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Guest Editorial

Advancing ketamine in the treatment hierarchy for refractory depression

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Evidence indicates that ketamine is highly effective, has a lower side effect profile and is better tolerated compared to many augmentation strategies for refractory depression. This, combined with data on psychiatric treatment outcome mediators, suggests that earlier intervention with ketamine could improve outcomes for patients suffering from refractory depression.

Keywords
Antidepressants; depressive disorders; psychopharmacology; general adult psychiatry; quality of life.

The past few decades have witnessed a surge of interest in rapid-acting treatments for refractory psychiatric conditions. The anaesthetic ketamine, a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, has increasingly been researched for psychiatric indications. Initial studies demonstrating rapid antidepressant effects drove research leading to the recent US Food and Drug Administration (FDA) approval of intranasal esketamine, the first (and at present, only) ketamine-derived pharmaceutical approved for depression.[1]

Current prescribing guidelines support the use of ketamine-based treatments for treatment-resistant depression, typically defined as lack of response to two adequate trials of oral antidepressant therapies. However, given the novelty and interventional nature of ketamine, providers often consider ketamine as an alternative to electroconvulsive therapy (ECT) – usually employed as a 'last resort' intervention. In such cases, patients can spend upwards of one year trialling first-line oral antidepressant therapies in addition to various augmentation strategies before clinicians may consider ketamine.[2]

A recent open-label, randomised, noninferiority trial of 403 patients with treatment-resistant depression demonstrated that intravenous ketamine may be at least as effective as ECT, psychiatry's most effective treatment for depression, and emerging data suggest ketamine's side effect profile is favourable compared to current antidepressant augmentation strategies.[3] Current validated models for ketamine delivery use intermittent dosing intervals, in contrast to daily dosing of antidepressants to achieve a steady state in the body. Therefore, common side effects of ketamine including nausea, hypertension and dissociation, have been shown to be time-limited and dissipate within 1–2 h of administration.[1] However, given the novelty of ketamine in psychiatric practice, potential long-term effects of repeated, intermittent ketamine dosing remain unknown.

The utilisation of ketamine-based treatments is limited by concerns about its potent psychoactive effects and addiction potential, as well as the risk of ketamine use disorder outside medical settings. Studies of patients with ketamine use disorder have shown evidence of cognitive decline and interstitial cystitis; however, these side effects are seen in individuals who use significantly greater quantities at higher frequencies than those used for treating depression. Studies investigating ketamine for depression in medical settings have shown neither evidence of misuse following treatment nor evidence of bladder pathology or cognitive decline when adhering to validated prescribing guidelines.[1] However, this may not be true with home-based ketamine treatment and, as such, it is important that ketamine treatment be administered in a medically supervised setting.

Given emerging evidence supporting ketamine-based treatments as a treatment for depression with high efficacy, rapid response time and low side effect burden, psychiatry must critically evaluate when it is most appropriate to utilise ketamine for this purpose. Schizophrenia provides an illustrative parallel from contemporary psychiatric practice, with evidence showing that prioritising higher-efficacy treatments such as clozapine earlier in the disease course leads to superior long-term outcomes. This approach is supported by data showing response rates are highest for the initial antipsychotic, with markedly diminishing response rates among patients who require subsequent trials. In addition, a longer duration of untreated psychosis diminishes likelihood of remission, and early use of effective treatments such as clozapine leads to longer periods of remission.[4] Given what is known about the impact of chronic stress on neuroplasticity and treatment outcomes, it is possible that early intervention with effective treatments might also lead to better long-term outcomes in depression. Data assessing clinical predictors of antidepressant response have supported this, showing an association between shorter duration of untreated depressive episode and superior treatment response and prognosis. In addition, shorter duration of response to antidepressant treatment is associated with better outcomes.[5] However, before the discovery of ketamine's antidepressant effects, early utilisation of treatments with higher efficacy was limited by the fact that depression treatments with higher relative efficacy usually came with increased side effects.

Esketamine is currently FDA-indicated as an adjunctive treatment after two failed antidepressant trials. Despite this, the psychiatric community currently holds ketamine as a third-line treatment after augmentation has failed.[6] Thus, we believe that it is most appropriate to compare ketamine to other commonly utilised augmentation strategies for depression refractory to first-line therapy.

