

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

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## **Priority Area 05: Depression and Other Mental Health Disorders**

**Prepared for:**

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## **Statement of Funding and Purpose**

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHS290-2010-00006-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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## **Financial Disclosure Statement**

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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, 540 Gaither Road, Rockville, MD 20850, or by email to: [effectivehealthcare@ahrq.hhs.gov](mailto: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 21,000 leads about potential topics has resulted in identification and tracking of about 2,250 topics across the 14 AHRQ priority areas and 1 cross-cutting area; more than 600 topics are being actively tracked in the system.

## Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice 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 170 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 preliminary late-phase clinical trial data for off-label drug indications) was available; (2) information was compiled and sent for expert comment before May 8, 2015, in this priority area; and (3) we received five to seven sets of comments from experts between July 1, 2014, and May 18, 2015. (Nineteen topics in this priority area were being tracked in the system as of May 8, 2015.) We present one summary of two topics (indicated below by an asterisk) that emerged as having some potential for higher impact on the basis of expert comments. Topics in this Executive Summary and report are organized alphabetically. Readers are encouraged to read the detailed information that follows the Executive Summary.

### Priority Area 05: Depression and Other Mental Health Disorders

Topic	High-Impact Potential
1. * Off-label ketamine for treatment-resistant bipolar depression and major depressive disorder	Moderately high
2. * Off-label scopolamine for treatment-resistant bipolar depression and major depressive disorder	Moderately high
3. Video game (SPARX) for cognitive behavior therapy for adolescents with major depressive disorder	Archived; U.S. diffusion halted

## Discussion

Within this priority area, the majority of interventions we are tracking in the Horizon Scanning System are interventions that potentially offer treatments for patients whose conditions fail to respond to available medications and behavioral therapies for bipolar depression (BPD), major depressive disorder (MDD), and posttraumatic stress disorder (PTSD). Recent research suggests that these disorders may involve dysregulation of various neurotransmitters and pathways that normally modulate aspects of patients’ moods. Investigational medications are targeting novel and well-characterized mechanisms in an effort to provide additional therapeutic options for patients with these disorders.

In parallel with broad pharmacotherapy development, basic research is making strides towards expanding understanding of the fundamental neurobiology that underlies personalized treatment for mental health disorders. Personalized drug therapy has traditionally lagged behind behavioral therapy in this regard because an incomplete understanding of phenotypic susceptibility and genetic correlates has hampered clinicians' ability to customize treatments. However, newly identified putative biomarkers and genotype-driven clinical trial research offer promise that optimized, "bespoke" medications could be forthcoming for patients with mental health disorders. Although few new formal topics were added to this priority area since the last report, the Healthcare Horizon Scanning system is aware of a host of these therapies and diagnostics and continues to monitor research developments to identify the most promising ones for our nation's patients and health care system.

This report addresses two topics, both off-label pharmacotherapies with potential use for treating multiple mental health indications, that experts determined to have high-impact potential during this reporting period.

### **Eligible Topic Not Deemed to Have High-Impact Potential**

- **Video game (SPARX™) for cognitive behavior therapy for adolescents with major depressive disorder:** Standard nonpharmaceutical treatments for adolescents with early-onset major depressive disorder (eoMDD) include supervised individual or group cognitive behavior therapy (CBT) sessions. Although effective, these sessions have high attrition rates and are poorly accepted by many adolescent patients. Consequently, patients build entrenched negative associations and fail to optimally benefit from treatment. A need exists for effective, well-tolerated behavioral therapy options for adolescent patients with eoMDD.

SPARX is a novel video game-based software, originally developed in New Zealand and intended for outpatient treatment of adolescents with eoMDD. The software incorporates traditional CBT concepts in a self-directed interactive virtual environment based on entertaining role-playing "quest" games. Clinical trial data support SPARX's efficacy and tolerability for treating eoMDD, with subsequent studies extending these findings to several adolescent subpopulations.

Previously, American patients could download a full beta version from LinkedWellness (Baltimore, MD), SPARX's North American commercial licensee. However, LinkedWellness' company Web site has been nonfunctional since early 2015, and SPARX's New Zealand-based portals have restricted software access solely to patients based in that country. Consequently, despite broad diffusion and government support in New Zealand, we archived this topic in May 2015 and presently deem it to lack high-impact potential for American patients. For a more detailed discussion of this topic, including a brief survey of published outcomes data available through late 2014, please refer to the December 2014 Potential High-Impact Interventions report published on the AHRQ Web site.

