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. HHSA290-2010-00006-C). 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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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 National Academy of Medicine (formerly 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, 5600 Fishers Lane, Rockville, MD 20857, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ’s interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as “interventions.” The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 24,500 leads about potential topics has resulted in identification and tracking of about 2,400 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 750 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop. The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 195 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest.
(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

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

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

**Results**

The table below lists the three topics for which (1) preliminary phase III data for drugs or programs were available; (2) information was compiled and sent for expert comment before November 6, 2015, in this priority area; and (3) we received six to eight sets of comments from experts between January 1, 2015, and November 16, 2015. (Twenty-five topics in this priority area were being tracked in the system as of November 6, 2015). Three topics were eligible for consideration and two were designated as having high-impact potential (indicated below with an asterisk) based on experts’ comments and their assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically. Readers are encouraged to read the detailed information on these interventions that follows the Executive Summary.

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**Discussion**

Pharmacotherapy regimens and behavioral therapy protocols are well established as treatment approaches for mental health disorders. Unfortunately, these therapeutic options have limited and inconsistent efficacy. Fewer than half of patients in whom bipolar depression (BPD), major depressive disorder (MDD), or post-traumatic stress disorder (PTSD) has been diagnosed achieve remission with available antidepressants; similarly, a meta-analysis published in September 2015 by Driessen and colleagues in PLoS One implies that behavioral therapies may be up to 25% less effective for treating depressive disorders than previously believed. Consequently, several interventions being tracked in the AHRQ Healthcare Horizon Scanning System in this priority area
are positioned as alternatives for patients whose conditions are refractory to available BPD, MDD, and PTSD treatments.

During the most recent reporting period for the Horizon Scanning System, we added several new topics on investigational drugs and behavioral therapies for the above-mentioned indications, as well as treatments for binge-eating disorder and schizophrenia. Growing evidence signals that while genotype-specific, “personalized” mental health medicines may be forthcoming, the most universally effective mental health treatments are comprehensive interventions incorporating early diagnosis and management using medications and cognitive therapy. Many of newly added topics use this integrated approach, and we look forward to the generation of safety and efficacy data.

This report addresses three topics that experts deemed to have high-impact potential: two topics are off-label pharmacotherapies for treating BPD and MDD and one uses telehealth services to expand the reach of behavior therapy resources for treating PTSD.

Eligible Topic Not Deemed High-Impact at This Time

- **Off-Label Scopolamine for Treatment-Resistant Bipolar Depression and Major Depressive Disorder**: Preclinical studies show that cholinergic pathway regulation is a key factor mediating patients’ susceptibility to depression and the severity of certain depressive symptoms. Accordingly, researchers are investigating various anticholinergic drugs as antidepressants to treat acute episodes of treatment-resistant BPD or MDD. Scopolamine, an anticholinergic and potential antidepressant approved by the U.S. Food and Drug Administration (FDA) and used as an antiemetic (to prevent nausea and vomiting) and to prevent motion sickness, is being studied off-label. Experts commenting on off-label scopolamine were highly skeptical of the drug’s utility as an effective, rapid-onset, therapy for patients with treatment-resistant BPD and MDD because of the data thus far. Although patients and clinicians might willingly try scopolamine after exhausting other pharmacotherapy options, experts expressed concerns about the drug’s safety profile and best administration method. Some experts also noted that a lack of third-party payer coverage could limit diffusion and increase health disparities. Based on this, we will continue to track the intervention for additional data from two small ongoing trials and, if warranted, seek additional expert comments after more data accumulate.

Topics Deemed to Have High-Impact Potential

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

- **Key Facts**: An unmet need exists for effective antidepressants for acute and long-term MDD, even though many FDA-approved medications are available. Standard antidepressant efficacy varies among patients, and previously effective drugs may have waning responses in a single patient or are ineffective for managing acute episodes. Worldwide, hundreds of ongoing and completed reports support ketamine’s rapid antidepressant properties, hypothesized to derive from ketamine’s high-affinity, nonselective N-methyl-D-aspartate receptor antagonism and other biological pathway activities.

