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Ketamine, Esketamine, *and Suicidality*

What the science actually shows about rapid relief of suicidal thinking, "psychache," and the still-unanswered question of suicide prevention

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READ THIS FIRST

This is a non-peer-reviewed educational white paper. It is a narrative review written for public dissemination — not a peer-reviewed publication, a systematic review, a clinical practice guideline, or an individualized medical recommendation. The science is moving quickly; several findings discussed here are from 2025–2026, and one meta-analysis of suicidal behavior remains a preprint. Conclusions should change as better data arrive. Suicidal thoughts, intent, or behavior require clinical assessment and safety planning. Ketamine or esketamine is never a substitute for hospitalization or another higher level of care when that is clinically indicated. **If you are in crisis: call or text 988 (US).**

The short version

1

IV racemic ketamine rapidly reduces suicidal ideation — often within hours — and this is now supported by randomized trials and a substantial 2026 meta-analysis of 26 trials[3].

2

The effect is only partly explained by improvement in depression. Psychological pain ("psychache"), hopelessness, anhedonia, reward processing and brain-network state may each contribute[2,1].

3

Intranasal esketamine produces rapid antidepressant effects in severely depressed, acutely suicidal patients — but its randomized trials did not show an additional benefit over intensive standard care on suicide-specific scales[9,10].

4

Neither has been proven to prevent suicide attempts or deaths. That is a different — and much harder — question, and the honest answer today is "we don't know yet"[7,8].

5

The most defensible clinical model is ketamine as a rapid bridge: an intervention that can reduce unbearable suicidal thinking quickly enough to create time for connection, means safety, psychotherapy, medication optimization and recovery. Reducing suicidal ideation is clinically meaningful. It is not the same as proving prevention.

FIGURE 1 **Key numbers at a glance**

FINDING	NUMBER	SOURCE
Response (≥50% drop in suicidal ideation) at 24 h, ketamine vs midazolam	**55% vs 30%** · NNT ≈ 4	2
Share of ketamine's anti-ideation effect explained by mood improvement	**≈ 34%**	2
Suicidal symptoms at 24 h after a single infusion, 26 RCTs (n=1,166)	**SMD −0.69** (95% CI −0.98 to −0.40)	3
Full remission of suicidal ideation at day 3, ketamine vs placebo (KETIS)	**63% vs 32%** · OR 3.7	4
Psychological pain lower with ketamine — from 40 min through 96 h; not at 2–6 weeks	**40 min → 96 h**	1
Esketamine vs placebo (both + hospitalization), MADRS at 24 h · CGI-SS-r	**−3.8 points · not significant**	9,10
Suicidal behavior, ketamine/esketamine vs placebo, 73 RCTs (n=5,671) — preprint	**1.63% vs 1.72%** · OR 0.98 (0.58–1.60)	7
Medically attended suicide attempt / self-harm, esketamine vs control, claims cohort (n=23,140)	**HR 1.02** (0.67–1.54)	8

Suicidality is not simply "very severe depression"

One assumption increasingly challenged by modern suicide research is that suicidality is merely a symptom sitting near the severe end of a depression scale.

Depression is one of the strongest clinical contexts in which suicidality occurs. But suicidal ideation has its own phenomenology: psychological pain, perceived entrapment, hopelessness, narrowing of perceived alternatives, altered reward processing, rumination, interpersonal disconnection — and, in some people, an extraordinary conviction that the current state is both unbearable and permanent. Contemporary models of suicide, such as O'Connor's integrated motivational–volitional model, treat defeat and entrapment as the engine of ideation and a separate set of "volitional" factors as what turns ideation into an attempt[11].

This distinction matters because ketamine sometimes produces a clinical phenomenon that is difficult to explain with a simple antidepressant model: suicidal thinking can improve dramatically *before* the rest of the depression does.

In an important randomized trial of 80 adults with major depression and clinically significant suicidal ideation, Grunebaum and colleagues compared IV ketamine with the active control midazolam. Twenty-four hours later, the reduction in Scale for Suicide Ideation scores was nearly five points greater with ketamine, with an effect size of Cohen's d = 0.75. Fifty-five percent of patients receiving ketamine achieved at least a 50% reduction in suicidal ideation, compared with 30% receiving midazolam — a number needed to treat of roughly four. Importantly, improvement in general depressive mood statistically explained only about one-third (33.6%) of ketamine's effect on suicidal ideation[2].