### **Fast-Acting Medications (Off-Label Ketamine and Scopolamine) for Treatment-Resistant Bipolar Depression and Major Depressive Disorder**

- **Key Facts:** Although several U.S Food and Drug Administration (FDA)-approved medications are available for treating BPD and MDD, half or more of patients with BPD or MDD fail to experience symptom improvement. Additionally, a substantial number of medically responsive patients demonstrate incomplete recovery or do not respond

immediately. These inadequate responses prolong patients' exposure to severe, potentially fatal symptoms, such as suicidal ideation. A significant unmet need exists for fast-acting treatments for this patient population. Ketamine and scopolamine are two FDA-approved drugs whose rapid antidepressant properties and purported efficacy for treating medically refractory BPD and MDD have spurred investigations into their potential role as prototypical medications for future antidepressant drug development.

*Ketamine.* Widely used as an analgesic, anesthetic, and sedative in intranasal, intravenous (IV), oral, and rectal formulations, ketamine was first described as having notable antidepressant activity in humans by American researchers 15 years ago. In the interim, numerous case reports and clinical trials have reported that ketamine, particularly when administered intravenously at subanesthetic doses, can effectively treat refractory BPD and MDD. For many patients, single ketamine doses often reduce depressive symptoms within 2 hours, with improvements reported as persisting for 2 weeks or longer. In smaller studies and case reports, IV ketamine also reduced comorbid suicidal ideation. Dozens of ongoing national and international clinical trials are exploring ketamine's optimal delivery route and administration protocols for treating depression indications. Further studies are also attempting to understand approaches to ameliorating ketamine's side effects and identifying predictive biomarkers of ketamine treatment response among various patient populations.

Ketamine is used off-label for treating depressive disorders; no major American or international manufacturers are pursuing labeling for treating BPD or MDD, and third-party payers generally do not reimburse its cost for these indications. Based on informal clinical practice listings and patient self-reports, IV ketamine treatments for BPD and MDD cost between \$525 and \$1,250 per infusion; equivalent intranasal doses are less expensive.

*Scopolamine.* Scopolamine is a muscarinic antagonist approved for treating several indications including motion sickness and postoperative nausea; the drug can be administered via eye drops, intravenously, orally, or as a transdermal patch. Although not as actively studied as ketamine, a handful of small studies since 2006 establish intravenously administered scopolamine as a second fast-acting general antidepressant. Preliminary findings suggest that scopolamine's and ketamine's antidepressant properties may partly arise from their shared effects on some key neural processes; however, scopolamine's antidepressant role also appears to involve cholinergic modulatory properties distinct from ketamine.

Researchers have not clarified phenotype-specific antidepressant response to ketamine, although early studies found that the drug might be more effective for treating female patients. Like ketamine, scopolamine's use for treating depression is considered off-label; however, scopolamine's antidepressant use has not substantially diffused beyond clinical trials. IV scopolamine is not advertised as a treatment by private clinics. However, oral and transdermal patch formulations are available at retail, with average monthly per-patient costs between \$100, for a monthly supply of oral tablets, and \$170, for 10 transdermal patches.

- **Key Expert Comments:** Experts evaluating these two interventions thought both drugs have potential to address a large unmet need for fast-acting antidepressants, especially for treating medically refractory cases. Consulted clinical, health systems, and research experts agreed that more clinical data are needed for both interventions. For ketamine, experts were most concerned about the lack of clear dosing protocols and potential adverse events associated with IV administration, while for scopolamine, the experts noted a dearth of randomized controlled trial data supporting the drug's efficacy. While both drugs have

potential for wide acceptance among patients and clinicians who have exhausted other treatment options or patients who require immediate symptom remediation, experts questioned whether adoption would be dampened by potential out-of-pocket patient costs and shifts from oral antidepressants to infusion treatments. Experts also stated that similar factors could exacerbate health disparities. Overall, experts were reasonably optimistic about both ketamine and scopolamine as options for treatment-resistant depression and thought that these drugs have relatively solid high-impact potential.

