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

Priority Area 05: Depression and Other Mental Health Disorders

Prepared for:
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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 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 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 five 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. (Twenty topics in this priority area were being tracked in the system as of October 29, 2013.) We present three summaries of four topics (indicated below by an asterisk) that emerged as having some potential for higher impact on the basis of expert comments. Topics in this Executive Summary and report are organized alphabetically. Readers are encouraged to read the detailed information that follows the Executive Summary.

Priority Area 05: Depression and Other Mental Health Disorders

Topic	High-Impact Potential
1. * Cortisol antagonist (mifepristone, Korlym) for treatment of psychotic depression	Lower end of the high-impact-potential range
2. * Deep brain stimulation (Reclaim DBS Therapy or Libra DBS) for treatment-resistant depression	Moderately high
3. Off-label intranasal oxytocin for treatment of schizophrenia	No high-impact potential at this time
4. * Off-label ketamine for treatment-resistant bipolar depression and major depressive disorder	Moderately high
5. * Off-label scopolamine for treatment-resistant bipolar depression and major depressive disorder	Moderately high

Discussion

One theme common to interventions being developed for mental health disorders is the search for options to address treatment-resistant bipolar depression (BPD), major depressive disorder (MDD), and posttraumatic stress disorder. Investigators are also seeking to identify effective, rapid-acting interventions they can prescribe to patients in crisis (i.e., those experiencing suicidal ideation or severe, debilitating depression symptoms).

We discuss mifepristone, a drug for psychotic major depression (PMD), a condition for which no U.S. Food and Drug Administration (FDA)-approved interventions are available, is being investigated in trials. We also discuss deep brain stimulation (DBS) devices, which offer a new

approach for treatment-resistant depression that departs from traditional pharmacotherapy and psychotherapy interventions. Finally, we combine discussion of two drugs researchers are exploring for potential antidepressant efficacy: ketamine, an FDA-approved anesthetic, and scopolamine, an FDA-approved antiemetic. Trials are ongoing to examine the proposed rapid antidepressant effects of these agents. Interventions that yield rapid response are critically needed for severely depressed patients at risk of suicide, and these agents could be prescribed off label to patients whose conditions are refractory to traditional interventions.

Cortisol Antagonist (Mifepristone, Korlym) for Treatment of Psychotic Depression

- **Key Facts:** PMD, a subcategory of MDD, is associated with a higher risk of hospitalization, suicide attempts, and completed suicides than nonpsychotic MDD. For this condition, no FDA-approved interventions are available, and treating this population remains a challenge. Cortisol, a hormone produced by the adrenal gland, mediates the body's response to stress. Patients with PMD secrete cortisol at higher rates than patients with nonpsychotic MDD. Conversely, in healthy people, administering glucocorticoids can induce cognitive deficits similar to those seen in patients with PMD, research has suggested. Because this evidence might point to an etiologic and pathophysiologic link between cortisol and PMD, researchers have proposed cortisol receptors as a therapeutic target for PMD. Mifepristone (Korlym™, Corcept Therapeutics, Inc., Menlo Park, CA) is an oral antiprogestin and glucocorticoid-II receptor (GR-II) antagonist under study in a phase III trial for treating PMD. Its manufacturer purports that blocking the GR-II receptor might prevent excessive cortisol activity and relieve PMD symptoms. Completed phase III trials did not demonstrate statistical superiority of mifepristone over placebo, but the data suggested a significant relationship between higher plasma concentrations of the drug and clinical response. Therefore, the manufacturer is studying mifepristone at a higher, oral dosage of 1,200 mg daily in the ongoing trial. Mifepristone is FDA-approved for medical terminating pregnancy up to 49 days (branded as Mifeprex®) and for treating hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome (branded as Korlym). It can be prescribed off label for treating PMD. FDA has granted fast-track status for this indication.
- **Key Expert Comments:** Experts agreed that the unmet need for effective treatment for PMD is important, especially considering the debilitating nature and risk of suicide attempts and completed suicides in this patient population. However, experts' opinions varied about whether this intervention will meet that need, and experts were eager to see data from the ongoing, phase III trial. They commented that if proved effective for this condition, the drug might reduce costs of care associated with untreated PMD or treatment-refractory PMD. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact range.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Deep Brain Stimulation (Reclaim/Activa DBS Therapy or Libra DBS) for Treatment-Resistant Depression

- **Key Facts:** Despite availability of oral pharmacotherapy and psychotherapy as first- and second-line therapies, and despite availability of electroconvulsive therapy or repetitive transcranial magnetic stimulation as second- and third-line therapies for BPD or MDD, a significant proportion of affected patients have treatment-refractory depression. DBS, a

standard modality for treating some movement disorders (e.g., essential tremor, Parkinson's disease, dystonia), is being studied for treating psychiatric conditions, including BPD and MDD. DBS employs a battery-operated, pacemaker-like neurostimulator implanted in the chest below the clavicle (collarbone) to deliver controlled electrical stimulation to specific brain regions via thin wire electrodes. The electrodes carry a high-frequency electrical signal that interferes with neural activity at the placement site and is intended to modulate the activity in that region of the brain. Currently, both the Reclaim® (also referred to as the Activa® device in trials of MDD; Medtronic, Inc., Minneapolis, MN) and the Libra® DBS device (St. Jude Medical, Inc., St. Paul, MN) are in phase III development for DBS for treating BPD and MDD. Reclaim/Activa trials for MDD have an anticipated completion date of October 2014; phase III trials of Libra were actively enrolling as of December 2013. The Reclaim device previously received FDA humanitarian device exemption approval for treating obsessive-compulsive disorder, which marked the first FDA approval of any DBS device for a psychiatric indication. DBS is expected to be positioned as an additional therapeutic option for patients who have treatment-resistant or refractory disease.

