Psychosomatic Medicine and General Practice
Том 11 № 2 (2026)
DOI: 10.26766/pmgp.v11i2.720

Psychotherapy and Ketamine: How Does This Combination Affect the Duration of the Antidepressant Effect?

Viacheslav Zaika — Yarmachenko Institute of Special Education and Psychology of the National Academy of Pedagogical Sciences of Ukraine
Yan Tytarenko — Bogomolets National Medical University

Background. Ketamine provides rapid but short-lived antidepressant effects for treatment-resistant depression (TRD). To prolong this response, ketamine-assisted therapy (KAT) combines the drug's pharmacological effects with psychotherapy.

Aim. This study aims to analyze scientific evidence regarding the synergistic interaction between ketamine's pharmacological effects and modern psychotherapeutic interventions, viewing the drug's effect as a foundation for therapy.

Materials and Methods. A review of scientific literature, including randomized controlled trials, open-label studies, and systematic reviews, was conducted to evaluate combining ketamine with psychotherapy.

Results. Evidence shows that structured approaches like cognitive-behavioral therapy (CBT), behavioral activation (BA), and automated computer training of implicit self-associations (ASAT) may moderately prolong ketamine's antidepressant effects, though data are heterogeneous. However, one study showed no clear advantage of ASAT combined with psychotherapy over ketamine monotherapy. Synergism may theoretically rely on utilizing a ketamine-induced “window of heightened neuroplasticity” to consolidate new cognitive-emotional and behavioral patterns.

Conclusions. Current scientific data require further accumulation and structuring to develop standardized KAT protocols. Large, well-designed RCTs are necessary to definitively confirm how much psychotherapy contributes to prolonging ketamine’s antidepressant efficacy.

Keywords: Ketamin, psychotherapy, depression, ketamin-assisted therapy, psychedelic-assisted therapy, antidepressants

Introduction

Depression is one of the most common mental disorders in the world and a leading cause of disability. According to estimates by the World Health Organization, approximately 280–350 million people worldwide suffer from depression, accounting for about 3.8–5% of the population (Chiriţă et al., 2015; Marcus et al., 2012; Stringaris, 2017; Sultana et al., 2023). Each year, about 1 in 20 people report an episode of depression (Marcus et al., 2012; Pragholapati, 2020). At the same time, depression is observed 1.5–3 times more frequently in women than in men (Sultana et al., 2023).

Depression is a significant public health problem, as it is the leading cause of disability worldwide (Marcus et al., 2012; Reddy, 2010; Stringaris, 2017). In the worst cases, depression can lead to

suicide. Each year, approximately 800,000 people die by suicide, making it the second leading cause of death among individuals aged 15 to 29 (Machado et al., 2024).

There is confirmed evidence of a trend toward increasing prevalence of depression that cannot be explained solely by changes in research methods (Goodwin et al., 2022; Moreno-Agostino et al., 2020). The prevalence of depression has increased particularly since 2020, when over 53 million new cases were reported, a rise attributed to the COVID-19 pandemic (Sultana et al., 2023).

Antidepressants are widely used to treat depression, and numerous large studies show that they are statistically more effective than placebo. However, complete remission is achieved in far from all patients: between 30% and 60% of patients do not achieve an adequate response to antidepressant therapy (Fanelli et al., 2020; Fava, 2003; Feltes et al., 2017; Mojtabai et al., 2021). This underscores the need for an individualized approach and the search for new therapeutic strategies.

The use of ketamine as part of ketamine-assisted therapy (KAT) or as a standalone pharmacological agent is one of the new methods for treating depression that is currently receiving significant attention and for which there are high hopes.

Esketamine (the S-enantiomer of ketamine), known under the brand name Spravato, is used as a pharmacological agent outside of KAT for the treatment of depressive disorders. It was officially approved by the FDA for the treatment of treatment-resistant depression in March 2019 as an adjunct to antidepressants (combination therapy) (Vekhova et al., 2025). In December 2019, the FDA and the European Medicines Agency (EMA) added the indication of treatment-resistant depression (TRD) for Spravato. In January 2025, the FDA approved changes allowing Spravato to be used as monotherapy for the treatment of treatment-resistant depression (TRD) (Rahrig et al., 2025). Ketamine has a rapid antidepressant effect, particularly in patients with suicidal thoughts, making it an important tool in modern psychopharmacotherapy (Berman et al., 2000; Krystal et al., 2019).

