

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

Priority Area 06: Developmental Delays, ADHD, and Autism

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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. HHS290201000006C). 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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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 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 two topics for which preliminary phase II (for off-label uses of approved interventions) or phase III data were available for an intervention. Information was compiled and sent for expert comment by May 15, 2014, in this priority area; and we received five to eight sets of comments from experts between July 1, 2013, and May 23, 2014. Eight topics in this priority area were being tracked in the system as of May 15, 2014, and two of them were eligible for high-impact consideration at this time. 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 this intervention following the Executive Summary.

Priority Area 06: Developmental Delays, ADHD, and Autism

Topic	High-Impact Potential
1. *Off-label intranasal oxytocin for treatment of autism spectrum disorders	Moderately high
2. Neuropsychiatric Interpretive Electroencephalograph Assessment Aid (NEBA) for assessment of attention-deficit/hyperactivity disorder	No high-impact potential based on expert comments; topic is being archived

Discussion

Although we conduct intensive scanning for interventions and innovations across this priority area, relatively few topics have been identified on developmental disorders (e.g., attention-deficit/hyperactivity disorder [ADHD] and autism spectrum disorders [ASDs]). This deficit in viable topics reflects the slower pace in advancing understanding of these disorders and their etiology. Although recent progress has been limited, researchers continue to investigate genetic and neurobiologic underpinnings of ADHD and ASDs to develop new potential therapeutic and diagnostic targets.

ASDs, sometimes referred to as pervasive developmental disorders, constitute a broad range of associated cognitive and neurobehavioral disorders that share core features, including persistent deficits in social communication and social interaction, restricted and repetitive patterns of behavior, and atypical language development. Preliminary research supports a hypothesis that

earlier diagnosis and intervention may result in improved developmental cognitive and social outcomes for affected children. Both behavioral therapy and pharmaceutical treatments are used as interventions to improve various symptoms in patients diagnosed with ASDs. To date, effective pharmacologic treatments for social deficits in individuals with ASD are lacking. One topic, an off-label medication purporting to address social dysfunction in patients with ASDs, emerged as having potential for high impact.

Eligible Topic Not Deemed High Impact

- The Neuropsychiatric Interpretive Electroencephalograph Assessment Aid (NEBA), a noninvasive diagnostic device that analyzes the ratio between patients' theta and beta brain waves as a purported biomarker of ADHD, received marketing clearance from the U.S. Food and Drug Administration in July 2013 as a clinician evaluation–adjunct assessment tool. However, experts commenting on this intervention did not consider it to have high-impact potential at this time, citing factors including NEBA's limited potential adoption by clinicians because at best it appears to have potential only as an incremental benefit—it is a confirmatory tool that does not replace the standard of care—and it carries a possible financial burden to patients because of lack of reimbursement. For this reason, we have archived this topic from the horizon scanning system.

Off-Label Intranasal Oxytocin for Treatment of Autism Spectrum Disorders

- **Key Facts:** Many patients with an ASD diagnosis are treated with structured behavioral programs intended to improve social cognition and functioning and mediate their most pervasive emotional symptoms. No effective pharmacologic treatments have been available for addressing social deficits in these patients. Recent preclinical research and small clinical trials link oxytocin hormone signaling with reinforcement of normal, positive social behaviors. Although oxytocin's role in childbirth and lactation is well understood and it is approved for these indications, oxytocin's function in mediating social behavior and social cognition is still being investigated. Several academic centers are investigating off-label, intranasal oxytocin for treating social cognitive deficits in patients with ASD, and one company is researching a proprietary intranasal delivery system for a similar indication. In ongoing and completed trials, oxytocin is administered via intranasal spray at a dosage of 24 IU, once or twice daily.

Recently completed trials investigating oxytocin efficacy in patients with ASDs have found that intranasal administration positively affects social functioning, assessed by a various measures including social responsiveness and comprehension. Ongoing trials may further establish optimal doses and frequency for both adult and adolescent patients.

- **Key Expert Comments:** Experts evaluating this intervention agreed that an important unmet need exists for an effective treatment for social dysfunction in ASD. However, experts indicated that additional data are needed to facilitate widespread adoption by patients and clinicians. Overall, experts acknowledged the potential for intranasal oxytocin to become the standard of care for treating social dysfunction in ASDs, because of the absence of other medications for this indication, the ease of oxytocin administration, and its favorable cost and safety profile.
- **Potential for High Impact:** Moderately high

Developmental Delays, ADHD, and Autism Intervention

Off-Label Intranasal Oxytocin for Treatment of Social Dysfunction in Autism Spectrum Disorders

