AHRQ Healthcare Horizon Scanning System – Potential High Impact Interventions Report

Priority Area 05: Depression and Other Mental Health Disorders

Potential High Impact Interventions Report

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA29020100006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual Topic Profiles are developed for technologies and programs that appear to be closer to diffusion into practice in the United States. Drafts of those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify those interventions that experts deem, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually, and topics included may change depending on expert comments received on interventions issued for comment during the preceding six months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in the horizon scanning, assessing the leads for topics, or provide opinions regarding potential impact of interventions.

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None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor target technologies and innovations in health care and to create an inventory of target technologies that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is the identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is the analysis of the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future utilization and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, more than 7,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0 to 4 years of potential diffusion (e.g., in phase III trials for pharmaceuticals or biotechnologies or in phase II or a trial with some preliminary efficacy data on the target population for devices and programs) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling a profile on topics and issuing topic profile drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest (COI).

Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the high impact potential designation. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the potential high impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as potential high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The material on interventions in this Executive Summary and report is organized according alphabetically by disease state. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary. The table below lists the 10 topics for which (1) preliminary phase III data on drugs or phase II data on devices were available, or a program innovation was being implemented; (2) information was compiled by November 2011 in this priority area; *and* (3) we received six to eight sets of comments from experts between February and November 1, 2011. (A total of 44 topics in this priority area were being tracked in the system as of November 2011.) For purposes of the Potential High Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present four summaries on five topics (indicated below by an asterisk) that emerged as potential high impact on the basis of experts' comments and their assessment of potential impact.

Priority Area 05: Depression and Other Mental Health Disorders
1. Adusuve Staccato (inhaled loxapine AZ-004) for rapid treatment of schizophrenia or bipolar agitation
2. Agomelatine (Valdoxan) for treatment of major depressive disorder
3. *Citizen soldier peer support outreach program (Buddy-to-Buddy) for returning veterans
4. *Deep brain stimulation for treatment-resistant depression
5. *Deep brain stimulation for treatment-resistant obsessive-compulsive disorder
6. Deep transcranial magnetic stimulation for treatment of major depressive disorder
7. *Extended intensive psychotherapy assisted by methylenedioxymethamphetamine for treatment of posttraumatic stress disorder
8. *Ketamine for treatment-resistant bipolar depression and major depressive disorder
9. Magnetoencephalography for diagnosis of posttraumatic stress disorder
10. Off-label riluzole (Rilutek) for treatment of major depressive disorder

Discussion

One theme common to health interventions being developed for mental health disorders is the search for options to address treatment resistance in disorders such as major depressive disorder (MDD), obsessive-compulsive disorder (OCD), bipolar disorder, and posttraumatic stress disorder (PTSD). The proposed use of implanted devices for treatment of mental health conditions represents a departure from traditional pharmacotherapy and psychotherapy approaches. Use of a technically banned substance in clinical trials for a new therapeutic purpose could herald a significant change in service delivery for treatment-resistant PTSD. In the absence of optimal, effective strategies for PTSD, one program captured experts' attention as having high potential to improve support for returning veterans with PTSD.

Bipolar Depression, Major Depressive and Obsessive Compulsive Disorder

Deep Brain Stimulation for MDD and OCD

- **Key facts**: According to the American Psychiatric Association, guidelines for first-line therapy of MDD and OCD recommend combination oral pharmacotherapy and psychotherapy. Second-line therapy for MDD includes drug therapy, combination therapy, and sometimes, electroconvulsive therapy or transcranial magnetic stimulation (TMS); second-line therapy for OCD includes different drugs, combination therapy, TMS or ablative neurosurgery. For patients with treatment-resistant MDD or OCD, investigators have sought new approaches. Deep brain stimulation (DBS), which has become an accepted modality to treat some movement disorders (e.g., Parkinson's disease, dystonia), is being explored as a treatment for psychiatric conditions, including MDD and OCD. 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 the neural activity at the placement site and is intended to inhibit the activity in that region of the brain. Currently, the Reclaim® device (Medtronic, Inc., Minneapolis, MN) and Libra® device (St. Jude Medical, Inc., St. Paul, MN) are in development for DBS for MDD. Reclaim is in phase III trials for MDD with an anticipated completion date of October 2014; Libra is also in phase III trials. The Reclaim device received humanitarian device exemption (HDE) approval for OCD, which marked the first U.S. Food and Drug Administration (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 intervention predicted that DBS could have a significant impact on many parameters of the health care system, including increased costs, a shift in care setting from outpatient to inpatient, changes in staffing models with the addition of a neurosurgical team, and barriers to clinical and patient acceptance because of the invasiveness of the procedure and need for a different type of followup than pharmacotherapy options involve. These experts generally believe that these potential changes would limit diffusion of DBS for MDD and OCD, possibly also minimizing access to DBS for these indications. If DBS does diffuse for these indications, it could potentially significantly change the landscape of care for both treatment-refractory MDD and OCD.