At the same time, ketamine in the form of a racemic mixture is used off-label by specialized clinics as an innovative treatment for treatment-resistant mental disorders, including depression, post-traumatic stress disorder (PTSD), anxiety disorders, and other mental disorders.

Ketamine at subanesthetic doses provides rapid relief of depressive symptoms in treatment-resistant depression; however, the median time to relapse after a single infusion is often 1–2 weeks (Corriger & Pickering, 2019; Walsh et al., 2021). Repeated or maintenance infusions may prolong the effect but raise concerns regarding cumulative toxicity, dependence, and treatment costs (Alnefeesi et al., 2022; Phillips et al., 2019; Smith-Apeldoorn et al., 2022). One promising approach is combining ketamine with psychotherapy, which theoretically allows for the use of a temporary “window of neuroplasticity” to enhance the effectiveness of psychotherapeutic learning and foster deeper and more lasting therapeutic changes (Drozdz et al., 2022; Lullau et al., 2023; Price et al., 2022). The aim of this article is to synthesize data on how psychotherapy influences the duration of the antidepressant effects of ketamine-assisted therapy.

Materials and methods

This review is based on published RCTs, systematic reviews, open-label trials, and case series evaluating ketamine in combination with psychotherapy for treatment-resistant depression and other mental disorders (Drozdz et al., 2022; Gomes & Novais, 2025; Joneborg et al., 2022; Kew et al., 2023; Kryst et al., 2020; Simpson & Juruena, 2026; Wilkinson et al., 2017; Wilkinson et al., 2021). The primary endpoints were duration of response/remission, time to relapse, and changes in depression scales over the medium-term (4–24 weeks) period. This review is based on published RCTs, systematic reviews, open-label trials, and case series evaluating ketamine in combination with psychotherapy for treatment-resistant depression and other mental disorders (Drozdz et al.,

2022; Gomes & Novais, 2025; Joneborg et al., 2022; Kew et al., 2023; Kryst et al., 2020; Simpson & Juruena, 2026; Wilkinson et al., 2017; Wilkinson et al., 2021). The primary endpoints were duration of response/remission, time to relapse, and changes in depressive scales over the medium-term (4–24 weeks) period.

Synthesis

Cognitive-behavioral therapy combined with CAT— we identified and analyzed two studies on this topic.

In an open-label study of TRD, the combination of 4 ketamine infusions with a 10-week course of CBT demonstrated that among responders, the median time to relapse was 12 weeks, and a subset of patients maintained remission for at least 8 weeks after the last infusion (Wilkinson et al., 2017).

A sequential RCT involving 6 ketamine infusions and 14 weeks of CBT showed a moderate-to-large effect on the maintenance of the antidepressant response on the QIDS scale (Cohen's d ≈ 0.71), which persisted up to 14 weeks after the last infusion compared to the control group (Wilkinson et al., 2021).

Behavioral activation as a psychotherapy method in combination with ketamine. A case series of patients with TRD who responded to a course of repeated ketamine infusions showed that 12–17 sessions of behavioral activation (BA) were associated with sustained improvement in depressive symptoms and functioning; especially when BA was initiated prior to clinical relapse (Phillips et al., 2023). This supports the idea that psychotherapy should be "embedded" during a period of heightened neuroplasticity rather than deferred until symptoms return.

ASAT (Automated Computerized Training of Implicit Self-Associations) combined with CAT. A randomized clinical trial of ASAT tested whether brief computerized training in positive self-associations, initiated 24 hours after a single ketamine infusion, could prolong the antidepressant effect. In the "ketamine+ASAT" group, depression levels remained consistently low for 30 days, whereas in the "ketamine+sham intervention" group, symptoms gradually returned to placebo levels (Price et al., 2022). This supports the concept that targeted cognitive intervention during the "window of neuroplasticity" may consolidate the benefits of CAT.

CAT on its own (with a psychotherapeutic component of various modalities included). Systematic reviews of CBT for TRD and other disorders (PTSD, addictions, chronic pain) generally demonstrate a significant reduction in symptoms, sometimes maintained for up to 3–6 months (Drozdz et al., 2022; Gomes & Novais, 2025; Kryst et al., 2020; Yermus et al., 2024). However, the quality of evidence is heterogeneous: small sample sizes, different types of psychotherapy, variable ketamine doses/administration routes, and short follow-up periods (Drozdz et al., 2022; Gomes & Novais, 2025; Joneborg et al., 2022; Simpson & Juruena, 2026).

