Next-Step Treatment Considerations for Patients With Treatment-Resistant Depression That Responds to Low-Dose Intravenous Ketamine

William V. Bobo, M.D., M.P.H., Patricio Riva-Posse, M.D., Fernando S. Goes, M.D., Sagar V. Parikh, M.D.

Numerous short-term randomized trials support the acute-phase efficacy of low-dose intravenous (IV) ketamine for patients with treatment-resistant unipolar or bipolar depression. Ketamine's antidepressive effects generally have limited duration, highlighting the need for maintenance treatment after an acute-phase response. It is increasingly likely that psychiatrists will be called upon to manage the care of patients with treatment-resistant unipolar or bipolar depression who have responded acutely to ketamine and to recommend or initiate next-step treatments. However, there is a paucity of controlled evidence to guide best practices for managing treatment of patients with treatment-resistant unipolar or bipolar depression who have had a positive initial response to ketamine. This article reviews the available evidence supporting specific strategies for extending and maintaining acute antidepressive responses to low-dose IV ketamine in patients with treatment-resistant unipolar or bipolar depression and provides some preliminary considerations for clinical practice.

Focus 2020; 18:181–192; doi: 10.1176/appi.focus.20190048

Numerous short-term randomized trials support the acute-phase efficacy of subanesthetic doses of ketamine (generally, 0.5 mg/kg infused intravenously [IV] over 40–60 minutes or administered intranasally) in patients with unipolar and bipolar depression who failed to respond to multiple therapeutic trials of traditional antidepressants or mood-stabilizing drugs (1). The most common adverse effects in these studies were mild and transient, and the risk of serious adverse effects from low-dose ketamine appears to be low when used in the short term for the acute treatment of unipolar or bipolar depression (2). The antidepressive effect of ketamine lasts about 7 days after a single infusion and can be extended for several more days if repeated infusions are given (3, 4). However, after repeated infusions end, depressive symptoms typically return within only a few weeks (3, 4), absent an alternative form of effective treatment.

The transient nature of ketamine's antidepressive effects highlights a compelling need to safely extend positive responses to ketamine, particularly for patients with treatment-resistant unipolar or bipolar depression. For individuals who have responded to a course of intravenous ketamine, maintenance treatment is generally necessary. However, the best practices for managing treatment of patients with treatment-resistant unipolar or bipolar depression who have had a positive initial response to ketamine are unclear. Still, it is increasingly likely that psychiatrists will be called upon to manage the care of patients who have received a successful trial of ketamine and to recommend or initiate next-step treatments.

Until evidence from adequately powered randomized trials becomes available, clinical guidance regarding best practices after a positive antidepressive response to ketamine must rely on expert recommendations, clinical experience, and preliminary research evidence where available. In keeping with that observation, this article reviews the available evidence supporting specific strategies for extending and maintaining acute antidepressive responses to subanesthetic ketamine in patients with treatment-resistant unipolar or bipolar depression and provides some preliminary considerations for clinical practice (Box 1).

POTENTIAL APPROACHES TO EXTENDING ACUTE RESPONSE TO KETAMINE

Maintenance Treatment With Intravenous or Intranasal Ketamine

For managing depression, it is common to extend treatment with an effective acute-phase therapeutic (antidepressants, some mood-stabilizing drugs, electroconvulsive therapy, etc.) in the hopes of maintaining clinical response. However,

there are no controlled trials that directly examine the maintenance phase efficacy of intravenous or intranasal racemic ketamine for treatment-resistant unipolar or bipolar depression. As such, the long-term antidepressive efficacy of repeated ketamine treatments is largely unknown. Additionally, the potential long-term safety concerns of repeated long-term ketamine infusions are not trivial and include abuse potential, cognitive dysfunction, psychosis, and urinary cystitis (5).

Most of the available evidence supporting the use of repeated continuation- or maintenance-phase ketamine treatments for patients with treatment-resistant unipolar or bipolar depression comes from small, open, uncontrolled studies or retrospective case series. For example, in an open-label pilot study, 12 hospitalized patients with treatment-resistant depression who were actively suicidal were given intravenous ketamine (0.5 mg/kg) thrice weekly over 14 days (6). Five of the 12 enrollees remitted within the first three acute-phase infusions. Remission was sustained for all five patients throughout a maintenance phase in which they received once-weekly ketamine infusions for 4 weeks. In another small, open-label pilot study, eight patients with treatment-resistant unipolar or bipolar depression received repeated intravenous infusions of ketamine (0.5 mg/kg) for 7 weeks after an initial positive response to three ketamine infusions (7). All eight patients sustained their positive responses through 60 days of follow-up.

Small retrospective case series have also reported the effective maintenance of acute responses to intravenous ketamine, using repeated infusions in elderly patients with treatment-resistant unipolar or bipolar depression (8) and in mixed groups of adults with treatment-resistant unipolar or bipolar depression (9, 10). In each of these reports, the repeated infusions of intravenous ketamine were well tolerated, including no evidence of cognitive decline, treatment-emergent psychosis, or the development of signs and symptoms consistent with cystitis after 12–45 treatments given over 14–126 weeks (10).