- **Potential for High Impact:** High

Off-Label Ketamine for Bipolar Depression and MDD

- **Key facts**: Despite widespread use, approved medications for bipolar depression treatment do not elicit the desired therapeutic response in many patients and are associated with considerable lag time in response. Only a fraction of patients respond within a week of administration. 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 (NIMH) for treatment-resistant bipolar depression and MDD. The drug is given intravenously, and preliminary data have indicated it has produced a rapid (within 2 hours) and relatively sustained (approximately 1 to 2 weeks long), significant reduction in the Hamilton Depression Rating scales in some patients with bipolar depression or MDD.
- **Key Expert Comments**: Overall, the experts commenting on the intervention were highly optimistic about its 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.
- **Potential for High Impact:** High

Posttraumatic Stress Disorder

Citizen Soldier Peer Support Outreach Program for Returning Veterans

- **Key facts**: Despite the high number of citizen soldiers who develop PTSD, clinical depression, substance abuse, sleep disturbances, or suicidal thoughts, only about half who need intervention receive care. Therefore, programs have been developed that are intended to link more soldiers to mental health services and support. One of these new programs, the Buddy-to-Buddy program, is a veteran peer-outreach support program that operates by training veterans to provide support and linkage to needed resources for returning civilian soldiers. The program is based on the theory that for returning soldiers, peer-to-peer "buddies" are uniquely positioned to offer emotional support and resources because of the shared experience of the war setting. This, in turn, might help reduce the stigma associated with seeking mental health care.
- **Key Expert Comments**: While data regarding the effectiveness of the program are limited, experts agreed that the unmet need this program purports to address is vast and important, and that this program is likely to meet this unmet need, especially for groups of people who are affected by health disparities (e.g., limited access to services, stigma associated with seeking mental health care). However, because the service is designed to link patients to existing services, experts did not predict that that this program would particularly disrupt current health care infrastructure or patient management models, other than potentially increasing patient volume in treatment centers.
- **Potential for High Impact:** Moderately high

Extended Intensive Psychotherapy Assisted by Methylenedioxymethamphetamine for Treatment of Posttraumatic Stress Disorder

- **Key facts**: Methylenedioxymethamphetamine (MDMA, also known as *Ecstasy*) is a synthetic, psychoactive drug with a chemical structure similar to both mescaline and methamphetamine. MDMA ingestion results in psychological effects that are characterized by feelings of increased energy, euphoria, and emotional warmth and distortions in time, perception, and tactile experiences. MDMA appears to be unique in that it gives rise to these emotional effects without apparently affecting other psychological functions, such as visual perception or cognitive processes. These effects have led to research on its use to assist in difficult-to-treat cases of PTSD during extra-long therapy sessions. It has been proposed that use of MDMA can enable patients to introspectively access their emotions and internal conflicts during a psychotherapeutic session without the concomitant fear normally associated with those emotions and memories. With this fear mitigated, patients might be better able to engage in psychotherapy with their therapists. When used for this purpose, the drug is administered only when it precedes a psychotherapy session of unusually long duration: 8 hours. The U.S. Government has approved the use of MDMA for clinical research, and a trial is ongoing. MDMA is on the list of Schedule I controlled substances and the process by which MDMA would become available for this clinical purpose is unclear.
- **Key Expert Comments**: In general, experts commenting on this intervention thought that, if adopted, it had the potential to markedly disrupt certain aspects of the existing mental health care system—prescribing patterns, psychotherapy practice patterns, coding systems, and therapy settings. Most experts thought this intervention would require extensive training on the part of the clinicians and/or therapists to be effective. They suggested clinicians would have to be trained in safe administration of MDMA and how to monitor for side effects and in the physically and emotionally demanding therapeutic style that this intervention would require. Experts were skeptical about the ability of MDMA-assisted psychotherapy to provide long-term improved patient health outcomes.
- **Potential for High Impact**: Moderately high

Bipolar Depression, Major Depressive, and Obsessive-Compulsive Disorder Interventions

Intervention

Deep brain stimulation for selected mental health disorders

Although medication and psychotherapy are the primary treatments for patients with treatment-resistant major depressive disorder (MDD) and patients with treatment-resistant obsessive-compulsive disorder (OCD), investigators have sought new approaches to treat each of these conditions when drugs and psychotherapy fail to adequately control symptoms. One approach, deep brain stimulation (DBS), an accepted treatment for movement disorders (e.g., Parkinson's disease, dystonia), is being explored as a treatment for psychiatric conditions, including MDD and OCD.[1,2]

DBS therapy uses a battery-operated, pacemaker-like neurostimulator, which a surgeon implants subcutaneously in the chest below the clavicle, to deliver controlled electrical stimulation to the brain via thin wire electrodes.[1] The electrodes carry a high-frequency electrical signal that interferes with the neural activity at the placement site and is intended to inhibit the activity in that region of the brain.[3]

Physicians often perform the device implantation in two separate procedures: lead placement and neurostimulator implantation.[1] The surgeon implants electrode leads in the brain using local anesthesia under stereotactic guidance; for this procedure, the patient is usually hospitalized overnight.[1] Neurostimulator implantation is performed under general anesthesia, usually as an outpatient procedure. The electrode leads connect to the neurostimulator through insulated extension wires, which are tunneled under the skin at the scalp and down the neck to the chest.[1] To treat OCD, a neurosurgeon implants electrode leads in the anterior limb of the internal capsule (AIC, also called the ventral capsule/ventral striatum) and connects the leads to the neurostimulator. Because DBS for OCD involves bilateral stimulation of the AIC, surgeons implant two neurostimulators in the chest.[2] For the treatment of MDD, different clinical investigators and manufacturers may target different areas of the brain with their respective DBS devices.[1]

