer's disease (AD)—its diagnosis and new disease-modifying (rather than symptom management) treatments in development.

The National Institute on Aging (NIA) describes AD as progressive and irreversible, gradually destroying memory and cognitive ability. AD is the most common cause of dementia, a group of brain disorders that cause progressive loss of intellectual and social skills to the point of interfering with daily life, according to the Mayo Clinic. The primary features of AD are the presence of amyloid plaques and neurofibrillary tangles in the brain and disconnection among neurons in the brain, according to NIA. Symptoms are typically not evident in early, preclinical AD; however, toxic changes begin to occur, such as proteins that are deposited abnormally and neurons that function less efficiently. Eventually, damage spreads to the hippocampus, the region of the brain

responsible for forming memories. In the final stages of AD, brain damage is widespread and brain tissue has shrunk significantly, according to NIA. The Alzheimer's Association indicates that the cause of AD is unknown and that researchers think it results from some combination of genetic, lifestyle, and environmental factors that affect the brain over time.

According to the Alzheimer's Association, 5.2 million people in the United States had AD in 2013. An estimated 11% of people aged 65 years or older and 32% of people aged 85 years or older have AD, although a definitive diagnosis can be made only postmortem upon examination of the brain. AD is the sixth leading cause of death in the United States, according to the Alzheimer's Association.

Much research into AD's causes has focused on two hallmark structures found in the brains of patients with AD: amyloid plaques and neurofibrillary tangles. Amyloid plaques are thought to disrupt and/or damage neurons in the brain. Neurofibrillary tangles may cause cell dysfunction and eventually cell death. Other researchers point to inflammation as a possible cause of the progressive cell death seen in the brains of patients with AD.

In the previous iteration of this report (June 2013), we discussed two new imaging agents closest to diffusion out of a class of six or seven similar positron emission tomography (PET) radiopharmaceuticals in development that are intended to aid in detecting beta-amyloid plaques. Proponents of these imaging agents purport that earlier diagnosis could enable earlier intervention for care planning by families and elder caregivers, even in the absence of effective treatment to slow or halt disease progression. The U.S. Food and Drug Administration (FDA) recently approved two PET-imaging drugs for detecting beta-amyloid plaques: florbetapir F 18 injection (Amyvid) in April 2012 and flutemetamol F 18 injection (Vizamyl) in October 2013. However, in September 2013, the Centers for Medicare and Medicaid Services (CMS) released a final decision memo limiting coverage for PET beta-amyloid imaging to the following two scenarios: "(1) to exclude Alzheimer's disease (AD) in narrowly defined and clinically difficult differential diagnoses, such as AD versus frontotemporal dementia (FTD); and (2) to enrich clinical trials seeking better treatments or prevention strategies for AD, by allowing for selection of patients on the basis of biological as well as clinical and epidemiological factors." Based on the available evidence, CMS determined that insufficient evidence existed to consider PET beta amyloid imaging as "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member for Medicare beneficiaries with dementia or neurodegenerative disease." Because of this decision to significantly restrict coverage for PET beta-amyloid imaging for diagnosing AD, these imaging agents were determined to have no high-impact potential at this time.

The search is on for ways to definitively diagnose AD and for drugs, biologics, and alternative or complementary interventions that modify the disease or better manage symptoms to keep patients as independent as possible for as long as possible. The Horizon Scanning System is tracking several drugs in late-phase development. In this report, we discuss the off-label use of insulin for treating AD. Researchers have uncovered a potential role for brain insulin signaling in the pathogenesis of AD and have begun to investigate intranasal insulin as a potential therapeutic intervention for patients with mild cognitive impairment or AD.

Off-Label Intranasal Insulin for Treatment of Alzheimer's Disease

- **Key Facts**: Insulin delivered intranasally is being investigated for treating AD, and some researchers think it might have potential to modify the disease's rate of progression. This approach is based on research findings that suggest that dysfunctional cerebral insulin signaling may contribute to AD pathogenesis and subsequent cognitive deficits. Insulin

receptors and insulin-sensitive glucose transporters, which regulate energy metabolism in the central nervous system by mediating glucose uptake in cells, are co-located in brain structures that are involved in memory and have been shown to be compromised in patients with AD. The rationale for using intranasal delivery is based on concerns that delivering insulin via other routes (e.g., intravenously) could adversely alter patients' blood glucose levels. Moreover, in some cases, insulin effects appear to be mediated by the presence of the ApoE4 allele, a genetic risk factor for developing AD. Intranasal insulin therapy is being explored by several research institutions, rather than by insulin manufacturers. In completed and ongoing clinical trials, intranasal delivery methods include needleless nostril syringes, a nasal drug electronic atomizer device, and nasal spray bottles. Initial clinical trial results suggest that insulin may improve certain cognitive measures in patients with AD or amnestic mild cognitive impairment. Because insulin is not approved for treating AD and no particular company appears to be pursuing trials to secure FDA approval for a labeled indication for AD, its use for treating AD is considered to be off label at this time.