One randomized acute trial of intravenous ketamine for patients with treatment-resistant unipolar or bipolar depression subsequently evaluated the maintenance efficacy of intravenous ketamine in a subset of participants (11). Forty-one patients with treatment-resistant depression who relapsed after participating in a randomized comparison of single-dose ketamine and midazolam (phase 1) received additional treatment with six open-label infusions of ketamine over two weeks (phase 2). Phase-2 participants with positive responses received four additional open-label infusions once weekly (phase 3). In phase 1, 27% (N=11) of patients met response criteria 24 hours after receiving ketamine. In phase 2, 23 (59%) participants who completed the study met response criteria, the majority of whom met response criteria after three of the maximum of six delivered infusions. In phase 3, 21 (91%) of the responders in phase 2 maintained positive responses through the end of follow-up. There were no spontaneous reports of drug seeking or drug craving.

In summary, the research evidence supporting the use of repeated intravenous ketamine treatments for maintenance of acute positive responses in patients with treatment-resistant unipolar or bipolar depression is encouraging but preliminary. The evidence reviewed here suggests that patients with treatment-resistant unipolar or bipolar depression who respond well to acute-phase ketamine usually continue to benefit from treatment with repeated infusions, without serious adverse effects. However, prospective studies are limited by relatively short durations of follow-up (up to six weeks) after acute-phase responses, although retrospective case series describe successful maintenance treatment over longer observation periods. The field awaits definitive evidence of long-term efficacy and safety of maintenance treatment with intravenous ketamine in people with treatment-resistant unipolar or bipolar depression. Whereas long-term randomized trials could take several years to complete, data of sufficient quality to guide clinical practice could be generated sooner with the development of linked national registries (12).

Maintenance Treatment With Esketamine

In March 2019, intranasal esketamine was approved by the U.S. Food and Drug Administration (FDA) for patients with treatment-resistant unipolar or bipolar depression. The approval was based on a phase III study that showed the superiority of intranasal esketamine over placebo for reducing depressive symptoms over 28 weeks (13) and a maintenance discontinuation trial of stable esketamine responders and remitters that showed a significantly lower rate of relapse in participants assigned to weekly or biweekly treatment compared with placebo (14). Notably, two additional Janssen Pharmaceuticals–sponsored phase III trials, including a dose-comparison acute-phase placebo-controlled trial (15) and a trial in older adults (16), failed to show significant differences in depressive symptom change versus placebo. However, the FDA panel considered the evidence from the two positive trials to be sufficient for approval.

Intranasal esketamine is available for acute and maintenance treatment, although high cost, variable insurance coverage, and FDA-mandated Risk Evaluation and Mitigation Strategies (REMS) may limit access for many patients with treatment-resistant unipolar or bipolar depression (16). Nevertheless, given that it is the only form of ketamine with a long-term efficacy and safety study (14), intranasal esketamine may be the safest and most effective means of maintaining the response achieved from an acute ketamine course. In that study, 297 patients with treatment-resistant unipolar or bipolar depression who achieved stable remission after 16 weeks of esketamine treatment were randomized to continued treatment with esketamine or placebo nasal spray, each in addition to antidepressants. Treatments were administered either once weekly or once every two weeks. Rates of relapse were significantly lower (27% versus 45%), and time to relapse was significantly longer with esketamine than with placebo (hazard ratio=0.49, 95%

confidence interval [CI]=0.39–0.84, number needed to treat [NNT]=6). Adverse effects were generally observed after dosing, were mild to moderate in intensity, and typically resolved during the same treatment day. There were no observed cases of psychosis, respiratory depression, or interstitial cystitis or reported cases of ketamine addiction.

In summary, there is controlled evidence supporting maintenance-phase intranasal esketamine after an initial and sustained acute-phase response. This result raises the possibility of maintenance-phase effectiveness of intranasal esketamine after a positive acute response to intravenous or intranasal racemic ketamine. However, the median period of esketamine exposure in the Janssen maintenance trial was only 19 weeks. Therefore, replication and extension of these effects over longer observation periods are needed. To our knowledge, there are no published data about prolonging the response to ketamine by switching to esketamine.

Oral Ketamine

The recent FDA approval of intranasal esketamine, the enormous research activity around intravenous ketamine, concerns about poor absorption pharmacokinetics, and off-patent status have all contributed to a relative lack of attention paid to the use of oral ketamine for patients with treatment-resistant unipolar or bipolar depression (17–19). Nevertheless, individual investigators have conducted clinical studies with oral ketamine for the acute treatment of depression. For instance, a recently completed randomized trial of 41 patients with treatment-resistant unipolar or bipolar depression showed significantly greater improvement in depressive symptoms with oral ketamine (1 mg/kg) than with placebo when added to antidepressants, given three times weekly over 21 days (20). Repeated oral ketamine resulted in antidepressant effects at 40 and 240 minutes postdosing and on days 3, 7, 14, and 21. After 21 days, six ketamine-treated participants (27%, N=6) and none of the patients who received placebo achieved remission (NNT=3.7).

Similar conclusions were reached in a randomized trial that compared the antidepressive effects of oral ketamine (25 mg twice a day as an adjunct to 150 mg sertraline) with those of sertraline+placebo in 90 adults with moderate-to-severe major depressive disorder over six weeks (21) and in a smaller randomized trial that enrolled 46 patients with mild-to-moderate depression and comorbid chronic headache and compared the antidepressive effects of oral ketamine (50 mg three times a day) with those of diclofenac over 6 weeks (22). In both studies, significantly greater improvement in depressive symptoms occurred over time for patients who received ketamine compared with controls, with no dissociative adverse effects or cases of abuse or dependence reported. In a recent systematic review that included these two active-comparator trials and 11 other reports of lower methodological quality, the authors cited the need for additional well-designed randomized trials and concluded that there appears to be initial evidence of significant antidepressant effects with oral ketamine, although the onset of efficacy is not as rapid as for intravenous ketamine (23).