- **Key Expert Comments:** Experts commenting on this topic believe that DBS could have an impact on several parameters of the health care system: adding neurosurgery to the clinical treatment pathway; increasing costs of care by adding a surgical procedure to treatment options; shifting some care from the outpatient setting to inpatient surgery; and possibly creating barriers to clinical and patient acceptance. Overall, experts were optimistic about the intervention's potential to improve patient outcomes for treatment-refractory MDD. A few experts, noting that the target population for this intervention is small, tempered expectations about its potential for high impact.
- **Potential for High Impact:** Moderately high

Off-Label Fast-acting Drugs (Ketamine, Scopolamine) for Treatment-resistant Bipolar Depression and Major Depressive Disorder

- **Key Facts:** Despite widespread use, approved medications for treating BPD and MDD do not elicit an adequate therapeutic response in many patients and are associated with considerable lag time in response. Only a fraction of treated patients responds within a week of starting any of the many medications available for BPD and MDD. This delay can increase suicide risk and mortality. Ketamine hydrochloride is a long-used general anesthetic (since 1966) now being investigated with funding from the National Institute of Mental Health for treatment-resistant BPD and MDD. The drug is given by a single intravenous infusion, and preliminary data have indicated it produces a rapid (within 2 hours) and relatively sustained (about 1–2 weeks long) significant reduction in the Hamilton Depression Rating scales in some patients with BPD or MDD. Scopolamine is an anticholinergic agent approved by FDA for treating peptic ulcer and as an antiemetic to prevent motion sickness and post-surgical nausea. The National Institute of Mental Health is sponsoring a large clinical trial to investigate its potential antidepressant efficacy. Data from several small trials suggest that it also has a rapid-acting antidepressant effect in patients with treatment-resistant BPD or MDD. The manufacturers of these drugs do not appear to be pursuing label expansions at present; both agents could be prescribed off label for treating depression.
- **Key Expert Comments:** Overall, experts who commented were highly optimistic about the potential of these drugs to meet the need for rapid-onset, effective treatment for BPD and

MDD. They thought that the drugs could have an important impact across many health system parameters, including lowering costs incurred from ineffective treatment, reducing suicide risk because of its rapid action, and changing care setting from outpatient oral therapy prescribed in a physician's office to outpatient infusion therapy administered by a different type of provider in an infusion clinic. However, experts also suggested that barriers to diffusion may exist, stemming from potential relapse. Experts also noted the requirement for additional patient monitoring, given that ketamine and scopolamine introduce unique adverse effect profiles compared with existing antidepressant medications.

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

Depression and Other Mental Health Disorder Interventions

Cortisol Antagonist (Mifepristone, Korlym) for Treatment of Psychotic Depression

Unmet need: Treatments in use for psychotic major depression (PMD)—a subcategory of MDD with a higher risk of hospitalization, suicide attempts, and suicides than nonpsychotic MDD—are associated with unwanted side effects, extensive lag time between start of medication and therapeutic effects, suboptimal efficacy, and stigma (especially in the case of electroconvulsive therapy [ECT]).[1,2] Furthermore, no interventions are specifically approved by the U.S. Food and Drug Administration (FDA) for treating PMD.[3] Effective medications are needed for this condition. If approved, mifepristone would be the first pharmacotherapy indicated for use in this population.

Intervention: Cortisol, a hormone produced by the adrenal gland, mediates the body's response to stress.[4] The hypothalamic-pituitary-adrenal (HPA) axis regulates the body's stress response and cortisol secretion. Research has implicated dysregulation of the HPA axis in various mood and psychiatric disorders,[5] and experts hypothesize that diminished suppression of the cortisol response may contribute to PMD.[6,7] In patients with PMD, cortisol has been observed to be secreted at higher rates (hypersecreted) than in patients with nonpsychotic MDD.[8] Further, research has suggested that administering glucocorticoids to healthy participants can induce cognitive deficits similar to those seen in patients with PMD.[8] Because this evidence might point to a causative and pathophysiologic link between cortisol and PMD, researchers have suggested cortisol signaling as a therapeutic target for PMD.[9]

Mifepristone (Korlym™) is an oral progesterone receptor antagonist at low doses and also inhibits glucocorticoid-II receptors (GR-II) at higher doses.[10] Cortisol binds to glucocorticoid receptors in the brain, including the GR-II.[8] Based on its mechanism of action on glucocorticoid receptors, investigators are studying mifepristone for treating PMD.[11] Mifepristone's manufacturer purports that blocking the GR-II receptor might prevent excessive cortisol activity, potentially relieving PMD symptoms.[11] For this indication, 1,200 mg of mifepristone is being administered orally, in four 300 mg tablets, once daily, for a week.[9]