- **Key Expert Comments**: Experts agreed that, in theory, an affordable, widely accessible, noninvasive, and easily administered therapy, such as intranasal insulin might improve patient health and also realize dramatic long-term health care cost savings in AD care. Experts stated that their enthusiasm is predicated on an assumption of efficacy in insulin's potential to modify the AD progression rate and that the preliminary data must be confirmed by larger trials.

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

Dementia (Including Alzheimer's Disease) Interventions

Off-Label Intranasal Insulin for Treatment of Alzheimer's Disease

Unmet need: According to the National Institute on Aging, available pharmacotherapies indicated for use in treating Alzheimer's disease (AD) address disease symptoms but not the underlying disease process. Moreover, these interventions are effective for some but not all patients and also may have a limited duration of therapeutic efficacy.[1] Therefore, an unmet need exists for novel, effective, disease-modifying agents for AD. Intranasal insulin, if proven effective, might be positioned as the first disease-modifying agent for AD.

Intervention: Preclinical and clinical research suggests that aberrant insulin signaling may contribute to the metabolic dysfunction underlying AD pathology. Insulin receptors and insulin-sensitive glucose transporters, which regulate energy metabolism in the central nervous system by mediating glucose uptake in cells, are colocated in brain structures that are involved in learning and memory and have been shown to be compromised in patients with AD.[2-4] Additionally, "peripheral insulin abnormalities" (e.g., insulin resistance) have been associated with increased risk of developing AD, and patients with AD have shown reduced insulin levels in their cerebrospinal fluid.[5]

In light of these findings, several research organizations have been begun investigating intranasal insulin as a potential therapy for AD and its prodromal condition, mild cognitive impairment (MCI).[5-7] Intranasal administration allows for direct delivery of therapeutic agents to the central nervous system via the olfactory and trigeminal neural pathways at doses low enough to avoid significant systemic effects.[6] In the case of intranasal insulin, this delivery mode bypasses the blood-brain barrier and also reduces the systemic risk of hypoglycemia.

Preliminary data suggest that the response to intranasal insulin in patients with AD or MCI may differ based on sex and/or the presence of the apolipoprotein e4 (*ApoE4*) allele, which is known to be a genetic risk factor for AD.[5,8,9] Additionally, studies have revealed dose-dependent effects on insulin on various cognitive measures.[5,8,9] Trials of intranasal insulin for treating AD or MCI have tested dosages ranging from 10 IU to 20 IU, intranasally, twice daily. In the largest clinical trial to date, insulin is administered at a dose of 20 IU, intranasally, twice daily, approximately 30 minutes after a meal.[10]

Clinical trials: In completed and ongoing clinical trials on intranasal insulin for AD, several intranasal delivery methods have been used: needleless syringes inserted into alternating nostrils, a nasal drug electronic atomizer device (ViaNase™), and nasal spray bottles.[5,7,11] In 2013, the Alzheimer's Disease Cooperative Study registered the largest randomized, controlled trial to date (n=240) for this intervention for treating AD and amnestic MCI.[10] Various insulin products already approved for diabetes treatment have been administered using a variety of intranasal administration devices; insulin products tested for treating cognitive dysfunction associated with AD and MCI include short-acting insulin (Novolin® R), rapid-acting insulin aspartate (NovoLog®), and long-acting insulin detemir (Levemir®).[5,7,9,11,12] In results reported in 2011, 104 adults with amnestic MCI or mild to moderate AD were given placebo or intranasal insulin for 4 months. Investigators reported that the insulin treatment "improved delayed memory (p <0.05)," "preserved caregiver-rated functional ability (p <0.01)," and "preserved general cognition as assessed by the [Alzheimer's Disease Assessment Scale - cognitive subscale] score for younger participants and functional abilities as assessed by the [Alzheimer's Disease Cooperative Study – activities of daily living] scale for adults with AD (p <0.05)."[7] Results reported in 2013 from a study using long-acting intranasal insulin detemir in patients with MCI or AD showed a significant impact of a daily 40 IU dose on various cognitive measures. Interestingly, immediate and delayed list and story recall

improved for patients carrying the *ApoE4* allele, but worsened for non-carriers. However, working memory improved with 40 IU daily insulin treatment regardless of *ApoE* status.[9] The data suggest a potential role for ApoE status in responsiveness to insulin therapy for treating MCI and AD, which will need to be further elucidated in ongoing trials.

