Systematic Reviews and Meta-Analyses of Ketamine Therapy for Depression (2020–2024)

A Comparative Evidence Summary

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Abstract

This report summarizes more than 25 systematic reviews and meta-analyses published between 2020 and 2025 on ketamine-based therapies for depression. It provides a comparative analysis of intravenous (IV) ketamine, esketamine nasal spray (Spravato), and oral ketamine, highlighting differences in response rates, remission rates, speed of symptom relief, and durability of results.

It also examines research on the impact of combining ketamine with psychotherapy. Drawing from high-quality peer-reviewed studies, the report is designed to offer patients, clinicians, journalists, and policymakers a clear, accessible overview of the most reliable evidence available.

While research on ketamine's use in psychiatry is still emerging, this summary is grounded in the most rigorous and credible studies to date—those that aggregate findings from randomized controlled trials and observational studies. By consolidating this data into one document, the report helps readers bypass the complexities of academic publishing and access the essential takeaways from years of scientific investigation.

Systematic Reviews and Meta-Analyses of Ketamine Therapy for Depression (2020–2024)

This document summarizes systematic reviews and meta-analyses published between January 2020 and December 2024 on the use of ketamine-based treatments for depression. The evidence is organized into:

IV and Injection Ketamine – Research on intravenous and intramuscular administration, the most studied forms.

Esketamine (Spravato Nasal Spray) – Findings on the FDA-approved intranasal formulation.

Oral Ketamine – Systematic reviews of ketamine in lozenge, capsule, or sublingual forms.

Ketamine vs. Esketamine – Head-to-head comparisons in clinical trials and pooled analyses.

Ketamine + Psychotherapy – Studies examining whether pairing ketamine with talk therapy leads to better outcomes.

(Removed) – This page focuses exclusively on ketamine therapy and does not include SSRI or SNRI research.

Only studies focused on depression (major depressive disorder or bipolar depression) were included. Reviews involving other conditions (e.g. PTSD, chronic pain, anxiety, addiction) were excluded. Each section draws only from systematic reviews and meta-analyses, which represent the highest level of evidence.

Frequently Asked Questions About Ketamine Therapy

Which is more effective for treating depression: IV ketamine or the esketamine nasal spray Spravato?

Twenty-five systematic reviews and meta-analyses—such as those published in *EClinicalMedicine* (2023), *Journal of Affective Disorders* (2024), and *Expert Opinion on Drug Safety* (2022)—consistently show that IV ketamine is substantially more effective than Spravato (esketamine nasal spray) for treating depression.

In pooled studies, IV ketamine tripled the likelihood of achieving symptom response compared to placebo (RR = 3.01), while esketamine showed only a modest improvement (RR = 1.38). Remission rates were also dramatically higher: patients receiving IV ketamine were 2.5 to 4 times more likely to achieve remission than those on placebo, whereas esketamine increased remission odds by just 28%–47%.

Effect sizes tell a similar story—IV ketamine scored a Cohen's d of -0.75 (a large effect), while esketamine averaged -0.38, only slightly above what's seen with SSRIs (≈0.30). These differences are not subtle. In fact, the antidepressant impact of IV ketamine is among the strongest seen in modern psychiatry. While esketamine acts quickly, its effects often fade within weeks unless continued, and dropout rates in trials were up to 80% higher than for IV ketamine.

Does oral ketamine work for depression?

Systematic reviews suggest that oral ketamine may reduce depression symptoms, but the results are slower, weaker, and less reliable than other forms like IV ketamine. Across four meta-analyses published since 2020, oral ketamine consistently took 2 to 6 weeks to show effects—about the same timeline as SSRIs *(Journal of Clinical Psychiatry, 2019; Psychopharmacology Bulletin, 2020)*. That's a major difference from IV ketamine, which often begins working within 24 hours *(Journal of Affective Disorders, 2020)*.

While one review reported a large effect size (SMD = -0.75) *(Psychopharmacology Bulletin, 2020)*, this didn't always translate into meaningful remission or lasting recovery. In fact, none of the systematic reviews provided strong evidence that oral ketamine can end depression the way IV ketamine sometimes does *(World Journal of Biological Psychiatry, 2023; Journal of Affective Disorders, 2020)*. Response and remission rates hovered around RR = 2.6–2.8, but these were only marginally statistically significant ($p \approx 0.06–0.07$), raising questions about how dependable they really are *(Psychopharmacology Bulletin, 2020)*.

The quality of evidence is also a concern. Reviews consistently flagged problems with small sample sizes, short follow-up periods, and inconsistent reporting of side effects *(World Journal of Biological Psychiatry, 2023; Journal of Clinical Psychiatry, 2019)*. As a result, the long-term safety and effectiveness of oral ketamine remain unclear *(Journal of Affective Disorders, 2020)*.

Bottom line: Oral ketamine shows early promise, but the research doesn't yet support it as a fast-acting or dependable treatment for depression—especially in treatment-resistant cases. It's not useless, but it's not ready for primetime either.

How effective is oral ketamine compared to other administration methods?

Oral ketamine appears significantly less effective than IV ketamine and shows weaker, slower results than esketamine nasal spray. In four systematic reviews published between 2020 and 2024, oral ketamine showed moderate antidepressant effects—but unlike IV ketamine, which often works within 24 hours, oral forms typically take 2 to 6 weeks to show any meaningful improvement (*Journal of Clinical Psychiatry*, 2019; *Psychopharmacology Bulletin*, 2020). That's on par with SSRIs, not psychedelics.

When response and remission rates were reported, they hovered around 2.6 to 2.8 times higher than placebo—but these findings barely cleared the bar for statistical significance and came from small, high-bias studies (*Psychopharmacology Bulletin*, 2020; *World Journal of Biological Psychiatry*, 2023). By contrast, IV ketamine tripled the chance of symptom response (RR = 3.01) and nearly quadrupled remission (RR = 3.78) in much larger and more rigorous reviews (*EClinical Medicine*, 2023; *Expert Opinion on Drug Safety*, 2022). Esketamine's performance was more modest than IV but still more consistent than oral: effect sizes ranged from 0.15 to 0.38, with a response rate of 1.38 over placebo (*American Journal of Psychiatry*, 2024).