In summary, the reasonably strong preliminary evidence of antidepressive effects sustained over three to six weeks and reassuring safety profile in the reviewed studies raises the hypothesis that oral ketamine could be used to safely extend the acute antidepressive effects of ketamine. However, we are not aware of any randomized trials testing the efficacy of oral ketamine for sustaining a positive initial antidepressive response to intravenous or intranasal racemic ketamine.

Other Glutamatergic Drugs

Although the exact mechanism by which ketamine exerts antidepressive effects has not been established, its known *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist activity has reinvigorated the search for alternative glutamatergic agents that could be more easily administered and that lack dissociative effects or potential concerns for abuse. Among the most studied is lanicemine, a once-weekly parenterally administered NMDA antagonist with no dissociative side effects. An initial phase IIb study (152 patients with major depressive disorder and a history of poor response to antidepressants) showed short-term efficacy (24); however, this was followed by a negative placebo-controlled trial (25). Mixed results have also been observed for several NMDA receptor (NMDAR) antagonists, including those that are specific to the NR2B subunit (26). Augmentation trials of memantine, an uncompetitive NMDAR antagonist approved for the treatment of Alzheimer's disease with a relatively benign safety profile, have yielded disappointing results for treating depressive symptoms of patients with major depressive disorder and bipolar disorder (27). Treatment with the NMDA antagonist riluzole failed to show efficacy in preventing relapse after a positive response to intravenous ketamine in a small, randomized, placebo-controlled continuation trial (28). Lithium, a mood-stabilizing drug that reduces glutamatergic neurotransmission and may share with ketamine a number of important effects on molecular second-messenger signaling pathways (29), also failed to demonstrate efficacy for extending the acute-phase response to intravenous ketamine in a small, randomized trial (30).

The antidepressive effects of two antimicrobial agents that affect glutamatergic neurotransmission—minocycline (an anti-inflammatory glutamate-modulating tetracycline) and D-cycloserine (an NMDAR antagonist antituberculosis drug)—have also been investigated as potential antidepressives. A recent meta-analysis of three small randomized trials (totaling 158 randomly assigned participants with major depressive disorder) yielded a large antidepressive effect for minocycline compared with placebo (standard mean difference=−0.78, 95% CI=−0.24 to −1.33), providing proof-of-concept evidence for acute-phase efficacy (31). However, we are unaware of any controlled studies of minocycline maintenance of acute antidepressive responses

to ketamine or other agents. A recent randomized trial of 32 patients with treatment-resistant unipolar or bipolar depression who responded to two open-label ketamine infusions showed that maintenance-phase treatment with adjunctive d-cycloserine (titrated to 1,000 mg daily) over six weeks resulted in lower scores on the 17-item Hamilton Depression Rating Scale (HAMD) (32) suicide item (item 3) than adjunctive placebo (33). However, the D-cycloserine and placebo maintenance groups did not differ significantly with respect to total depression severity scores, both overall and in separate analyses of participants with major depressive disorder and with bipolar disorders.

At least two glutamatergic compounds are being tested in larger phase III trials: rapastinel and the combination of dextromethorphan and bupropion. Rapastinel is an injectable partial agonist of the glycine-binding site of the NMDAR (34). In a randomized proof-of-concept trial of 116 participants with major depressive disorder who failed to respond to a trial of at least one conventional antidepressant, a single dose of intravenous rapastinel infused over three to 15 minutes resulted in rapid improvement in HAMD scores at 24 hours, with 5 mg/kg and 10 mg/kg doses achieving significantly greater improvement in depression severity than saline placebo (35). However, in three phase-III randomized trials (NCT02932943, NCT02943564, and NCT02943577) that collectively enrolled 1,510 patients with major depressive disorder who had a partial response to conventional antidepressants, adjunctive rapastinel did not result in a significantly greater reduction in depressive symptoms than that seen with placebo. A phase-III evaluation of AXS-05—a combination of dextromethorphan, a widely available antitussive with mild NMDA antagonistic properties, and bupropion, an antidepressant and CYP2D6 inhibitor coadministered to increase dextromethorphan exposure—has been completed (NCT04019704). A total of 327 adults with major depressive disorder were randomized to 6 weeks of treatment with AXS-05 or placebo. In December 2019, the trial sponsor announced that AXS-05 treatment resulted in significantly greater improvement in depressive symptoms than placebo over 6 weeks (the primary study endpoint) and significantly greater improvement in depressive symptoms with AXS-05 after one week (36). In a six-week, randomized, phase-II trial of 80 adults with severe major depressive disorder (NCT03595579), treatment with AXS-05 resulted in significantly greater reduction in depressive symptoms than that with bupropion monotherapy (37). The results of these studies have not been published and are not yet available on the ClinicalTrials.gov website.