Clinical trials: Using mifepristone to treat PMD is under study in one ongoing phase III clinical trial.[9] Three completed phase III trials did not demonstrate superiority of mifepristone over placebo.[11] However, phase III data revealed a statistically significant linear association between mifepristone plasma concentration and clinical response. Therefore, the manufacturers proposed that higher doses of mifepristone might yield significant antidepressant effects[12] and stated the following:

> While the studies did not meet their primary endpoints individually, data aggregated from Corcept's major efficacy studies of similar design, involving 724 observed cases, indicate that the response rate in patients who received CORLUX [mifepristone] separated from the placebo group with statistical significance for the endpoint, 50% improvement in the BPRS PSS [Brief Psychiatric Rating Scale Positive Symptom Subscale] at Day 7 and at Day 56. In addition, using the same endpoint, the response rates for patients who achieved a drug level in their plasma that was greater than the 1660 nanogram per milliliter threshold mentioned above, statistically separated from both those patients whose plasma levels were below this threshold and those patients who received placebo.[11]

The manufacturer continues to develop mifepristone for this condition at a 1,200 mg, oral daily dosage, which is higher than that used in previous trials. In a third-quarter 2013 report, the manufacturer reported faster-than-anticipated enrollment for the ongoing phase III trial in PMD and

anticipated that an interim analysis of study data would take place ahead of schedule, in the second quarter of 2014.[13]

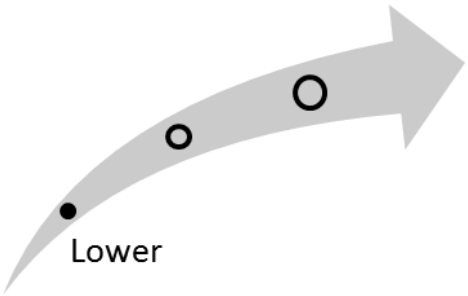
Manufacturer and regulatory status: Korlym is made by Corcept Therapeutics, Inc., of Menlo Park, CA. FDA has granted the agent fast-track status for this indication.[1] FDA approved Korlym in 2012 for treating Cushing's disease.[14] Mifepristone is also approved for the medical termination of pregnancy at up to 49 days gestation.[15]

Diffusion: Physicians can prescribe mifepristone off label for treating PMD, even with its ongoing study for the labeled indication to treat PMD. A search of 11 representative, private, third-party payers that publish their coverage policies online (Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) identified 2 payers with policies that specifically address the use of mifepristone for patients with PMD. These payers consider mifepristone investigational or unproven for this indication and do not provide coverage at this time.[16,17]

Clinical Pathway at Point of This Intervention

Although no treatments are FDA approved for PMD, pharmacotherapy used for MDD is typically the first-line PMD treatment and involves concomitant use of antidepressant and antipsychotic medications.[1,18] ECT is sometimes used as second- or third-line therapy.[18] Mifepristone would likely be positioned as a first-line treatment.

Figure 1. Overall high-impact potential: cortisol antagonist (mifepristone, Korlym) for treatment of psychotic depression



Experts commenting on this intervention agreed that the unmet need for an effective, fast-acting, FDA-approved treatment for PMD is important, especially considering the debilitating nature of this condition and the associated poor outcomes. However, opinions varied on whether this intervention can meet that need. Some experts opined that even though the drug is available off label, more data are needed before clinicians could be expected to adopt use. If the drug is proven effective for this condition, experts thought, it could have important impacts not only on improving patient outcomes, but also on lowering costs of care. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided comments on this topic.[19-24] We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: The unmet need for interventions for PMD is high and important, the experts agreed. They cited suboptimal treatments, lack of an FDA-approved treatment for this condition, and the condition's debilitating nature. One expert with clinical experience treating this patient population stated that treating PMD has been a major challenge,

because “the presence of psychotic features (often not identified or diagnosed) is a major reason for treatment resistance.”[24]

However, experts varied in their opinions about whether mifepristone will meet this need. On one hand, some experts noted that available trial data are not particularly compelling, given the trial designs and reported outcomes thus far. These experts wanted to see data demonstrating a clear benefit. On the other hand, one clinical expert, who did additional research into this topic, commented that he finds the available literature compelling and believes that unsatisfactory trial data thus far reflect poor trial design and not necessarily lack of efficacy of the drug. Another research-based expert pointed out that the FDA fast-track designation suggests this idea may have merit.

Acceptance and adoption: Patients would be extremely accepting of the intervention, experts thought. They said the following factors would contribute to diffusion of mifepristone, if approved: its oral administration would be a benefit, especially compared with ECT; virtually no training would be needed to prescribe it; and it would carry markedly less stigma with patients than ECT. Similarly, the experts anticipated that clinicians would readily adopt the use of the drug, considering the lack of effective treatments available.

Health care delivery infrastructure and patient management: If the drug is shown to be effective, most experts believe, it would reduce the need for some hospitalizations and the need for ECT, which has high costs. In light of this, experts agreed that mifepristone has potential to reduce long-term treatment costs associated with PMD. Experts also noted that any improvement in functional ability in these patients might be associated with reduced societal costs and improved function and productivity of the treated patients.