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

# **Depression and Other Mental Health Disorder Interventions**

# Fast-Acting Medications (Off-Label Ketamine and Scopolamine) for Treatment-Resistant Bipolar Depression and Major Depressive Disorder

**Unmet need:** The majority of patients diagnosed with bipolar depression (BPD) or major depressive disorder (MDD) cannot tolerate or fail to respond satisfactorily to approved medications.<sup>1</sup> Available pharmacotherapies have slow time courses for relieving depression symptoms, limiting their utility for treating acute depression events, in which immediate intervention is vital to reduce the risk of serious harm to patients.<sup>1,2</sup> An unmet need exists for fast-acting, well-tolerated medications for treatment-resistant BPD or MDD. Ketamine and scopolamine may offer effective, off-label treatment alternatives for these patients.

**Intervention: Pharmacology.** Ketamine is a high-affinity, noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, approved for use as a general anesthetic.<sup>1,3</sup> NMDA is a global glutamate receptor and also contributes to synaptic plasticity control.<sup>1,4</sup> Abnormal glutamate neurotransmission may be a key modulator of symptoms in MDD and BPD, although the exact mechanism of action is unclear.<sup>1,4,5</sup> Evidence also suggests that NMDA receptor signaling may mediate glutamate dysregulation, leading some researchers to hypothesize ketamine and other NMDA antagonists could be potent antidepressants.<sup>5,6</sup>

In contrast, scopolamine is a belladonna alkaloid and strong anticholinergic, acting as a competitive inhibitor at muscarinic acetylcholine receptors (mAChRs).<sup>7</sup> While not definitive, recent findings suggest that the central nervous system–cholinergic system plays a key role in MDD and BPD pathophysiology; linkage studies also associate mAChRs genetic variants with increased clinical depression susceptibility.<sup>8</sup> Hypothetically, scopolamine’s inhibition of aberrant cholinergic system activity might make the drug a viable antidepressant.

Neurobiologic studies have not definitively revealed mechanisms underlying ketamine’s and scopolamine’s novel antidepressant properties.<sup>9</sup> The drugs’ differing compositions imply divergent modulatory pathways; however, converging studies have identified that ketamine and scopolamine both mediate processes leading to mammalian target of rapamycin (mTOR) activation and increased mTOR signaling, purportedly central to rapid antidepressant activity.<sup>9-11</sup> Corresponding clinical data demonstrate that infusing ketamine or scopolamine can ease depressive symptoms within a few hours or days, exponentially faster than many approved antidepressants.<sup>12,13</sup>

**Dosage.** In most clinical trials, single subanesthetic ketamine doses are given by IV or intramuscular injection for treating MDD and BPD; smaller studies have also investigated daily or weekly dosages for these indications. The most commonly reported ketamine dosing protocol is a single, 0.5 mg/kg IV injection; ketamine appears to have potential as a monotherapy or adjunct to other drugs and approved treatments such as electroconvulsive therapy (ECT).

Similarly, the most frequently investigated scopolamine protocol is three 4 mcg/kg infusions, administered 3–5 days apart.<sup>8,14</sup> Small clinical trials and case reports have inconclusively reported antidepressant efficacy using oral, intranasal, and rectal ketamine formulations;<sup>15,16</sup> oral and transdermal patch scopolamine are also being studied and may also effectively treat depression symptoms.<sup>17</sup>

**Clinical trials:** In the past 5 years alone, almost 100 American and international studies and cases have reported ketamine’s efficacy for treating BPD and MDD.<sup>13,18,19</sup> Dozens of ongoing clinical trials are also investigating off-label ketamine for treatment-resistant BPD or MDD.<sup>20-25</sup> Additional trials and case studies are also expanding research into ketamine’s efficacy for treating suicidal ideation and as an adjunct treatment to behavior and brain-stimulation therapies.<sup>26,27</sup> Numerous clinical trials and case studies report rapid, sustained antidepressant effects of single

intravenous ketamine infusions in these patient populations, along with rapid reductions in severe suicidal ideation and acute depression levels.<sup>1,2,18,23,28,29</sup> Comparatively, repeated ketamine doses have shown inconsistent efficacy, and reports suggest that this protocol's efficacy varies among patients and is contingent upon pretreatment symptom severity and the selected administration regimen.<sup>18,30,31</sup>