That does not prove a unique anti-suicide mechanism. But it argues against the simplest explanation — that ketamine merely improves depression and suicidal thinking passively follows.

The evidence for IV ketamine and suicidal ideation is now substantial

The strongest quantitative summary to date was published in *JAMA Psychiatry* in May 2026. Shim and colleagues synthesized 26 randomized clinical trials involving 1,166 patients with a major depressive episode. A single IV ketamine infusion was associated with significantly lower suicidal symptoms at 24 hours compared with control, with a standardized mean difference of −0.69 (95% CI −0.98 to −0.40). A signal remained at one month (SMD −0.70), although considerably less long-term evidence was available. Repeated infusions produced a similar reduction at the end of treatment (SMD −0.72)[3].

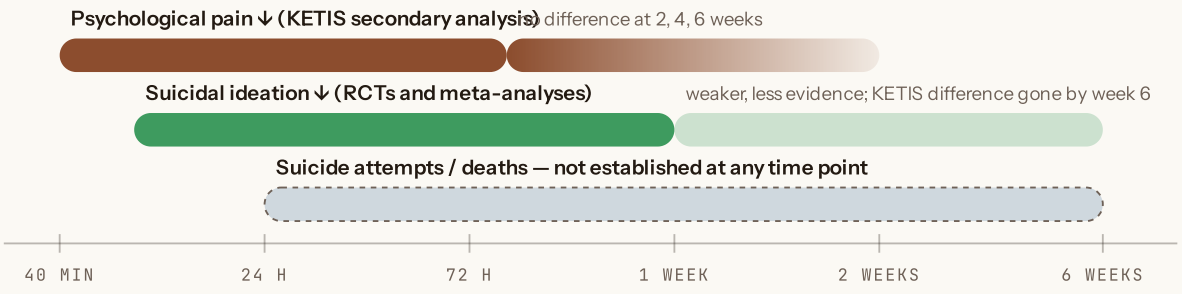
This extends what earlier syntheses had shown. Wilkinson's 2018 individual-participant-data meta-analysis of 10 trials found that 55% of ketamine-treated participants were free of suicidal ideation one day after a single dose, versus 20% of controls, with moderate-to-large effect sizes persisting through one week[5]; Witt's 2020 meta-analysis found the effect clearest in the first 72 hours and strongest for the intravenous route[6].

Those are meaningful effect sizes. The meta-analyses also illustrate ketamine's defining characteristic: speed. Anti-suicidal and antidepressant effects can emerge within hours, while longer-term outcomes remain much less certain.

Another particularly important trial is the French multicenter KETIS study reported by Abbar and colleagues in *The BMJ*. Investigators randomized 156 voluntarily hospitalized patients experiencing severe suicidal ideation to two IV infusions of ketamine 0.5 mg/kg or saline placebo, 24 hours apart, in addition to usual care. By day 3, 63.0% of ketamine-treated patients had achieved full remission of suicidal ideation versus 31.6% with placebo — an odds ratio of 3.7. The difference began remarkably quickly: suicidal remission was already apparent within hours[4].

There are important nuances. Diagnostic subgroup effects differed, and the especially large signal in bipolar disorder should not be over-interpreted from subgroup analyses. By six weeks, the between-group difference in suicidal remission was no longer statistically significant. Ketamine's value may lie less in permanently eliminating suicide risk with one treatment than in rapidly changing the state of a person trapped inside an acute suicidal crisis.

FIGURE 2 **The time course — what changes, and when**



The pattern is consistent: the earliest change is in *how the pain feels*, then in suicidal thinking, and the evidence thins the further out y
Sources: psychological pain 1; ideation 2 3 4 5 6; behavior 7 8.

Psychache: perhaps the most important clue

One of the most compelling developments in this literature concerns psychological pain, sometimes called *psychache*. The term was introduced by suicidologist Edwin Shneidman, who argued that unbearable psychological pain lies close to the heart of the suicidal state. In his formulation, suicide is often not best understood as a wish for death; it can be an effort to stop conscious psychological suffering that has become intolerable[12].