  As an antidepressant, ketamine is usually administered as a single intravenous infusion. Clinical data suggest that this dose can relieve symptoms within 2 hours, with observed effects persisting for 2 weeks or more, making ketamine a viable treatment-resistant BPD and MDD therapy. In small studies, ketamine administration also reduced suicidal ideation in depressed inpatients and may be a useful emergency antidepressant. Ongoing clinical
trials are investigating optimal ketamine dosing, long-term effect durability, and adverse event profiles. Ketamine’s treatment efficacy is also motivating the development of biochemically similar antidepressants, including esketamine and other ketamine derivatives. Compared with standard daily antidepressant regimens, ketamine therapy is relatively inexpensive. However, as an off-label therapy without third-party payer coverage, patients incur higher direct costs, with average per-treatment prices of $525 to $1,250 from private providers nationwide. Ketamine’s use is also severely constrained by the U.S. Drug Enforcement Administration, which classifies it as a Schedule III drug requiring a license and prescription to obtain.

- **Key Expert Comments:** Experts regarded ketamine as having good antidepressant potential, citing positive data from several clinical trials and studies, along with its novelty as a rapid-acting treatment for acute BPD and MDD. Although intravenous ketamine has known safety risks and might require increased infrastructure or staffing models to administer and monitor, experts noted that these effects would be moderated by the patient health benefits. Some experts also thought off-label ketamine use might be limited by cost concerns and suggested that additional clinical data are needed to provide the basis for third-party payer coverage.

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

**Telemedicine-Facilitated Psychotherapy for Treatment of Post-Traumatic Stress Disorder**

- **Key Facts:** Although effective evidence-based psychotherapies are available for treating PTSD, a significant number of Americans who experience PTSD—including a large percentage of military personnel with the disorder—fail to receive adequate care. Two factors driving PTSD resource under-use are a lack of geographic access to providers and a strong stigma associated with openly seeking mental health resources. Additional interventions and delivery systems could increase treatment rates and reduce health care burdens typically associated with poorly treated or under-treated PTSD.

  Telemedicine-facilitated psychotherapy is an alternative care delivery model used to administer PTSD behavior therapies. This model removes geographic constraints and also affords discreet treatment. In clinical trials and small studies, telemedicine facilitates delivery of one, or a combination, of several standard PTSD psychotherapies, including cognitive behavior therapy, cognitive processing therapy, eye movement desensitization and reprocessing, and prolonged exposure therapy. Telemedicine-facilitated psychotherapy has also shown broad efficacy for treating PTSD and common comorbid indications and in case studies was also effective for treating military patients deployed in combat areas.

  This delivery model can be effectively used adjunct to or in place of in-person psychotherapy, and many experts consider telemedicine-facilitated psychotherapy to be a cost-effective service with treatment efficacy comparable to in-person therapy. Telemedicine-facilitated psychotherapy can also potentially be rapidly diffused because it is extensively supported by national clinical, military, and scientific agencies and covered by Medicaid and several other third-party payers.

- **Key Expert Comments:** Experts evaluating telemedicine-facilitated psychotherapy concluded these services could address an underserved population, offering effective mental health treatment to patients who are unable to receive standard of care due to geographic distance from providers or other factors. As an alternative delivery method covered by third-party payers and supported by government organizations, this intervention could diffuse
widely and would be readily accepted by patients, experts thought, although some clinicians may have reservations when comparing remote therapy to in-person sessions. Overall, clinical and research experts anticipated that telemedicine-facilitated psychotherapy would improve patient health outcomes.

- **High-Impact Potential:** Moderately high
Depression and Other Mental Health Disorder Interventions
Off-Label Ketamine for Treatment-Resistant Bipolar Depression and Major Depressive Disorder

Unmet need: Many patients with bipolar depression (BPD) or major depressive disorder (MDD) are unable to achieve symptom relief with available antidepressants; these drugs also have sometimes intolerable side effects, further limiting their effectiveness. Additionally, few options are available for patients experiencing acute depressive episodes, for which rapid symptom remediation is paramount. An unmet need exists for fast-acting, well-tolerated antidepressants to effectively treat medically refractory BPD and MDD.

Intervention: Ketamine is a racemic, noncompetitive, high-affinity N-methyl-D-aspartate (NMDA) receptor antagonist long approved and widely used as general anesthetic. The drug is one of many NMDA antagonists under investigation as a putative antidepressant, partly due to a hypothesized link between dysfunctional glutamate neurotransmission and depressive symptoms observed in BPD and MDD.