Systematic reviews and meta-analyses published in 2014 and 2015 summarize reported trials studying ketamine administration for treating MDD and BPD. These reviews agreed that ketamine treatment was associated with higher rates of clinical remission and response than placebo or a comparator anesthetic.<sup>18,29,32</sup> This finding was sustained in analyses focused on treatment-resistant depression in patients administered single or repeated ketamine doses.<sup>18,33</sup> As an adjunct therapy, however, ketamine's efficacy was reportedly inconclusive, with some studies reporting significant depression resolution and other trials reporting no effect.<sup>18,34</sup>

Adverse-event reporting is not available from all clinical trials, but one systematic review of ketamine administration in patients with 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.<sup>35</sup> However, some case reports have observed severe adverse events, including delayed-onset suicidal ideation, dysphoria, and anxiety.<sup>36</sup>

Fewer published trials report scopolamine's antidepressant activity. A phase II/III trial enrolling patients with MDD (n=40) found that intravenous scopolamine, administered adjunct to citalopram, was superior to placebo for increasing response rates (65% vs. 30%; p=0.027) and remission rates (65% vs. 20%; p=0.004).<sup>37</sup> The most common treatment-related adverse events were blurred vision, dizziness, and dry mouth.<sup>37</sup> A recent systematic review concluded that all available scopolamine formulations had some degree of antidepressant efficacy, with one identified study showing differentially greater treatment effects among female patients.<sup>14,38</sup>

Multiple small studies have reported that IV ketamine, when administered to patients who have BPD, produces significant improvements in depressive symptoms and suicidal ideation within 40 minutes compared with placebo. A 2012 National Institute of Mental Health trial reported that 79% of patients with BPD (n=15) responded positively to ketamine.<sup>2</sup> These same investigators observed that single ketamine infusions also improved patients' (n=36) BPD-associated anhedonia (diminished pleasure from, or interest in, previously rewarding activities).<sup>39</sup> In the same year, Polish researchers enrolling adult inpatients with treatment-resistant BPD (n=25) reported similar efficacy.<sup>24</sup>

*Ongoing trials.* Several ongoing, large clinical trials are investigating ketamine's efficacy for treating MDD, BPD, and comorbid suicidal ideation.<sup>40-42</sup> Trials are also probing the efficacy of repeated ketamine administrations in treating depressive disorders and associated predictive biomarkers of ketamine antidepressant response. Two ongoing clinical trials continue to study scopolamine's antidepressant efficacy.<sup>17</sup>

**Manufacturer and regulatory status:** Ketamine and scopolamine are available in branded and generic formulations for approved indications. We found no listed manufacturers actively engaged in clinical trials investigating these drugs' use for treating MDD or BPD. In the absence of formal development programs, ketamine and scopolamine use is off-label for depression indications.

**Diffusion and costs:** Ketamine is classified as a Schedule III controlled substance and cannot be purchased and administered without a U.S. Drug Enforcement Administration license.<sup>43,44</sup> Higher-dose ketamine is colloquially known as "Special K," and is sometimes abused as a street drug, further hampering attempts to expand approvals and availability for off-label use.<sup>45,46</sup>

Several active private clinical practices offer off-label ketamine infusion therapy for treatment refractory depression.<sup>47</sup> As listed online, per-infusion ketamine costs range from \$525 to \$1,250; anecdotal evidence suggests that intranasal ketamine treatments are less expensive.<sup>48-51</sup>

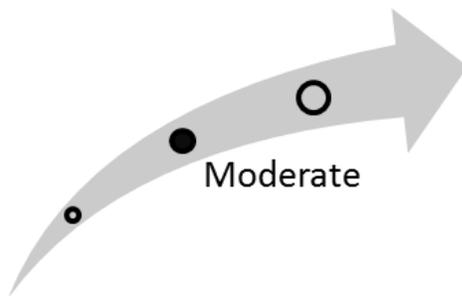
Although scopolamine has fewer severe side effects and no acknowledged abuse potential, unlike ketamine, off-label scopolamine antidepressant use is primarily restricted to clinical trials, and scopolamine infusions are not publicly available. Accordingly, IV scopolamine's anticipated per-patient and per-treatment costs are unknown. Oral and transdermal patch scopolamine, however, are available for purchase with a prescription. One month's worth of methscopolamine bromide tablets costs about \$100, while a similar supply of transdermal patches costs approximately \$170.<sup>52,53</sup>