Unmet need: Autism spectrum disorders (ASDs) are a group of developmental brain disorders whose symptoms include varying levels of cognitive and behavioral impairments, affecting language, motor, and social skills.^{1,2} According to recent data from the U.S. Centers for Disease Control and Prevention's Autism and Developmental Disabilities Monitoring Network, 1 in 68 children aged 8 years old meets diagnostic criteria for an ASD.³ Although ASD symptoms vary across patients, they generally fall into one or more of three areas: social dysfunction, communication difficulties, and repetitive and stereotypic behaviors.^{2,4} Children with an ASD who manifest social dysfunction symptoms may make little eye contact with other people, exhibit lower social attention and responsiveness than other children do, display no positive affect for toys and activities, and may respond unusually to others' emotional displays; these symptoms may persist into adulthood.^{1,4}

Many patients diagnosed with an ASD are treated using behavioral therapy programs designed to improve social cognition and functioning.⁴ These programs include use of music, assistive technology, and pharmacologic therapies to manage ASD-associated symptoms.^{5,6} Although various medications are employed to treat agitation, aggression, and depression symptoms, few effective pharmacological therapies are available for treating social deficits in patients with ASD; a viable pharmacological intervention targeting brain circuits involved in social behavior and cognition might reduce social dysfunction in patients with ASD and improve overall patient outcomes.⁷ If proved effective, intranasal oxytocin therapy would likely be used as an adjunct to ongoing behavior therapy regimens, and it may replace other prescribed medications.

Intervention: In the human body, oxytocin is a neuromodulator and neurotransmitter synthesized in the paraventricular and supraoptic nuclei of the hypothalamus.⁸ Oxytocin is stored and secreted by the pituitary gland and distributed directly to regions known to be involved in emotion regulation, memory, and social function, including the amygdala, hippocampus, suprachiasmatic nucleus, and brain stem.⁹ Oxytocin's mechanism of action in treating ASDs is still unknown, but it may be mediated by either oxytocin receptor changes or oxytocin-dopamine, oxytocin-opioid, or oxytocin-arginine vasopressin brain reward pathways that have been found to be genetically altered in patients with ASDs.¹⁰⁻¹³ Research in both healthy patients and patients diagnosed with ASDs has determined that exogenous oxytocin positively affects social interaction, possibly promoting affiliative (group bonding) behaviors, reducing anxiety, and increasing emotional actions including eye contact, trust, and generosity.¹⁴⁻¹⁷ Conversely, recent studies have also demonstrated that oxytocin facilitates socially exclusionary behaviors such as envy, in-group conformity, and defensiveness towards persons outside one's social group.¹⁸⁻²⁰

Clinical trials: In nine ongoing and completed trials, intranasal oxytocin has been most frequently administered once or twice daily, at a dose of 24 IU, for periods between 1 and 8 weeks.²¹⁻²⁹ A large review of adverse-event reports from completed studies demonstrated that intranasal oxytocin can be safely administered at dosages up to 40 IU daily in short-term research environments;³⁰ a small trial of eight Japanese boys with ASDs, aged 10–14 years old, also provided preliminary evidence supporting safe long-term oxytocin administration (i.e., longer than 6 continuous months).³¹

Investigators from four completed studies have reported that intranasal oxytocin increases systemic oxytocin levels that may be linked to improved communication, social task functioning, and emotional and linguistic comprehension in patients with ASDs.³¹⁻³⁴ For example, investigators from a trial on effects of intranasal oxytocin administration on social psychological task completion

in high-functioning adult males with ASDs (n=40) reported that a single 24 IU oxytocin dose improved patients' ability to more frequently ($p=0.03$) and more rapidly ($p=0.02$) make nonverbal judgments; oxytocin administration was also associated with improving diminished brain activity ($p<0.001$) and enhancing functional coordination ($p<0.001$) in medial prefrontal cortex, a brain region previously demonstrated to be involved in modulating social cognition.^{9,35} Additionally, in two recent clinical trials enrolling adolescent patients with ASDs (n=16), two different oxytocin dosages were associated with improved performance on tasks measuring emotional comprehension.^{32,36}

The majority of ongoing and completed trials have investigated the effects of intranasal oxytocin on improving social cognition and functioning in small patient populations, with most studies enrolling fewer than 20 patients. However, three clinical trials are registered, each with an intended enrollment of more than 140 total patients; study sites are in the United States and Canada.^{21,25,37}

Manufacturer and regulatory status: The U.S. Food and Drug Administration (FDA) has approved intranasal oxytocin for inducing or augmenting labor and for inducing uterine contractions postpartum to reduce bleeding.³⁸ Its use in treating ASD is off label. In the United States, generic forms of oxytocin are available through several manufacturers and sold as an injectable solution.^{38,39} Clinical trials investigating oxytocin for treating ASDs, however, primarily use intranasal spray formulations of the drug. The intranasal formulation of oxytocin, branded as Syntocinon® (Novartis International AG, Basel, Switzerland) was discontinued in the United States but is available abroad and has been successfully obtained for use by U.S.-based clinical trial investigators.^{22,40} Generic intranasal oxytocin spray formulations are also available without prescription on the Internet from various companies, including at least one with headquarters in the United States (ABC Nutraceuticals, Boise, ID), but safety and efficacy information for these products has not been made publicly available.^{41,42}