Preclinical studies indicate that ketamine’s antidepressant properties may result from one or more biochemical functions. In particular, ketamine administration affects brain-derived neurotrophic factor–mediated synaptic plasticity and synaptogenesis and also leads to upregulation of the mammalian target of rapamycin (mTOR) protein kinase. These processes could potentially facilitate ketamine’s rapid antidepressant timecourse.

Racemic ketamine is usually intravenously or intramuscularly injected at subanesthetic doses to treat BPD and MDD. The most commonly reported clinical trial protocols use single or chronic 0.5 mg/kg intravenous infusions. Oral, intranasal, and rectal ketamine administrations have been successfully employed, and researchers are also investigating the antidepressant properties of ketamine’s R- and S-enantiomer forms.

Clinical trials: Ketamine is one of the most extensively studied off-label antidepressants. Since 2010, more than 100 unique peer-reviewed clinical trials and case studies have reported on ketamine’s efficacy for treating BPD and MDD. Dozens of ongoing clinical trials are investigating ketamine for treatment-resistant BPD or MDD, with additional studies probing ketamine’s efficacy for treating acute depression. Limited evidence suggests that single ketamine infusions may also augment standard oral antidepressants and electroconvulsive therapy for treating MDD and offer an effective first-line option for acute BPD or MDD with comorbid suicidal ideation. In contrast, chronic ketamine treatments have inconsistent efficacy that vary based on patients’ pretreatment symptom severity and clinicians’ administration parameters.

In 2014 and 2015, systematic reviews analyzed several trials studying ketamine for treating MDD and BPD. Several of these reviews agreed that ketamine treatment was associated with higher rates of clinical remission and response than placebo or a comparator anesthetic. Review authors found that this result was stable in analyses focused on treatment-resistant depression in patients administered single or repeated ketamine doses. However, two Cochrane Reviews concluded that insufficient clinical trial evidence existed to support ketamine antidepressant efficacy for either indication. One systematic review of subanesthetic ketamine administration for treating MDD reported that treatment-related adverse events were generally mild, with some patients experiencing brief, reversible changes in blood pressure, heart rate, or respiratory rate. However, smaller studies have observed severe adverse events, including delayed-onset suicidal ideation, dysphoria, and anxiety; a 2015 case report also noted that patients administered frequent, poorly monitored injections could develop ketamine addiction.

Manufacturer and regulatory status: Infusible ketamine (racemic ketamine hydrochloride solution) is the only formulation sold commercially in the United States; several manufacturers
produce generic versions, and a branded formulation, Ketalar®, is marketed by JHP Pharmaceuticals, LLC (Parsippany, NJ). Ketamine is approved as a general anesthetic for diagnostic and surgical applications but has no approval for antidepressant use. To date, no manufacturers are pursuing expanded labeling, so ketamine is diffusing as an off-label BPD and MDD treatment.

**Diffusion and costs:** Several American academic, government, and medical institutions sponsor clinical trials studying ketamine’s antidepressant efficacy. Additionally, private clinicians increasingly offer outpatient ketamine therapy for treating depression, charging between $525 and $1,250 per infusion, with adapter-delivered intranasal ketamine costing less.

Ketamine is a Schedule III controlled substance and cannot be legally purchased and administered without a U.S. Drug Enforcement Administration license. High-dose ketamine can be abused as a street drug known as “Special K”; the notoriety associated with this illicit use may negatively impact expanded approval or availability.

**Clinical Pathway at Point of This Intervention**

Available treatments for BPD and MDD include pharmacotherapy, individual and group cognitive behavior therapy, and other forms of individual psychotherapy. Anticonvulsants, antipsychotics, benzodiazepine, and lithium are frequently prescribed to treat BPD. Common antidepressants for treating MDD include selective serotonin reuptake inhibitors, atypical antidepressants, and monoamine oxidase inhibitors used as monotherapies and in combination. For treatment-resistant disease, physicians may also prescribe ECT, forms of transcranial magnetic stimulation (TMS), or implanted vagus nerve stimulation.

Ketamine’s mechanism of action and molecular targets differ from commonly used depression pharmacotherapies, leading to its potential to augment the effects of other medications. As a rapid-acting antidepressant, ketamine could be used as a bridge therapeutic, providing acute symptom management until slower-acting, chronically administered antidepressants become effective. Ketamine may also be prescribed adjunct to ECT, TMS, vagus nerve stimulation, and psychotherapy.