A systematic review of Al-Garni's ketamine maintenance therapy indicates that adjunctive psychotherapy was associated with a reduced risk of relapse (HR ≈ 0.72), although this estimate is based on a small number of observations and requires confirmation (Al-Garni et al., 2025).

At the same time, a study by Moore et al. (2025) found no additional benefits or synergistic effects from combining ketamine with psychotherapeutic interventions compared to ketamine alone over a 30–180-day follow-up period when treating patients with depression and PTSD (Moore et al., 2025). Similarly, in a systematic review of KAT for TRD by Simpson & Juruena (2026), no convincing advantage over control conditions was found where comparison groups were present, despite overall improvement in both groups. Another review cautiously concludes that the addition of psychotherapy is "often associated" with better duration and depth of effect, but due to the heterogeneity of the studies, it is impossible to formally confirm the causal contribution of psychotherapy (Joneborg et al., 2022; Kew et al., 2023).

Comparison with pharmacological strategies without a psychotherapeutic component. Systematic reviews of real-world practice and RCTs consistently demonstrate that repeat and maintenance infusions (or nasal esketamine) effectively prolong the antidepressant response, often for months (Alnefeesi et al., 2022; Kryst et al., 2020; McMullen et al., 2021; Phillips et al., 2019; Smith-Apeldoorn et al., 2022). A separate review of strategies for prolonging the effects of ketamine concludes that no non-pharmacological strategy (including psychotherapy) currently has the same clear evidence base as repeated infusions (McMullen et al., 2021).

Discussion

Current neurobiological models view ketamine as a means of rapidly activating synaptogenesis, restoring dendritic spines, and normalizing stress-induced, inflammatory, and neurotoxic changes (Lullau et al., 2023). This creates a temporary state of heightened neuroplasticity, during which psychotherapeutic interventions more strongly modify neural networks.

Clinical evidence supporting this model is still limited, but the results of CBT studies, the BA series, and the ASAT trials are consistent with the concept of synergy between “pharmacological priming” and targeted training (Phillips et al., 2023; Price et al., 2022; Wilkinson et al., 2017; Wilkinson et al., 2021).

A possible explanation for the neurophysiological mechanism of the synergistic action of ketamine and psychotherapeutic interventions could be as follows: ketamine creates a “window of heightened neuroplasticity,” and psychotherapy conducted within the first 24–48 hours after infusion theoretically better consolidates new cognitive and behavioral patterns (Hasler, 2019; McCartney et al., 2022; Muscat et al., 2021; Muscat et al., 2022; Sakopoulos & Todman, 2025).

Limitations of the evidence:

- small sample sizes, high likelihood of sampling error (Phillips et al., 2023; Wilkinson et al., 2017; Wilkinson et al., 2021).

- heterogeneity of protocols: varying ketamine doses/routes, infusion frequency, duration of psychotherapy, and its theoretical models (Drozdz et al., 2022; Gomes & Novais, 2025; Joneborg et al., 2022; Kew et al., 2023; Simpson & Juruena, 2026).

- "Pure" control groups (ketamine without psychotherapy or psychotherapy without ketamine) with equivalent contact intensity are often absent (Drozdz et al., 2022; Gomes & Novais, 2025; Simpson & Juruena, 2026)

- Short follow-up periods (30 days to 3–6 months) are insufficient to assess long-term maintenance and safety (Drozdz et al., 2022; Gomes & Novais, 2025; Joneborg et al., 2022; Smith-Apeldoorn et al., 2022).

Despite these limitations, current data allow for several preliminary recommendations:

- Structured, manualized approaches (CBT, behavioral activation) appear to be the most promising for prolonging the response based on currently available information (Phillips et al., 2023; Wilkinson et al., 2017; Wilkinson et al., 2021).

- Optimal timing involves initiating or intensifying psychotherapy before the completion of the infusion course and continuing for at least 8–14 weeks, when the risk of relapse is high (Phillips et al., 2023; Wilkinson et al., 2017; Wilkinson et al., 2021).

- Computer-based or low-resource interventions (ASAT) can be a scalable tool for consolidating change, particularly in systems with limited access to in-person psychotherapy (Price et al., 2022).