So while oral ketamine might help some people, the current evidence shows it's slower, less powerful, and far more uncertain than either IV or nasal administration. It doesn't yet offer the reliability or rapid relief that define ketamine's clinical reputation.

How quickly does ketamine therapy work to reduce or eliminate depression symptoms or suicidal ideation?

Ketamine therapy can begin reducing depression symptoms or suicidal thoughts in as little as 40 minutes, with peak antidepressant effects typically emerging within 24 hours of a single infusion. This finding, backed by multiple systematic reviews and meta-analyses, makes ketamine one of the fastest-acting depression treatments in psychiatry (*Current Neuropharmacology*, 2014; *Molecular Psychiatry*, 2022; *Frontiers in Psychiatry*, 2024).

In clinical trials of IV ketamine, response rates (meaning a ≥50% reduction in symptoms) were seen in 45% to 65% of patients within 24 hours—compared to just 5%–20% for placebo (*Therapeutic Advances in Psychopharmacology*, 2023; *Brain Sciences*, 2023). Remission (few or no symptoms) occurred in up to 30% of patients after one infusion, and repeated infusions increased the odds to 40% or more (*Brain Sciences*, 2023; *Current Neuropharmacology*, 2014).

Suicidal ideation often drops even faster. Some reviews found that suicidal thoughts diminished within 40 minutes, though this wasn't consistent across all studies (*Current Neuropharmacology*, 2014; *Therapeutic Advances in Psychopharmacology*, 2023). One large meta-analysis reported that patients receiving ketamine were 10 times more likely to show improvement in suicidal ideation by Day 1 compared to placebo (*Translational Psychiatry*, 2024). Repeated infusions further extended this benefit, helping keep suicidal thoughts lower for days or even weeks in some cases (*Translational Psychiatry*, 2024).

The speed of action is one of ketamine's most defining strengths. No other approved antidepressant—including SSRIs or esketamine nasal spray—matches the rapid onset consistently observed with IV ketamine.

What percent of people who undergo ketamine therapy report at least a 50% reduction in symptoms?

According to twelve systematic reviews and meta-analyses published between 2020 and 2024, between 30% and 76% of patients who undergo ketamine therapy for depression report at least a 50% reduction in symptoms—a benchmark known as clinical response (*Therapeutic Advances in Psychopharmacology*, 2023; *Brain Sciences*, 2023; *Molecular Psychiatry*, 2022; *Current Neuropharmacology*, 2014).

The median response rate across these reviews was 55%, meaning that over half of patients experienced a major drop in depressive symptoms, often after just one or two infusions (*Frontiers in Psychiatry*, 2024). In randomized controlled trials of IV ketamine, the results were even stronger, with response rates reaching 63%, compared to 5%–20% for placebo (*Therapeutic Advances in Psychopharmacology*, 2023; *Brain Sciences*, 2023). By contrast, real-world studies found slightly lower rates, around 30%—a pattern commonly observed in psychiatric research when trial controls are removed (*Therapeutic Advances in Psychopharmacology*, 2023).

These numbers place IV ketamine among the most effective depression treatments ever studied—especially for people who haven't responded to SSRIs, psychotherapy, or other standard options.

What percent of people who undergo ketamine therapy report going into remission (little or no symptoms)?

Across five major systematic reviews and meta-analyses published between 2020 and 2024, between 27% and 43% of patients who received ketamine therapy for depression reported going into remission—meaning their symptoms became minimal or disappeared altogether (*Brain Sciences*, 2023; *Molecular Psychiatry*, 2022; *Current Neuropharmacology*, 2014; *Frontiers in Psychiatry*, 2024; *Therapeutic Advances in Psychopharmacology*, 2023).

The median remission rate was 29%, typically measured after just one or two IV ketamine infusions. Some studies reported even higher remission rates (up to 40%) with

“serial” infusions, though the exact number of treatments varied and wasn’t always clearly defined (*Brain Sciences*, 2023).

While these results are impressive for such a short course of treatment, long-term remission data is scarce. Most studies tracked patients for only a week or two. So while ketamine shows striking short-term potential to bring depression into remission—faster than any traditional antidepressant—we still don’t know how often that remission lasts without continued treatment.

Does combining ketamine with psychotherapy improve outcomes?

Early evidence suggests it might—but the science is still catching up. Across four systematic reviews published between 2020 and 2024, combining ketamine with psychotherapy showed signs of improving outcomes, especially for people who initially responded well to ketamine.

In several studies, patients who received therapy after ketamine experienced longer-lasting antidepressant effects and lower relapse rates compared to those who didn’t (*Journal of Pain Research*, 2022; *British Journal of Psychiatry*, 2023). One trial found that 44% of patients reached remission when ketamine was paired with cognitive behavioral therapy—an encouraging signal, even if based on small sample sizes (*British Journal of Psychiatry*, 2023).

But in the only randomized trial focused on depression, combining psychotherapy with ketamine showed no significant benefit over ketamine alone (*Journal of Affective Disorders*, 2022). And most of the strongest results came from PTSD studies, not depression. The meta-analyses noted that therapy might help extend ketamine’s effects, but the data were too limited to explain why—or to say which therapeutic approach works best, or when to deliver it (*Journal of Clinical Psychiatry*, 2023).

The likeliest explanation? Ketamine may open a temporary “therapeutic window”—a period of heightened neuroplasticity and emotional openness—when therapy hits harder and sticks longer. That window could be the key. But for now, ketamine-assisted psychotherapy remains promising but unproven, and larger, better-controlled trials are still needed to turn that promise into certainty.

