THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 12 Issue 7

EDITORIAL ARTICLE

Ketamine-Assisted Psychotherapy: opportunities and challenges

Daniël Kleinloog, MD, PhD[1,2]
Anesthesiologist, Clinical Pharmacologist, Augmented Psychotherapist (in training)

[1]Medische Kliniek Velsen, Velsen-Noord, The Netherlands
[2]Embracing Psychedelics, Amsterdam, The Netherlands

OPEN ACCESS

PUBLISHED
31 July 2024

CITATION
Kleinloog, D., 2024. Ketamine-Assisted Psychotherapy: opportunities and challenges. Medical Research Archives, [online] 12(7). https://doi.org/10.18103/mra.v12i7.5630

DOI
https://doi.org/10.18103/mra.v12i7.5630

ISSN
2375-1924

ABSTRACT

Ketamine is a dissociative anesthetic with unique pharmacological and psychological properties. Its antidepressant effects are mediated through the glutamatergic system and subsequent neuroplasticity and can be amplified when combined with psychotherapy. The ketamine-induced dissociative state should not be seen as an unwanted side-effect, but as a unique opportunity for psychotherapeutic intervention. When psychotherapy is augmented by subanesthetic doses of ketamine, a synergistic effect is seen that increases and prolongs the effect on depressive symptoms, general well-being and quality of life.

Keywords: Ketamine, NMDA antagonist, psychotherapy, psychedelic, consciousness

Introduction

On August 3rd, 1964, in a clinical research unit in a prison in the U.S. State of Michigan, a pharmacologist and an anesthesiologist administered the first dose of ketamine to a human volunteer.[1] The dose of ketamine was slowly increased from having no effect, to a sub-anesthetic effect (described as "conscious but 'spaced out'"), and then further to general anesthesia.[1] Even during this very first administration of ketamine, it was clear that this drug had unique and remarkable effects.[1-2] The results from the phase I study mention the hemodynamic stability, limited effects on respiration and airway reflexes, analgesic properties, and the dream-like experiences in subanesthetic doses.[2] The term 'dissociative anesthesia' is introduced to descibe the dream-like effects of ketamine.[2,3]

During the sixty years that followed this first administration, ketamine has proven to be a unique and versatile drug in the fields of anesthesiology and, more recently, in the field of psychiatry.[3,4]

The aim of this article is to create awareness on the opportunities and challenges that are provided by ketamine-assisted psychotherapy (KAP).

Overview on ketamine

Pharmacology

The main pharmacologic mechanism of action of ketamine is non-competitive antagonism of the *N*-methyl-D-aspartate (NMDA) receptor.[3-6] Ketamine binds to the PCP binding site on the inside of the NMDA receptor channel, which results in a blocking of the influx of calcium ions through the channel (see Figure 1).[3-5] While ketamine blocks NMDA receptors, a paradoxical increase in brain levels of glutamate is seen in subanesthetic levels.[7-8]

Two optical isomers exist: S(+)-ketamine (esketamine) and R(-)-ketamine (arketamine).[3-5,9] The affinity for the NMDA receptor and the anesthetic potency of esketamine is three to four times that of arketamine.[4,5,9] The same is often thought for their respective ability to induce dissociative effects, but instead the isomers appear to induce distinct psychological effects.[9] Esketamine is more likely to induce sensations such as ego-dissolution, illusions and hallucinations, thought disturbances and paranoia, whereas arketamine induces feelings of relaxation and wellbeing.[9-10]

Many different routes of administration are available, including intravenous, intramuscular, intranasal, sublingual and oral; although oral and rectal bioavailablity is low and variable (10-25%).[3-5,11] Both isomers are metabolised into active norketamine and non-active hydroxyketamine.[4,6,9]