SIDEBAR · A 30-YEAR-OLD IDEA, SUDDENLY RELEVANT

Edwin S. Shneidman, one of the founders of modern suicidology, used "psychache" to describe intense mental pain — the hurt, anguish, shame, grief, humiliation, guilt, loneliness, rejection or fear that can become subjectively unbearable. His 1993 paper "Suicide as Psychache" proposed that many suicidal states are better understood as attempts to end intolerable conscious pain than as an abstract desire for death. In shorthand, the internal experience may be closer to *"I cannot continue experiencing this"* than *"I want to be dead."*

Modern research does not treat psychache as the sole cause of suicide, but psychological pain has remained an important construct because it overlaps with — yet is not identical to — depression and hopelessness. That makes the ketamine findings unusually interesting: more than 30 years after Shneidman articulated the construct, randomized data now suggest that psychological pain itself can fall within roughly an hour of a ketamine infusion and remain lower for several days. This does not prove that relief of psychache *causes* ketamine's anti-suicidal effect. But it is a compelling mechanistic hypothesis.

The original KETIS study found evidence that mental pain mediated part of ketamine's anti-suicidal effect[4]. A 2026 secondary analysis examined this directly. Baryshnikov and colleagues analyzed psychological-pain measurements collected repeatedly during the KETIS trial. Psychological pain was significantly lower with ketamine than placebo beginning approximately 40 minutes after treatment and continuing through 96 hours. The early difference remained significant after accounting statistically for depressive symptoms and hopelessness. At weeks 2, 4 and 6, however, ketamine and placebo no longer differed[1].

That time course is fascinating. Ketamine may function, at least temporarily, as a kind of psychological analgesic. It does not resolve grief, trauma, relationship loss, financial stress or loneliness — but it may rapidly make the internal experience less unbearable. The suicidal state

may be driven not only by how bad a person feels, but by the conviction that the pain is intolerable, inescapable and permanent.

A useful conceptual sequence is: **psychological pain → entrapment → perceived absence of alternatives → suicidal ideation → suicidal intent.** If ketamine rapidly interrupts that sequence near its beginning, it could help explain why suicidal thinking sometimes falls faster than overall depression severity. Note how this converges with a separate fact from the suicide literature: roughly half of people who survive an attempt describe the interval between deciding and acting as ten minutes or less[13]. The crisis is fast. So is ketamine.

Hopelessness: changing the prediction that "this will never end"

Hopelessness deserves separate attention because it is not identical to sadness. A person can tolerate enormous suffering if they believe it will end. Suicidal crises frequently include something different: a highly convincing prediction that the present state is permanent.

A 2024 randomized ketamine-versus-midazolam study involving 84 patients with treatment-resistant depression and prominent suicidal ideation found early changes in dimensions of hopelessness as well as suicidal thinking, and early change in hopelessness was associated with subsequent improvement in suicidality[14].

One way of conceptualizing this — still partly theoretical — is that suicidal states involve a form of *temporal constriction*: "I feel this way now" becomes "I will always feel this way." The perceived future collapses into the present. Ketamine may temporarily weaken the certainty of that prediction.

Anhedonia and the return of anticipated reward

Another clue comes from anhedonia. NIMH investigators examined data from ketamine trials in treatment-resistant major depression and bipolar depression. Improvement in anhedonia, measured with the Snaith–Hamilton Pleasure Scale, accounted for an additional 13% of the variance in improvement in suicidal thoughts even after accounting for changes in general depressive symptoms[15].

There is a major psychological difference between "My life hurts" and "My life hurts, and nothing in my future could possibly feel rewarding." The return of even a small ability to anticipate

pleasure, connection, curiosity, relief or meaning may alter the internal calculation that sustains suicidal thinking. This does not make anhedonia *the* mechanism — suicide is far too complex for a single-variable explanation. But psychological pain, hopelessness and anhedonia together suggest that ketamine acts on dimensions of suicidality that are related to, but not reducible to, depression severity.

A working biological model: rescue first, repair second

A 2026 review proposed a "rescue–repair" model of ketamine's anti-suicidal action[16]. This is a theoretical synthesis, not an experimentally proven unified mechanism, but it is a useful frame.

FIGURE 3 **The rescue–repair model, in one picture**

PHASE 1 · RESCUE · MINUTES TO HOURS

1. NMDA blockade, preferentially on inhibitory interneurons
2. Transient cortical disinhibition → glutamate surge
3. AMPA-receptor signaling ↑
4. Rigid loop loosens: pain → rumination → hopelessness → entrapment

Felt as: psychological pain drops; other mental states become reachable.