IV Ketamine Therapy: Systematic Review Findings

Based on Six Systematic Reviews & Meta-Analyses Published in The Last 5 Years (2020-2024)

Key Findings

– IV ketamine consistently produced rapid antidepressant effects, often within 24 hours of a single infusion.
– Response rates in clinical trials ranged from 45% to 65%, compared to placebo rates between 5% and 20%.
– Remission occurred in up to 30% of patients after just one infusion—a striking result given the brevity and intensity of the treatment.
– Serial infusions led to remission rates of up to 40%, though the term "serial" was not always clearly defined (most likely 2 infusions)
– Some studies reported significant reductions in suicidal ideation within 40 minutes, though these effects were not universally found to be statistically significant.
– Antidepressant effects were sustained in many patients for up to 7 days, and in some cases, longer—especially with repeated infusions.
– Real-world response rates (~30%) were lower than those in controlled clinical trials (~63%), a pattern commonly observed in psychiatric research.
– These outcomes were observed across five large-scale systematic reviews and meta-analyses published between 2014 and 2024.

What This Research Suggests About IV Ketamine

Across five systematic reviews and meta-analyses, IV ketamine consistently demonstrated rapid antidepressant effects, often within 24 hours of a single infusion. Response rates in clinical trials ranged from 45% to 65%, and remission rates of 30% after a single treatment were not uncommon—a striking outcome for such a brief intervention. Some studies also reported reductions in suicidal ideation within 40 minutes, though these effects were not universally found to be statistically significant.

While “serial infusions” were often associated with even higher remission rates (up to 40%), most reviews did not specify how many infusions these protocols included. Based on the source studies referenced in these reviews, it appears that the vast majority involved just one or two infusions, making it difficult to draw conclusions about longer treatment courses. Overall, the evidence strongly supports IV ketamine as a fast-acting and clinically meaningful option for treatment-resistant depression, while also highlighting the need for greater clarity and consistency in how treatment protocols are defined and reported.

Systematic Reviews Cited

🟨 Therapeutic Advances in Psychopharmacology (2023)

Title: *Ketamine For Bipolar Depression: An Updated Systematic Review*

– 48% of IV ketamine patients achieved ≥50% symptom reduction; placebo group: 5%
– Controlled trial response rate: 63%; real-world studies: 30%
– Some reductions in suicidal ideation were observed, though findings varied

🟨 Brain Sciences (2023)

Title: *An Update on the Efficacy of Single and Serial Intravenous Ketamine Infusions and Esketamine for Bipolar Depression*

– MADRS scores dropped by 11–12 points within 2 days
– Response rates: 54% (single), 55% (serial); remission: 30% (single), 40% (serial)
– Esketamine data was limited but showed similar MADRS reductions

Note: a reduction of 11 to 12 points represents a substantial improvement and can be characterized as a high or very high change in the context of clinical depression treatments. This kind of improvement can make a noticeable difference in a patient's daily functioning and overall quality of life, particularly in acute settings where rapid relief from symptoms is critical.

🟨 **Current Neuropharmacology (2014)**
Title: *The Role of Ketamine in Treatment-Resistant Depression: A Systematic Review*

– 65% response rate within 24 hours of a single infusion
– Suicidal ideation dropped within 40 minutes and remained lower for hours
– Some patients maintained remission for up to 3 months
– Repeated infusions prolonged antidepressant effects

🟨 **Frontiers in Psychiatry (2024)**
Title: *Efficacy And Safety Of Ketamine And Esketamine For Unipolar And Bipolar Depression: An Overview Of Systematic Reviews With Meta-Analysis*

– Ketamine increased short-term response and remission rates vs. placebo
– Strongest effects were in unipolar depression; bipolar results were mixed
– For bipolar depression, most studies found no significant difference between ketamine and placebo after 1–2 weeks

🟨 **Molecular Psychiatry (2022)**
Title: *International Pooled Patient-Level Meta-Analysis Of Ketamine Infusion For Depression: In Search Of Clinical Moderators*

– 24-hour response: 45.5% for ketamine vs. 20.5% for placebo (NNT = 4)
– 7-day response: 37.7% vs. 18.3% (NNT = 5.2)
– Remission: 27% at 24 hours vs. 13% placebo; 25% at 7 days vs. 12%

Key Takeaways

RESPONSE RATES (50%+ reduction in symptoms)

Range: 30% – 76%

(read as "between 30% and 76% of patients saw depressive symptoms reduced by half or more.")

Median: 55%*

(read as "the median response rate for a 50% or greater reduction in depression symptoms was 55%, meaning that half of the reported study response rates were below this value and half were above.")

Notes:

• Out of 12 systematic reviews, there were 9 published Response Rates

• Many of the studies simply concluded that IV ketamine was "effective or highly effective" without mentioning numbers.

REMISSION RATES (few or no symptoms–basically ending the depression)

Range: 27% – 43%

The median Remission Rate (few or no symptoms): 29%*

Out of 12 systematic reviews, there were only 5 published Remission Rates

* These numbers are very misleading

Most systematic reviews and meta-analyses on IV ketamine measure response and remission rates after just one or two infusions, typically within a few days. That tells us one thing: ketamine works fast. But it tells us almost nothing about what really matters to patients—what are the chances that a full protocol of IV ketamine can end or nearly end their depression?

Long-term data on IV or injection ketamine therapy simply doesn't exist in the published literature. The studies we do have are limited, typically capping out at six infusions.

For instance, this open-label study found a **79% remission rate** after a **9-month follow-up**, but it lacks the controlled rigor of a randomized trial.

Another study showed that six infusions over four weeks led to 69% of patients with suicidal ideation achieving full remission—but frustratingly, it doesn't report remission rates for depression itself.

And while this study here followed patients for a full 12 months, it was based on just six infusions. The remission rate was 46%.

These studies were not included in my analysis because I focused strictly on **systematic reviews and meta-analyses**—the highest level of evidence. Individual studies lack the broader synthesis and methodological rigor that systematic reviews provide in assessing long-term efficacy and safety.

Esketamine Research (the Nasal Spray Spravato)

Based on Six Systematic Reviews & Meta-Analyses Published in The Last 5 Years (2020-2024)

Key Findings

– Esketamine produced modest but statistically significant antidepressant effects, often within 2 to 4 hours of the first dose, sustained through the 28-day induction phase.
– Response and remission rates were consistently higher than placebo, though the effect sizes were small.
– Some reviews reported early reductions in suicidal ideation (at 2–4 hours), but these effects did not persist at 24 hours or beyond.
– Continuing esketamine beyond the induction phase may help prevent relapse, but benefits often diminished after discontinuation.
– Adverse events were common and included dissociation, increased blood pressure, nausea, dizziness, and somnolence—but were generally described as tolerable.
– One review found that most published esketamine trials underreported serious and non-serious adverse events compared to what was listed in trial registries, especially for psychiatric and cardiovascular side effects.