**Figure 1.** Overall high-impact potential: off-label ketamine for treatment of bipolar depression and major depressive disorder

Experts commenting on this topic had favorable impressions of ketamine’s potential as an effective, rapid-onset intervention for treatment-resistant BPD and MDD. These experts anticipated that intravenous ketamine use could increase health care delivery service needs and patient management; however, if equally effective oral or intranasal ketamine formulations became available, the increased burden of IV administration could be avoided. Optimism for this intervention’s potential was tempered by available efficacy and safety data; several experts stated that larger, long-term clinical trials are needed to validate this intervention’s utility. Experts thought that its off-label status for MDD and BPD, lack of third-party payer coverage, and its abuse
potential could limit diffusion, but still considered the intervention to be promising. 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 off-label ketamine for treating BPD and MDD. We have organized the following discussion of expert comments by the parameters on which they commented.

**Unmet need and health outcomes:** All experts acknowledged a substantial unmet need exists for additional pharmacotherapies for treatment-resistant BPD and MDD and thought that ketamine’s efficacy suggests that it could address some of this need, particularly for acute cases. Although most experts thought that available data indicated ketamine’s treatment efficacy, every expert wanted evidentiary support from larger, tightly controlled trials and long-term studies to clearly establish the drug’s therapeutic benefits and limitations and complete adverse event profile among patients with BPD or MDD.

**Acceptance and adoption:** Experts anticipated that ketamine would be widely accepted by patients, particularly if an effective intranasal formulation were to be available. Additionally, experts thought that third-party payer reimbursement would also encourage patient adoption. In contrast, several experts predicted that ketamine’s unclear adverse event profiles and abuse risk, additional attendant resources and monitoring requirements, and lack of indication-specific FDA approval could significantly limit clinician acceptance and adoption.

**Health care delivery infrastructure and patient management:** Compared with oral antidepressants, off-label intravenous ketamine would require facilities equipped for infusion therapies, experts remarked; an intranasal ketamine formulation could alleviate this infrastructure burden. Several experts were concerned about ketamine’s adverse event profile and noted that safety risks could dictate additional patient management resources. Two experts remarked that these increases might be offset by reduced burdens associated with managing previously ineffectively treated patients.

**Health disparities:** Without FDA approval and subsequent third-party payer reimbursement, off-label ketamine use would increase health disparities, most experts concluded, with one research expert framing this intervention, in its current context, as “most likely a treatment only available to the wealthy.”
Telemedicine-Facilitated Psychotherapy for Treatment of Post-Traumatic Stress Disorder

Unmet need: More than 21 million Americans—including at least 500,000 military veterans—have received a diagnosis of post-traumatic stress disorder (PTSD). Despite the existence of validated psychotherapy options for treating PTSD, many patients remain untreated or receive suboptimal care. Poor treatment rates are particularly pronounced among first responders, military veterans, and patients residing in areas lacking quality care providers. Factors hindering effective treatment include geographic proximity to quality services and the threat of social stigma associated with the disorder. An unmet need exists for effective interventions and care delivery options that can reduce these treatment disparities.

Intervention: Telemedicine-facilitated psychotherapy for treating PTSD encompasses any psychotherapy program or delivery system that uses telecommunications, including phone and Internet technologies, to provide real-time, evidence-based primary care for patients with PTSD. This care model can remotely deliver effective psychiatric and psychological services, clinician consultation and pharmacotherapy prescription, and patient management. Typically, telemedicine facilitates delivery of one, or a combination, of several standard PTSD psychotherapies, including cognitive behavior therapy (CBT), cognitive processing therapy (CPT), eye movement desensitization and reprocessing (EMDR), and prolonged exposure (PE) therapy on schedules identical to those recommended for in-person therapy. Remote service providers can also collaborate with local clinicians to reinforce and enhance face-to-face care.

Clinical trials: Data from several late-phase clinical trials support telemedicine-facilitated psychotherapy’s efficacy as an effective complement or substitute for in-person psychotherapy. This delivery system has also shown efficacy for treating common comorbid indications in patients with PTSD, including depression, insomnia, and substance abuse. Although CBT and PE have the largest body of supporting data for treating American patients, researchers report comparable results with patient populations administered CPT or EMDR psychotherapy, suggesting telemedicine-facilitated psychotherapy’s potential as a universally applicable care delivery system.

