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

Priority Area 05: Depression and Other Mental Health Disorders

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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 identifying 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 4 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 16,000 leads about potential topics has resulted in identification and tracking of about 1,800 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 600 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 annually. Topics eligible for inclusion are those interventions expected to be within 0–4 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 on drugs or phase II or III data on devices and procedures were available or a program innovation was being implemented; (2) information was compiled by May 16, 2013, in this priority area; *and* (3) we received five to nine sets of comments from experts between October 25, 2011, and May 18, 2013. (Twenty-one topics in this priority area were being tracked in the system as of May 18, 2013.) For program topics, we often extend the timeframe over which we track the topics because programs can take longer to demonstrate their potential. One topic, the citizen soldier peer support outreach program (Buddy-to-Buddy) was designated as having high-impact potential in the previous report. However, after 2.5 years of tracking, it has not diffused outside the State in which it was implemented; thus, its impact has not borne out a high potential, and it will be archived in the system after this report. We present three summaries of three 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. Citizen soldier peer support outreach program (Buddy-to-Buddy) for returning veterans	No high-impact potential at this time
2. * Cortisol antagonist (mifepristone, Korlym) for treatment of psychotic depression	Lower end of the high-impact-potential range
3. * Deep brain stimulation (Reclaim DBS Therapy or Libra DBS) for treatment-resistant depression	Moderately high
4. Off-label intranasal oxytocin for treatment of schizophrenia	No high-impact potential at this time
5. * Off-label ketamine 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 resistance in major depressive disorder (MDD), bipolar disorder,

and posttraumatic stress disorder. 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. A second approach, the proposed use of an implanted deep brain stimulator for treating depression, represents a departure from traditional pharmacotherapy and psychotherapy. Finally, an FDA-approved anesthetic is being investigated for its rapid antidepressant effects; interventions that yield rapid response in severely depressed patients at risk of suicide are critically needed.

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. In patients with PMD, cortisol is secreted at higher rates than in 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 etiological and pathophysiological link between cortisol and PMD, cortisol has been proposed as a therapeutic target for PMD. Mifepristone (Korlym™, Corcept Therapeutics, Inc., Menlo Park, CA) is an oral 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. Three completed phase III trials did not demonstrate statistical superiority of mifepristone over placebo, but the manufacturer asserts this is because of the low dosages used in the trials and is studying mifepristone at higher doses in the ongoing trial.
- **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 improve patient outcomes and 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 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 electroconvulsive therapy or repetitive transcranial magnetic stimulation as second- or third-line therapies for MDD, a proportion of patients affected by MDD have treatment-refractory disease. Therefore, investigators are seeking new approaches for treatment-refractory disease. Deep brain stimulation (DBS), which has become an accepted modality to treat some movement disorders (e.g., Parkinson's disease, dystonia), is being studied for treating psychiatric conditions, including MDD. DBS employs a battery-operated, pacemaker-like neurostimulator implanted in the chest below the clavicle (collarbone) to deliver controlled electrical stimulation to the brain 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 inhibit the activity in that region of the brain. Currently, both the Reclaim® device (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 MDD. Reclaim trials for MDD have an anticipated completion date of October 2014; the BROADEN phase III trial of Libra had yet to complete enrollment in its trial as of June 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 second-line therapeutic option.

- **Key Expert Comments**: Experts commenting on this topic believe that DBS could have an impact on several parameters of the health care system: increasing costs of care by adding a surgical procedure to the options, shifting some of the care from the outpatient setting to inpatient surgery, adding neurosurgery to the clinical treatment pathway, 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 their thoughts about high-impact potential.
- **Potential for High Impact:** Moderately high

Off-Label Ketamine for Treatment-Resistant Bipolar Depression and Major Depressive Disorder

- **Key Facts**: Despite widespread use, approved medications for treating bipolar depression do not elicit the desired therapeutic response in many patients and are associated with considerable lag time in response. Only a fraction of treated patients respond within a week of starting any of the many medications available for bipolar depression 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 bipolar depression 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 bipolar depression or MDD.
- **Key Expert Comments**: Overall, experts who commented were highly optimistic about the drug's potential to meet the need for rapid-onset, effective treatment for bipolar depression and MDD. They thought that the drug 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 the potential of relapse.
- **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 major depressive disorder (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 pharmacotherapeutic agent indicated for use in this population.