What This Research Suggests About Esketamine

Across six systematic reviews published between 2020 and 2024, esketamine was consistently shown to deliver a fast-acting antidepressant effect—often within hours of the first dose. However, the magnitude of that benefit was modest. Effect sizes were small (ranging from 0.15 to 0.23), with remission and response rates only modestly better than placebo. Several reviews reported improvements in suicidal ideation within 2 to 4

hours, but these benefits typically faded by 24 hours and were no longer significant at 28 days.

The most consistent theme across reviews was that esketamine may help prevent relapse if continued beyond the 4-week induction phase—but its effectiveness after discontinuation was inconsistent or unclear. The evidence for long-term efficacy remains mixed, and the overall quality of the data was frequently described as low. Multiple reviews called for larger, independent trials to clarify esketamine's long-term value.

While esketamine was generally considered tolerable, adverse effects like dissociation, dizziness, nausea, and elevated blood pressure were commonly reported. One review raised concerns that adverse events may be underreported in the published literature compared to trial registries. However, this was not a finding echoed across all six reviews and should be interpreted cautiously.

Collectively, these systematic reviews offer a more conservative—and arguably more realistic—portrait of esketamine than the data submitted to the FDA, which reported much higher remission and response rates after long-term treatment. The discrepancy likely reflects the difference between manufacturer-sponsored clinical trials and broader, more independent evidence synthesis. These reviews suggest that esketamine offers fast relief for some—but its overall impact is modest, short-lived unless continued, and still not well understood in the long term.

Systematic Reviews Cited

🟨 **American Journal of Psychiatry 2024**
Title: *Esketamine Treatment for Depression in Adults: A PRISMA Systematic Review and Meta-Analysis*

– Esketamine produced a modest antidepressant effect, with effect sizes ranging from 0.15 to 0.23 on a scale where 0 indicates no effect and 1 indicates a very strong effect.

– This level of improvement is roughly equivalent to the benefit seen when adding an antipsychotic to an antidepressant for treatment-resistant depression.
– No reduction in suicidal thoughts was observed at any point in the studies reviewed.
– The findings suggest that while esketamine may provide some benefit, its overall impact appears limited, especially in cases where rapid relief from suicidal ideation is needed.

🟨 Clinical Psychopharmacology and Neuroscience (2021)

Title: *Rapid Onset of Intranasal Esketamine in Patients with Treatment Resistant Depression and Major Depression with Suicide Ideation: A Meta-Analysis*

– Esketamine produced a rapid antidepressant effect within 2–4 hours of the first dose, significantly reducing MADRS scores compared to placebo.
– This antidepressant effect remained statistically significant through 28 days in patients with MDD, including those with TRD and MDSI.
– In patients with suicidal ideation (MDSI), esketamine reduced suicidal thoughts at 2–4 hours, but this effect was not statistically different from placebo at 24 hours or day 28.

🟨 International Journal of Molecular Sciences (2021)

Title: *Long-Term Efficacy of Intranasal Esketamine in Treatment-Resistant Major Depression: A Systematic Review*

– Continuing esketamine treatment beyond the 4-week induction phase may help maintain antidepressant effects and prevent relapse in patients with TRD.
– The antidepressant effect of esketamine appears to diminish or become inconsistent after discontinuation.
– Long-term results are mixed, and the overall level of evidence for esketamine's sustained efficacy in TRD remains low.
– More high-quality randomized controlled trials with larger sample sizes are needed to assess long-term outcomes.

🟨 Expert Opinion on Drug Safety (2022)

Title: *The Efficacy and Safety of Adjunctive Intranasal Esketamine Treatment in Major Depressive Disorder: A Systematic Review and Meta-Analysis*

– Adjunctive intranasal esketamine significantly reduced depressive symptoms compared to placebo, with a small but statistically significant effect size (d = -0.239).
– Response rates were 22% higher with esketamine than placebo (RR = 1.221), and remission rates were 37% higher (RR = 1.366).
– One-year trials indicated that esketamine helped lower relapse rates without notable long-term side effects.
– Esketamine was found to be safe, well tolerated, and rapidly effective in patients with treatment-resistant depression and suicidal ideation.

🟨 Psychological Medicine (2023)

Title: *Reporting Of Harms In Clinical Trials Of Esketamine In Depression: A Systematic Review*

– Nine out of ten esketamine trials were rated as "low quality" in their reporting of adverse events; only one reached "moderate quality."
– 41.5% of serious adverse events and 39% of non-serious adverse events listed on ClinicalTrials.gov were not reported in published journal articles.
– Most missing adverse events were psychiatric or cardiovascular and occurred in patients receiving esketamine.
– The study concluded that current published data significantly underrepresents harms, making benefit-risk assessments based solely on journal articles unreliable.

🟨 Journal of Psychiatric Research (2024)

Title: *Intranasal Esketamine for Patients with Major Depressive Disorder: A Systematic Review and Meta-Analysis*

– Intranasal esketamine led to significantly higher remission rates than placebo in patients with MDD and TRD (RR = 1.371; 95% CI: 1.194 to 1.574; $p < 0.0001$).
– Response rates were also higher with esketamine (RR = 1.274; 95% CI: 1.108 to 1.465; $p = 0.001$).
– Subgroup analysis showed that 84 mg and flexible dosing regimens were especially effective.
– Adverse events were common but generally tolerable; long-term safety and subgroup-specific efficacy require further study.

Comparing IV Ketamine Research to the Esketamine Nasal Spray Spravato

Based on 10 Systematic Reviews & Meta-Analyses Published in The Last 5 Years (2020-2024)

Key Findings

Across 10 systematic reviews published between 2020 and 2024, the evidence consistently points to IV ketamine (racemic ketamine) as the more effective treatment for depression when compared to intranasal esketamine (Spravato). While both treatments were associated with rapid symptom relief and were generally effective for treatment-resistant depression, the magnitude and durability of benefit differed significantly.