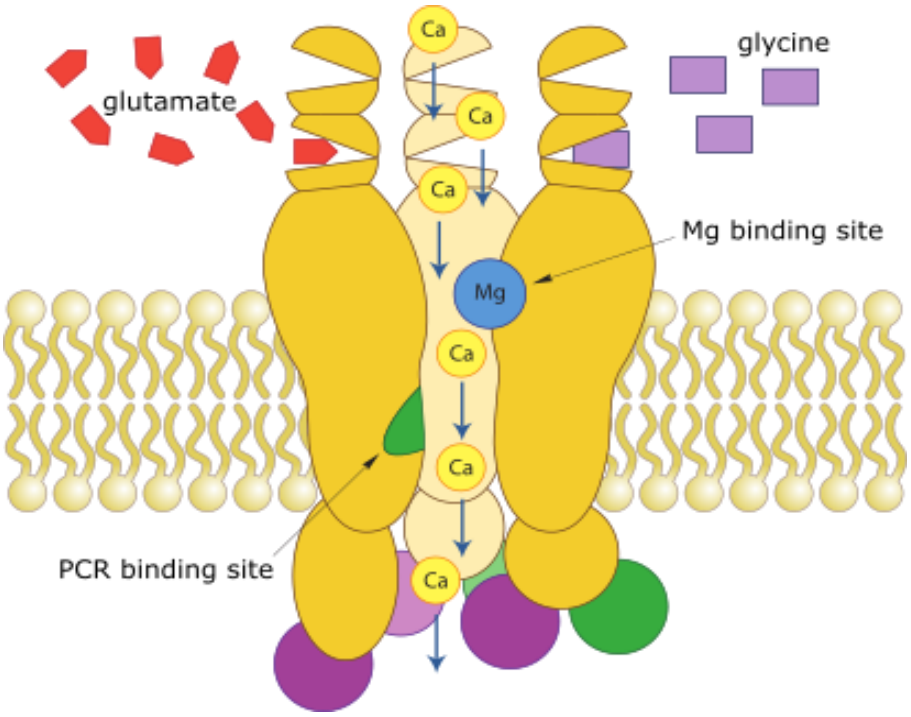
Ketamine for anesthesiology

Ketamine has been introduced as one of the first intravenous anesthetic agents. From the beginning, it has been seen as a nearly ideal agent, in particular for uses outside the operating room, due to the maintenance of homeostasis (cardiovascular stability, maintenance of respiration and respiratory reflexes).[3-6] Ketamine also has antinociceptive and analgesic properties and can be used to treat acute, post-operative and chronic pain.[6,12-14]

During ketamine anesthesia, induction doses of 1-2 mg/kg are used, followed by a maintenance dose of 1-6 mg/kg/hr and steady-state plasma concentrations of ketamine are 1200-2400 ng/mL and awakening from anesthesia occurs at plasma concentrations of 640-1100 ng/mL.[3,4,6]

The use of ketamine as a recreative drug and the subsequent repressive actions and schedulling of the substance led to a stigma and a decreased use of ketamine as an anesthetic agent. The introduction of propofol as an alternative intravenous anesthetic agent, drove the use of ketamine further to the background.

Figure 1: Overview of the NMDA-receptor



Concurrent with the resurgence of ketamine in the field of psychiatry, interest in its uses in anesthesiology have also resurfaced. The widespread misuse of opioids (the so-called 'opioid epidemic') has increased the use of multimodal pain management strategies, which often include ketamine.[4] Its use as an adjuvant in both anesthesia and pain management has increased a lot in the last two decades.[4] The addition of a subanesthetic dose of ketamine to a general anesthesia regimen decreases the need for opiods during and after surgery (up to six weeks postoperatively), as well as the dose of anesthetic agents used, which reduces side effects related to general anesthesia.[3,4,14]

Ketamine for psychiatric illnesses

The potential usefulness of ketamine in a psychotherapeutic setting was already explored in the 1970s.[3,11,15-16] However, it took until the early 2000s for larger, controlled trials to provide evidence for the effectiveness of ketamine as a treatment for depressive disorder.[17-18] In contrast to other pharmacological treatments of depressive disorder, ketamine is characterized by a rapid onset, effectiveness for symptoms that are considered treatment-resistant and independence of an increase of serotonin in the synapse.[3,5,8,19]

For uses outside of anesthesia, the use of a subanesthetic dosing regimen is common. A subanesthetic dose can be defined as a dose that is high enough to induce a desired effect (such as the induction of a dissociative state or remission of psychiatric symptoms or pain) but not so high that it induces full dissociation or anesthesia. Different desired or undesired effects might require a different target plasma concentration and therefore a different dosing regimen. The most common subanesthetic intravenous dosing regimen is 0.5 mg/kg, administered during 40 minutes, which results in plasma concentrations of 100-250 ng/mL (in comparison, plasma concentrations during anesthesia are between 1200-2400 ng/mL).[3,6] Within the subanesthetic dosing range there appears to be a positive dose-effect relation for both antidepressant and psychomimetic effects.[3,11,20-22]

Ketamine appears to be most promising for the treatment of treatment-resistant depression (TRD) and could be seen as an alternative to electroconvulsive

therapy (ECT).[23-28] Treatment-resistant depression is associated with a high burden of disease, major costs for healthcare and affects millions of individuals worldwide.[27] Ketamine also shows promise in the treatment of post-traumatic stress disorder (PTSD) and substance-use disorders.[3]

Ketamine as a recreative drug

Soon after its introduction as an anesthestic agent ketamine was already used as a recreative drug.[1,5] There is likely a relation between the widespread use of ketamine in the Vietnam war and the start of its use as a recreative drug, especially in veterans.[1] Concerns have been raised that ketamine-assisted psychotherapy might lead to an increase in recreative use of ketamine. There have been no reports that participants in ketamine-assisted psychotherapy are more likely to start using ketamine for recreative purposes.[11,16]