Several academic medical centers—including Children's Hospital of Philadelphia, PA; Holland Bloorview Kids Rehabilitation Hospital, Ontario, Toronto, Canada; Massachusetts General Hospital, Boston; Montefiore Medical Center of Albert Einstein Hospital, New York, NY; and Stanford University School of Medicine, Stanford, CA—are investigating intranasal oxytocin for treating social cognitive deficits in patients with ASDs.^{21-29,37} Additionally, in 2012, OptiNose US Inc. (Yardley, PA), was awarded a grant by the Research Council of Norway to fund a study of oxytocin for treating ASDs using the company's "bi-directional" nasal drug delivery technology; OptiNose recently completed a phase I dose delivery efficacy study in healthy adults, with results pending.^{43,44}

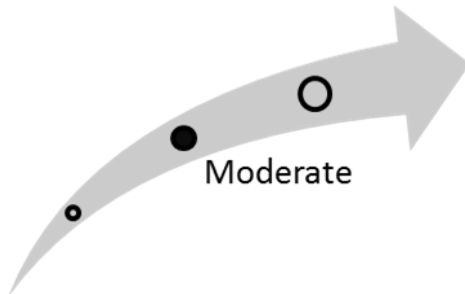
Clinical Pathway at Point of This Intervention

No single standard of care exists for treating behavioral or cognitive symptoms of ASDs. Dietary and medical interventions that are used to control ASD symptoms include antidepressants, antipsychotic medications, immune system moderators, and nutritional supplements.^{45,46} Additionally, cognitive behavior therapies and speech-language pathology interventions have been used to treat social and communication deficits in patients with autism. In 2006, FDA approved risperidone for treating irritability in children with a diagnosis of autism. However, no approved medications are available that effectively treat ASD core symptoms, including deficits in social cognition and associated behaviors.⁴⁵

Patients who have been given intranasal oxytocin spray for treating symptoms of ASDs are expected to experience little modification to their routines, and no health staffing and infrastructure

implications are expected. Intranasal oxytocin is expected to be used as an adjunct to present interventions, including behavior therapy and other medications.

Figure 1. Overall high-impact potential: off-label intranasal oxytocin for treatment of autism spectrum disorders



Experts evaluating this intervention agreed that an unmet need exists for an effective treatment for social dysfunction in ASD, considering the burdens this condition poses to patients, family and caregivers, and society. Experts also agreed that this intervention has potential to address this unmet need but commented that more data would be required to foster widespread adoption. Overall, experts anticipated that intranasal oxytocin has moderate-to-high potential to diffuse widely among clinicians and patients and could become the standard of care for treating social dysfunction in ASDs. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this topic.⁴⁷⁻⁵² We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Social dysfunction in ASDs represents a significant unmet need, the experts agreed; they cited the lack of treatment options and the debilitating nature of social dysfunction symptoms on patients, caregivers, and others. However, the experts' consensus opinion was that this intervention needs more data to show efficacy and long-term effects, leaving oxytocin's potential to address an unmet need unresolved. Although some experts we consulted considered existing clinical trial results promising, the remaining experts refrained from making conclusions based on this limited data set. One clinical expert noted, however, that both the theoretical and empirical support for this intervention exceeded that of previously tested treatments.⁵⁰

Acceptance and adoption: Citing the convenience and relatively low cost of oxytocin along with patients' and clinicians' desire for effective treatments, experts anticipated a potential for widespread acceptance and adoption. Experts also remarked that additional data supporting oxytocin's efficacy would also increase patient and provider adoption rates.

Health care delivery infrastructure and patient management: Most of the experts stated that, as a previously approved and diffused medication, off-label use of oxytocin would not present significant changes to health care delivery infrastructure. Experts also remarked that oxytocin intranasal spray would likely be added to existing treatment regimens and would not add to patient management loads.

A health systems expert commenting on this intervention noted that adoption of intranasal oxytocin for this indication may result in significant, positive disruptions to both delivery infrastructure and patient management, as the present standard of care places large resource burdens

on caregivers, treatment providers, and educational facilities, particularly public schools.⁴⁹ Reviewing this intervention, a clinical expert also cautioned that without proper preparation, initial adoption of oxytocin for treating ASDs could have a substantially negative effect on health care delivery, as intranasal oxytocin would not be immediately accessible to patients, despite receiving prior FDA approval.⁵⁰

Health disparities: Most experts noted that this intervention is not likely to increase health disparities, due to its relatively low cost and availability, in comparison to intensive therapy programs that are the present standard of care. Although one expert with a research perspective noted that affluent patients and caregivers may be more likely to be informed of and use this intervention, overall, experts concluded that intranasal oxytocin, if adopted for this indication, would not significantly impact health disparities.⁵¹

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