→

PHASE 2 · REPAIR · HOURS TO DAYS

1. BDNF–TrkB, mTORC1, ERK pathways engage
2. Protein synthesis, synaptic remodeling, synaptogenesis
3. Prefrontal–limbic and reward networks partially restored
4. Endogenous opioid signaling likely modulates the whole cascade

Felt as: mood and anticipated reward improve over days — the window for durable treatment.

Adapted from the rescue–repair synthesis[16] and the glutamate/AMPA/BDNF literature it draws on. A model, not a proof.

Phase 1: acute rescue

Ketamine is an NMDA glutamate-receptor antagonist, but "ketamine blocks NMDA receptors" does not adequately explain its clinical effects. One leading model proposes preferential interference with NMDA signaling on inhibitory GABA interneurons, producing transient cortical disinhibition and an increase in glutamatergic throughput. Downstream, relative signaling

through AMPA receptors increases, followed by activation of neuroplasticity-related pathways. At the experiential and circuit level, this acute perturbation may temporarily disrupt entrenched patterns involving rumination, threat, salience, self-referential processing and psychological pain — a transient loosening of an abnormally rigid brain state. That idea is appealing, but it remains a model rather than established fact.

Phase 2: repair and neuroplasticity

At approximately the same time, slower intracellular processes are being initiated. AMPA signaling interacts with pathways including BDNF–TrkB, mTORC1, ERK, protein synthesis, synaptic remodeling and synaptogenesis. Over hours to days, these changes may support restoration of impaired prefrontal–limbic and reward-network function. This may help explain an apparent paradox: the subjective rescue can begin within minutes or hours, while biological repair unfolds over days. The two processes need not be mutually exclusive.

The opioid system: an unexpectedly persistent piece of the puzzle

The opioid contribution to ketamine's antidepressant — and potentially anti-suicidal — effects remains controversial, but it has become difficult to dismiss. In a small but influential 2018 randomized crossover study, Williams and colleagues found that pretreatment with the opioid antagonist naltrexone markedly attenuated ketamine's antidepressant response[17]. A 2025 *Nature Medicine* study added another layer: in 26 adults with MDD who received ketamine after placebo or 50 mg of naltrexone in a double-blind crossover design, naltrexone attenuated both ketamine's acute increase in anterior cingulate glutamate-plus-glutamine signaling and its antidepressant effect the following day[18]. Preclinical work provides a possible biological bridge: ketamine increased β-endorphin signaling in medial prefrontal cortex in an animal model, and interfering with opioid-receptor signaling disrupted both behavioral effects and AMPA-associated molecular changes[19].

At the same time, contradictory human evidence matters. A 2025 randomized trial in adults with major depression and alcohol-use disorder did not find that naltrexone abolished ketamine's antidepressant efficacy[20]. The responsible conclusion is therefore not that ketamine "works because it is an opioid." A better summary: endogenous opioid signaling probably interacts with ketamine's glutamatergic and neuroplastic effects, while its precise importance — and whether it contributes specifically to anti-suicidal effects — remains unresolved.

Ketamine and esketamine are not interchangeable evidence bases

Racemic ketamine contains both R- and S-ketamine. Esketamine is the S-enantiomer, administered intranasally in its FDA-approved formulation. Both have rapid antidepressant effects. But the evidence regarding suicidal ideation specifically is not identical.

TABLE 1 **Two medicines, two evidence bases**

	IV RACEMIC KETAMINE	INTRANASAL ESKETAMINE (SPRAVATO)
Molecule	R- and S-ketamine, 50/50	S-enantiomer only
Typical antidepressant dose	0.5 mg/kg over 40 min	56 or 84 mg, twice weekly for 4 weeks, then tapering
US regulatory status for depression	Off-label	FDA-approved: treatment-resistant depression (2019); MDD with acute suicidal ideation or behavior (2020)[21]
Comparator in the key suicidality trials	Saline or midazolam, usual care[2,4]	Placebo spray, *both arms hospitalized* with antidepressant started or optimized[9,10]
Suicide-specific scale result	Separates from control at 24 h – 72 h in multiple RCTs and meta-analyses[3,5]	CGI-SS-r did not separate from placebo at 24 h in ASPIRE I or II[9,10]
Depression scale result	Large, rapid	MADRS ≈ 3.8 points better than placebo at 24 h[9]
Suicide attempts / deaths	Not established	Not established; label says so explicitly[21,8]
Setting	Clinic or hospital with monitoring	REMS-certified site; 2 h observation; no driving that day[21]