To date, the largest trials examining this intervention have enrolled veterans of the Vietnam War, Persian Gulf conflict, Operation Enduring Freedom, or Operation Iraqi Freedom. In a 2014 study enrolling rurally residing veterans (n=125), Morland and colleagues found that 12 telemedicine-facilitated psychotherapy sessions were as effective as 12 in-person CPT sessions for reducing PTSD symptoms; this treatment response was sustained for 6 months after therapy concluded, and investigators also reported high therapeutic alliance, treatment compliance, and patient satisfaction with telemedicine-facilitated psychotherapy. A 2015 study (n=265) by Fortney and colleagues based at 3 regional Veterans Affairs facilities also reported efficacy for telemedicine-facilitated psychotherapy compared with usual care, with rurally residing veterans randomly assigned to the telemedicine psychotherapy study arm displaying statistically significantly
larger decreases in PTSD symptoms after 6 and 12 treatment months (mean 6-month Posttraumatic Diagnostic Scale score change, -5.9; mean 12-month Posttraumatic Diagnostic Scale score change, -4.9) compared with those in the usual care arm (mean 6-month Posttraumatic Diagnostic Scale score change, -1.4; mean 12-month Posttraumatic Diagnostic Scale score change, -1.8) [6-month $\beta = -3.81$; $p=0.002$; 12-month $\beta = -2.49$; $p=0.04$].61

In 2015, investigators described an active duty soldier with acute stress disorder, deployed at a remote combat outpost, who was successfully treated across 10 psychotherapy sessions, including 5 sessions conducted via videoconferencing.71 This and other preliminary findings suggest that telemedicine-facilitated psychotherapy may have added potential as an effective intervention for treating prodromal PTSD, advancing treatment timelines and enhancing long-term patient health outcomes.

A 2015 systematic review of 11 published studies—totaling 472 patients—found that telemedicine-facilitated psychotherapy was associated with significant improvements in patients’ mental health symptoms up to 6 months after treatment.72 Telemedicine-facilitated psychotherapy’s long-term efficacy for treating PTSD has not been established. A lack of standardized intervention protocols across completed studies has also hindered efforts to determine this intervention’s broader efficacy. Although some studies have reported treatment efficacy in followups conducted up to 18 months after treatment, other trials failed to show sustained efficacy at later time points.73

**Manufacturer and regulatory status:** Academic and government institutions involved in clinical trials and implementation of telemedicine-facilitated psychotherapy for treating PTSD include the U.S. Department of Defense (Arlington, VA); the U.S. Department of Veterans Affairs (Washington, DC), with study sites in States including Arkansas, California, Hawaii, Louisiana, and Washington; Medical University of South Carolina (Charleston); University of Wisconsin, Madison; and the Veterans Medical Research Foundation (San Diego, CA).61,74,75

The Department of Defense, acting on longstanding recommendations from clinical experts and military personnel advocates, has invested significant resources towards formally implementing telemedicine-facilitated psychotherapy for veterans living in rural areas.64,68 The infrastructure for this intervention, in concert with local Veterans Affairs facilities, is well established.62 Telemedicine-facilitated psychotherapy is also available to civilian patients, often directly through a primary care provider or entity affiliated with a third-party payer.

**Diffusion and costs:** Despite broad support, telemedicine-facilitated psychotherapy is not yet widely diffused. According to a 2015 analysis, only 1.5% of all Veterans Healthcare Administration mental health encounters involved a telemedicine component, despite surveys indicating that 38% of VA patients with a PTSD diagnosis live in rural areas and two-thirds of patients live closer to one of VA’s community-based outpatient clinics than to a large, well-equipped medical center.76 We anticipate that diffusion and use will increase in coming years, fostered by additional clinical evidence and continued support from large institutions.