In summary, the development of glutamatergic drugs for treatment-resistant unipolar or bipolar depression that lack ketamine's dissociative and potentially habit-forming properties is an area of active research. Several well-studied agents have yielded inconsistent results in short-term efficacy trials, and almost none are currently available for clinical use. The results supporting possible maintenance-phase efficacy of D-cycloserine after acute-phase antidepressive response to ketamine are only preliminary and are not yet convincing with respect to maintaining long-term antidepressive effects.

Electroconvulsive Therapy (ECT) and Other Neuromodulatory Treatments

ECT is an effective treatment for patients with severe and treatment-resistant unipolar or bipolar depression (38). Although repeated ECT administrations are often used in maintenance-phase treatment, this is typically after a positive acute antidepressive response to ECT, not to other treatment modalities, including ketamine. There is no specific guidance from the literature that addresses the role of ECT or other neuromodulatory treatments (e.g., transcranial magnetic stimulation [TMS], vagal nerve stimulation [VNS], and others) for maintaining acute antidepressive responses to ketamine in patients with treatment-resistant unipolar or bipolar depression.

Additionally, there is no consistent evidence that the use of ketamine as an anesthetic either strengthens or extends the antidepressive effects of ECT. Two influential meta-analyses that examined the antidepressive effects of ketamine anesthesia for depressed patients undergoing ECT had contradictory results. One report documented significantly greater and more rapid antidepressive responses—but also more side effects and longer postanesthesia recovery times—with add-on ketamine anesthesia (39). The second meta-analysis documented mixed findings across 24 reviewed studies, limiting the conclusions that could be drawn regarding the overall antidepressive benefit of ketamine relative to other forms of anesthesia for ECT (40).

In summary, there is no evidence supporting the efficacy of ECT for maintenance-phase treatment after an acute response to ketamine. Given the need for general anesthesia in ECT, there has been considerable interest in exploring whether ketamine as an anesthetic can improve or extend antidepressive responses to ECT. However, it is currently unknown whether ketamine should be the anesthetic of choice for people who have responded to acute ketamine infusions who then receive ECT.

Switching Conventional Antidepressants or Mood Stabilizers

In clinical practice, most patients who receive antidepressive treatment with ketamine will not have a history of having failed to respond to every available antidepressant medication or mood-stabilizing drug. For example, in our experience, many ketamine-treated patients with treatment-resistant unipolar major depression have not been offered (or have previously refused) a therapeutic trial of third-line or fourth-line treatments, including tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs). This likelihood raises the possibility that many depressed patients who are treated acutely with ketamine could be transitioned to a new antidepressant, mood stabilizer, or medication

combination that had not been previously trialed in hopes of avoiding or limiting the duration of maintenance treatment with ketamine. To our knowledge, this question has not been addressed empirically.

PRACTICAL CONSIDERATIONS

Although there are several potential approaches to consider for maintaining an initial acute antidepressive response to intravenous ketamine, none of the reviewed options have direct empirical support for this specific indication. This lack of evidence substantially weakens the ability to make strong clinical recommendations, which require a reasonably high degree of certainty about the comparative utility of the proposed treatments and their respective risks of harm, over the long term, to people with treatment-resistant unipolar or bipolar depression who have responded acutely to intravenous ketamine. Mindful of not only these large knowledge gaps but also the need to address an increasingly common clinical scenario, we provide some preliminary guidance that can be considered based on the available but limited clinical evidence and on practice experience.

When Maintenance Treatment With Ketamine Is Chosen

In our experience, most patients who respond to intravenous ketamine will opt for additional ketamine treatments, either as a sole therapy or in the context of changing or modifying treatment with antidepressants or mood-stabilizing medications (discussed later). Given the lack of established efficacy and safety of maintenance treatment with repeated doses of ketamine, due caution is warranted, given the unknown efficacy and safety profile over the long term (5, 41).

Before acute-phase ketamine treatment is started, patients should be made aware that additional ketamine treatment is only one of potentially several options available for maintaining clinical benefit (see Box 1). The potential risks should also be revisited with patients who are considering ketamine maintenance treatment, even if they have tolerated repeated acute-phase treatments. In our experience, continuation of the effective acute-phase dose (nearly always 0.5 mg/kg IV, infused over 40–60 minutes) can be safely administered for maintenance-phase treatment. After an acute response to ketamine, we typically provide continuation-phase infusions administered once weekly for four weeks, followed by a systematic increase in the time interval between infusions, usually with a concurrent change in treatment with conventional antidepressants or mood-stabilizing medications and psychosocial treatment.

Although long-term safety and benefit are still relatively uncertain, maintenance-phase treatment with ketamine may be practicable in the context of a rigorous informed consent process combined with protocol-driven treatment decisions. The informed consent process emphasizes the reasonable expectation (but not a guarantee) of short-term benefit and the relative absence of evidence of long-term effectiveness and safety. Clinical protocols should include a clear delineation of team members and their roles, specific treatment procedures, eligibility criteria, procedures for clinical evaluation by an anesthesiologist when necessary, specific go– no-go decision rules for providing and discontinuing acute- and maintenance-phase treatment with ketamine, and procedures for systematically assessing and managing adverse effects (Box 2). A gradual decrease in the frequency of ketamine infusions should be conducted with the goal of eventually stopping ketamine treatment, if possible. When stopping ketamine is not possible, the systematic approach to symptom and side-effect monitoring described earlier is crucial for identifying a minimum frequency of ketamine administrations needed to maintain therapeutic benefit and the earliest point in time when treatment-limiting adverse effects may be occurring.