– IV ketamine was repeatedly found to be more effective than esketamine in both response and remission rates. Meta-analyses reported that racemic ketamine tripled the likelihood of response compared to placebo (RR = 3.01), while esketamine showed only modest improvements (RR ~1.2–1.4). Remission rates followed a similar pattern, with ketamine nearly quadrupling the chance of remission (RR = 3.70) compared to esketamine (RR = 1.28–1.47).

– Effect sizes also strongly favored IV ketamine. With Hedges' g values around 1.52 and Cohen's d reaching -0.75 in some pooled analyses, IV ketamine demonstrated a much larger impact on depressive symptoms than esketamine, which averaged d = -0.38—similar to standard SSRIs.

– Esketamine produced faster initial symptom relief in some studies, with Number Needed to Treat (NNT) as low as 2 at 1 day, compared to ketamine's NNT of 3. But by 4 weeks, esketamine's NNT increased to 11, while ketamine's was 9, suggesting a sharper decline in benefit over time for esketamine.

– Suicidal ideation improved significantly with ketamine, particularly within the first 24 hours. In one review, patients were 10 times more likely to show improvement in suicidal thoughts after ketamine compared to placebo. Esketamine did not show a statistically significant reduction in suicidal ideation beyond the first few hours.

– Both treatments were generally safe and tolerable, though dissociation and dizziness were more commonly reported with esketamine. However, dropout rates were 80% higher with esketamine than with IV ketamine in some studies.

– Placebo effects played a major role in both treatments, accounting for up to 78% of the observed benefit in ketamine trials and 64% in esketamine trials. This high placebo response highlights the importance of control conditions and rigorous study design when interpreting these results.

– Evidence quality across reviews was generally low, limiting the strength of conclusions. Many studies had small sample sizes, publication bias, or inconsistent definitions of response and remission. This was especially true in esketamine research, where fewer trials exist and long-term outcomes are less well studied.

– Overall, systematic reviews offer a more conservative view than the manufacturer-sponsored clinical trials used for FDA approval of Spravato, which reported remission rates of 58.2% and response rates of 76.5%. The discrepancy likely stems from the broader dataset and inclusion of negative or unpublished studies in independent systematic reviews.

Taken together, these findings suggest that while both treatments offer fast-acting relief, IV ketamine delivers a significantly stronger and more consistent antidepressant effect than the esketamine nasal spray. Esketamine's initial impact may appear promising, but its benefits tend to wane more quickly, and its long-term advantage is less well established in the literature.

What This Research Suggests About IV Ketamine vs. Esketamine

Across 10 systematic reviews published between 2020 and 2024, IV ketamine consistently outperformed esketamine nasal spray in nearly every key measure of antidepressant effectiveness. Racemic ketamine (typically administered intravenously) was associated with much stronger response and remission rates, larger effect sizes, and more sustained results. In contrast, esketamine often produced modest symptom relief that appeared quickly but faded more rapidly over time.

The difference in treatment potency is striking: ketamine tripled the likelihood of response compared to placebo, while esketamine's benefit hovered near the threshold of statistical significance. Effect sizes followed the same pattern—ketamine's impact was more than twice as large as esketamine's and significantly greater than what's typically seen with SSRIs. Suicidal ideation improved dramatically within 24 hours of ketamine treatment; no such reliable effect was observed for esketamine.

Tolerability was acceptable for both drugs, though dropout rates were significantly higher with esketamine in some trials. Notably, placebo responses were substantial in both treatment arms—especially with ketamine—accounting for over half of the observed benefit, a finding that raises important questions about study design and the interpretation of results.

The gap between these systematic reviews and the clinical trial data submitted for FDA approval of Spravato is also worth noting. Manufacturer-sponsored studies reported high remission and response rates for esketamine over the long term, yet those outcomes were not consistently replicated across independent reviews. Systematic reviews draw from broader datasets and include negative or unpublished results, making their findings a more conservative and possibly more accurate reflection of real-world performance.

In sum, while both esketamine and ketamine are fast-acting treatments for depression, the evidence clearly favors IV ketamine for stronger, longer-lasting relief—especially in patients with treatment-resistant depression or suicidal ideation.

Systematic Reviews Cited

🟨 Translational Psychiatry 2024

Title: *A meta-analysis of the effects of ketamine on suicidal ideation in depression patients*

– Ketamine significantly reduced suicidal thoughts within one day of treatment.
– Patients given ketamine were 10 times more likely to show improvement in suicidal thoughts on Day 1 compared to placebo (RR = 10.02).
– Ketamine was more effective than esketamine (4.8 times) and midazolam (3.1 times) on Day 1.
– Repeated ketamine treatments increased effectiveness; patients were 44% more likely to improve after multiple doses than after a single treatment (RR = 0.56).
– By Day 26, ketamine remained significantly more effective than placebo in reducing suicidal thoughts (RR = 4.29).
– Repeated treatments extended the duration of improvement in suicidal ideation.
– Esketamine and midazolam did not significantly reduce suicidal thoughts compared to placebo.

🟨 Journal of Affective Disorders 2024

Title: *Efficacy of intravenous ketamine and intranasal esketamine with dose escalation for Major Depression*

– IV ketamine was nearly five times more effective than intranasal esketamine at reducing depression symptoms.
– IV ketamine showed a very large effect size (Hedges' g = 1.52), indicating a strong impact on depressive symptoms.
– In contrast, intranasal esketamine produced only a small effect (Hedges' g = 0.31).
– IV ketamine was effective even at low doses (as little as 0.2 mg/kg), with the strongest results at 0.5 mg/kg.
– Higher IV ketamine doses above 0.5 mg/kg did not improve outcomes further.
– Esketamine was more effective at 56–84 mg than at the lower 28 mg dose.

– The overall quality of evidence was considered low due to a small number of studies and potential publication bias.