Conclusions

Psychotherapy integrated with ketamine therapy is a promising strategy for prolonging antidepressant effects, with particularly encouraging results for CBT, behavioral activation, and targeted cognitive interventions conducted during the period of heightened neuroplasticity following ketamine infusions. However, the available data have methodological limitations, and the results do not always unequivocally demonstrate an advantage over ketamine without psychotherapy. Large, well-controlled RCTs with standardized KAP protocols, clearly defined follow-up durations, and mechanistic markers (neuroimaging, cognitive measures) are needed to accurately assess the extent to which psychotherapy can increase the duration and depth of ketamine’s antidepressant effects.

Conflict of Interest

The authors declare that there is no conflict of interest.

Acknowledgments

The authors would also like to express their sincere gratitude to AmA Holding for funding the research presented in this article.

References

1. Al-Garni, A., Vazquez, G., Alotibi, T., Hernandorena, C., & Knyahnytska, Y. (2025). Efficacy and safety of ketamine maintenance therapy in treatment-resistant depression: A systematic review of treatment protocols and clinical outcomes.. Journal of affective disorders, 120475. https://doi.org/10.1016/j.jad.2025.120475
2. Alnefeesi, Y., Chen-Li, D., Krane, E., Jawad, M., Rodrigues, N., Ceban, F., Di Vincenzo, J., Meshkat, S., Ho, R., Gill, H., Teopiz, K., Cao, B., Lee, Y., McIntyre, R., & Rosenblat, J. (2022). Real-world effectiveness of ketamine in treatment-resistant depression: A systematic review & meta-analysis.. Journal of psychiatric research, 151, 693-709. https://doi.org/10.1016/j.jpsychires.2022.04.037
3. Argento, E., Petker, T., Vig, J., Robertson, C., Jaeger, A., Necyk, C., Thielking, P., & Walsh, Z. (2024). “This is you teaching you:” Exploring providers’ perspectives on experiential learning and enhancing patient safety and outcomes in ketamine-assisted therapy. PLOS ONE, 19. https://doi.org/10.1371/journal.pone.0306381
4. Berman, R. M., Cappiello, A., Anand, A., Oren, D. A., Heninger, G. R., Charney, D. S., & Krystal, J. H. (2000). Antidepressant effects of ketamine in depressed patients. Biological Psychiatry, 47(4), 351-354. https://doi.org/10.1016/S0006-3223(99)00230-9
5. Chiriţă, A. L., Gheorman, V., Bondari, D., & Rogoveanu, I. (2015). Current understanding of the neurobiology of major depressive disorder. Romanian journal of morphology and embryology = Revue roumaine de morphologie et embryologie, 56(2 Suppl), 651–658.
6. Corriger, A., & Pickering, G. (2019). Ketamine and depression: a narrative review. Drug Design, Development and Therapy, 13, 3051 - 3067. https://doi.org/10.2147/dddt.s221437
7. Da Costa Gonçalves, K., De Tavares, V., De Morais Barros, M., De Brito, A., Cavalcanti-Ribeiro, P., Palhano-Fontes, F., Falchi-Carvalho, M., Arcoverde, E., Santos, R., Hallak, J., De Araujo, D., & Galvão-Coelho, N. (2024). Ketamine-induced altered states of consciousness: a systematic review of implications for therapeutic outcomes in psychiatric practices. European Archives of Psychiatry and Clinical Neuroscience, 275, 1271 - 1299. https://doi.org/10.1007/s00406-024-01925-6
8. Dames, S., Kryskow, P., & Watler, C. (2022). A Cohort-Based Case Report: The Impact of Ketamine-Assisted Therapy Embedded in a Community of Practice Framework for Healthcare Providers With PTSD and Depression. Frontiers in Psychiatry, 12. https://doi.org/10.3389/fpsyt.2021.803279