We believe that rigorous informed consent and protocol-driven procedures can help strike a reasonable balance between a compelling clinical need for rapid-acting antidepressive therapy with ketamine against its unknown longer term effectiveness and safety profile—all within the context of very close psychiatric follow-up (42). Such an approach should also include regular communication with the clinician who is administering ketamine treatments and regular assessment of efficacy (supplemented by the use of standardized depression and adverse effect rating scales), short- and long-term side effects, and behaviors suggesting a heightened risk of addiction to ketamine and other substances. Repeated doses of ketamine carried out over an indefinite period may be expected to lead to a high cumulative out-of-pocket cost burden, which may limit this approach for many patients.

BOX 1. Approaches to extending acute response to ketamine

- Continued intravenous or intranasal ketamine
- Intranasal esketamine
- Oral ketamine
- Other glutamatergic drugs
- Electroconvulsive therapy
- Other neuromodulatory therapies
- Switching conventional antidepressants or mood-stabilizing medications
- Continuation of effective psychotherapy

Can Intranasal Esketamine Be Used?

The strong but preliminary evidence of the maintenance-phase benefit of repeated intranasal esketamine is encouraging and invites some speculation about its potential role in routine practice (Box 3). How long and how often to continue administration of esketamine treatment for this purpose are uncertain. The dosing scheme used in the Janssen maintenance trial (weekly or biweekly administration) provides, arguably, the best preliminary guidance for

BOX 2. Clinical considerations and recommendations for racemic ketamine maintenance

- Most evidence supporting maintenance-phase treatment with repeated infusions of racemic ketamine for people with treatment-resistant unipolar or bipolar depression consists of small, uncontrolled studies with relatively short durations of follow-up.
- Long-term effectiveness and safety of maintenance-phase therapy with racemic ketamine is unknown.
- The informed consent process for both acute-phase and maintenance-phase treatment with ketamine should explicitly state these unknown factors. Potential risks of treatment-emergent psychosis, cognitive dysfunction, addiction or abuse, and urinary cystitis should be specifically discussed.
- There should be close coordination with the clinical service providing ketamine infusions and frequent follow-up with patients with treatment-resistant unipolar or bipolar depression receiving ketamine maintenance.
- Ideally, repeated maintenance-phase ketamine infusions are provided under the auspices of a clinical protocol that specifies criteria for major treatment decisions and delineates procedures for systematic assessments of effectiveness and safety.
- Changing to a potentially more effective conventional antidepressant or mood-stabilizing medication and optimization of psychosocial treatment may enable a gradual reduction in the frequency of ketamine administration and, perhaps, eventual discontinuation of ketamine.

maintenance treatment. Whether the acute and long-term efficacy of racemic ketamine is similar to esketamine and whether repeated esketamine can extend a positive response to racemic ketamine are empirical questions that have not yet been answered. Given similar initial results in early proof-of concept trials (43), it may not be unreasonable to assume that specific formulations are likely to be comparable in efficacy.

The potential long-term safety concerns with racemic ketamine must also be considered to apply to intranasal esketamine until results of rigorously conducted long-term safety studies show otherwise (44). The development of an intranasal esketamine treatment registry and REMS program may be expected to reduce some of these risks. However, as others have cautioned, important concerns will still remain untracked, including switching from the medically sound use of esketamine to the overuse or illegal (nonprescribed) use of racemic ketamine (45). Therefore, we urge the same degree of caution and rigor of practice with the use of intranasal esketamine as was recommended earlier for racemic ketamine. Finally, the cost of treatment with esketamine may be excessive for many patients, which may limit its utility as a long-term repeated-dose maintenance-phase therapy.

How About Oral Ketamine?

As discussed earlier, antidepressive effects of oral ketamine have been demonstrated in a handful of studies with varying methodological quality, but research into the efficacy of oral ketamine for extending the acute antidepressive effects of intravenous or intranasal ketamine is lacking. Still, oral ketamine has some practical advantages that may increase its appeal for some patients (Box 4). Oral ketamine is available at a relatively low cost and can be administered outside of medical settings, without direct clinical monitoring. Additionally, oral administration of ketamine follows traditional antidepressant-prescribing practices involving licensed prescribers and community pharmacies, suggesting ease of implementation and dissemination. Oral ketamine (created in compounding pharmacies) has been used worldwide for chronic pain for decades—particularly in the United Kingdom, where oral ketamine pain guidelines exist (46) and advice is offered through the National Institute for Clinical Excellence (47).