Intervention: Cortisol, a hormone produced by the adrenal gland, mediates the body's response to stress.[4] In patients with PMD, cortisol has been observed to be secreted at higher rates (hypersecreted) than in patients with nonpsychotic MDD.[5] Further, research has suggested that administering glucocorticoids to healthy participants can induce cognitive deficits similar to those seen in patients with PMD.[5] Because this evidence might point to an etiological and pathophysiological link between cortisol and PMD, cortisol has been proposed as a therapeutic target for PMD.[5]

Mifepristone (Korlym™, formerly CORLUX) is an oral glucocorticoid-II receptor (GR-II) antagonist that is being investigated for treating PMD.[6] Cortisol binds to glucocorticoid receptors in the brain, including the GR-II.[5] Mifepristone's manufacturer purports that blocking the GR-II receptor might prevent excessive cortisol activity, potentially relieving PMD symptoms.[6] For this condition, 1,200 mg of mifepristone is being administered orally, in four 300 mg tablets, once daily, for several days.[7]

Clinical trials: Using mifepristone to treat PMD is being investigated in one ongoing phase III clinical trial.[7] Three completed phase III trials did not demonstrate superiority of mifepristone over placebo.[6] However, the manufacturer continues to develop mifepristone for this condition at a higher dose than that used in the three earlier trials, stating 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 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.[6]

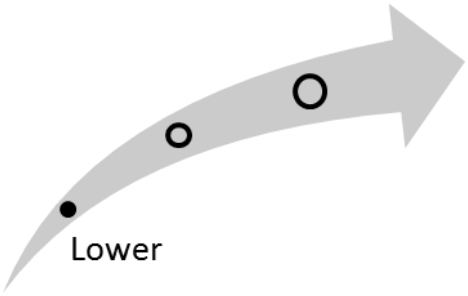
This finding prompted the manufacturer to design a new phase III trial using a higher dosage, stating that this change may allow "more patients to achieve higher plasma concentrations of [the] drug and improve the efficacy 'signal.' "[6] In "Study 14," it is testing a 1,200 mg, once-daily dosage given for 7 days. It expects to complete patient enrollment at 20 clinical sites in 2013.

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] Korlym was FDA approved in 2012 for treating Cushing's disease.[8] Currently, it can be used off label for PMD.

Clinical Pathway at Point of This Intervention

Although no treatments are FDA approved for PMD, pharmacotherapy used for MDD is typically the first-line treatment and involves concomitant use of antidepressant and antipsychotic medications.[1,9] For patients who do not respond to pharmacotherapy, ECT is sometimes used.[9] 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 would be needed before clinicians adopted use. If the drug is proved to be effective for this condition, experts thought, it could have important impacts on improving patient outcomes and 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.[10-15] 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 current 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."[15]

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 DBS Therapy or Libra DBS) for Treatment-Resistant Depression

Unmet need: Although medication and psychotherapy are the primary interventions for treatment-resistant 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., Parkinson's disease, dystonia), is being studied as a treatment for psychiatric conditions, including MDD, and is already FDA approved under a humanitarian device exemption for treatment-refractory obsessive-compulsive disorder.

Intervention: DBS is a surgical intervention in which a neurostimulator device delivers electrical signals to the brain.[16] It consists of an insulated wire electrode that is placed into the brain, a pacemaker-like neurostimulator, and another insulated wire that connects the brain lead to the device.[16] The transmitted electrical signal interferes with brain activity at the placement site, thereby inhibiting activity in that region of the brain.[17] In treating MDD, different clinical investigators and manufacturers are targeting different areas of the brain with their respective devices.

DBS implantation is typically a two-phase process: electrode placement and neurostimulator implantation.[16] In phase 1, using local anesthesia, a neurosurgeon drills into the patient's skull and places the electrodes, sometimes aided by imaging-guided techniques.[16] In phase 2 with the patient under general anesthesia, a neurosurgeon implants the neurostimulator just below the collarbone.[16] The extension wire is passed 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.[16]

Between 2 and 4 weeks after implantation, the device is activated and programmed through a wireless programming computer.[17] As instructed by their physicians, patients can turn the neurostimulator on and off with a control magnet.[17] About every 6–12 months, followup surgery is needed to replace the device's batteries.[17]

Clinical trials: 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])."[18] According to Medtronic, patients who undergo DBS for MDD 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).[19] 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.[19] As of June 2013, the trial Web site (www.broadenstudy.com) indicated that enrollment remained open.