9. Dore, J., Turnipseed, B., Dwyer, S., Turnipseed, A., Andries, J., Ascani, G., Monnette, C., Huidekoper, A., Strauss, N., & Wolfson, P. (2019). Ketamine Assisted Psychotherapy (KAP): Patient Demographics, Clinical Data and Outcomes in Three Large Practices Administering Ketamine with Psychotherapy. Journal of Psychoactive Drugs, 51, 189 - 198. https://doi.org/10.1080/02791072.2019.1587556
10. Drozdz, S., Goel, A., McGarr, M., Katz, J., Ritvo, P., Mattina, G., Bhat, V., Diep, C., & Ladha, K. (2022). Ketamine Assisted Psychotherapy: A Systematic Narrative Review of the Literature. Journal of Pain Research, 15, 1691 - 1706. https://doi.org/10.2147/jpr.s360733
11. Fanelli, G., Benedetti, F., Kasper, S., Kautzky, A., Zohar, J., Souery, D., Montgomery, S., Albani, D., Ferentinos, P., Rujescu, D., Mendlewicz, J., Serretti, A., & Fabbri, C. (2020). Higher polygenic risk scores for schizophrenia may be suggestive of treatment non-response in major depressive disorder. medRxiv. https://doi.org/10.1101/2020.01.15.20017699
12. Fava M. (2003). Diagnosis and definition of treatment-resistant depression. Biological psychiatry, 53(8), 649–659. https://doi.org/10.1016/s0006-3223(03)00231-2
13. Feltes, K. P., Doorduin, J., Klein, H. C., Juárez-Orozco, L. E., Dierckx, R. A., Moriguchi-Jeckel, C. M., & de Vries, E. F. (2017). Anti-inflammatory treatment for major depressive disorder: implications for patients with an elevated immune profile and non-responders to standard antidepressant therapy. Journal of psychopharmacology (Oxford, England), 31(9), 1149–1165. https://doi.org/10.1177/0269881117711708
14. Gomes, A., & Novais, F. (2025). Ketamine-Assisted Psychotherapy for Treatment-Resistant Depression: a Systematic Review. Current Treatment Options in Psychiatry, 12. https://doi.org/10.1007/s40501-025-00346-z
15. Goodwin, R. D., Dierker, L. C., Wu, M., Galea, S., Hoven, C. W., & Weinberger, A. H. (2022). Trends in U.S. Depression Prevalence From 2015 to 2020: The Widening Treatment Gap. American journal of preventive medicine, 63(5), 726–733. https://doi.org/10.1016/j.amepre.2022.05.014
16. Hasler, G. (2019). Toward specific ways to combine ketamine and psychotherapy in treating depression. CNS Spectrums, 25, 445 - 447. https://doi.org/10.1017/s1092852919001007
17. Joneborg, I., Lee, Y., Di Vincenzo, J., Ceban, F., Meshkat, S., Lui, L., Fancy, F., Rosenblat, J., & McIntyre, R. (2022). Active mechanisms of ketamine-assisted psychotherapy: A systematic review.. Journal of affective disorders. https://doi.org/10.1016/j.jad.2022.07.030
18. Kew, B., Porter, R., Douglas, K., Glue, P., Mentzel, C., & Beaglehole, B. (2023). Ketamine and psychotherapy for the treatment of psychiatric disorders: systematic review. BJPsych Open, 9. https://doi.org/10.1192/bjo.2023.53
19. Kryst, J., Kawalec, P., Mitoraj, A., Pilc, A., Lasoń, W., & Brzostek, T. (2020). Efficacy of single and repeated administration of ketamine in unipolar and bipolar depression: a meta-analysis of randomized clinical trials. Pharmacological Reports, 72, 543 - 562. https://doi.org/10.1007/s43440-020-00097-z
20. Krystal, J. H., Abdallah, C. G., Sanacora, G., Charney, D. S., & Duman, R. S. (2019). Ketamine: A paradigm shift for depression research and treatment. Neuron, 101(5), 774–778. https://doi.org/10.1016/j.neuron.2019.02.005
21. Lullau, A., Haga, E., Ronold, E., & Dwyer, G. (2023). Antidepressant mechanisms of ketamine: a review of actions with relevance to treatment-resistance and neuroprogression. Frontiers in Neuroscience, 17. https://doi.org/10.3389/fnins.2023.1223145
22. Machado, R. A., Vicente, R. S. P., Serra, E. R. N., Souza, J. C., Silva, D. S., Reis, G. S., Mota, S. M. B., Farias, S. T. S., Rodrigues, R. C. M., Paz, J. L., Silva, B. R. P. P., & Lopes, I. M. (2024). The benefits of physical activity for depression. International Seven Journal of Health Research, 3(2), 738–741. https://doi.org/10.56238/isevjhv3n2-031
23. Marcus, M., Yasamy, M. T., van Ommeren, M., Chisholm, D., & Saxena, S. (2012). Depression: A global public health concern. World Health Organization. https://www.researchgate.net/publication/285075782_Depression_A_global_public_health_concern
24. McCartney, A., McGovern, H., & De Foe, A. (2022). Psychedelic assisted therapy for major depressive disorder: Recent work and clinical directions. Journal of Psychedelic Studies. https://doi.org/10.1556/2054.2022.00211