On the other hand, oral ketamine is poorly absorbed, with estimates ranging from 15% to 25% absorption with oral ingestion and up to 30% with sublingual dosing (19, 48). The erratic absorption pharmacokinetics of oral ketamine may lead to practical challenges when trying to select potentially

BOX 3. Clinical considerations and recommendations for intranasal esketamine maintenance

- The maintenance-phase efficacy of intranasal esketamine administered weekly or biweekly is supported by a randomized trial. Patients in that study responded acutely to intranasal esketamine, not intravenous racemic ketamine.
- The efficacy and safety of intranasal esketamine maintenance-phase treatment beyond 19 weeks are unknown for patients with treatment-resistant unipolar or bipolar depression, as is the efficacy of maintenance-phase intranasal esketamine treatment after an acute response to intravenous racemic ketamine.
- Intranasal esketamine is administered under the aegis of an FDA-mandated Risk Evaluation and Mitigation Strategies (REMS) program.
- Encouraging results from the randomized maintenance-phase trial and availability of a REMS program could lead to a false sense of security about the long-term safety and effectiveness of repeated intranasal ketamine.
- The informed consent and follow-up procedures with Intranasal esketamine maintenance should be similar to those used in maintenance-phase treatment with intravenous racemic ketamine.
- Although there is little evidence-based support, optimizing next-step pharmacotherapy and psychosocial treatment may be possible to enable a gradual lengthening of the time interval between doses, with the goal of eventually stopping esketamine maintenance.

BOX 4. Clinical considerations and recommendations for oral ketamine maintenance

- Research into the efficacy of oral ketamine for treatment-resistant unipolar or bipolar depression is confined to the acute phase of treatment only, although case reports summarize longer-term use of ketamine.
- The efficacy of oral ketamine for maintenance-phase treatment after an acute response to intravenous ketamine in people with treatment-resistant unipolar or bipolar depression is unknown.
- The absorption of oral ketamine is poor; thus, identifying an effective dose for treating depression may be challenging and lead to problems, considering the high risk of depressive relapse soon after acute-phase ketamine infusions are stopped.
- If oral ketamine is chosen as a maintenance-phase treatment, informed consent and follow-up procedures should be similar to those for maintenance-phase treatment with intravenous racemic ketamine, including optimizing next-step pharmacotherapy and psychosocial treatment with the goal of tapering and discontinuing oral ketamine maintenance.

effective antidepressive doses. Extrapolation of a typical intravenous ketamine dose of 0.5 mg/kg to oral dosing is only approximate, suggesting a three- to fivefold initial target; for an 80 kg individual getting a 40-mg IV dose, an oral dose may range from 120 to 200 mg. The published literature also documents very wide ranges and frequencies of dose administration, ranging from once weekly to three times daily (20, 23). Our own clinical experience parallels that of the Toronto case series report of 100 to 300 mg every three days (49), with occasional higher doses and more frequent administrations. Twice-weekly dosing of 100–300 mg resembles, pharmacokinetically, the dose delivered by the FDA-approved twice-weekly intranasal esketamine. In our experience, compounding pharmacies are often able to formulate oral capsules or tablets with a typical monthly prescription cost of under $100 USD.

Because of the lack of studies investigating oral ketamine for extending acute antidepressive responses to intravenous ketamine, the use of oral ketamine for this specific purpose must be considered a low-priority option. However, for patients with treatment-resistant unipolar or bipolar depression who express a desire to undergo a therapeutic trial of oral ketamine after an acute response to intravenous ketamine, preliminary considerations for clinical use can be provided based on clinical experience and available but limited research. Once a patient consents to treatment with oral ketamine, their prior experience on intravenous ketamine should be reviewed with respect to dosing, efficacy, and side effects. As with most oral agents, lower doses would be initiated, efficacy and side effects would be monitored, and dosing would be adjusted. An initial upper limit of dosing of five times the previous intravenous dose can be declared, and procedures for the first dose should be discussed. The first dose may be administered in the office with clinical monitoring by staff and a family member for two hours. The typical dosing strategy is 100 mg of oral ketamine every Monday and Thursday at bedtime, with the patient reporting both efficacy and side effects by phone the next day. As is the case with ketamine and esketamine, the long-term antidepressive efficacy and safety of oral ketamine for treatment-resistant unipolar or bipolar depression is unknown. Once there is confidence in the safety of oral ketamine, doses are increased by 50 mg per dose every one to two weeks, until a maximum of 300 mg twice per week is achieved. The patient can be seen every two to three weeks face to face during the titration period. Otherwise, we again

BOX 5. Clinical considerations and recommendations for use of ECT and other neuromodulatory treatments after acute response to ketamine

- The efficacy of electroconvulsive therapy (ECT) and other neuromodulatory treatments, such as transcranial magnetic stimulation and vagus nerve stimulation, is unknown for extending an acute antidepressive response to ketamine in people with treatment-resistant unipolar or bipolar depression.
- Ketamine is often discussed as a safer and equally efficacious alternative to ECT for the acute management of treatment-resistant unipolar or bipolar depression; however, no evidence currently supports such an assertion.
- Ketamine may be a reasonable alternative for patients with treatment-resistant unipolar or bipolar depression who have responded poorly to ECT or who cannot tolerate the procedure.
- ECT may be a useful alternative for patients with treatment-resistant unipolar or bipolar depression who have a positive initial response to ketamine but experience a recurrence of depressive symptoms despite ongoing ketamine treatment.
- Although empirical evidence is sparse, ECT may be preferred over ketamine for patients with treatment-resistant unipolar or bipolar depression who have lost reliable transportation, have active substance use disorders, or have psychotic symptoms, catatonic features, or mixed depressive symptoms.
- The choice of anesthesia for patients with treatment-resistant unipolar or bipolar depression who are undergoing ECT should be made in consultation with the collaborating anesthesiologist based on standard guidance, even for patients with prior positive antidepressive response to ketamine. Using intravenous ketamine as a standard anesthetic with ECT has not been shown to enhance ECT's antidepressive effect.