About 2 to 4 weeks after implantation surgery, physicians activate and program the neurostimulator through a wireless programming computer, with followup therapeutic adjustment performed as needed.[1] As instructed by their physicians, patients can turn the neurostimulator on and off with a control magnet. The DBS battery lasts from 6 to 16 months on average, depending on device programming and the frequency of stimulation required.[1] When the battery is depleted, a surgeon must perform a minor surgical procedure to replace the neurostimulator device. In most cases, the new device can be connected to the existing electrode leads.[1]

Currently, Medtronic, Inc. (Minneapolis, MN), and St. Jude Medical, Inc. (St. Paul, MN), are each developing DBS technology for mental health applications.[4,5]

Medtronic is evaluating its Reclaim® DBS Therapy for treatment-resistant depression in phase III clinical trials in the United States under an investigational device exemption (IDE) from U.S. Food and Drug Administration (FDA).[4,6] In results from a 2010 clinical trial of 10 patients with severe treatment-resistant MDD that had not responded to pharmacotherapy, psychotherapy, or electroconvulsive therapy (ECT), and in whom a DBS system was implanted, researchers for the Medtronic device concluded 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])."[7] According to Medtronic, patients who undergo DBS to treat MDD would face risks similar to those faced by patients who undergo DBS for other indications.

In February 2009, the FDA granted Medtronic approval for Reclaim DBS therapy for OCD under a humanitarian device exemption, which was the first FDA approval of any kind for a DBS device for a psychiatric indication.[4] The Reclaim device is indicated for bilateral stimulation of the AIC as an adjunct to medications and as an alternative to anterior capsulotomy for treatment of chronic, severe,

treatment-resistant OCD in adult patients whose disease has failed to respond to at least three selective serotonin reuptake inhibitors. The device has been on the market for treatment of OCD in Europe since July 2009.[2]

In a 2010 clinical trial of the Medtronic device in patients with treatment-refractory OCD, in which primary endpoints included change from baseline in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores and in which responders were defined as having at least 35% decrease in Y-BOCS score, investigators concluded, "In the open phase, the mean (SD) Y-BOCS score decreased by 46%, from 33.7 (3.6) at baseline to 18.0 (11.4) after 8 months ($p < 0.001$). Nine of 16 patients were responders, with a mean (SD) Y-BOCS score decrease of 23.7 (7.0), or 72%. In the double-blind, sham-controlled phase ($n = 14$), the mean (SD) Y-BOCS score difference between active and sham stimulation was 8.3 (2.3), or 25% ($p = 0.004$)."[8]

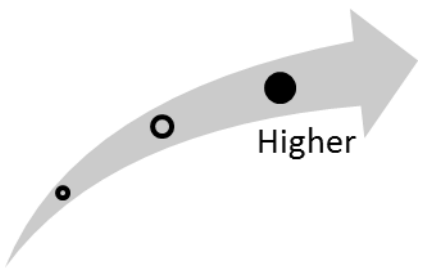
According to St. Jude Medical, the company is evaluating its Libra® DBS system for treatment-resistant depression in the phase III BROADEN (Brodmann Area 25 Deep Brain Neurostimulation) clinical trial under an IDE.[5] According to a July 2011 company press release, FDA approved an expansion of the trial to 20 sites across the U.S., and expanded enrollment to 125 patients.[5] As of November 2011, the company had not stated when it anticipated having results from the trial.

Clinical Pathway at Point of This Intervention

According to the American Psychiatric Association, guidelines for treatment of MDD and treatment of OCD recommend a combination of oral pharmacotherapy and psychotherapy. Second-line therapy for MDD includes ECT or transcranial magnetic stimulation (TMS); second-line therapy for OCD includes TMS or ablative neurosurgery. If approved for these separate indications, DBS is expected to be positioned as an additional second-line therapeutic option.

Because DBS is invasive in nature, pharmacotherapy and psychotherapy are expected to remain first-line treatments for MDD and for OCD. DBS is indicated to complement conventional drug therapy for MDD or OCD. Depending on DBS treatment efficacy in individuals, DBS might allow some patients to use lower drug dosages or different drug regimens. 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. Additionally, 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 1. Overall High Impact Potential: Deep brain stimulation for selected mental health disorders



Experts commenting on this topic predicted that DBS could have a significant impact on many parameters of the health care system, including markedly increased costs, a shift in care setting from outpatient to inpatient, the addition of a neurosurgical team, and barriers to clinical and patient acceptance. These experts generally believe that these potential changes could limit diffusion of DBS for MDD and OCD. However, if DBS does diffuse for these indications, it might potentially improve patient outcomes, but would significantly change the landscape of care for both MDD and OCD. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact 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.[9-14] One expert reported a slight conflict of interest (a clinician involved in research related to DBS), and this interest was balanced by perspectives of five experts without conflicts of interest. Six other experts, also with backgrounds in clinical work, health systems, and/or research, offered their perspectives on the potential impact of DBS for OCD.[15-20]

Most of the experts agreed that because not all patients respond to currently available treatments for MDD or OCD, an important unmet need exists. However, some dissenting experts stated that the unmet need is not very significant, because the number of patients who do not respond to (first-, second-, or third-line) treatments represents a small fraction of the total number of patients with these conditions.

