Editorial

When Still Water Runs Deep: The Complexities of Clinically Repurposing FDA Approved Therapies


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In this month's issue of *Clinical Therapeutics*, Karkare et al[1] have reported an analysis of real-world data that heightens the awareness of an increasingly important patient population: patients with treatment-resistant depression (TRD). Underneath the surface, however, they have highlighted the regulatory, safety, and cost-effectiveness issues associated with repurposing a commonly used drug for the treatment of a new disorder.

There are several interesting and important aspects to this study.[1] From a clinical standpoint, major depressive disorder (MDD) is a recurrent psychiatric condition. One major insurer reported that pre-pandemic, MDD had a diagnosis rate of 4.4% and that women were diagnosed with MDD twice as often (6%) as men. People diagnosed with MDD are nearly 30% less healthy than people without an MDD diagnosis, which translates to nearly 10 years of healthy life lost for both women and men. Up to 85% of patients with MDD have one or more additional concurrent chronic health conditions, and 30% have 4 or more. Finally, patients with MDD use health care services more than other commercially insured Americans, resulting in more than twice the overall health care spending ($10,673 compared with $4283).[2] In an updated survey in 2022, this insurer reported that major depression goes undiagnosed and untreated at disproportionately greater rates in Black and Hispanic communities, where it is associated with higher rates of major depression diagnoses.[3]

Today, there is a wide range of therapeutic modalities and pharmacotherapeutics available that align with the degree of symptomatology. However, among the most difficult-to-treat of these patients, ~30% of the total, are those patients who experience an inadequate response to 2 or more different antidepressant treatment courses. This patient population, identified as having TRD,[4] is responsible for approximately one half of the annual treatment costs of medication-treated MDD. Thus, there continues to be a driving interest in the development of novel or repurposed therapies to treat those patients who are unresponsive to existing therapies.

In recent years, ketamine has come to the forefront as an alternative treatment for TRD. Ketamine first received US Food and Drug Administration (FDA) approval in 1970 as a sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation.[5] Ketamine has since found a place as expanded, unlabeled use in the management of acute pain through multiple consensus guidelines from professional societies and academies.[6] The interest in ketamine's potential use as an antidepressant began in the 1990s when attention in psychiatric fields shifted from targeting monoamine neurotransmitters (norepinephrine, dopamine, and serotonin) to glutamate neurotransmission through the fortuitous research of Krystal and Charney.[7] They showed that ketamine blocked the glutamate receptor *N*-methyl-D-aspartate, which resulted in surprisingly salient effects on depressive symptoms.

Ketamine, a Schedule III nonnarcotic substance under the Controlled Substances Act,[8] is actually a chiral compound consisting of a racemic mixture of *S*-ketamine (esketamine) and *R*-ketamine (arketamine). The racemic mixture of the injectable formulation of ketamine had gone off-patent in 2002, driving the commercial manufacturer to advance the doubly patent-protected, nasal spray formulation of the esketamine enantiomer to commercial development. Nasal spray esketamine received FDA approval in 2019 as a breakthrough therapy[9] for use as an adjunct therapy with an oral antidepressant for TRD in adults with depressive symptoms and in adults with MDD with acute suicidal ideation or behavior.[10] This treatment regimen requires a cautious, escalating schedule of nasal sprays to achieve its effect.[11]

Schatzberg[12] has critiqued the pivotal clinical trial resulting in approval, highlighting esketamine's underappreciated opioid properties, the higher relapse rate in the treatment arm of the randomized blinded withdrawal study, and the 3 versus 0 suicides in the treatment arm that occurred 4 to 20 days after the last dose of esketamine. These events presaged the assignment of a Risk Evaluation and Mitigation Strategy to the approval.

Approval of esketamine was in fact accompanied by a Risk Evaluation and Mitigation Strategy,[13] with the goal of mitigating "risks of serious adverse outcomes resulting from sedation and dissociation caused by [esketamine] administration, and abuse and misuse of [esketamine]." To achieve this goal, the drug must fall under the auspices of medically supervised dispensing centers for administration; there must be certification of pharmacies and health care settings to administer; there must be assurance that patients are informed about serious adverse outcomes and need for monitoring while on treatment; and there must be enrollment of all patients in a registry to further characterize risks and to support safe use. On February 16, 2022, the FDA published a detailed alert raising awareness of the use of compounded intranasal racemic ketamine prepared by pharmacists, not the optical isomer esketamine, to treat psychiatric disorders.[14] The FDA has also advised health care professionals about preclinical studies that raise safety alarms.[15]

Reliable estimates on the cost-effectiveness of esketamine are difficult to obtain. Drugs.com cites a price for a 2-spray pack as $729.[16] Ross and Soeteman[17] provide a cost-effectiveness analysis which concludes that esketamine is "unlikely to be cost-effective for management of treatment-resistant depression in the United States unless its price falls by more than 40%" from $240 per dose to approximately $140 per dose.

Beyond use of esketamine for TRD, researchers are finding other applications for ketamine. In February 2022, PharmaTher was granted orphan drug designation by the FDA for ketamine to treat status epilepticus.[18] Another congener of ketamine, methoxetamine, found early, popular use and availability from online vendors[19] but was recently placed in Schedule I of controlled substances.[20] Looking beyond ketamine and its congeners, Murphy et al[21] are exploring AV-101 for its ketamine-like antidepressant effects and reduced potential for behavioral side effects, described in mice.