Manufacturer and regulatory status: Novo Nordisk a/s, of Bagsvaerd, Denmark, makes Novolin R, NovoLog, and Levemir; Kurve Technology, Inc., of Lynnwood, WA, makes ViaNase. Currently, insulin manufacturers do not appear to be pursuing development of their products for this indication. Instead, ongoing trials are sponsored by various research groups, including the University of Kansas (Lawrence), the HealthPartners Research Foundation (Minneapolis, MN), the University of Washington (Seattle), and Wake Forest University (Winston-Salem, NC) in collaboration with the Alzheimer's Disease Cooperative Study, a service of the National Institute on Aging and University of California, San Diego.[10,13-15] Because insulin is not approved for treating AD, use of the drug for AD or MCI is considered off label.

Clinical Pathway at Point of This Intervention

Donepezil (Aricept®), galantamine (Razadyne®), rivastigmine (Exelon®), and tacrine (Cognex®) are FDA-approved cholinesterase inhibitors, and, depending on the drug, are used to treat AD symptoms for mild to severe disease stages. Memantine, an N-methyl-D-aspartate receptor antagonist, is approved to treat the symptoms of moderate to severe AD.[1] None of these drugs has been shown to be disease-modifying.[1] Intranasal insulin would likely be used in conjunction with other AD pharmacotherapy and supportive care measures.

Figure 1. Overall high-impact potential: off-label intranasal insulin for treatment of Alzheimer's disease
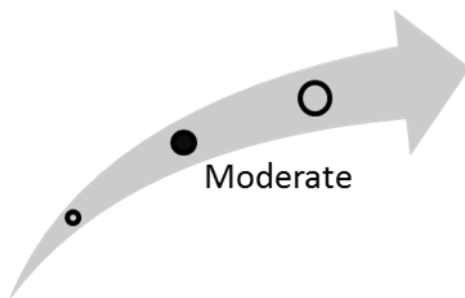
Experts commenting on this intervention agreed that the need for disease-modifying treatments for AD is extremely important and that intranasal insulin is, in theory, an affordable, widely accessible, and easily administered therapy that might realize health improvements and cost savings. This enthusiasm, however, is predicated on the assumption that the agent is efficacious in modifying AD's rate of progression. Experts stated that the available clinical trial data are not yet robust enough to assume efficacy and some were skeptical about the agent's potential to improve health outcomes. 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, and health systems backgrounds, offered perspectives on this intervention.[16-21] We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: The need for disease-modifying treatments for AD is extremely important, the experts unanimously agreed, citing both the debilitating nature of the disease and the expected increase in its prevalence as the number of aging persons in the United States grows over the next 30 years.

However, several experts expressed some uncertainty about intranasal insulin's ability to meet this need. Although most agreed that preliminary trial data appear somewhat promising, several experts noted that these results do not yet demonstrate the slowing or halting of disease or regression of AD. Further, only one of two insulin doses used in the trial appeared to be effective, one expert with a research background noted. Another research-based expert commented that whether the therapy can provide ongoing benefit or whether patients develop insulin resistance is unclear thus far. Another expert with research experience stated that although many researchers are investigating the use of intranasal proteins for brain-related conditions, these attempts have been generally ineffective because of variability in the percentage of the drug that actually reaches the brain or because they do not provide benefit to patients.

Acceptance and adoption: Experts anticipated that the drug's well-known safety profile and long history of use (in diabetes) would increase physician acceptance and adoption of the intervention. Patient and caregiver acceptance of the therapy would likely be widespread because of its ease of use and lack of invasiveness, the experts generally thought.

Health care delivery infrastructure and patient management: Despite skepticism about efficacy, most experts agreed that using intranasal insulin would dramatically affect the health care system if it were proved to be effective in modifying AD's course. The main reason experts gave is that it would be the first agent to treat the underlying cause of AD, rather than only addressing AD symptoms for some period.

Health disparities: Because insulin is widely available and relatively inexpensive, it would likely be accessible to patients, experts noted. In terms of cost, most experts agreed that the minimal cost of adding insulin to a patient's treatment regimen in the short term would be outweighed by the potentially significant long-term cost savings that might be realized if this agent is proved to modify AD progression. If insulin can improve the functional capabilities of patients with AD, experts noted, the costs of patient care would decrease or at least be postponed. As such, experts noted that intranasal insulin could potentially alleviate health disparities among patients with AD.

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