Overall, experts commenting on material on these topics supported the theory underlying use of DBS in these populations, which may reflect their knowledge about the efficacy that DBS has shown in patients with movement disorders. While most of these experts agreed that the available data suggest that the intervention shows promise in MDD and OCD, most offered a caveat with this view calling for more efficacy data, especially from larger double-blind trials with a sham control or comparison to other second- or third-line interventions.

These experts asserted that DBS has the potential to markedly disrupt many aspects of the health care system—care models, treatment paradigms, and patient management—not only because it provides a new treatment modality (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 dissented in a fashion, stating that because DBS would be indicated for use in only a small subpopulation of patients with MDD or OCD, basic care models and treatment paradigms for the majority of patients would not change. That is, all patients would still be initiated on pharmacotherapy and psychotherapy, and if their responses were not satisfactory, they would be considered for a different intervention, such as TMS. Because DBS is positioned at the same point in the clinical pathway as TMS, ECT, or ablative neurosurgery, these experts contend that the clinical pathway would not change.

Experts agreed that this intervention would require a dramatic change in 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, the new multidisciplinary care team will require a referring psychiatrist, a neurosurgeon, a neurosurgical team for implantation, and a neurologist for patient monitoring. Several of the experts noted that this would require a great deal of clinician training, claiming, as one expert opined, “It will demand that more surgeons be trained in stereotactic, functional neurosurgery, and [have] greater familiarity with DBS technology, theory, and procedures.” Experts also noted that psychiatrists would need to be trained in identifying patients who are appropriate for referral for DBS. Most experts providing comments also spoke to the predicted patient learning curve, citing the need to educate patients on how to turn the device on or off, how to provide feedback to clinicians about the stimulation parameters, and how to recognize safety concerns.

In light of those changes, most experts predicted, DBS could have a notable impact on cost of care for the intended patient population: treatment-resistant MDD and OCD. First, the upfront costs are significant, given that “neurosurgical procedures to implant the DBS devices typically cost between $60,000 and $80,000” and that “cost of battery replacement is about $10,000 to $20,000.”[21] Also, battery replacement involves a surgical procedure. It should be noted that experts commenting tended to compare their cost change estimates to pharmacotherapy, though DBS is not likely to compete with pharmacotherapy, but rather is expected compete with most costly third-line interventions such as

TMS, ECT, and ablative neurosurgery. Therefore, the expected change in upfront costs might not be quite as significant as these experts predict. Second, experts predicted that if DBS is effective at controlling symptoms for MDD or OCD, it has potential to decrease the significant financial burden associated with ongoing, uncontrolled MDD and OCD.

Experts commenting on these topics predicted a great deal of controversy for this intervention, which they thought could affect patient and clinical acceptance. Some experts thought the invasiveness and possible side effects of the procedure might be barriers to acceptance, while others thought that patients with intractable MDD or OCD would be willing to accept an intervention that potentially could improve symptoms and quality of life, regardless of its invasiveness. Overall, these experts thought clinicians would be reluctant to offer this intervention because of high costs, invasiveness, infrastructure requirements, potential risks, and the amount of training required to implement the intervention. However, one expert, speaking from a health systems perspective, pointed out that prior peer-reviewed studies predicted clinical acceptance for this intervention. This point was echoed by an expert with a research perspective who stated, "DBS is fairly well established for other diagnoses."[22] Experts also thought controversy might arise in light of the debate over using neurosurgical interventions for mental health conditions, and one expert predicted public push-back over what may be considered or perceived as a form of "mind control."

Intervention

Off-Label Ketamine for Treatment of Bipolar Depression

Despite their widespread use, currently approved medications for bipolar depression do not elicit a therapeutic response in many patients.[23] Also, these medications are associated with a considerable lag time in response, with only a fraction of patients responding by the end of the first week of treatment. This delay can result in increased suicide risk and mortality.[23] Therefore, an unmet need exists for effective medications that offer a rapid time to elicit a response.