Although ketamine is an example of a successfully repurposed drug that gained FDA approval as an optical isomer with an altered route of administration, Karkare et al[1] remind us of the complexities associated with the task of repurposing and the risk of inequity to access. They confirm continuing evidence of the disparate access by women and highlight the importance of ongoing health economic modeling to ensure proper acceptance and uptake of newly designated drugs. Ensuring safety, efficacy, equity, and cost-effectiveness is required for the successful repurposing of any drug, whether targeting an orphan disease or one as prevalent as MDD.

Shakespeare recognized that a calm exterior may mask turbulent undercurrents, as he expressed in *Henry VI* [c. 1590; Part 2, Act 3, Scene 1; Duke of Suffolk]: "Smooth runs the water where the brook is deep; And in his simple show he harbours treason."[22] Still water indeed runs deep, and we have just scratched the surface of the complexities related to the clinical repurposing of drugs.

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REFERENCES

1. Karkare S, Zhdanava M, Pilon D, Nash AI, Morrison L, et al. Characteristics of real-world commercially insured patients with treatment-resistant depression initiated on esketamine nasal spray or conventional therapies in the United States. *Clin Ther*. 2022;44.
2. BlueCross BlueShield. Major depression: the impact on overall health. https://www.bcbs.com/the-health-of-america/reports/major-depression-the-impact-overall-health. Published May 10, 2018. Accessed November 11, 2022.
3. BlueCross BlueShield. Racial disparities in diagnosis and treatment of major depression. https://www.bcbs.com/the-health-of-america/reports/racial-disparities-diagnosis-and-treatment-of-major-depression. Published May 31, 2022. Accessed November 11, 2022.
4. Bruce DF. Treatment-Resistant Depression. WebMD. https://www.webmd.com/depression/guide/treatment-resistant-depression-what-is-treatment-resistant-depression. Posted May 2, 2022. Accessed November 11, 2022.
5. Ketamine. Wikipedia. https://en.wikipedia.org/wiki/Ketamine. Last edited September 25, 2022. Accessed November 11, 2022.
6. Schwenk ES, Viscusi ER, Buvanendran A, Hurley RW, Wasan AD, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med*. 2018;43:456–466.
7. Gordon J. New hope for treatment-resistant depression: guessing right on ketamine. https://www.nimh.nih.gov/about/director/messages/2019/new-hope-for-treatment-resistant-depression-guessing-right-on-ketamine. Posted August 13, 2019. Accessed November 11, 2022.
8. Drug Enforcement Agency. US Department of Justice. Drug Fact Sheet. Ketamine. https://www.dea.gov/sites/default/files/2020-06/Ketamine-2020.pdf. Posted April 2020. Accessed November 11, 2022.
9. US Food and Drug Administration (FDA). US Department of Health and Human Services. FDA Briefing document. Psychopharmacologic drugs advisory committee (PDAC) and Drug safety and risk management (DSaRM) advisory committee meeting. February 12, 2019. https://www.fda.gov/advisory-committees/february-12-2019-joint-meeting-psychopharmacologic-drugs-advisory-committee-pdac-and-drug-safety-and. Content current as of 02/16/2022. Accessed November 11, 2022
10. Papova V, Daly E, Trivedi M, Cooper K, Lane R, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled trial. *Am J Psychiatry*. 2019;176:428–438.
11. Esketamine nasal spray. Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211243s004lbl.pdf. Revised July 2020. Accessed November 11, 2022.
12. Schatzberg AF. A word to the wise about intranasal esketamine. *Am J Psychiatry*. 2019;176:422–424.
13. US Food and Drug Administration (FDA). US Department of Health and Human Services. Approved Risk Evaluation and Mitigation Strategies (REMS). Esketamine. https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=386. Last updated January 3, 2022. Accessed November 11, 2022.
14. US Food and Drug Administration (FDA). US Department of Health and Human Services. FDA alerts health care professionals of potential risks associated with compounded ketamine nasal spray. https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-professionals-potential-risks-associated-compounded-ketamine-nasal-spray. Content current as of February 16, 2022. Accessed November 11, 2022.
15. Olney JW, Labruyere J, Price MT. Pathologic changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science*. 1989;244:1360–1362.

16. Drugs.com. Spravato prices, coupons and patient assistance programs. https://www.drugs.com/price-guide/spravato. Accessed November 11, 2022.
17. Ross EL, Soeteman DI. Cost-effectiveness of esketamine nasal spray for patients with treatment-resistant depression in the United States. *Psychiatr Serv*. 2020;71:988–997.
18. PharmaTher Granted FDA Orphan Drug Status for Ketamine. https://microdose.buzz/news/pharmather-granted-fda-orphan-drug-status-for-ketamine/. Posted February 1, 2022. Accessed November 11, 2022.
19. Ward J, Rhyee S, Plansky J. Methoxetamine: a novel ketamine analog and growing health-care concern. *Clin Toxicol*. 2011;49:874–875.
20. Federal Register. Schedules of Controlled Substances: Placement of Methoxetamine (MXE) in Schedule I. June 6, 2022. https://www.federalregister.gov/documents/2022/06/06/2022-11933/schedules-of-controlled-substances-placement-of-methoxetamine-mxe-in-schedule-i. Accessed November 11, 2022.
21. Murphy N, Ramakrishnan N, By Vo-Le, Br Vo-Le, Smith MA, et al. A randomized cross-over trial to define neurophysiological correlates of AV-101 N-methyl-D-aspartate receptor blockage in healthy veterans. *Neuropsychopharmacology*. 2021;46:820–827.
22. Great Books Online. Shakespeare. https://www.bartleby.com/345/authors/444.html. Accessed November 4, 2022.