The ASPIRE esketamine studies

The phase 3 ASPIRE I and ASPIRE II trials enrolled adults with major depressive disorder who had active suicidal ideation with intent and required hospitalization — an unusually important population, because many antidepressant trials exclude the people at greatest acute risk. In

ASPIRE I, 226 patients were randomized to intranasal esketamine 84 mg or placebo, each added to comprehensive standard care including hospitalization and initiation or optimization of an oral antidepressant. At 24 hours, depressive symptoms measured by the MADRS improved significantly more with esketamine — a between-group difference of about 3.8 points. However, the prespecified key secondary measure of suicidality, the CGI-SS-r, did not show a statistically significant difference[9]. ASPIRE II produced the same pattern[10].

That does not mean esketamine failed suicidal patients. Suicidality improved dramatically in *both* groups. The methodological challenge is that everybody received a potent package of acute suicide treatment: hospitalization, intensive clinical contact, containment, monitoring, and antidepressant therapy. When standard care produces a very large fall in suicidality, an additional drug–placebo difference becomes statistically much harder to detect.

The current US prescribing information reflects this. Esketamine is approved for depressive symptoms in adults with MDD with acute suicidal ideation or behavior, but its effectiveness in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated, and improvement after esketamine does not remove the need for hospitalization when that is clinically warranted[21].

The adolescent data reinforce the same distinction

A 2026 phase 2b randomized study examined intranasal esketamine in 147 adolescents aged 12 to under 18 with MDD at imminent suicide risk. All participants received comprehensive standard care, including hospitalization, antidepressant treatment and evidence-based psychotherapy. Esketamine met its primary endpoint for rapid improvement in depressive symptoms, but suicidality improved across all treatment groups rather than producing an esketamine-specific suicide signal[22]. The pattern resembles the adult ASPIRE findings.

The hardest question: does ketamine actually prevent attempts or deaths?

This remains unanswered. Most ketamine research has been powered to detect changes in rating scales, not rare outcomes such as suicide attempts or deaths. A reduction in suicidal ideation is clinically valuable in its own right. But ideation and behavior are imperfectly correlated, and we cannot assume that an intervention that lowers a suicide-rating score will necessarily reduce completed suicide.

An updated systematic review and meta-analysis, currently available as a medRxiv preprint and **not yet peer reviewed**, analyzed 73 randomized trials comprising 5,671 participants. Suicidal behavior occurred in 1.63% of ketamine/esketamine participants and 1.72% of placebo participants — an estimated odds ratio of 0.98 (95% credible interval 0.58–1.60). There were 42 suicide attempts in ketamine/esketamine groups versus 41 with placebo, and six versus two suicide deaths. None of these comparisons demonstrated a statistically reliable difference, and the investigators rated the evidence as low or very low certainty because events were rare and estimates imprecise[7].

Those raw counts should not be read as evidence that ketamine increases suicide. With so few events, the uncertainty is enormous. What the analysis demonstrates is simpler: we do not yet have enough randomized evidence to know.

FIGURE 4 **Two questions, two very different answers**

"Does it reduce suicidal *thinking*?"

Yes — rapidly, in randomized trials.

26 RCTs, SMD −0.69 at 24 h[3] · 63% vs 32% remission at day 3[4] · 55% vs 30% response at 24 h[2]

STRONG EVIDENCE

"Does it prevent suicide *attempts or deaths*?"

Unknown.

73 RCTs, 83 attempts total, OR 0.98 (0.58–1.60) — preprint[7] · claims cohort HR 1.02 (0.67–1.54)[8] · FDA label: not demonstrated[21]

INSUFFICIENT EVIDENCE

What do real-world data tell us?

Two large 2026 observational studies are useful precisely because they point in somewhat different directions. Liu and colleagues conducted a target-trial emulation in a large electronic-health-record network, comparing 3,383 matched pairs of patients with MDD treated with esketamine or conventional antidepressants. Esketamine was associated with fewer composite "suicide-related events" over several follow-up windows and lower all-cause mortality. But the composite was largely driven by reductions in *coded suicidal ideation*; there were too few

attempts and self-harm events to establish whether esketamine reduced those specifically, and residual confounding remains possible[23].