Researchers believe that dysfunction in glutamate neurotransmission could play a major role in the etiology of depressive symptoms, although its exact mechanism of action is still unknown.[24] Research suggests that N-methyl-D-aspartate (NMDA) receptors might mediate this glutamatergic dysregulation. This has given rise to the hypothesis that NMDA receptor antagonists might have antidepressant effects.[24] Data from both preclinical and clinical studies have suggested that NMDA receptors are viable therapeutic targets to investigate for the treatment of bipolar depression.[24]

Ketamine hydrochloride (ketamine) is a nonopiate NMDA receptor antagonist under study for use in the treatment of bipolar depression.[25] The drug was originally launched by King Pharmaceuticals, now a unit of Pfizer, Inc. (New York, NY), in 1966 as a general anesthetic agent.[25] In results from a clinical trial, researchers reported that a single infusion of ketamine (0.5 mg/kg of body weight for 40 minutes) produced a rapid (within 2 hours) and relatively sustained (approximately 1 to 2 weeks long) significant reduction in Hamilton Depression Rating scales in patients with MDD.[25,26]

The National Institute of Mental Health is funding the research and also investigating the drug for treatment of MDD.[27] In results from a completed clinical trial on the use of ketamine in 18 patients with bipolar depression, investigators concluded, "Within 40 minutes, depressive symptoms significantly improved in subjects receiving ketamine compared with placebo; this improvement remained significant through day 3. The drug different effect size was largest at day 2. Seventy-one percent of subjects responded to ketamine and 6% responded to placebo at some point during the trial. Ketamine was generally well-tolerated; the most common adverse effect was dissociative symptoms, only at the 40-minute point."[23] According to FDA, ketamine is currently listed as a Schedule III controlled substance.[28] Manufacturers of the drug do not appear to be pursuing regulatory approval for a labeled indication change for ketamine, so the potential regulatory process for using the drug in this capacity is unknown at this time.

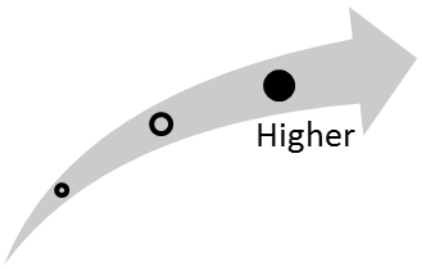
Clinical Pathway at Point of This Intervention

According to the U.S. Department of Veterans Affairs, clinical guidelines for treatment of an acute depressive episode in a patient with bipolar disorder recommend the following: referring for hospitalization if necessary; prescribing pharmacotherapy; providing psychoeducation, psychotherapy (e.g., counseling), and family intervention as indicated; and considering ECT or alternative therapies.[29]

Currently approved pharmacologic treatments for bipolar depression include lithium, quetiapine, and the combination of olanzapine and fluoxetine; other treatments include lamotrigine, antidepressants, and atypical antipsychotics.[23] Despite their widespread use, these medications do not elicit a therapeutic response in many patients.[23] Also, researchers purport that these medications are associated with a considerable lag of onset, with only a fraction of patients responding by the end of the first week of treatment; this delay can result in increased suicide risk and mortality.[23] Furthermore, these drugs operate via a different mechanism of action from that of ketamine. All of these factors suggest that ketamine, if approved for marketing, has the potential to both compete with and complement currently approved medications. Nonpharmacologic interventions used in the treatment of

bipolar depression (e.g., psychoeducation, counseling, family intervention, ECT) will likely remain as complementary therapies to ketamine, if the drug is approved for marketing.

Figure 2. Overall High Impact Potential: Ketamine for treatment of bipolar depression



Overall, the experts commenting on this material were highly optimistic about this intervention's potential to meet the need for a rapid-onset, effective treatment for bipolar depression. They predicted that the drug would have an important impact across many health system parameters, including processes of care and care-setting shift from self-administration of an oral drug to administration of medication at an infusion center. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.[30-36] The experts strongly agreed that the unmet need for rapidly effective medications for bipolar depression is extremely important, citing issues such as prevalence and societal burden of the illness and efficacy of current medications. Furthermore, most of the experts strongly supported the rationale underlying the use of ketamine to meet this unmet need. One expert, however, stated that the role of glutamatergic neurotransmission in bipolar depression is not completely understood, and thus, questioned whether this intervention would produce benefits. This view was balanced by other experts who asserted that evidence is growing to support the role of NMDA receptors in this condition.

Experts commenting on this topic were generally certain about ketamine's potential to improve health outcomes in this population, citing data from a pilot trial that showed both efficacy and safety. Two experts, however, pointed out that long-term data on the intervention's benefits have not accrued yet, and uptake of this intervention might be limited until such data become available. These experts were confident that, if available for use in this indication, ketamine has potential to affect the current understanding of bipolar depression, disrupt current care models, shift the way the conditions are treated, and shift the way patients are managed. Within these parameters, two salient themes emerged. First, if ketamine is proven effective, it would likely shift the focus of research and treatment to the role of the glutamatergic pathway. Second, because drug is given by infusion, care would shift from home care (e.g., oral therapy) to the clinical setting. One expert, speaking from a research perspective, noted that because of ketamine's rapid effect, it might prove useful as a diagnostic tool.

In light of the potential change in care setting, experts noted, this intervention would be likely to affect staffing levels and health care processes for treating this population. That is, patient volume in infusion centers would increase, which in turn would require increased staffing to administer the drug and monitor patients. For these reasons, most experts predicted, this intervention would increase the per-patient cost of care for these patient populations. One clinical expert, however, predicted that costs of care would be reduced over time because a rapid-action, efficacious drug might obviate the need for inpatient stays, frequent visits to clinician's offices, and treatment in partial-hospital care settings.