Per-patient costs for telemedicine-facilitated psychotherapy vary, depending on the program and provider. Patients are often responsible for none or a small portion of these costs, particularly in cases in which patients are receiving services as part of military benefits.62,63 Civilian patients may also obtain subsidized services through insurance coverage provided by third-party payers.63

Service providers’ per-patient telemedicine-facilitated psychotherapy costs are expected to be similar to those for standard psychotherapy programs. However providers may incur minor additional costs during program implementation to cover telecommunications equipment, infrastructure and management, and personnel training.58 Recent cost-analysis studies suggest that these expenses are offset by later savings from reduced resource use and fewer secondary treatment outlays.63
The U.S. Centers for Medicare and Medicaid Services (CMS) considers telemedicine, as a broad application, as “a cost-effective alternative to the more traditional face-to-face way of providing medical care (e.g., face-to-face consultations or examinations between provider and patient) that states can choose to cover….”

No official compendium exists listing States with specific policies for telemedicine-facilitated psychotherapy, but unofficial sources indicate that at least 40 States offer at least partial coverage for this intervention (often cataloged as telepsychiatry or telepsychology).

In 2014, CMS released a proposed rule expanding reimbursable telemedicine services to include forms of telemedicine-facilitated psychotherapy, with unique coding. Although PTSD and other disorders are not explicitly listed, this rule, which observers indicate could become effective as early as 2016, could provide more extensive coverage nationwide.

Similarly to CMS, many private third-party payers regard telemedicine-facilitated psychotherapy as an effective and financially sound health intervention and explicitly or implicitly provide coverage or reimbursement for related services.

Clinical Pathway at Point of This Intervention

Various in-person psychotherapies, including CBT, exposure therapy, brief psychodynamic therapy, and EMDR are standard treatments for PTSD. Additionally, two selective serotonin reuptake inhibitors, paroxetine (Paxil®) and sertraline (Zoloft®), are FDA-approved for treating PTSD, and off-label antidepressants, antipsychotics, and benzodiazepines are often prescribed for this indication. Based on clinical evidence, telemedicine-facilitated psychotherapy can viably complement or replace in-person psychotherapy, including as an adjunct to prescribed medications and patient- and clinician-managed mental health monitoring and reinforcement devices.

Figure 2. Overall high-impact potential: telemedicine-facilitated psychotherapy for treatment of post-traumatic stress disorder

Experts commenting on telemedicine-facilitated psychotherapy agreed that this intervention could address a service gap among patients with PTSD. They also noted that psychotherapy through this delivery method is identical to in-person therapy, potentially allowing underserved populations to receive standard of care behavior therapy. Although the experts were divided on this intervention’s projected adoption rate among clinicians, the majority of experts thought that patients would welcome this alternative treatment option. Overall, consulted experts supported telemedicine-facilitated psychotherapy as a valuable addition to clinicians’ armamentariums. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.
Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on telemedicine-facilitated psychotherapy for treating PTSD.\textsuperscript{87-92} We have organized the following discussion of expert comments by the parameters on which they commented.

**Unmet need and health outcomes:** Consensus expert opinion held that a substantial unmet need exists for widespread effective treatment of patients with PTSD, and they concluded that telemedicine-facilitated psychotherapy offers a treatment option that could increase treatment rates and improve patient health outcomes for this indication.

**Acceptance and adoption:** Overall, experts anticipated that this intervention would be relatively widely accepted among patients, particularly those who stand to benefit most from expanded access to psychotherapy. However, in evaluating potential adoption among clinicians, experts were divided. Half of the experts thought that many clinicians would willingly adopt telemedicine-facilitated therapy as a way to effectively treat patients. In contrast, the remaining experts cited concerns including limited reimbursement for setup and technical costs, potential insurance liability for adverse events occurring during remote treatment, and general clinician preference for in-person therapy as factors that may limit clinician adoption.\textsuperscript{88,90,91}

**Health care delivery infrastructure and patient management:** Experts concluded that wider diffusion of this intervention could require additional infrastructure to support equipment and maintenance of associated technology. Outside of these concerns, though, experts thought that with the alternative delivery system for behavioral therapy, patient management would not significantly change.

**Health disparities:** All experts stated that this intervention has potential to reduce health disparities by increasing access to behavioral therapy for traditionally underserved patients—particularly rurally located, disabled, or economically disadvantaged individuals. One expert also noted that telemedicine-facilitated therapy could address an unmet need for critical services among deployed military personnel experiencing acute PTSD symptoms, while another expert cited this intervention’s potential to provide personalized therapy for patients with varied cultural backgrounds who otherwise would not be matched with therapists who share their backgrounds.\textsuperscript{89,90}
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