🟨 Front. Psychiatry (2024)

Title: *Efficacy and safety of ketamine and esketamine for unipolar and bipolar depression: an overview of systematic reviews with meta-analysis*

- No significant difference was found in effectiveness or tolerability between ketamine and esketamine.
– Both ketamine and esketamine were effective in treating major depressive disorder and bipolar depression, including treatment-resistant forms.
– Ketamine produced rapid symptom relief, though its effects in bipolar depression tended to decline after two weeks.
– Esketamine showed consistent effectiveness in unipolar depression, but fewer studies were available compared to ketamine.
– Dissociation and dizziness were reported more often with esketamine than with placebo.
– The overall quality of the studies was low, limiting the strength of the conclusions.

🟨 Children (Basel) (2024)

Title: *A Systematic Review on Ketamine and Esketamine for Treatment-Resistant Depression and Suicidality in Adolescents: A New Hope?*

– Ketamine response rates typically range from 35% to 76%, depending on factors such as depression severity, dosage, and individual variability.
– Esketamine response rates also vary widely, with rapid symptom reductions reported—particularly in adolescents—though specific numerical rates were not provided.
– Ketamine remission rates are generally lower than response rates, but some studies report sustained remission lasting several weeks.
– Esketamine remission rates are less frequently reported, but remain an important metric for evaluating treatment effectiveness.

🟨 Frontiers in Psychiatry 2024

Title: *Hype or hope? High placebo response in major depression treatment with ketamine and esketamine: a systematic review and meta-analysis*

- Ketamine and esketamine show strong antidepressant effects, but placebo response accounts for 62-71% of the total treatment response.
- Seven days after treatment, placebo response still made up 66% of the effect, meaning only 34% of the antidepressant effect was likely due to the medication itself.- In studies using ketamine, 78% of the treatment effect could be attributed to the placebo response.
- In studies using esketamine, 64% of the treatment effect was due to the placebo response.
- Sensitivity analysis showed that even when accounting for biases, at least 43% of the antidepressant effect remained placebo-driven.

🟨 EClinical Medicine 2023

Title: *Ketamine for the treatment of major depression: a systematic review and meta-analysis*

– Ketamine (racemic and esketamine combined) more than doubled the likelihood of treatment response compared to placebo (RR = 2.14; 95% CI: 1.72–2.66).
– For context, SSRIs typically show a response rate of 50% over placebo (RR = 1.5), making ketamine approximately 143% more effective in absolute terms.
– Racemic ketamine was far more effective than esketamine: RR = 3.01 (95% CI: 2.24–4.03) vs. RR = 1.20 (95% CI: 0.96–1.49).
– This means racemic ketamine tripled the chance of response, while esketamine showed only a modest improvement over placebo.

– Ketamine increased remission rates by 64% compared to placebo (RR = 1.64; 95% CI: 1.33–2.02), about 22% better than typical SSRI remission rates.
– Racemic ketamine had the highest remission impact: RR = 3.78 (95% CI: 2.44–5.78), nearly quadrupling the chance of remission.
– Esketamine had a more modest remission benefit: RR = 1.28 (95% CI: 1.11–1.47).

– The average symptom reduction (effect size) for ketamine (racemic + esketamine) was Cohen's d = -0.63 (95% CI: -0.80 to -0.45), about twice that of traditional SSRIs (effect size ≈ 0.30).
– Racemic ketamine's effect size was d = -0.75, while esketamine's was d =

-0.38 (p = 0.03), meaning esketamine's average effect is closer to standard antidepressants, while racemic ketamine is significantly more powerful.

🟨 Expert Opinion on Drug Safety 2022

Title: *Efficacy and Safety of Racemic Ketamine and Esketamine for Depression: A Systematic Review and Meta-Analysis*

Response Rates

– Ketamine (racemic + esketamine) more than doubled the likelihood of response compared to placebo (RR = 2.14; 95% CI: 1.72–2.66).
– For context, SSRIs typically show a 50% improvement over placebo (RR = 1.5), meaning ketamine is 143% more effective in absolute terms.
– Racemic ketamine was significantly more effective than esketamine: RR = 3.01 (95% CI: 2.24–4.03) vs. RR = 1.20 (95% CI: 0.96–1.49).
– Racemic ketamine tripled the chance of response, while esketamine offered only a small improvement over placebo.

Remission Rates

– Ketamine increased the likelihood of remission by 64% compared to placebo (RR = 1.64; 95% CI: 1.33–2.02).
– This represents a 22% advantage over the average remission rate seen with SSRIs.
– Racemic ketamine was especially effective, nearly quadrupling the chance of remission (RR = 3.78; 95% CI: 2.44–5.78).
– Esketamine offered a modest remission benefit (RR = 1.28; 95% CI: 1.11–1.47).

Effect Sizes

– When pooled, racemic ketamine and esketamine had an average effect size of Cohen's d = -0.63 (95% CI: -0.80 to -0.45).
– This is approximately twice the effect size of traditional SSRIs, which average around d = 0.30.
– Racemic ketamine had a stronger effect (d = -0.75) than esketamine (d = -0.38), a statistically significant difference (p = 0.03).
– Esketamine's effect size aligns with standard antidepressants, while racemic ketamine is more than twice as effective.

🟨 J Affect Disord (2021)

Title: *Comparative Efficacy of Racemic Ketamine and Esketamine for Depression*

– Ketamine's response rate was three times higher than esketamine's (RR = 3.01 vs. RR = 1.38).
– Remission with ketamine was 2.5 times more likely than with esketamine (RR = 3.70 vs. RR = 1.47).
– Patients were 80% more likely to discontinue treatment when using esketamine compared to ketamine (RR = 1.37 vs. RR = 0.76).

🟨 Journal Of Affective Disorders 2022

Title: *Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis*

– Racemic (IV) ketamine had a 118% higher response rate than esketamine, making it 2.18 times more effective at reducing depression symptoms.
– Response rates: racemic ketamine (RR = 3.01) vs. esketamine (RR = 1.38).
– Racemic ketamine's remission rate was 152% higher than esketamine's, making it 2.52 times more effective at achieving full remission.
– Remission rates: racemic ketamine (RR = 3.70) vs. esketamine (RR = 1.47).
– IV ketamine outperformed nasal esketamine in both symptom reduction and full recovery from depression.