Though the experts all agreed that uptake of this therapy could both influence and be heavily influenced by patient and clinical acceptance, experts were divided on whether acceptance would be broad or narrow. 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, while other experts thought that the infusion method of administration and required frequent office visits could be a barrier. In terms of clinical acceptance, rapid uptake because of the potential for increased revenues and the intervention's potential efficacy and safety profile was predicted by some of the experts.

Others predicted reluctance because of the increased cost of staffing and administration. Because ketamine is associated with dissociative reactions, and because it is a "street drug" that might prompt drug users to seek medically inappropriate treatment, several experts thought the intervention has a high potential for controversy.

Posttraumatic Stress Disorder Interventions

Program

Citizen Soldier Peer Support Outreach Program (Buddy-to-Buddy) for Returning Veterans

Twenty-five percent to 40% of citizen soldiers (National Guard and Reserves) who were deployed to Afghanistan and Iraq develop posttraumatic stress disorder (PTSD), clinical depression, substance abuse, sleep disturbances, or suicidal thoughts.[37,38] Of these, only about half of those who need intervention receive care.[37] The Buddy-to-Buddy program is intended to meet the current need to link more veterans with appropriate medical and psychological resources.

The Buddy-to-Buddy program, developed at the University of Michigan (Ann Arbor, MI) in partnership with the Michigan Army National Guard (MI ARNG, Lansing, MI) and Michigan State University (East Lansing, MI), is intended to be a veteran peer outreach support program and operates by training veterans to provide support and linkage to needed resources for returning civilian soldiers.[39] Goals of the program include improvement in treatment entry, adherence, and clinical outcomes and reductions in suicide.[37] The program is based on the theory that for returning soldiers, peer-to-peer "buddies" can be uniquely positioned to offer emotional support and resources because they understand the experience of the war setting, which in turn may help reduce the stigma associated with seeking mental health care.[40,41]

Program volunteers are divided into two groups: "Buddy Ones" and "Buddy Twos."[40] According to program developers, all returning soldiers are assigned a "Buddy One." This is a veteran within a National Guard unit who has received training in peer support and systematically makes contact (via telephone) with each of his or her assigned veterans to try to identify those who might benefit from further evaluation or referral.[40,42] Once soldiers in need are identified, Buddy Ones encourage registration and entry into Veterans Administration Hospital or military programs, develop strategies to enhance enrollment in community treatment programs, and support adherence after treatment is begun.[37] The Buddy One tier is operated and overseen by MI ARNG.[37]

"Buddy Two" volunteers are veterans from outside the National Guard who are intended to serve as backup for the Buddy Ones.[37] They receive more intensive training in motivational interviewing and local resources, and also receive weekly telephone supervision. These Buddies visit armories during drill weekends, are available by telephone to all soldiers, and work with individuals who are beyond the Buddy Ones' scope of training.[37,40,42,43] Buddy Twos are overseen by University of Michigan staff.[40]

As of October 2010, the Buddy-to-Buddy program had trained about 350 Buddy Ones and 32 Buddy Twos; the program is currently available only in the State of Michigan.[37] One published journal article on the program does not state the number of program participants who have been served, but notes that "more than 20% have been referred to formal treatment by their buddy, reflecting previously unmet clinical needs," and 53% of participants have used resources or services suggested by their buddy.[37,40] Based on the program's success, the developers have recommended expansion to a national program for all returning citizen soldiers, and urge that "these efforts be linked with evaluation outcome assessments."[37,40] Program developers have stated that program referrals that have been made are "in the process of being evaluated in greater detail and longer-term outcome evaluations are being proposed."[37]

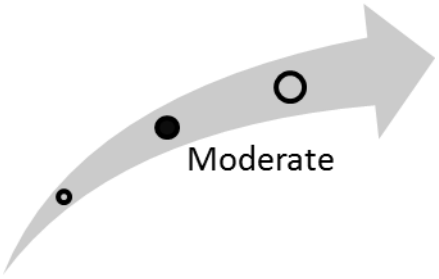
Current Approach to Care

Though both medical and psychological interventions for PTSD and clinical depression are available, only about half of citizen soldiers returning from war with these conditions seek or receive

these interventions. Of soldiers referred via the Post Deployment Health Assessment screening process, only 54% follow through with a mental health visit, and only 30% report receiving minimally adequate treatment.[37] The majority of reserve soldiers who seek care do so in the civilian sector, rather than the military sector, which may be due to the lack of military medical/psychiatric facilities in many civilian communities.[37,44] Outcomes in this population remain poor, and the Buddy-to-Buddy program is intended to mitigate some of the barriers that exist for returning civilian soldiers who need medical or psychological intervention.

The success of the Buddy-to-Buddy program relies on its ability to match veterans in need with appropriate mental health services. Therefore, medical and psychological interventions are necessary complements to this program, as are local community resources that are intended to aid veterans in adjusting to life back home.

