This issue of *Psychiatric Annals* brings together several leading clinical research groups who review the evidence for ketamine in mood disorders. The articles highlight progress since the initial report in 2000 from Yale investigators of intravenous (IV) ketamine’s rapid antidepressant efficacy, and the subsequent larger replication study at the National Institute of Mental Health published in 2006. Since that time, there has been an explosion of interest in the off-label use of ketamine, primarily for serious depressive disorders, as well as pharmaceutical industry interest in developing variants of ketamine for psychiatric indications. The first commercial success in this regard was the US Food and Drug Administration (FDA) approval in March 2019 of an intranasal (IN) spray form of ketamine (esketamine, the S-isomer of racemic ketamine) as an adjunctive therapy for treatment-resistant depression (TRD).

Many challenges and questions remain for clinicians and researchers in the ketamine field.

**HOW DOES KETAMINE WORK?**

The article, “Neurobiological Mechanisms of Ketamine: Depression, Suicide, Trauma, and Chronic Stress Pathologies,” by Dr. Lynnette A. Averill, Christopher L. Averill, and Dr. Chadi G. Abdallah delves into the neurobiological mechanisms underlying ketamine’s antidepressant actions. This is an interesting and evolving story. Insights into ketamine’s mechanisms of action are important because understanding how ketamine works is critical to rationally developing the next iteration of drugs that are “ketamine-like” but may be devoid of ketamine’s psychotomimetic side effects. It is critical to understand which of the many steps beyond ketamine’s initial N-methyl-D-aspartate receptor channel blockade are essential for its antidepressant effects—is it enhancement of other ionotrophic receptors such as alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic, proliferation of neurotrophic factors, or formation of new synapses? What is the role of non-glutamatergic mechanisms such as opioid signaling?

**WHAT ARE THE BEST METHODS TO PROLONG KETAMINE’S TRANSIENT ANTIDEPRESSANT AND ANTISUICIDAL EFFECTS?**

This is likely the most relevant clinical issue. Many patients have shown benefit with short-term treatment over several weeks. How are these gains to be maintained? Some patients may require chronic indefinite receipt of ketamine or esketamine, administered according to a fixed- or variable-dosing schedule. However, as discussed in the article, “Ketamine, Esketamine, and A New Generation of Antidepressants,” by Drs. Samuel T. Wilkinson and Brandon M. Kitay, treatment with esketamine mandates onsite clinical monitoring for at least 2 hours after medication administration and poses restrictions on same-day driving. For some patients, this will not be feasible in the long term. Oral

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agents for take-home use might have a role in prolonging response and could offer a more clinically feasible approach for long-term relapse prevention. Several oral agents for major depressive disorder (MDD) and TRD that impact amino acid neurotransmitter systems are currently in late-stage clinical development. Nonpharmacological approaches involving cognitive training and focused psychotherapy are also in development for this vulnerable post-ketamine period.

**HOW DOES THE EFFECTIVENESS OF KETAMINE COMPARE TO MEDICATION AND NEUROSTIMULATION ALTERNATIVES?**

Currently, three atypical antipsychotics (aripiprazole, quetiapine XR, brexpiprazole) are FDA-approved for the adjunctive treatment of MDD, whereas the combination of olanzapine and fluoxetine is approved for TRD. A priority for future investigations will be evaluating the relative effectiveness of ketamine/esketamine compared to these approved medications. The Department of Veterans Affairs is planning such a trial, comparing IN esketamine to aripiprazole for TRD. Also, as discussed in the article, “Comparative Efficacy of Ketamine in Treatment-Resistant Depression,” by Drs. Hatice Guncu Kurt, Murat Altinay, and Amit Anand, an ongoing multicenter trial compares the effectiveness of an acute course of electroconvulsive therapy to an induction course of IV ketamine (administered twice per week for 3 weeks).

**WHICH ADDITIONAL PSYCHIATRIC INDICATIONS ARE THE MOST PROMISING?**

Beyond mood disorders (including bipolar depression) and suicidal ideation/behaviors, posttraumatic stress disorder (PTSD) is likely the psychiatric indication of greatest promise. The article, “Development of Ketamine Administration as a Treatment for Chronic PTSD,” by Abigail B. Collins, Sarah B. Rutter, and Dr. Adriana Feder summarizes work to date in trauma-related conditions. There is accruing evidence of rapid improvements in core PTSD symptoms after ketamine, although the evidence base is still in its infancy. Given the paucity of effective pharmacotherapies in PTSD, this is undoubtedly an area of massive unmet need.

We hope these articles provide an informative introduction for the novice clinician and offer more experienced clinicians a helpful and concise review.

**REFERENCES**