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Topic: racemic ketamine

Research Question: Is racemic ketamine more effective than J&J’s FDA-approved esketamine for treating Treatment-Resistant Depression?

In 1962, a drug called racemic ketamine was first synthesized, and after promising clinical trials, it received FDA approval as an anesthetic drug to sedate patients. However, over the decades, ketamine became a street or party drug, usually sold under the codenames “Special K” and “Psychedelic Heroin.” In an attempt to stop its illicit use, the US government made ketamine a federally controlled substance in 1999. In the 2000s, medical professionals began going off-label by prescribing it for treating Treatment-Resistant Depression (TRD). Although it was seen as a lifesaving drug for many, the FDA did not perform clinical trials on racemic ketamine as a treatment for mental health. Instead, in 2019, the FDA approved as a therapy for TRD a drug called esketamine (Janssen Pharmaceutical Companies). This leads me to question the various ethical and clinical concerns, particularly Johnson & Johnson’s, or “Big Pharm’s,” role in this drug. Esketamine’s development and funding appear to be driven by the ability to obtain a patent and exclusive market rights, prioritizing money over the accessibility and affordability of an already potent drug potentially more effective in TRD than the drug the FDA approved.

A 2000 study was performed by Robert M. Berman et al. to assess ketamine’s potential antidepressant effects. Finding that racemic ketamine had rapid antidepressant effects, this study incited further research into its potential use as a treatment for TRD. Berman et al. also contrasted ketamine with how SSRIs function. Typically, they take weeks to reduce suicidal ideation, while ketamine only takes hours. Complementing the results from Berman et al.’s study, Colleen Loo et al.’s 2023 study reinforced the safety and effectiveness of ketamine. This was done through a rigorously designed double-blind clinical trial, establishing a strong case for the clinical application of ketamine in treating TRD. Jennifer Chen’s 2022 article discusses how the drug works: ketamine prompts new neural connections. She further explains that when ketamine prompts the production of GABA and Glutamate, new neural pathways are created. Together these sources establish the efficacy of ketamine in the treatment of TRD.

Racemic ketamine’s superiority to esketamine can be observed from the initial research. Stevan Nikolin et al.’s 2023 systematic review and meta-analysis is one of the first clinical comparisons between ketamine and esketamine. While their work suggests that racemic ketamine is the superior drug, they highlight the need for more testing between the two, noting that there are currently limited studies comparing their efficacy, optimal dosing, and response times. Singh Balwinder et al.’s observational comparative study found that racemic ketamine infusions via IV required fewer treatments compared to intranasal esketamine to show results. The cost-effectiveness of racemic ketamine, as analyzed by Madeline Brendle, Ph.D., et al. builds on the idea of racemic ketamine being the better drug. She points out that it is cheaper to produce ketamine ($4 a unit) compared to esketamine ($780 for two sprays). And yet, insurance coverage complicates this, as noted by Dr. Allison Wells in her 2023 commentary on racemic ketamine. Even though racemic ketamine is cheaper to produce, it appears less financially attractive to pharmaceutical companies because it is not FDA-approved (and thus considered “experimental”).

The role of Johnson & Johnson in the FDA’s approval and marketing of ketamine and esketamine is the subject of Derek Beres’s 2022 article. He notes that the FDA’s approval of esketamine did not follow their established guidelines. He gathered his evidence from an analysis published in *The British Journal of Psychiatry*, which revealed that the trials were shorter than the FDA-required minimum and that only one of three trials showed significant results. Beres adds that suicides were deemed an anomaly and removed from the data pool, ignoring their possible relation to esketamine. While concluding that the efficacy of esketamine was inflated, he cites data from a single site in Poland that skewed the results; when this data was removed, esketamine did not significantly outperform the placebo. This raises questions about esketamine’s efficacy and why its FDA approval was rushed. It also points to the greedy nature of pharmaceutical companies.

The societal implications of these pharmaceutical practices become evident when examining the real-world impact. A news article from CBS8 and the Veterans Association illustrates the consequences of using esketamine over ketamine. It speaks about the case of Jodi Marone, a patient suffering from PTSD and TRD. Due to the VA’s decision to swap from racemic ketamine to esketamine, in which patients had no say, she suddenly killed herself. In her goodbye email, she stated that the sudden change in prescription prompted her decision (CBS8 n.p.). She wasn’t the only one, as further down the page, the article states that many veterans typically felt suicidal and unmotivated after the change.

These sources help support my hypothesis that, with adequate funding, we could conduct comprehensive long-term clinical trials on ketamine, initiate the FDA approval process, and make the promising treatment of racemic ketamine accessible to millions of Americans in dire need.

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