Health disparities: Several experts believe that this intervention, if shown to be effective, would have positive effects on health disparities of affected patients by offering a lower-cost and more widely diffusible intervention than ECT. Thus, its availability might improve access to care for some patients. The agent might also improve the ability of marginalized patients to return to the work force or otherwise engage socially and to seek medical treatment when necessary.

Deep Brain Stimulation (Reclaim/Activa DBS Therapy or Libra DBS) for Treatment-resistant Depression

Unmet need: Although medication and psychotherapy are the primary interventions for treatment-resistant major depressive disorder (MDD), investigators have sought new approaches because available drugs and psychotherapy often fail to control symptoms adequately. One approach, deep brain stimulation (DBS), an established treatment for movement disorders (e.g., essential tremor, Parkinson's disease, dystonia), is being studied as a treatment for psychiatric conditions, including MDD and bipolar depression (BPD). FDA recently approved a DBS system under a humanitarian device exemption for the first mood disorder indication—treatment-refractory obsessive-compulsive disorder (OCD).

Intervention: DBS is a surgical intervention in which an implanted neurostimulator device is programmed to deliver electrical signals to specific brain regions in the patient's brain. It consists of an insulated wire electrode that a neurosurgeon implants in the brain, a pacemaker-like neurostimulator implanted under the collarbone, and another insulated wire that connects the lead in the brain to the device.[25] The transmitted electrical signal modulates brain activity at the lead placement site, thereby inhibiting or activating activity within the targeted brain circuit.[26] In treating MDD and BPD, different clinical investigators and manufacturers are targeting various areas of the brain using their respective devices. Brain regions that have been individually targeted using DBS for treating depression include the subgenual cingulate region, medial forebrain bundle, and the nucleus accumbens.[27-30] Research has implicated these regions in emotional processing and the etiology of depression.

DBS implantation is typically a two-phase process: electrode placement and neurostimulator implantation. In phase 1, using local anesthesia, a neurosurgeon drills burr holes into the patient's skull and places bilateral electrodes on or in the targeted brain areas using imaging-guided techniques. In phase 2 with the patient under general anesthesia, a neurosurgeon implants the neurostimulator just below the collarbone. The surgeon passes the extension wire under the skin of the patient's head, neck, and shoulder via a small opening behind the ear and connects the electrode to the neurostimulator.[25]

Between 2 and 4 weeks after implantation, the device is activated and programmed through a wireless programming computer. As instructed by their physicians, patients can turn the neurostimulator on and off with a control magnet. About every 6–12 months, followup is needed; the device's batteries require replacement every 3 to 5 years, which involves a surgical procedure.[26]

Clinical trials: Multiple investigator-sponsored trials are examining neuromodulation of various brain regions to improve depression symptoms due to BPD or MDD. These trials test the Reclaim® DBS Therapy system using the Activa® neurostimulator (Medtronic, Minneapolis, MN[31-35] or the Libra® DBS System (St. Jude Medical, Inc., St. Paul, MN).[36,37] Ongoing DBS trials at academic medical centers target various different brain regions, including the superolateral medial forebrain bundle,[31] subgenual cingulate region (including Brodmann area 25),[34,36-39] the lateral habenulae,[32] and the nucleus accumbens.[33,35]

Several groups have reported positive findings from pilot trials. In one study, DBS of the medial forebrain bundle rapidly reduced depression symptoms in seven patients with treatment-refractory MDD.[27] Two studies in patients (n=17, n=21) with BPD or MDD who underwent DBS to the subcallosal cingulate white matter supported the long-term safety and antidepressant efficacy of this approach.[28,29] Finally, cognitive performance improved in a study of 10 patients with treatment-resistant depression who received DBS to the nucleus accumbens.[30]

Investigators concluded from a 2010 Reclaim DBS Therapy trial of 10 patients with severe, treatment-resistant MDD, that "twelve months following initiation of DBS treatment, 5 patients

reached 50% reduction of the HDRS [Hamilton Depression Rating scale] (responders, HDRS = 15.4 [+/-2.8]).”[40] According to the Reclaim manufacturer, patients who undergo DBS for depression would face risks similar to those faced by patients who undergo DBS for other indications.

The Libra DBS system trial is known as the phase III BROADEN (Brodmann Area 25 Deep Brain Neurostimulation).[41] According to a July 2011 company press release, FDA approved an expansion of the trial to 20 sites across the United States and expanded enrollment to 125 patients.[41] As of December 2013, the trial Web site (www.broadenstudy.com) indicated that enrollment remained open.