On September 2, 2026, Wang and colleagues published a large US administrative-claims analysis in *Drug Safety*. The matched cohort included 5,785 esketamine-treated patients and 17,355 controls. Current esketamine exposure was not associated with a statistically distinguishable difference in medically attended non-fatal suicide attempts or intentional self-harm: HR 1.017 (95% CI 0.670–1.544). That interval remains compatible with clinically meaningful benefit *or* harm[8].

> We have considerably better evidence that ketamine reduces suicidal thoughts than we do that ketamine or esketamine reduces suicidal behavior.

Why might IV racemic ketamine show a clearer suicide-specific signal?

We do not know. The apparent difference could reflect pharmacology, route and pharmacokinetics, dose, subjective-state effects, network effects, metabolites, or opioid–glutamate interactions. But an enormous part of it may simply be trial design. Many IV ketamine studies compared ketamine with saline or midazolam and measured suicide-specific outcomes over hours or days. The ASPIRE trials gave every participant a package of aggressive standard-of-care suicide treatment. It would be premature to conclude that racemic ketamine possesses a suicide-specific biological property that esketamine lacks. The clinical evidence bases differ; the biological explanation for that difference remains open.

HOW TO READ A KETAMINE-AND-SUICIDE STUDY · FIVE QUESTIONS

1. **What was the comparator?** Saline, midazolam (which mimics sedation), or placebo on top of hospitalization? The last makes any drug look smaller.
2. **Which outcome?** A depression scale (MADRS), an ideation scale (SSI, C-SSRS, CGI-SS-r), or actual attempts and deaths? Only the last answers the prevention question.
3. **At what time point?** 24 hours, 72 hours, 1 week, 6 weeks? Ketamine's effects are front-loaded; the later the time point, the smaller the difference.
4. **Who was enrolled?** Treatment-resistant depression, or people with active intent who needed a hospital bed? The latter is the population that matters and the hardest to study.
5. **How many events?** With attempts at ~1–2% over weeks, a trial needs thousands of participants to say anything. None has that yet.

Safety and practical considerations

A paper about ketamine in crisis would be incomplete without the risks, because they shape where and how it should be used.

- **Acute effects.** Dissociation, dizziness, nausea, blurred vision and a transient rise in blood pressure and heart rate are common during and shortly after dosing and typically resolve within an hour or two; a systematic review of ketamine trials in depression found these to be the dominant adverse effects, with few serious events at antidepressant doses[24]. Monitoring is standard — and required for esketamine[21].
- **Who needs extra caution.** Uncontrolled hypertension or significant cardiovascular disease; a history of psychosis; active substance-use disorder; pregnancy. These are reasons for careful assessment, not absolute bars, and they belong to the treating clinician.
- **Longer-term and misuse risks.** With frequent, prolonged or unsupervised use — patterns seen in recreational use far more than in clinic protocols — ketamine can cause bladder inflammation and cognitive effects, and it carries abuse liability[24]. This is the strongest argument for supervised administration and against self-sourced use during a crisis.
- **Route matters for the evidence.** The suicidal-ideation evidence is strongest for intravenous racemic ketamine; oral, intramuscular and intranasal routes have less and more variable

data[6].

- **Driving and the day of treatment.** Patients should not drive or operate machinery the day of treatment; esketamine's label formalizes this[21].

What I think this means clinically

I should say where I stand. I founded Utah's first esketamine clinic, have run ketamine treatment programs and research, and have watched this medicine change the arc of a bad week for many people. I am not neutral. That is exactly why I want to be careful here.

For patients with acute suicidal depression, the most defensible way to conceptualize ketamine is as a **rapid-acting bridge**. The goal is not to administer ketamine and declare the risk solved. The goal is to rapidly reduce the intensity of the state that is making survival difficult. If psychological pain falls, hopelessness loosens, anhedonia improves and suicidal ideation recedes, a previously inaccessible therapeutic window can open.

Inside that window, the real work of durable recovery can happen: connection with family and clinicians; putting time and distance between the person and lethal means; a written safety plan, which on its own roughly halves suicidal behavior in the months after an emergency visit[25]; treatment of the underlying mood disorder; psychotherapy; sleep restoration; substance-use treatment when needed; attention to trauma or interpersonal crises; medication optimization; and a realistic path forward.