Figure 3. Overall High Impact Potential: Citizen soldier peer support outreach program (Buddy-to-Buddy) for returning veterans



Experts agreed that the unmet need this program purports to address is vast and important, and that this program is likely to meet this unmet need to some extent, especially for groups affected by health disparities. However, because the service is intended to link patients to existing services, experts did not predict that that this program would particularly disrupt current health care infrastructure or patient management models, other than potentially increasing patient volume in treatment centers. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, provided perspectives on this topic.[45-51] Experts strongly agreed that the unmet need for linking citizen soldiers with mental health services is important, because of the size of the affected patient population, the current underutilization of mental health services by this population, and the negative impact that mental illness can have on soldiers, their families, and society. Experts were moderately certain that this program has potential to improve health outcomes because it is intended to link patients with extant and proven services and interventions. This view, however, was tempered by the lack of data available at this time. Most of the expert comments received were consistent with the following comment of one research-based expert: "This program seems to provide a resource that was essentially lacking before for these veterans. Although little data are available about the program's effectiveness, its very existence should be an improvement compared to the void that existed before."[47]

Most experts predicted that this program would be particularly effective in reducing health disparities across several dimensions, because of the following: (1) some minority populations do not traditionally seek mental health services, and "the kind of support that may come from the…program could provide needed encouragement;" (2) the program could lead to an increase in access to health care resources for individuals in rural communities, where resources are traditionally less available; and (3) soldiers with "low economic status, low literacy level, etc. are more likely to have difficulty navigating the health care system and to not know about available services [so] having a buddy might be more helpful to these individuals in improving their access to health care."[48,51]

Experts generally did not expect that this program would significantly disrupt the current health care infrastructure or the ways in which clinicians manage patients. Because the program is designed only to link patients with currently available services, its greatest impact would be a potential increase in patient volume seeking mental health services, most experts predicted. Similarly, most expert comments reflected the view that clinicians and providers would readily accept this program, because it requires little work on their end and could increase the number of patients who are linked with appropriate care.

Some experts predicted acceptance of the program by the intended patient population, especially because of the data (though limited) thus far that suggest that soldiers in the program generally feel comfortable talking to their Buddy about mental health issues. However, some experts cautioned that the stigma against seeking mental health services still exists in the military, and though the Buddy-to-Buddy program is intended to lessen this stigma, the fear of having a record of mental health treatment could be a barrier to program use. One expert, speaking from a research perspective, suggested that to gain the most patient support, the Buddies must be "supportive, knowledgeable, and trained in engaging individuals who might have reservations, such as fear, stigma, and indifference, about receiving mental health services."[51]

Experts were divided on how this program would affect health care costs. On one hand, if the program is proven effective in increasing patient use of services, an increase in short-term costs could occur as new patients enter the health care system. However, if more patients with mental health conditions are appropriately managed, long-term costs associated with untreated mental health conditions may be reduced.

Intervention

Extended Intensive Psychotherapy Session Assisted by Methylenedioxymethamphetamine for Treatment of Posttraumatic Stress Disorder

Despite the availability of pharmaceutical and psychological interventions for the treatment of PTSD, many treated patients still experience ongoing PTSD. The need for novel, effective treatment modalities for PTSD is significant.

Methylenedioxymethamphetamine (MDMA), also known as *Ecstasy*, is a synthetic, psychoactive drug that has a chemical structure similar to both mescaline and methamphetamine.[52] MDMA is known to bind to the serotonin transporter in the brain, thereby increasing and prolonging serotonin signaling, and to enter serotonergic neurons, thereby triggering excessive release of serotonin from the neurons.[52] This results in psychological effects that are characterized by feelings of increased energy, euphoria, and emotional warmth and distortions in time, perception, and tactile experiences. MDMA appears to be unique in that it gives rise to these emotional effects without apparently affecting other psychological functions, such as visual perception or cognitive processes.[53]

MDMA is being investigated for use immediately preceding a long-duration (e.g., 8-hour) psychotherapy session for patients with PTSD.[54] Some researchers assert that because MDMA temporarily reduces or eliminates fear and anxiety, it might allow patients with PTSD to introspectively access their emotions and internal conflicts during an extended psychotherapeutic session without the concomitant fear normally associated with those emotions and memories. With this fear mitigated, patients might be better able to communicate with their therapists about their disorder, which may enhance the therapeutic alliance, the psychotherapeutic process, and patient outcomes.[53] Within the field of psychotherapy, these first two components—introspection and strength of the therapeutic alliance—are believed to be the primary variables predicting therapeutic outcomes. Thus, MDMA is proposed as a tool for improving the efficacy of psychotherapy sessions in patients with PTSD.[53] MDMA had been widely diffused for treatment of many psychological disorders in the United States prior to its prohibition and inclusion in the list of Schedule I controlled substances in 1985.[53] In a clinical trials studying MDMA for this population, participants were given a single, oral dose of MDMA before undergoing an 8-hour psychotherapy session (including periods of rest or introspection).[53,54]

The U.S. Government has approved clinical trials assessing the safety and efficacy of MDMA for the treatment of PTSD during intensive psychotherapy.[53] One trial, sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS), is ongoing. In published results in one safety trial investigating MDMA-assisted psychotherapy in women with PTSD, investigators reported that low doses of MDMA (from 50 to 75 mg) were both psychologically and physiologically safe for all participants.[53] In a second clinical trial of 20 patients with chronic, refractory PTSD, published results reported, "Decrease in Clinician-Administered PTSD Scale scores from baseline was significantly greater for the group that received MDMA than for the placebo group at all three time points after baseline. The rate of clinical response was 10/12 (83%) in the active treatment group versus 2/8 (25%) in the placebo group. There were no drug-related serious adverse events, adverse neurocognitive effects or clinically significant blood pressure increases."[54]