Manufacturer and regulatory status: Medtronic, Inc., of Minneapolis, MN, manufactures the Reclaim DBS Therapy system and the Activa neurostimulator device used in several of the above trials.[42] St. Jude Medical, Inc., of St. Paul, MN, is developing its Libra® DBS system for treatment-resistant depression.[43] Reclaim is in a phase III trial under FDA investigational device exemption (IDE) status,[44] and Libra is in two IDE trials for treatment-resistant MDD.[36,41] Multiple academic medical centers are also investigating the efficacy of DBS for treatment-resistant depression; these investigators include Dartmouth-Hitchcock Medical Center, Lebanon, NH; Emory University, Atlanta, GA; Mount Sinai School of Medicine, New York, NY; Rennes University Hospital, Rennes, France; University of Calgary, Calgary, Canada; and University Hospital Bonn, Bonn, Germany.[31-35,37-39]

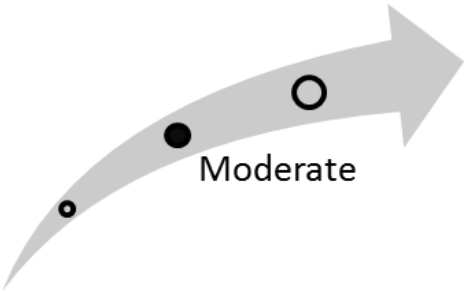
In February 2009, the Reclaim DBS system was approved by FDA for treatment-resistant OCD.[45]

Diffusion: A search of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) identified 7 payers with policies that address deep brain stimulation.[46-52] At present, these payers consider DBS for treating neuropsychiatric disorders such as OCD or depression to be investigational and do not provide coverage.

Clinical Pathway at Point of This Intervention

American Psychiatric Association guidelines for treating BPD or MDD recommend a combination of oral pharmacotherapy and psychotherapy. The Association’s recommended second-line therapy includes ECT or transcranial magnetic stimulation (TMS). If approved, DBS is expected to be positioned as an additional option for patients with treatment-resistant or refractory BPD and MDD. Because DBS is invasive, pharmacotherapy and psychotherapy are expected to remain first-line treatments; DBS would follow as an option when drug therapy has failed. Depending on DBS efficacy, its use might allow some patients to eliminate or lower their drug; however, no data are yet available to support this hypothesis. DBS therapy is incompatible and contraindicated with some other device-based depression treatments, such as TMS. The safety of ECT in patients with an implanted DBS system has not been established. Also, patients with an implanted DBS system may be unable to undergo procedures that use electrocautery devices or certain types of magnetic resonance imaging exams.

Figure 2. Overall high-impact potential: deep brain stimulation (Reclaim/Activa DBS Therapy or Libra DBS) for treatment-resistant depression



Experts commenting on this topic thought that DBS could have an impact on several parameters of the health care system, including increasing costs because it adds surgery to the treatment options, shifting the care setting from outpatient management to inpatient surgery and adding neurosurgery to the clinical pathway; a barrier to clinical and patient acceptance may be its invasiveness. Overall, experts were optimistic about the intervention's potential to improve patient outcomes, but a few noted that the target population for this intervention is small, which tempered their overall opinions about potential impact. 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, offered perspectives on the potential impact of DBS for MDD.[53-58] We have organized the following discussion of expert comments by the parameters on which the experts commented.

Unmet need and health outcomes: The unmet need for novel, effective interventions for treatment-resistant BPD or MDD is very important, given the debilitating nature of the condition and the accompanying societal and financial burdens, most experts agreed. However, they moderated this opinion somewhat because of the relatively small number of patients whose conditions do not respond to available (first-, second-, or third-line) treatments.

Overall, experts supported the theory underlying use of DBS for treatment-refractory MDD, which may reflect their awareness about DBS efficacy in patients with movement disorders. Although most of these experts agreed that available data suggest the intervention shows promise for treating MDD, several offered a caveat, calling for more efficacy data from larger study populations.

Acceptance and adoption: In terms of patient and clinical acceptance, some experts thought the invasiveness and possible side effects might be barriers to acceptance, but others thought that patients with intractable MDD or BPD would be willing to accept an intervention that potentially could improve symptoms and quality of life, regardless of its invasiveness. Some experts also thought controversy might arise in light of debate over using neurosurgical interventions for treating MDD and BPD.

Health care delivery infrastructure and patient management: DBS has the potential to markedly disrupt care models, treatment paradigms, and patient management, the experts asserted. This is because DBS involves inpatient neurosurgery and device implantation, rather than outpatient pharmacotherapy and psychotherapy. Thus the care setting would shift. However, several experts stated that because DBS would be indicated for use in only a small subpopulation of patients with BPD or MDD, these changes would not dramatically affect the health care system as a whole.

Because the intervention necessitates a shift from medical therapy at home to the neurosurgical operating room and inpatient hospital setting, DBS would require changes to staffing mix, care

setting, and clinician training practices, the experts generally agreed. Whether DBS use would require much clinician training was a matter of divided opinion. Several experts thought it would, but others disagreed, stating that neurosurgeons are already familiar with DBS implantation (for movement disorders).

Health disparities: Experts agreed that this intervention would have dramatic cost impacts for the small population for which the treatment is intended. The upfront costs of the device and implantation procedure are significant (tens of thousands of dollars) and may pose a barrier to uptake. Additionally, battery replacement is required every several years and involves a surgical procedure, which will also be costly. It should be noted that experts commenting tended to compare their cost-change estimates to pharmacotherapy, although DBS is not likely to compete with pharmacotherapy but rather is expected compete with more costly, third-line interventions such as repetitive TMS, ECT, and ablative neurosurgery. Therefore, the expected change in upfront costs might be less significant than these experts believe. Experts also thought that if DBS were effective at controlling MDD symptoms, it might decrease the significant financial burden of ongoing, uncontrolled MDD.