🟨 Journal of Affective Disorders 2024

Title: *Number needed to treat (NNT) for ketamine and esketamine in adults with treatment-resistant depression*

– Both ketamine and esketamine are effective for treating depression, but esketamine shows faster symptom relief that fades more quickly over time.
– Racemic ketamine maintains its effectiveness longer than esketamine, with more patients benefiting over time.

– The Number Needed to Treat (NNT) for ketamine was 3 at 1 day, meaning only 3 people needed treatment for 1 to benefit—a strong effect.
– By 4 weeks, ketamine’s NNT increased to 9, indicating reduced effectiveness over time.
– Esketamine had an even stronger initial effect with an NNT of 2 at 1 day.
– By 4 weeks, esketamine’s NNT increased to 11, suggesting a sharper decline in benefit compared to ketamine.

Oral Ketamine Research

Based on 4 Systematic Reviews & Meta-Analyses Published in The Last 5 Years (2020-2024)

Key Findings

– Oral ketamine appears to offer a moderate antidepressant effect, but the evidence base remains small, methodologically limited, and inconsistent in clinical impact.
– Unlike IV ketamine or esketamine nasal spray—which often show symptom relief within hours or days—oral ketamine consistently takes 2 to 6 weeks to produce measurable improvement, a timeline that mirrors traditional antidepressants.
– While some meta-analyses reported statistically significant reductions in depression severity (e.g., SMD = -0.75), the reviews raised doubts about whether this improvement translates into meaningful clinical benefit for most patients.
– Remission and response rates (RR ≈ 2.6–2.8) were only marginally statistically significant (p-values near 0.06–0.07), leaving it unclear whether these effects are robust or replicable.
– Importantly, no systematic review provided convincing data that oral ketamine achieves the full remission or rapid response observed with IV formulations—especially in treatment-resistant cases.
– Across the reviews, methodological issues were common: high risk of bias, small sample sizes, brief follow-up periods, and inconsistent tracking of adverse events. These limitations make it difficult to draw confident conclusions about safety or long-term benefit.
– Overall, while early results suggest oral ketamine has potential as an antidepressant, the current evidence lacks the clarity, strength, and consistency needed to support its widespread use. The treatment may be promising, but much stronger studies are required to determine whether it is truly effective, for whom, and under what conditions.

What This Research Suggests About Oral Ketamine

The collective evidence from four systematic reviews suggests that oral ketamine may offer moderate antidepressant effects, but its clinical value remains uncertain. Unlike intravenous ketamine or esketamine nasal spray—both known for their rapid onset of action—oral ketamine consistently demonstrated a delayed therapeutic effect, with improvements typically emerging between 2 and 6 weeks. This timeline mirrors traditional antidepressants, raising questions about whether oral ketamine offers any distinct advantage in urgent or treatment-resistant cases.

Although some pooled analyses showed statistically significant reductions in depression symptoms, the data on response and remission rates were marginally significant at best, with wide confidence intervals and p-values hovering just above conventional thresholds for reliability. More importantly, none of the reviews provided compelling evidence that oral ketamine achieves the high remission rates seen with IV formulations.

Methodological limitations were a consistent concern across reviews. Most of the included studies were small, short in duration, and carried a high risk of bias—particularly in how they monitored adverse effects. The lack of rigorous, long-term trials means the durability of oral ketamine's antidepressant effects—and its safety profile—are still largely unknown.

In short, oral ketamine shows early promise but lacks the evidentiary strength needed to support confident clinical use. For patients and clinicians hoping for a fast-acting, game-changing alternative, the current data are underwhelming. Until larger, higher-quality trials are conducted, oral ketamine should be considered an experimental option—one that may help some, but cannot yet be relied on as a robust treatment for depression.

Systematic Reviews Cited

🟨 Journal of Clinical Psychiatry 2019

Title: *Oral Ketamine for Depression: A Systematic Review*

– Oral ketamine did not produce immediate effects; statistically significant improvements in depression symptoms typically appeared after 2 to 6 weeks of treatment.
– This delayed onset mirrors the timeline of traditional antidepressants, contrasting sharply with the rapid effects of IV ketamine.
– The improvement was statistically significant ($p < .05$), suggesting the results were unlikely due to chance—but the reviews did not confirm whether this translated into meaningful clinical benefit for patients.
– Systematic reviews emphasized the slower onset of oral ketamine's antidepressant effects compared to IV formulations, raising questions about its usefulness for patients needing rapid relief.

🟨 Psychopharmacology Bulletin 2020

Title: *An Update on the Efficacy and Tolerability of Oral Ketamine for Major Depression: A Systematic Review and Meta-Analysis*

– Oral ketamine produced a moderate reduction in depressive symptoms compared to placebo (SMD = -0.75; 95% CI: -1.08 to -0.43; $p < 0.0001$).
– Significant benefits were observed by the second week of treatment (SMD = -0.71; 95% CI: -1.08 to -0.35; $p = 0.001$; $I^2 = 0\%$), suggesting a quicker onset than traditional antidepressants.
– Patients were about 2.6 to 2.8 times more likely to achieve response or remission compared to placebo, but these findings were only marginally statistically significant (RR = 2.58 for response; RR = 2.77 for remission; $p \approx 0.06–0.07$).
– While oral ketamine appears safe and moderately effective, its ability to deliver full remission remains uncertain and requires confirmation from larger studies.

🟨 World Journal of Biological Psychiatry 2023

Title: *Oral ketamine for depression: An updated systematic review*

– All included studies reported significant improvements in depressive symptoms following oral ketamine treatment.

– The randomized controlled trials were marked by a high risk of bias, largely due to flawed analysis methods and inadequate monitoring of adverse events.
– Early evidence supports oral ketamine's antidepressant potential, but larger studies with longer follow-up periods are needed to confirm its antisuicidal effects and effectiveness in treatment-resistant depression.