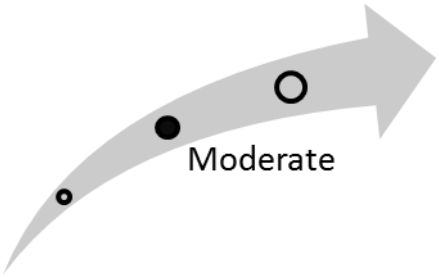
Manufacturer and regulatory status: Medtronic, Inc., of Minneapolis, MN, is developing the Reclaim® DBS Therapy device, and St. Jude Medical, Inc., of St. Paul, MN, is developing its Libra® DBS system for treatment-resistant depression. Reclaim is in a phase III trial under an FDA investigational device exemption (IDE), and Libra is recruiting for its FDA-approved IDE trial.[19-21]

Clinical Pathway at Point of This Intervention

American Psychiatric Association guidelines for treating 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 for this indication, DBS is expected to be positioned as an additional second-line option. Because DBS is invasive, pharmacotherapy and psychotherapy are expected to remain first-line treatments for MDD with

DBS as a complement to drug therapy. Depending on DBS treatment efficacy in individuals, its use might allow some patients to use lower drug dosages or eliminate medication use; however, no data are yet available to support this hypothesis. DBS therapy is incompatible with some other device-based depression treatments. For example, TMS is contraindicated in patients with implanted DBS devices, and 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 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.[22-27] We 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 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 who 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 of this procedure, some experts thought the invasiveness and possible side effects might be barriers to acceptance, but others thought that patients with intractable MDD 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.

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 not only because DBS provides a new treatment modality in this patient population (surgical implant rather than medical and talk therapy), but because it has the potential to shift care from oral pharmacotherapy to neurosurgery. However, several experts stated that because DBS would be indicated for use in only a small subpopulation of patients with MDD, these changes would not dramatically affect the health care system as a whole.

Generally, experts agreed DBS would require changes to staffing mix, care setting, and clinician training practices because the intervention necessitates a shift from medical therapy at home to the neurosurgical operating room and inpatient hospital setting. 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).

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 Ketamine for Treatment-Resistant Bipolar Depression and Major Depressive Disorder

Unmet need: Many cases of bipolar depression and MDD fail to respond adequately to available therapies.[28] Also, because available pharmacotherapies have a delayed onset of action and once active, do not exert effects rapidly (i.e., within hours), they are ineffective for alleviating acute episodes associated with these conditions.[28,29] Further, available agents are associated with undesirable side effects that may limit patient adherence to recommended treatment plans.[28] Therefore, an unmet need exists for novel, effective, fast-acting, and well-tolerated interventions for treating depressive episodes that occur with bipolar disorder or MDD. Glutamate is known to be the major excitatory neurotransmitter in the brain.[28] Researchers believe that dysfunction in glutamate neurotransmission may play a major role in the etiology of depressive symptoms in both bipolar disorder and MDD, although its exact mechanism of action is still unknown.[28,30] Research has suggested that glutamate N-methyl-D-aspartate (NMDA) receptors mediate this glutamatergic dysregulation, giving rise to the hypothesis that NMDA receptor antagonists may have antidepressant effects.[30] Data from both preclinical and clinical studies have suggested that NMDA receptors are viable therapeutic targets to investigate for treating bipolar depression.[30]

Intervention: Ketamine hydrochloride (ketamine) is a noncompetitive, high-affinity NMDA antagonist that is approved in the United States for use as a general anesthetic.[28] Now, ketamine is being investigated for the intravenous treatment of treatment-resistant or acute severe depressive episodes in patients with bipolar disorder or MDD.[28,31] 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.[28,32]

Clinical trials: Clinical trials have shown ketamine to have a rapid (e.g., within minutes or hours) therapeutic effect; research suggests that this rapid effect may be due to the agent's high affinity for NMDA receptors and to its intravenous administration route.[28] In clinical trials for these indications, ketamine is generally administered as a single intravenous infusion, at dosages lower than those used for anesthesia.[31] 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.[29,33,34]

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."[35] 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.[35] This statistically significant superiority was maintained 7 days after administration.[35]