Off-Label Fast-acting Drugs (Ketamine, Scopolamine) for Treatment-resistant Bipolar Depression and Major Depressive Disorder

Unmet need: Many cases of BPD and MDD are not effectively managed with available pharmacotherapies.[59] Because many existing pharmacotherapies do not exert effects rapidly, they are ineffective in managing severe, acute episodes associated with these conditions.[59,60] Furthermore, many therapies are associated with undesirable side effects that may limit adherence to medical treatment in patients with these conditions.[59] An unmet need exists for novel, effective, fast-acting, and well-tolerated interventions for treating depressive episodes that occur in patients with BPD or MDD. Ketamine is a compound being studied for treating depression off label that exerts its antidepressant activity through a unique mechanism (i.e., N-methyl-D-aspartate [NMDA] receptor antagonism) that is different from that of existing pharmacologic interventions. Another compound being studied for treating depression off label is scopolamine, which is also purported to have rapid antidepressant activity via a novel molecular pathway (i.e., muscarinic acetylcholine receptor antagonism). If proved effective, off-label ketamine or scopolamine could be an option for patients who have exhausted all other treatment options or as an adjunctive option to other therapeutic regimens for BPD or MDD.

Intervention: Ketamine hydrochloride (ketamine) is a noncompetitive, high-affinity NMDA receptor antagonist that is FDA approved for use as a general anesthetic.[59] Glutamate is the major excitatory neurotransmitter in the brain; this neurotransmitter binds various types of glutamate receptors, including the NMDA receptor.[59] Researchers believe that dysfunctional glutamate neurotransmission may play a major role in causing depressive symptoms in both BPD and MDD, although its exact mechanism of action is still unknown.[59,61] Studies have suggested that NMDA receptor signaling mediates this glutamatergic dysregulation, giving rise to the hypothesis that NMDA receptor antagonists may have antidepressant effects.[61,62] Although this area of research is in its relative infancy, preliminary data suggest that ketamine may exert its antidepressant effects through its impact on synaptic plasticity and synaptogenesis, mediated at least in part by increased brain-derived neurotrophic factor levels.[62-66] Recently identified molecular targets of ketamine that appear to play a role in its antidepressant properties also include mammalian target of rapamycin (mTOR) and eukaryotic elongation factor 2 kinase, both of which have demonstrated roles in synaptic plasticity.[63,66,67]

These data led to the investigation of ketamine for treatment-resistant or acute severe depressive episodes in patients with BPD or MDD.[59,68] Ketamine (in 30 mg/kg doses) has been shown to increase "the firing rate of glutamatergic neurons and the presynaptic release of glutamate" in vitro, and these characteristics are believed to contribute to the agent's antidepressant effects.[59,69]

Standard administration of ketamine for general anesthesia is typically 2 mg/kg, intravenously, or 9–13 mg/kg via intramuscular injection. Because individual responses vary, the dose is often titrated to achieve the desired anesthetic effect.[70] For this off-label indication for treating BPD or MDD, a subanesthetic dose is often used; multiple trials have tested intravenous ketamine infusions at a dose of 0.5 mg/kg.

Scopolamine is a belladonna alkaloid that acts as a competitive inhibitor at muscarinic acetylcholine receptors (mAchRs) to exert potent anticholinergic properties.[71] Research has implicated the central nervous system–cholinergic system in the pathophysiology of depressive disorders. Patients with unipolar depression or BPD demonstrate physiological signs of cholinergic hypersensitivity that include exaggerated neuroendocrine and pupillary responses and characteristic disturbances to normal REM (rapid eye movement) sleep cycles.[72] Additionally, certain genetic

variations of muscarinic cholinergic receptors are associated with an increased risk of developing depression.[73] Although the mechanism of central nervous system cholinergic dysfunction in depression is not fully understood, data suggest that increased cholinergic pathway activity contributes to the negative emotional-processing bias observed in many mood disorders.[74] Along these lines, researchers believe that cholinergic hyperactivity can lead to overrepresentation of negative emotion, thereby promoting depression symptoms.[74] Through inhibition of mAchRs, scopolamine purportedly counteracts the hypersensitivity/hyperactivity of the cholinergic system in patients with depression. By inhibiting this cholinergic hyperactivity, it may be possible to restore normal emotional processing and lessen the signs of depression.[73] Clinical data suggest that these changes may be evident as soon as 3 days after treatment, which could provide a therapeutic advantage over standard antidepressants with delayed therapeutic onset.[75,76]

For this off-label scopolamine indication, clinical trials have investigated oral and intravenous routes of administration. When administered intravenously for treating depression, dosage was 4 mcg/kg, given during 3 separate sessions spaced 3–5 days apart.[73,77] In a trial of orally administered scopolamine, a dosage of 0.5 mg, twice daily, was used in conjunction with the orally administered, selective serotonin reuptake inhibitor citalopram.[76]

Other forms of scopolamine exist, but they have not been tested for treating depression. These include investigational intranasal formulations and the FDA-approved transdermal patch.