🟨 Journal of Affective Disorders 2020

Title: *The effect of intravenous, intranasal, and oral ketamine in mood disorders: A meta-analysis*

– Both intravenous and intranasal ketamine formulations show strong short-term effectiveness in reducing symptoms of treatment-resistant depression, while oral ketamine demonstrates a more gradual but still meaningful benefit.
– Intranasal ketamine or esketamine reduced depressive symptoms within 24 hours, with a large and statistically significant effect size (Hedges' g = 1.247; 95% CI: 0.591–1.903; $p < 0.01$).
– Intravenous ketamine or esketamine showed a large effect size at 2–6 days (g = 0.949), but results were not statistically significant (95% CI: -0.308–2.206; $p = 0.139$), limiting confidence in the finding.
– Intranasal ketamine sustained a large and statistically significant effect between 7–20 days post-treatment (g = 1.018; 95% CI: 0.499–1.538; $p < 0.01$).
– Oral ketamine showed a moderate but statistically significant effect by days 21–28 (g = 0.633; 95% CI: 0.368–0.898; $p < 0.01$), indicating delayed but meaningful symptom improvement.

Research Comparing Ketamine Alone vs. Ketamine Combined with Psychotherapy

Based on 4 Systematic Reviews & Meta-Analyses Published in The Last 5 Years (2020-2024)

Key Insights

– Combining ketamine with psychotherapy appears to extend antidepressant effects and reduce relapse, especially in patients who initially respond to ketamine.
– Studies in PTSD show large symptom reductions, but evidence in depression is more mixed.
– Research quality is still low, and better trials are needed to confirm how and when psychotherapy adds value.
– Early findings suggest ketamine may create a “therapeutic window” in which talk therapy is more effective.

What This Research Suggests About Ketamine Combined with Psychotherapy

Across four systematic reviews published between 2020 and 2024, early findings suggest that combining ketamine with psychotherapy may help prolong the antidepressant effects of ketamine, reduce relapse, and produce greater symptom improvement than ketamine alone. This is especially true in studies of posttraumatic stress disorder (PTSD), where combined treatment led to large reductions in symptom severity—including a pooled effect size (SMD) of –7.26 for clinician-assessed outcomes.

In depression, the results were more mixed and preliminary, with only one randomized trial reporting no additional benefit of ketamine-assisted psychotherapy (KAP) over standard care. Still, other reviews observed that

patients who received psychotherapy after ketamine showed more sustained improvements than those who didn't—suggesting that therapy may help extend remission and possibly prevent relapse in those who initially respond to ketamine.

While these findings are promising, the evidence base is still limited. Most studies used small sample sizes, employed varying psychotherapeutic techniques, and differed in ketamine dosing and timing. Few trials were randomized, and the overall quality of evidence was considered low to moderate. Additionally, none of the studies directly tested the mechanisms behind why or how psychotherapy might amplify or prolong ketamine's effects.

Taken together, the research suggests that ketamine may create a temporary therapeutic window—through mechanisms like enhanced neuroplasticity, altered perspective, or increased emotional openness—during which psychotherapy could be more effective. But for now, the combined use of ketamine and psychotherapy should be seen as experimental but promising, with a clear need for larger, well-controlled studies to determine when, how, and for whom this combination works best.

Systematic Reviews Cited

🟨 **J Affect Disord (2022)**
Time: *Active mechanisms of ketamine-assisted psychotherapy: A systematic review*

– Ketamine-assisted psychotherapy (KAP) may help reduce symptoms of substance use disorders, but evidence is still limited and results are mixed.
– In the only randomized trial focused on treatment-resistant depression, KAP did **not** show a benefit over standard care.
– None of the studies directly tested how KAP works, but researchers believe ketamine's short-term effects on brain chemistry—like blocking NMDA receptors and boosting neuroplasticity—may support psychotherapy.

– The review also suggests that ketamine's impact on mindset—such as enhancing insight, shifting perspective, or evoking spiritual experiences—might make therapy more effective.
– Overall, the science behind KAP is still emerging. The review highlights a need for larger, high-quality trials to understand when and how this treatment works.

🟨 Journal of Clinical Psychiatry (2023)

Time: *Combining Ketamine and Psychotherapy for the Treatment of Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis*

– Combining ketamine with psychotherapy significantly reduced PTSD symptoms across all studies included in the review.
– The pooled symptom reduction was substantial, with a standardized mean difference (SMD) of –7.26 for clinician-assessed symptoms and –5.17 for patient-reported symptoms—both statistically significant.
– All four studies involved different combinations of ketamine administration and psychotherapeutic techniques, but each reported meaningful improvements in PTSD symptoms.
– While the results are promising, the sample size was small (only 34 patients), and two of the four studies were rated as low quality.
– Because of the limited data and methodological weaknesses, the overall quality of the evidence is low, but early findings suggest that ketamine-assisted psychotherapy may offer a powerful new option for treating PTSD.

🟨 Journal of Pain Research 2022

Time: *Ketamine Assisted Psychotherapy: A Systematic Narrative Review of the Literature*

– Among those who initially responded to ketamine, patients who received psychotherapy afterward experienced more sustained improvements in depression scores over 14 weeks. (Exact numbers were not reported.)

– Adding psychotherapy to ketamine treatment appears to prolong remission and reduce the risk of relapse.
– Evidence suggests that psychotherapy may help extend ketamine's antidepressant effects, but most studies had small sample sizes and limited methodological rigor.
– While early findings are promising, larger and more robust randomized controlled trials are needed to confirm these outcomes.

🟨 British Journal of Psychiatry 2023

Time: *Ketamine and psychotherapy for the treatment of psychiatric disorders: systematic review*

– When psychotherapy was added to ketamine treatment for depression, patients experienced greater and more sustained improvement compared to those receiving ketamine alone.
– One study combining cognitive behavioral therapy (CBT) with ketamine for treatment-resistant depression found that 50% of patients showed significant improvement, and nearly 44% achieved remission.
– These results suggest that therapy may help maintain the antidepressant effects of ketamine, potentially reducing relapse.
– However, due to differences in therapy types, ketamine dosing, treatment schedules, and small sample sizes, researchers caution that current findings are preliminary. Larger, standardized studies are needed to confirm how best to combine ketamine and psychotherapy.

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