BOX 6. Clinical considerations for switching to conventional antidepressants or mood stabilizers after acute response to ketamine

- No studies have investigated the effectiveness of extending an acute-phase antidepressive response to ketamine by switching to conventional antidepressants or mood stabilizers, although some unconventional agents, such as D-cycloserine, show promise.
- Most patients who undergo acute treatment with ketamine will be switched to an alternative antidepressant or mood-stabilizing treatment without having had adequate therapeutic trials of third- or fourth-line pharmacotherapies or evidence-supported psychosocial treatment.
- With few exceptions, most patients can be expected to tolerate a transition to a new antidepressant or mood-stabilizing medication while completing their acute-phase treatments with ketamine; CYP450 2B6 and 3A4 inducers (carbamazepine, etc.) and benzodiazepines may diminish or delay the onset of antidepressive effects with ketamine.
- A thorough review of drug treatment histories may uncover medications that were inadequately used, prematurely abandoned, or avoided altogether; such medications may now be next-step therapeutic options.
- The role of pharmacogenetics-guided treatment selection for patients with treatment-resistant unipolar or bipolar depression is unclear. However, when pharmacogenetics testing results have already been obtained, this information can be considered when making clinical decisions about next-step medication selection and dosing.

advise adopting the same protocol-driven practices for follow-up and monitoring with the use of oral ketamine as was recommended earlier for intranasal esketamine and intravenous racemic ketamine.

When Might ECT Be Preferred?

There is no evidence supporting the use of ECT or other neuromodulatory therapies for maintaining an initial positive antidepressive response to ketamine. However, ECT may be offered to patients with treatment-resistant unipolar or bipolar depression, those who did not respond to ketamine and have not previously undergone a therapeutic trial of ECT, those who experience a recurrence of depressive symptoms despite ongoing treatment with ketamine following an initial positive response, or those with a depressive relapse after successful ketamine treatment but who may not tolerate additional ketamine doses (Box 5). Examples of the latter include patients with a relapse of comorbid substance use; individuals who have lost reliable access to adequate transportation; and those presenting with pronounced mixed depressive symptoms, catatonia, or psychosis. There is even less guidance from the literature or clinical experience regarding the role of other neuromodulatory therapies such as TMS for maintaining initial positive antidepressive responses to ketamine. Therefore, we are hesitant to make specific recommendations about neuromodulatory treatments other than ECT.

Should Antidepressive Response to Ketamine Influence Choice of ECT Anesthesia?

Currently, there is no consistent evidence that the use of ketamine as an anesthetic either strengthens or extends the antidepressive effects of ECT. In our opinion, having a history of positive antidepressive response to ketamine, followed by a relapse requiring ECT treatment, provides no clear indication that ketamine should be the anesthetic drug of choice. The choice of anesthetic agent for ECT should be made in consultation with the collaborating anesthesiologist based on standard clinical guidance (42, 50, 51).

When Switching Conventional Antidepressants or Mood Stabilizers

In our experience, patients with treatment-resistant unipolar major depression who present for ketamine therapy often have not been offered or have refused therapeutic trials of older antidepressants, including TCAs or MAOIs. Broadly, most antidepressants are about equally effective, with only small advantages for some (52). Although this observation is based mainly on studies of patients who were not necessarily treatment resistant, it suggests that there may be considerable latitude in choosing another antidepressant after ketamine (Box 6). If an antidepressant has not been previously used, one recommendation, based on the Cipriani et al. study (52), is to consider using one of the three antidepressants with the best margin of efficacy and tolerability, specifically, agomelatine, escitalopram, or vortioxetine (53). Another approach is to consider TCAs or MAOIs as a maintenance strategy after acute response to ketamine, although efficacy is not proven. However, there is evidence suggesting that oral MAOIs and TCAs may be effective for at least some patients who do not respond to other types of antidepressants (54–60), although remission rates are often very low at the stage of treatment resistance when these medications are considered (54, 61). Still, we typically recommend that patients and their families consider these treatments before undergoing a therapeutic trial of ketamine.

For purposes of extending a positive antidepressive response to ketamine, case literature and a drug interactions database search suggest that depressed patients can be safely transitioned to TCAs, oral MAOIs, or newer antidepressants while receiving ketamine without clinically significant drug-drug interactions (18, 62–65). There is a hypothetical risk of sympathetic overactivation with the use of ketamine for patients who are being treated with MAOIs (65). Therefore, close monitoring is warranted, and consultation with a colleague in anesthesia may be helpful when transitioning to new antidepressants, especially MAOIs. If possible, the transition to TCAs or oral MAOIs should occur before initiating acute ketamine treatment; otherwise, more ketamine

infusions may be needed to ensure that antidepressive benefits are maintained during the several weeks required for the new antidepressant to achieve therapeutic effects. This may be especially important for treatment with MAOIs, which requires a washout period after tapering and stopping the previous antidepressant and other interacting drugs.