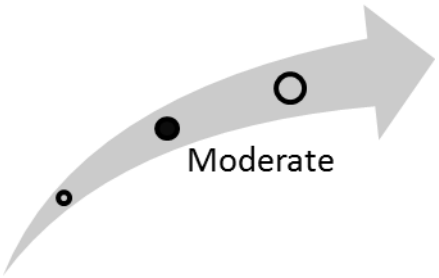
Although MAPS is conducting the studies for this indication, Merck & Co., Inc. (Whitehouse Station, NJ), originally synthesized MDMA in 1912, but did not test it in either humans or animals at that time. In the 1970s, the then-titled Bureau of Narcotics and Dangerous Drugs (now the Drug Enforcement Administration) identified street use of MDMA. This eventually led to its prohibition and

listing in 1985 as a controlled substance.[53] MDMA remains on the list of Schedule I controlled substances, which suggests that its regulatory approval process will be lengthy, though the process by which MDMA would become available for this clinical purpose is unclear at this time.

Clinical Pathway at Point of This Intervention

According to the National Institute of Mental Health,[55] treatment options for PTSD include psychotherapy (e.g., cognitive-behavior therapy) and pharmacotherapy (sertraline or paroxetine, which are both approved for the treatment of PTSD). No medications are currently approved by the U.S. Food and Drug Administration for use to enhance psychotherapy sessions for treatment of PTSD. MDMA is not being studied as a stand-alone therapy to treat PTSD, but as a means for improving the therapeutic value of an intensive, protracted psychotherapy session. Thus, MDMA would complement individual psychotherapy sessions, but not be used as continuous, long-term pharmacotherapy. If MDMA proves to be effective in improving the psychotherapy outcomes, it might have potential to displace some use of the two drugs that are currently approved for ongoing, long-term pharmacotherapy (sertraline or paroxetine) for PTSD.

Figure 4. Overall High Impact Potential: Extended intensive psychotherapy assisted by methylenedioxymethamphetamine for treatment of posttraumatic stress disorder



In general, experts commenting on this topic believe that this intervention has high potential for controversy and for marked disruption of certain aspects of the health care system. The disruption could arise due to the controversy over the drug itself and the proposed manner of using it to facilitate a therapy session of extended duration (up to 8 hours in one day), which is not currently easily accommodated in the health care system. Experts were also somewhat skeptical about the ability of MDMA-assisted psychotherapy to actually improve PTSD outcomes over the long term. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Six experts, with clinical, research and health systems backgrounds, provided comments on this topic.[56-61] Most agreed that the unmet need for effective PTSD interventions is vast and very important, particularly in light of the number of soldiers returning from wars. However, one expert, a former therapist, opined that there is virtually no need for pharmaceutically assisted psychotherapy because a "good therapist should be able to help a patient overcome their fear without the aid of drugs." While these experts agreed with the theory that helping patients become more emotionally available during therapy could be beneficial, most were skeptical about the potential for long-term improvement in health outcomes. Specific concerns included the following: (1) the major role that the skill level of the therapist plays in this intervention; (2) the potential for inter-patient variability and dose dependency issues in terms of MDMA efficacy; (3) the possibility that any progress achieved in the therapeutic session would be temporary, because the drug isn't intended to be used outside this arena; and (4) the fact that the health system and current practices do not accommodate extended (8-hour-long) therapy sessions.

Experts generally predicted that, if adopted, this intervention has high potential to disrupt current PTSD care models and the way patients are managed. Much of this discussion was based on the dramatic shift in psychotherapy session length (from 1 hour to 8 hours) that the intervention requires, and several experts commented that this change would profoundly affect the way patients currently

receive care, because no coverage or coding policies are in place for such a care model. However, several experts also noted that despite the initial increase in therapy time, the intervention has potential to reduce the long-term need for ongoing therapy if the intervention is proven effective for PTSD. However, a medical physician would need to prescribe the drug and closely coordinate with the psychotherapist how and when the patient actually receives it.

In general, experts commenting on this material thought that this intervention would heavily influence the nature of the provider-patient relationship, because the success of the intervention depends so heavily on the skill level of the therapist. Most experts thought this intervention would require extensive training on the part of the clinicians and/or therapists if it were to have any chance of being effective. They suggested clinicians would have to be trained in safe administration of MDMA and how to monitor for side effects and in the physically and emotionally demanding therapeutic style that this intervention would require.

Most of the experts predicted that both patients and clinicians would be extremely reluctant to accept or adopt this intervention. Patients might be unwilling to take an "illegal" or "street" drug as part of therapy, even if it is administered legally, both for fear of the drug's side effects and because MDMA has received recent negative press. Also, patients might be unwilling to undergo such an extended therapeutic session. Clinicians delivering the therapy would need to collaborate in a new way and provide a session that is much longer and more intensive than standard 1-hour sessions.

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