25. McMullen, E., Lee, Y., Lipsitz, O., Lui, L., Vinberg, M., Ho, R., Rodrigues, N., Rosenblat, J., Cao, B., Gill, H., Teopiz, K., Cha, D., & McIntyre, R. (2021). Strategies to Prolong Ketamine’s Efficacy in Adults with Treatment-Resistant Depression. Advances in Therapy, 38, 2795 - 2820. https://doi.org/10.1007/s12325-021-01732-8
26. Mojtabai, R., Amin-Esmaeili, M., Spivak, S., & Olfson, M. (2021). Remission and Treatment Augmentation of Depression in the United States.. The Journal of clinical psychiatry, 82 6. https://doi.org/10.4088/jcp.21m13988
27. Mollaahmetoglu, O., Keeler, J., Ashbullby, K., Ketzitzidou-Argyri, E., Grabski, M., & Morgan, C. (2021). “This Is Something That Changed My Life”: A Qualitative Study of Patients' Experiences in a Clinical Trial of Ketamine Treatment for Alcohol Use Disorders. Frontiers in Psychiatry, 12. https://doi.org/10.3389/fpsyt.2021.695335
28. Moore, T., Walker, K., Tung, E., Teed, A., Hell, F., Kinreich, S., Jung, R., Abdel, F., Hanson, R., & Ahmed, S. (2025). Combined ketamine and psychotherapy provide no additional benefit beyond ketamine alone in treating depression or PTSD: Evidence from a help-seeking sample.. Journal of affective disorders. https://doi.org/10.1016/j.jad.2025.04.041
29. Moreno-Agostino, D., Wu, Y. T., Daskalopoulou, C., Hasan, M. T., Huisman, M., & Prina, M. (2021). Global trends in the prevalence and incidence of depression:a systematic review and meta-analysis. Journal of affective disorders, 281, 235–243. https://doi.org/10.1016/j.jad.2020.12.035
30. Muscat, S., Hartelius, G., Crouch, C., & Morin, K. (2021). An Integrative Approach to Ketamine Therapy May Enhance Multiple Dimensions of Efficacy: Improving Therapeutic Outcomes With Treatment Resistant Depression. Frontiers in Psychiatry, 12. https://doi.org/10.3389/fpsyt.2021.710338
31. Muscat, S., Hartelius, G., Crouch, C., & Morin, K. (2022). Optimized Clinical Strategies for Treatment-Resistant Depression: Integrating Ketamine Protocols with Trauma- and Attachment-Informed Psychotherapy. Psych. https://doi.org/10.3390/psych4010012
32. Phillips, J., Blier, P., & Talbot, J. (2023). Sustaining the benefits of intravenous ketamine with behavioural activation therapy for depression: A case series. Journal of Affective Disorders Reports. https://doi.org/10.1016/j.jadr.2023.100613
33. Phillips, J., Norris, S., Talbot, J., Birmingham, M., Hatchard, T., Ortiz, A., Owoeye, O., Batten, L., & Blier, P. (2019). Single, Repeated, and Maintenance Ketamine Infusions for Treatment-Resistant Depression: A Randomized Controlled Trial.. The American journal of psychiatry, 176 5, 401-409. https://doi.org/10.1176/appi.ajp.2018.18070834
34. Pragholapati, A. (2020). Depression in someone who has divorce. OSF Preprints. https://doi.org/10.31234/osf.io/78xhm
35. Price, R., Spotts, C., Panny, B., Griffo, A., Degutis, M., Cruz, N., Bell, E., Do-Nguyen, K., Wallace, M., Mathew, S., & Howland, R. (2022). A Novel, Brief, Fully Automated Intervention to Extend the Antidepressant Effect of a Single Ketamine Infusion: A Randomized Clinical Trial.. The American journal of psychiatry, appiajp20220216. https://doi.org/10.1176/appi.ajp.20220216
36. Rahrig, R., Kosikowski, K., Whyde, H., Devoll, K., Honigford, A., Davis, M., Honaker, J., McCord, S., & D’Souza, M. (2025). Spravato® FDA-approved as monotherapy for adults with treatment-resistant depression. Pharmacy and Wellness Review, 16(2), Article 2. https://digitalcommons.onu.edu/cgi/viewcontent.cgi?article=1202&context=paw_review
37. Reddy M. S. (2010). Depression: the disorder and the burden. Indian journal of psychological medicine, 32(1), 1–2. https://doi.org/10.4103/0253-7176.70510
38. Sakopoulos, S., & Todman, M. (2025). The Effects of Psychotherapy on Single and Repeated Ketamine Infusion(s) Therapy for Treatment-Resistant Depression: The Convergence of Molecular and Psychological Treatment. International Journal of Molecular Sciences, 26. https://doi.org/10.3390/ijms26146673
39. Simpson, R., & Juruena, M. (2026). Effectiveness of ketamine-assisted psychotherapy as a treatment for treatment-resistant depression: a systematic review.. Psychopharmacology. https://doi.org/10.1007/s00213-026-07003-0
40. Smith-Apeldoorn, S., Veraart, J., Spijker, J., Kamphuis, J., & Schoevers, R. (2022). Maintenance ketamine treatment for depression: a systematic review of efficacy, safety, and