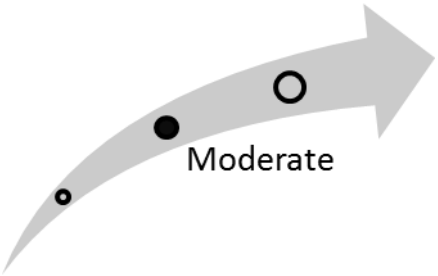
Manufacturer and regulatory status: The drug was launched in 1966 by King Pharmaceuticals, now a unit of Pfizer, Inc., of New York, NY, as a general anesthetic agent, and both branded and generic versions are sold by several manufacturers.[36] However, the drug's manufacturers do not appear to be seeking marketing approval for an expanded label. Instead, ketamine's off-label use in bipolar disorder and MDD is being investigated by research institutions, such as Baylor College of Medicine (Houston, TX), Mount Sinai School of Medicine (New York, NY), National Institute of Mental Health (Rockville, MD), and the National Institutes of Health Clinical Center (Bethesda, MD).[37-39]

Ketamine is classified as a Schedule III nonnarcotic controlled substance and, at higher doses, is sometimes abused as a street drug ("Special K"), which may affect the regulatory pathway for this indication and its availability for off-label use.[31,40]

Clinical Pathway at Point of This Intervention

According to the U.S. Department of Veterans Affairs, acute depressive episodes of bipolar disorder are treated with combinations of pharmacotherapy (e.g., quetiapine, lamotrigine, lithium), psychoeducation, and psychotherapy (e.g., counseling). ECT or alternative therapies are also sometimes considered.[41] According to the National Institute of Mental Health, MDD is usually treated with pharmacotherapy (e.g., selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors) and psychotherapy.[42] In some cases in which drugs and other therapies are not effective, clinicians might recommend ECT, vagus nerve stimulation, or TMS.[42] If ketamine is determined to be effective in treating these mood disorders, it is expected to be positioned for treating acute depressive episodes in patients with either acute bipolar depression or MDD.[28]

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



Overall, experts commenting on this topic were highly optimistic about this intervention's potential to meet the need for a rapid-onset, effective treatment for treatment-refractory bipolar depression and MDD. They thought the drug would have an important impact across many health system parameters, including shifting care from outpatient to the clinical setting for infusion therapy and potentially reducing long-term health care costs of treatment. However, support for this intervention was somewhat tempered by fact that the drug requires office-based administration and is known to be a street drug of abuse. 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 this intervention.[43-49] We organized the following discussion of expert comments by the parameters on which experts commented.

Please note that expert comments were received before the recent abstract publication by APA; however, the results presented in the abstract were consistent with previously published data.

Unmet need and health outcomes: An extremely important unmet need exists for rapidly effective medications for treatment-refractory bipolar depression or MDD, the experts strongly agreed, citing issues such as prevalence, societal burden of the illness, and lag time for efficacy of current medications. Furthermore, most of the experts were highly optimistic about this agent's ability to meet this need, citing both the underlying mechanism of action and the promising clinical trial data to date. Experts suggested that because of ketamine's rapid efficacy, it may be most useful in patients who are experiencing suicidal ideation and are brought to the emergency department.

Acceptance and adoption: Although the experts agreed that uptake of this therapy could both influence and be heavily influenced by patient and clinical acceptance, they were divided on whether acceptance would be broad or narrow. On one hand, some experts thought that patients

with treatment-refractory depression would readily accept a novel intervention that has the potential to improve their quality of life, and one clinical expert went so far as to suggest that this will become a "standard practice in emergency departments in the management of suicidal patients."[47] However, other experts suggested that medication infusion would require more office visits and could be a barrier to use. Other barriers indicated by some experts are that ketamine is associated with dissociative reactions and that it has a reputation as a "street drug" with a known risk of abuse.

Health care delivery infrastructure and patient management: Ketamine would affect the way patients are managed for these conditions because the drug is administered via an infusion and must, therefore, be given by a medical professional, the experts generally agreed. They noted that this intervention would shift care (oral pharmacotherapy) from an outpatient home setting to a clinical setting. Even more, experts stated that this would be the first agent that might be able to produce rapid antidepressant effects, which would represent a significant departure from current patient management.

In light of the potential change in care setting, experts noted, this intervention would likely affect staffing levels and health care processes for treating this population. Case volume in infusion centers and emergency rooms delivering mental health care might increase, which, in turn, would require increased staffing to administer the drug and monitor patients. For these reasons, most experts believe, this intervention would increase the per-patient cost of care for this patient population, although the drug itself is not expected to be particularly costly. Several experts believe that these initial costs of care would be recouped over time because a rapid-action, efficacious drug might obviate the need for inpatient stays, reduce the frequency of visits to clinician's offices, and move treatment to partial-hospital or outpatient care settings.

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