Clinical trials: Multiple clinical trials sponsored primarily by academic medical centers are investigating off-label ketamine for treatment-resistant depression in patients with BPD or MDD. Numerous studies have presented positive antidepressant effects of ketamine in these patient populations.[60,78-87] Clinical trials have shown ketamine to have a rapid therapeutic effect (e.g., within minutes or hours); research suggests that this rapid effect may be due to the agent's high affinity for NMDA receptors and to its intravenous administration route.[59] Data from these trials suggested that depressive symptoms improved both significantly and rapidly and that these effects lasted from 3 days to several weeks, following a single infusion.[60,83,86]

A 2013 abstract of a study presented at the American Psychiatric Association (APA) reported that "a single intravenous infusion of ketamine [0.5 mg/kg over a 40 minute period] had large and rapid antidepressant effects with[in] 24 hours of administration in several small studies in depressed patients."[88] Ketamine demonstrated a 16.5 point decrease on the Montgomery-Asberg Depression Rating Scale whereas the active placebo, midazolam, showed an 8.8 point decrease. This statistically significant superiority was maintained 7 days after administration.[88]

Several trials of off-label scopolamine for treatment-resistant depression are ongoing, including two pilot trials sponsored by Massachusetts General Hospital, Boston, and a larger, controlled trial (n=328) run by the National Institute of Mental Health (NIMH; Bethesda, MD).[89-91] In 2012, data from a phase II/III trial (n=40) suggested that scopolamine was an effective augmentation therapy to citalopram for treating depression.[76] In 2010, phase II data supported the antidepressant efficacy of intravenous scopolamine and also indicated a potential sex-dependent effect, with larger treatment effect sizes observed among women.[77] Preliminary data from a small cohort (n=15) in the NIMH-sponsored trial demonstrated that antidepressant efficacy may be correlated with an observable response on functional magnetic resonance imaging.[74] A systematic review published in 2013 supported the overall antidepressant efficacy of scopolamine across several routes of administration.[92]

Manufacturer and regulatory status: Ketamine is available in generic form from several manufacturers. It is also available as the branded drug Ketalar from JHP Pharmaceuticals, LLC, of Parsippany, NJ. Ketamine is FDA approved as an anesthetic for diagnostic and surgical procedures.[70] At present, ketamine's manufacturers do not appear to be pursuing marketing approval for an expanded label. Ketamine is classified as a Schedule III nonnarcotic controlled

substance and, at higher doses, is sometimes abused as a street drug ("Special K"), which could affect the regulatory pathway for this indication and its availability for off-label use.[68,93]

Several institutions and one company are investigating off-label ketamine for treating BPD and MDD. These include the following:

- Columbia University (New York, NY)[94]
- Janssen Research and Development, LLC, unit of Johnson & Johnson (New Brunswick, NJ)[95]
- Juvenile Bipolar Research Foundation (Maplewood, NJ)[96]
- Mount Sinai School of Medicine (New York, NY)[97,98]
- Massachusetts General Hospital (Boston)[99]
- Mayo Clinic (Rochester, MN)[100]
- NIMH[101] (also a cosponsor of trials at many of these institutions)
- New York State Psychiatric Institute (New York, NY),[102,103]
- North Shore Long Island Jewish Health System (Manhasset, NY)[104]
- Yale University (New Haven, CT)[105]

Oral scopolamine (methscopolamine bromide) is FDA approved and available in generic form from several manufacturers. It is indicated as adjunctive therapy for treating peptic ulcer.[106,107] Scopolamine is also available as a transdermal, extended-release patch (Transderm Scōp; Novartis International AG, Basel, Switzerland).[71] Transdermal scopolamine is indicated for treating motion sickness and postoperative nausea and vomiting. Manufacturers of scopolamine do not appear to be pursuing an official indication for treating depression.

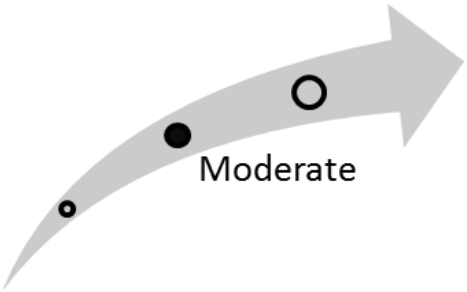
Two institutions are investigating off-label scopolamine for treating BPD and MDD: Massachusetts General Hospital and NIMH. Two trials at Massachusetts General Hospital are testing intravenously administered scopolamine for treating MDD.[90,91] NIMH's large trial of scopolamine for treating MDD uses a commercially available transdermal scopolamine patch.[89]

Clinical Pathway at Point of This Intervention

Treatment for BPD or MDD often comprises pharmacotherapy and psychotherapy. Pharmacologic management of MDD symptoms may involve monotherapy or combination therapy with several different classes of antidepressants (e.g., serotonin or norepinephrine reuptake inhibitors, atypical antidepressants, tricyclic/tetracyclic antidepressants, monoamine oxidase inhibitors).[108,109] Pharmacologic management of BPD may include some combination of lithium, anticonvulsants, antipsychotics, antidepressants, and benzodiazepines.[110] In patients whose condition is refractory to all attempted pharmacologic interventions and psychotherapy, physicians may try ECT, TMS, or vagus nerve stimulation.[110]

Because ketamine and scopolamine have different mechanisms of action from most pharmacologic interventions for depression, these agents could complement approved medications. Some clinical researchers see the rapid onset of action as a possible therapeutic bridge until standard antidepressants can take effect. Ketamine and scopolamine could also complement nonpharmacologic interventions such as ECT, TMS, vagus nerve stimulation, and psychotherapy.