Ketamine can potentially move somebody from *"I cannot survive this state"* to *"This state might change."* That is not a trivial effect. In an acute suicidal crisis, time matters. But buying time is different from curing the illness, and reducing suicidal thinking is different from proving prevention of suicidal behavior. Both truths can coexist.

FOR PATIENTS AND FAMILIES · THE PLAIN-LANGUAGE VERSION

- Ketamine can make suicidal thoughts and the pain behind them much lighter within hours. This is real and well-studied.
- The relief usually fades over one to two weeks unless something else is put in place. Think of it as a bridge, not a destination.
- No study has yet shown that it prevents suicide attempts or deaths. Nobody knows that yet — including the people selling it.
- It is given in a clinic or hospital with monitoring, by a clinician. It is not something to obtain on your own during a crisis.
- The best use of the window it opens is a safety plan, a follow-up appointment within days, and people around you. If you are in crisis now: call or text 988.

Where the science needs to go next

The next generation of studies should move beyond asking only whether MADRS or C-SSRS scores fall after ketamine. We need adequately powered trials and registries that follow suicide attempts, self-harm, emergency visits, hospitalizations and mortality over meaningful periods of time.

We also need better mechanistic phenotyping. In addition to conventional depression and suicide scales, future trials should repeatedly measure psychological pain, entrapment, hopelessness, anhedonia, rumination, cognitive flexibility, perceived burdensomeness, belongingness, reward anticipation and reasons for living. The recent psychological-pain findings are especially intriguing because psychache may be closer to what ketamine changes during the first hours of a suicidal crisis than a total depression score is.

Biomarker work — glutamate dynamics, neuroplasticity markers, functional connectivity, inflammatory biology, endogenous opioid activity, sleep and circadian changes — may eventually identify different suicidal phenotypes with different treatment responses. And we should investigate a question clinicians encounter constantly: what should happen during the window after the suicidal state improves? A rapidly plastic brain state combined with relief from psychological pain may represent an unusually valuable moment for psychotherapy, connection, meaning-making, behavioral change and treatment engagement.

Conclusion

Ketamine has changed the way psychiatry thinks about time. For decades, clinicians treating a severely depressed and suicidal patient largely accepted that biological treatment might take weeks to work. Ketamine demonstrated that this assumption was not a law of nature.

Within hours, suicidal thinking can sometimes change dramatically. The most recent evidence strengthens the conclusion that IV racemic ketamine has a genuine rapid effect on suicidal ideation that is at least partly separable from its overall antidepressant effect. Psychological pain, hopelessness, anhedonia, reward processing, glutamate/AMPA-mediated plasticity, brain-network dynamics and endogenous opioid signaling may all contribute. Esketamine similarly provides rapid antidepressant benefit in acutely suicidal depressed patients, although its pivotal trials have not demonstrated the same clear separation from intensive standard care on suicide-specific measures.

And there is one boundary we should state clearly: **we do not yet know whether ketamine or esketamine prevents suicide.**

That statement does not diminish ketamine's importance. Rapidly relieving unbearable psychological pain and suicidal thinking may be one of the most clinically meaningful things a psychiatric treatment can do. We simply need to describe accurately what the evidence has — and has not — shown. Ketamine is one of the best-supported rapid pharmacologic interventions for reducing acute suicidal ideation. Its greatest immediate value may be its ability to interrupt a suicidal state and create a window for safety, connection and durable treatment. Whether that translates into fewer suicide attempts or suicide deaths remains an urgent, unanswered question.

Disclosures and limitations

This article is a narrative educational review written for public dissemination and has not undergone external peer review. It should not be interpreted as a systematic review, a clinical practice guideline, or a treatment recommendation for any individual. The literature is evolving rapidly; some mechanistic interpretations discussed here — particularly the rescue–repair framework, network-state models, and proposed relationships between psychological pain and specific neurobiological pathways — are hypotheses supported to varying degrees rather than established causal mechanisms. One meta-analysis of suicide attempts and deaths cited here is

a preprint that has not completed peer review. Several 2026 citations were current at the time of writing and should be re-verified against journal records before any formal reuse. IV racemic ketamine is used off-label for depression in the United States; esketamine has FDA-approved psychiatric indications and is subject to specific prescribing, administration and monitoring requirements.

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