tolerability.. The lancet. Psychiatry, 9 11, 907-921. https://doi.org/10.1016/s2215-0366(22)00317-0

41. Stringaris A. (2017). Editorial: What is depression?. Journal of child psychology and psychiatry, and allied disciplines, 58(12), 1287–1289. https://doi.org/10.1111/jcpp.12844
42. Sultana, S., Muhammad, F., & Chowdhury, A. B. M. A. (2023). Women's depression: Before or after marriage, when women are more depressed? The Open Psychology Journal, 16, Article e187435012212221. https://doi.org/10.2174/18743501-v16-e230130-2022-47
43. Vekhova, K. A., Namiot, E. D., Jonsson, J., & Schiöth, H. B. (2025). Ketamine and esketamine in clinical trials: FDA-approved and emerging indications, trial trends with putative mechanistic explanations. https://doi.org/10.1002/cpt.3478
44. Walsh, Z., Mollaahmetoglu, O., Rootman, J., Golsof, S., Keeler, J., Marsh, B., Nutt, D., & Morgan, C. (2021). Ketamine for the treatment of mental health and substance use disorders: comprehensive systematic review. BJPsych Open, 8. https://doi.org/10.1192/bjo.2021.1061
45. Wilkinson, S., Wright, D., Fasula, M., Fenton, L., Griepp, M., Ostroff, R., & Sanacora, G. (2017). Cognitive Behavior Therapy May Sustain Antidepressant Effects of Intravenous Ketamine in Treatment-Resistant Depression. Psychotherapy and Psychosomatics, 86, 162 - 167. https://doi.org/10.1159/000457960
46. Wilkinson, S., Rhee, T., Joormann, J., Webler, R., Lopez, M., Kitay, B., Fasula, M., Elder, C., Fenton, L., & Sanacora, G. (2021). Cognitive Behavioral Therapy to Sustain the Antidepressant Effects of Ketamine in Treatment-Resistant Depression: A Randomized Clinical Trial. Psychotherapy and Psychosomatics, 90, 318 - 327. https://doi.org/10.1159/000517074
47. Wolfson, P., & Vaid, G. (2024). Ketamine-assisted psychotherapy, psychedelic methodologies, and the impregnable value of the subjective—a new and evolving approach. Frontiers in Psychiatry, 15. https://doi.org/10.3389/fpsyt.2024.1209419
48. Yermus, R., Bottos, J., Bryson, N., De Leo, J., Earleywine, M., Hackenburg, E., Kennedy, S., Kezemidis, M., Kratina, S., McMaster, R., Medrano, B., Mina, M., Morisano, D., Muench, M., Pillai, S., Scharlach, R., Setlur, V., Verbora, M., Wolfson, E., Zaer, N., & Lo, C. (2024). Ketamine-Assisted Psychotherapy Provides Lasting and Effective Results in the Treatment of Depression, Anxiety, and Post-Traumatic Stress Disorder at 3 and 6 Months: Findings from a Large Retrospective Effectiveness Study. Psychedelic Medicine, 2, 87 - 95. https://doi.org/10.1089/psymed.2023.0021