Similarly, for patients with bipolar disorders, it may be necessary to consider switching to medications or medication combinations that have not been used during the current depressive episode. For instance, in our experience, many ketamine-treated patients with bipolar disorders have not been offered therapeutic trials of at least one (and often more than one) second- or third-line option for bipolar depression, as defined by practice guidelines (66–70). In our experience, these agents have usually been avoided owing to their adverse effect profiles or potential for clinically significant drug-drug interactions. Most of these agents can be safely administered while acute-phase ketamine is being given (62). Theoretically, CYP2B6 and CYP3A4 inducers, such as carbamazepine, may reduce the overall exposure and, by extension, the therapeutic effects of ketamine (18). As such, carbamazepine may be a low-priority treatment option for patients receiving acute- or maintenance-phase ketamine.

Common adjuncts to antidepressants or mood-stabilizing medications may be expected to be reasonably well tolerated while patients are receiving ketamine or esketamine, although there may be a risk of added sedation with some agents, such as trazodone; other sleep-promoting medications; buspirone; and certain second-generation antipsychotic drugs (62). There is a possible risk of further reduction in seizure threshold when bupropion is administered with ketamine, although this specific interaction has not been previously reported (62). Benzodiazepines, often used with mood stabilizers and antidepressants to manage comorbid anxiety symptoms and associated distress, may limit or delay the therapeutic effects of ketamine (71, 72) and are, therefore, best avoided, especially within 24 hours of ketamine treatment. Intravenous ketamine appears to be about equally efficacious for anxious and nonanxious treatment-resistant major depressive disorder (73), suggesting that concomitant benzodiazepines may not be needed for such patients when treated with ketamine.

There is no evidence related to prioritizing and sequencing potential next-step conventional antidepressants or mood-stabilizing therapies after successful treatment with ketamine for people with treatment-resistant unipolar or bipolar depression. As such, the process of selecting and trialing subsequent treatments will be iterative, and much support and encouragement by the treatment team will be needed. The entire treatment armamentarium should be considered, including evidence-supported psychosocial treatment, which, in our experience, is often overlooked. Empirical evidence is limited regarding the use of pharmacogenetics testing as a decision support tool for selecting antidepressants, although some studies have demonstrated clinical utility for pharmacogenomics testing–guided prescription of antidepressants (74). When pharmacogenetics testing results have already been obtained, this information can be considered when making decisions about next-step treatment selection and dosing (75). HLA-A and HLA-B testing is recommended before the use of carbamazepine and oxcarbazepine for reducing the risk of severe cutaneous drug reactions, regardless of the patient's ethnic group (76). For patients who appear to have tried nearly all available options, it may be necessary to conduct a detailed review of therapeutic trials of medication to determine whether any involved inadequate doses, drug levels, or time on a given medication or medication combination. Medications not associated with any discernible benefit after an adequate therapeutic trial may be excluded from further consideration. However, agents that were associated with a partial response can be considered for another trial at a more optimal (usually higher) dose relative to the previous trial or in combination with other medications in the hopes of achieving a better overall response.

Medications that were previously tried and found to be potentially beneficial but poorly tolerated may also be revisited—for these medications, alternative formulations (liquids, orally dissolving tablets, sprinkles, etc.) may be better tolerated than solid tablets. Some patients may be willing to undergo therapeutic trials of medications associated with a more burdensome adverse effect profile, absent any significant safety concerns, after lacking response to several rounds of treatment with other medications. The practice of conducting such a detailed review of past medication trials requires patience on the part of the patient and practitioner and, often, the help of pharmacy records, additional medical records, and collateral historians.

CONCLUSIONS

Managing the next phases of treatment after an acute-phase response to ketamine in patients with treatment-resistant unipolar or bipolar depression is challenging, owing to the serious and often life-threatening nature of treatment-resistant unipolar or bipolar depression and the high rates of depressive relapses after ketamine infusions are stopped. Although several treatment options reviewed herein have promising preliminary support and pragmatic advantages, none have strong empirical support for safely and effectively extending acute-phase responses to ketamine into the maintenance phase. Still, several of the suggested therapeutic approaches, including conventional pharmacotherapies and ECT, are reasonable to consider for patients with treatment-resistant unipolar or bipolar depression, regardless of ketamine treatments, and can be safely deployed on the basis of a long history of sound clinical evidence and years of clinical experience. Other options, such as maintenance-phase ketamine or esketamine, will require an even greater level of rigor in terms of patient screening, monitoring, and follow-up procedures, given the lack of long-term efficacy and

safety data, potentially serious adverse effects, and limited clinical experience thus far. Funding agencies are encouraged to support large-scale, collaborative, multisite studies that investigate the long-term effectiveness and safety of ketamine as a maintenance-phase antidepressive treatment, as well as other promising approaches to extending a positive acute-phase response to intravenous or intranasal ketamine, including those reviewed herein.

AUTHOR AND ARTICLE INFORMATION

Department of Psychiatry and Psychology, Mayo Clinic, Jacksonville, Florida (Bobo); Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta (Riva-Posse); Department of Psychiatry and Behavioral Science, Johns Hopkins University School of Medicine, Baltimore (Goes); Department of Psychiatry, University of Michigan, Ann Arbor (Parikh). Send correspondence to Dr. Bobo (bobo.william@mayo.edu).

Dr. Riva-Posse served on an advisory board for Janssen Pharmaceuticals. Dr. Goes has received research support from Janssen Pharmaceuticals. Dr. Parikh has received research support from Assurex, Sage, and Takeda; has served as a consultant for Assurex, Janssen, Mensante, and Takeda; and owns shares of Mensante. Dr. Bobo reports no financial relationships with commercial interests.

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