Many current augmentation strategies for first-line depression treatments, although effective, are associated with significant side effects. Prescribing guidelines for refractory depression include augmentation with antipsychotics, mood stabilisers or atypical antidepressants like mirtazapine. Strong evidence supports augmentation with antipsychotics; however, antipsychotics are associated with significant cardiometabolic risks that predispose patients to diabetes, hyperlipidaemia and hypercholesterolemia, as well as increased mortality over time. Mirtazapine carries similar metabolic risks, thought to be due in part to the antihistaminergic effects on appetite stimulation. Lithium and other mood stabilisers are also effective augmentation strategies but must be maintained within a narrow therapeutic window and thus require frequent monitoring, with the potential risk of end-organ damage with

chronic administration. A recent trial compared the efficacy of augmenting first-line depression treatments with quetiapine versus intranasal esketamine and found the esketamine group was 1.54 times more like to achieve remission after 8 weeks of treatment and were 1.55 times more likely to sustain remission at 32 weeks. They also noted patients had an earlier response with esketamine and a lower incidence of treatment discontinuation as compared to quetiapine.[7]

Despite clinical evidence supporting ketamine as an effective augmentation strategy, economic considerations present an additional barrier to increased utilisation. While ketamine itself is a generic medication and carries a low unit cost, the interventional nature of administration results in additional expenses that add to the cost of treatment. Off-label use of generic ketamine often costs patients thousands of dollars because of overhead clinic expenses and treatments are rarely covered by insurance. Patients may be eligible for insurance coverage of intranasal esketamine treatment after two failed antidepressant trials, making it the most financially accessible ketamine option for the general population. However, administration of esketamine requires the clinic to enrol in a risk evaluation and mitigation strategy (REMS) programme, requiring adherence to regulations that require increased resources and financially limit administration to settings with high patient throughput. While those same regulations do not currently apply to ketamine administration when used as an off-label treatment for depression, FDA approval of ketamine for depression treatment would also likely require a REMS programme, placing similar logistical and economic barriers on ketamine administration. Additional research is needed to determine the overall cost-effectiveness of earlier utilisation of ketamine and esketamine in comparison to existing augmentation strategies to determine if doing so may lead to better long-term outcomes and reduced disease burden, thereby reducing the overall economic impact of depression (unemployment rates, healthcare expenditures, etc.) and improving patient quality of life. As with clozapine for schizophrenia, such data could inform treatment algorithms, and also promote improved coverage of ketamine by insurance carriers, thereby increasing accessibility.

Both parenteral ketamine and intranasal esketamine have shown rapid and robust treatment responses. However, some studies suggest that parenteral ketamine may be more effective than intranasal esketamine.[8] Despite this, the choice between the two often depends on logistical, financial and comfort considerations. Intranasal esketamine typically requires more frequent clinic visits, ranging from twice a week to every 2 weeks, while parenteral ketamine is usually administered about once a month. From a financial perspective, intranasal esketamine is FDA approved, allowing for insurance coverage. In contrast, parenteral ketamine, often used off-label, usually requires out-of-pocket payment, although some insurance plans are beginning to provide reimbursement. In addition, esketamine may be perceived as a safer option because of the FDA's rigorous approval standards and mandated safeguards for its administration.

Although the relevance of the psychoactive properties of ketamine to its antidepressant effects remain unclear, some studies have demonstrated the potential efficacy of ketamine-assisted psychotherapy (KAP), where the state induced by ketamine is combined with therapeutic support to catalyse psychotherapy. KAP can be appealing for patients for whom psychotherapy is an option, as it requires no regular dosing schedule, theoretically minimising side effects and medication dependence by catalysing changes in underlying psychological functioning that support depression recovery. Interestingly, the earliest studies demonstrating ketamine's efficacy utilised a KAP model, and recent studies have shown that active therapy during ketamine treatment may prolong its therapeutic effects.[1] However, despite historical precedent for using ketamine to augment psychotherapy, current evidence is limited, and further research is needed before conclusions can be drawn about the efficacy of KAP compared to ketamine treatment alone.

Given the potential impact that earlier utilisation of ketamine for refractory depression may have on disease outcomes, patient quality of life and cumulative economic burden of disease, we submit that now is the time for psychiatry to critically consider where ketamine-based treatments should be most appropriately situated within the treatment hierarchy for refractory depression. Urgent research priorities should include head-to-head comparisons of side effects, feasibility, tolerability and treatment outcomes of early ketamine augmentation versus current standard-of-care augmentation. While current research has demonstrated the high efficacy of ketamine in the acute phase of treatment, the sustainability of acute ketamine treatment varies, with current protocols requiring periodic 'boosters'. As such, research is also needed to determine the optimal dosing regimen to sustain efficacy as well as monitoring of the long-term side effects of the various medically supervised dosing regimens. Lastly, economic analyses are needed to investigate the overall cost benefits of earlier intervention with ketamine on the cumulative healthcare costs associated with refractory depression, potentially leading to improved coverage by insurance companies and increasing accessibility to care. Nevertheless, we posit that the current research creates an ethical obligation to consider medically supervised ketamine treatment earlier in the treatment hierarchy given data showing potentially superior efficacy with significantly lower side effects, possibly reducing long-term morbidity and mortality as compared with existing augmentation regimens for patients suffering from refractory depression.

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F.K. owns personal stock in Compass Pathways and Cybin, has received consulting fees from Cybin, research support from Tryp Therapeutics and is on the Science Advisory Board and holds stock equity for Apex Labs. K.N. and F.E.F. have no conflicts of interest to report.

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