Figure 3. Overall high-impact potential: off-label ketamine for treatment of BPD and major depressive disorder



Overall, experts commenting on this topic were highly optimistic about the potential of these interventions to meet the need for a rapid-onset, effective treatment for treatment-refractory BPD and MDD. They thought ketamine and scopolamine could have an important impact across many health system parameters, including shifting care from self-administered oral therapy to infusion therapy administered in a clinical setting and potentially reducing long-term health care costs of treatment. However, support for ketamine was somewhat tempered by fact that the drug requires clinical administration and is known to be a street drug of abuse. Additionally, enthusiasm for scopolamine was somewhat tempered by the need for intravenous administration and risk of anticholinergic effects associated with this drug. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, provided perspectives on off-label ketamine;[111-117] six experts commented on off-label scopolamine;[118-123] both of these drugs were discussed for use in treatment-resistant BPD and MDD. We have organized the following discussion of expert comments by the parameters on which experts commented.

Unmet need and health outcomes: Experts commenting on ketamine generally cited a moderate unmet need for new therapy options for treatment-refractory BPD and MDD, particularly fast-acting interventions. Experts' perspectives differed about the potential health impact of ketamine for treatment-resistant depression. Citing the invasiveness of other options (i.e., ECT), several experts anticipated that ketamine would have a moderate to large impact on health outcomes for this patient population. However, other experts thought that ketamine would have a minimal impact on health outcomes in the absence of data on long-term effects, safety, and small sizes of studies thus far. These individuals agreed that efficacy data from larger, well-controlled studies with extended follow-up periods would be needed to predict more substantial impacts on health outcomes.

Experts commenting on scopolamine remarked on the moderate-to-significant importance of the unmet need in treatment-resistant BPD and MDD, highlighting the need for fast-acting therapies with manageable adverse event profiles. Experts indicated that early results for scopolamine were promising, but several cited the need for longer-term efficacy and safety data before definitively deciding about impact on health outcomes. Overall, the majority of experts thought that the scopolamine data indicated efficacy for treatment-resistant BPD and MDD and anticipated a moderate to large impact on health outcomes in this patient population. However, two experts with health research backgrounds anticipated a small impact on health outcomes, citing the short followup times of the studies and data from inconsistent routes of scopolamine administration.

Acceptance and adoption: Commenting on ketamine, most experts anticipated that many clinicians and patients would readily welcome the therapy if it is proved to be an effective option for treatment-resistant disease. Several experts noted the lack of other effective or acceptable pharmacologic therapies as a key driver of acceptance and adoption. But other experts discussed barriers. A few experts with a research background noted that ketamine's classification as a controlled substance and illegal use as a social drug could generate stigma that would impede acceptance and adoption. And another expert postulated that the intravenous route of administration and dosing schedule for ketamine could deter patients.

Commenting on scopolamine, the experts expected moderate to widespread acceptance and adoption by both patients and clinicians. However, two clinical experts noted that the side effects and potential contraindications for anticholinergic medication could limit adoption, and that caution would be needed when selecting appropriate patients to receive scopolamine. An expert with a research background also noted that, as with ketamine, intravenous administration of scopolamine could present a barrier to acceptance and adoption.

Health care delivery infrastructure and patient management: Most standard antidepressant therapies are self-administered oral medications, and experts anticipated a minimal to moderate disruption of health care delivery infrastructure and patient management with the implementation of intravenous ketamine therapy. Disruptions to infrastructure and patient management would primarily result from the addition of multiple visits per week and patient monitoring requirements after ketamine administration, experts concluded.

Experts generally anticipated minimal to no disruption to health care delivery infrastructure and patient management with oral or transdermal scopolamine, indicating that it would likely be a complementary agent added to existing therapy regimens. However, several experts acknowledged that intravenous administration could be significantly more disruptive, and a clinical expert anticipated that this formulation might be provided only to inpatients. Another clinical expert pondered whether scopolamine could reduce the need for inpatient stays or more costly interventions.

Health Disparities: The majority of experts thought that the availability of ketamine in an inexpensive generic form could help to minimize health disparities. However, they also acknowledged that regular travel to a health facility for intravenous ketamine administration may promote health disparities among economically disadvantaged patients. A clinical expert pointed out the potential advantages of this therapy if it were affordable for patients of low socioeconomic status who have limited coverage for often-expensive psychotherapy sessions.

Several experts noted that the impact of scopolamine on health disparities was dependent upon the available/required route of administration and subsequent accessibility of the treatment. Generally, most experts did not anticipate a large impact on disparate populations, but noted that cost could be a factor. They thought that generic, inexpensive forms of the drug could potentially reduce disparities.

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