## Clinical Pathway at Point of This Intervention

Pharmacotherapy and various group and individual psychotherapy programs are standard treatments for BPD and MDD. Atypical antidepressants, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors are standard antidepressants for treating MDD and are used as monotherapies or in combination regimens.<sup>54-56</sup> For treating BPD, anticonvulsants, antipsychotics, benzodiazepine, and lithium are standard medications.<sup>57</sup> Clinicians with patients whose conditions do not respond to pharmacotherapy can also prescribe ECT, forms of transcranial magnetic stimulation (TMS), or implanted vagus nerve stimulation.<sup>56,57</sup>

The mechanisms of action for ketamine and scopolamine vary from standard pharmacotherapies; as a result, these interventions might replace or complement other interventions. Recent small studies suggest that single or repeated ketamine infusions augment the efficacy of standard oral antidepressants; similar research is ongoing with scopolamine, along with studies investigating ketamine in combination with ECT and TMS.<sup>18,19</sup> Some clinical researchers also posit that investigational fast-acting antidepressants could act as possible therapeutic bridges, providing relief from acute symptoms until standard, chronic antidepressants begin working.<sup>29</sup>

**Figure 1. Overall high-impact potential: fast-acting medications (off-label ketamine and scopolamine) for treatment-resistant bipolar depression and major depressive disorder**



Experts commenting on ketamine and scopolamine thought that both drugs have potential as fast-acting, effective treatments for BPD and MDD. Experts noted that, if IV delivery is the most effective administration route, adoption of these drugs could shift patient care settings and management from oral medications with intermittent monitoring toward regular appointments at clinician offices and infusion clinics. These experts were encouraged by reported clinical trial data demonstrating rapid symptom relief and the potential applications for indications such as comorbid suicidal ideation, but they noted a lack of large, definitive clinical trials. Multiple experts also opined that direct cost to patients, unresolved dosing protocols, and safety risks could limit adoption. Based on this input, our overall assessment is that these interventions are in the moderate high-impact-potential range.

## Results and Discussion of Comments

Six experts, with clinical, health systems, and research backgrounds, provided perspectives on off-label ketamine for treating MDD and BPD,<sup>58-63</sup> while five experts, with clinical and research backgrounds, commented on off-label scopolamine for the same indications.<sup>64-68</sup> Of the consulted experts, two clinical respondents offered opinions on both interventions.<sup>62,66</sup> We have organized the following discussion of expert comments by the parameters on which they commented; expert comments primarily assess intravenously administered ketamine and scopolamine for treating BPD and MDD, because this specific administration route is more established than other delivery options.

**Unmet need and health outcomes:** Experts concluded that a significant unmet need exists for additional treatment options for patients with treatment-resistant BPD and MDD. Similarly, experts agreed that ketamine and scopolamine could fill this unmet need as fast-acting alternative pharmacotherapies for these conditions. Overall, experts thought that these drugs could have a moderate-to-large impact on patient outcomes, although unsettled safety and long-term efficacy data led three experts to state that ketamine and scopolamine might not adequately address these needs.<sup>61,66,67</sup>

**Acceptance and adoption:** These drugs' expected acceptance and adoption were a matter of divergent opinions. Multiple experts, focusing on immediate patient and clinician adoption, predicted that ketamine and scopolamine would not be widely accepted for treating MDD and BPD, citing treatment costs, potential adverse events, and unclear clinical trial data. However, several experts concluded that clinician and patient acceptance and adoption rates would be high, with patients possibly preferring ketamine and scopolamine to treatments such as TMS and ECT for these indications.<sup>59,62,66,67</sup>

**Health care delivery infrastructure and patient management:** Experts predicted that, for these indications, IV ketamine and scopolamine would cause little disruption to health care delivery infrastructure. However, experts also stated that because these interventions require increased monitoring and must be administered by clinicians, patient management could be moderately affected. Two experts evaluating ketamine also speculated that an effective oral or intranasal ketamine formulation would mitigate these concerns.<sup>60,63</sup>

**Health disparities:** Many experts thought that these interventions could increase health disparities among economically disadvantaged patients, because of higher direct patient treatment costs in comparison to medications approved for treating MDD and BPD.<sup>58,60,63,65,67</sup> Additionally, experts considered that patients with limited access to infusion centers could be disproportionately underserved by these interventions.<sup>61,65</sup>

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