There is evidence that recreative use of ketamine is prevalent and has increased in recent years.[29] A large survey in the Netherlands estimates 2.6% of adults have used ketamine in their lifetime.[30] Use is most common in young adult males and most often infrequent (90.7% report use less than once a month).[30] Within the European Union, ketamine accounts for 9% of the seized psychoactive substances.[29] The number of ketamine-related health problems remains low.[29]

Although adequate information on doses are lacking, doses used for recreational purposes are general between 1-2 mg/kg (intravenous), 100-500 mg (oral) or 30-400 mg (intranasal insufflation), with an estimated plasma concentration of 50-200 ng/mL.[6]

Long-term, frequent and high-dose recreational use of ketamine is associated with attentional and cognitive disfunctions, flashbacks and urological complications (including ulcerative cystitis).[6,16,30-31] Although concerns have been raised that these effects might also occur following ketamine-assisted psychotherapy, these long-term effects of recreational use have not been described in a research or clinical setting.[16,31]

Ketamine-Assisted Psychotherapy

Biomedical model

When the efficacy of ketamine in the treatment of psychiatric illnesses is explained, the first approach is usually a biomedical or biochemical framework.[3,15]

Subanesthetic (but not anesthetic) doses of ketamine lead to a paradoxal increase in glutamate, mediated through disinhibition of gamma-aminobutyric acid (GABA) neurons.[7-9,19] The magnitude of glutamate release is related to the antidepressant effects.[19] When the initial effects of ketamine (antagonism of the NDMA receptor and its dissociative effects) wear off, those increased levels of glutamate lead to activation of both NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, resulting in the rapid release of brain-derived neurotrophic factor (BDNF) and activation of the mammalian target of rapamycin (mTOR) signalling pathway.[3-7,16,19,26,32-33] This leads to an increase in synaptic connections on excitatory neurons, known as structural neuroplasticity.[3,7-8,19,32-33] In this way, ketamine administration is hypothesised to correct the atrophy and loss of synapses that are seen in depressed patients.[7-8,19,32] Furthermore, ketamine-induced blocking of NMDA receptors might reset the imbalance between excitation and inhibition within microcircuits seen in patients with depression.[8,19] This ultimately leads to increases in methyl CpG binding protein 2 (MeCP2) phosphorylation at the Serine 421 (Ser421) site, which translates into prolonged therapeutic effects.[19]

Within this biomedical explanatory model, the dissociative effects of ketamine are generally seen as a limitation to the tolerability of ketamine administration.[3,15,27] Some have argued that the dissociative effects are not needed for the therapeutic effect, although all attempts to synthesize an antidepressant NMDA antagonist without dissociative effects have so far failed.[33-35] Interestingly, the dissociative effects have been shown to predict antidepressant effect in patients with major depressive

disorder and treatment-resistant depression.[36-37] And depressed patients who were given ketamine during general anesthesie for elective surgery did not show a reduction in depressive symptoms compared to placebo.[38]

Psychedelic model

Another approach to the use of ketamine as an antidepressant agent is to utilize the dissociative effects of ketamine.[11,15,27] The unique state of mind, often referred to as an altered or expanded state of consciousness, creates unique opportunities to promote psychological flexibility and induce long-lasting changes in behaviour and general well-being.[15,27,39-41] The altered or expanded state of consciousness can be seen as an amplifier, or a cathalyst, of psychotherapeutic mechanisms of change.[39-43]

In this regard, ketamine-induced subjective effects have similarities to the effects of psychedelic drugs.[11,43] Although ketamine is not considered a classic psychedelic (serotonergic 5-HT_{2A} receptor agonists, such as lysergic acid diethylamide -LSD-, psilocybin or N,N,-dimethyltryptamine -DMT-) it is often considered an atypical psychedelic drug.[27,43]

One of the debates that surrounds ketamine-assisted psychotherapy (and psychedelic-assisted psychotherapy in general) is whether or not there is synergism between the biochemical effects of ketamine and psychotherapy. The argument for synergism claims that the subjective effects induced by the pharmacological agent are of inherent value and are an integral part of the therapeutic process.[11,15,39-42] This argument appears to contradict the way Western medicine is usually approaching its examination of the efficacy of a pharmacological agent, purely within a biomedical framework.[39-42]

The combination of pharmacotherapy and psychotherapy in itself is not a novel idea.[15] Many different models of psychotherapy could be applied and have been studied (as reviewed by Mathai et al).[15,42] It is generally believed that administration of ketamine can best be combined with a psychotherapeutic framework that promotes psychological flexibility, and improves quality of life and overall functioning.[15,42] Efficacy should therefore also be measured as more than symptom reduction alone, and include measures of quality of life and general well-being.[15]

The administration of ketamine (or other psychedelics) within a therapeutic context generally consists of three phases: preparation, dosing sessions and integration.[42-43] Almost all settings use a form of psychological support with the intent of harm reduction and improving safety.[15,42]

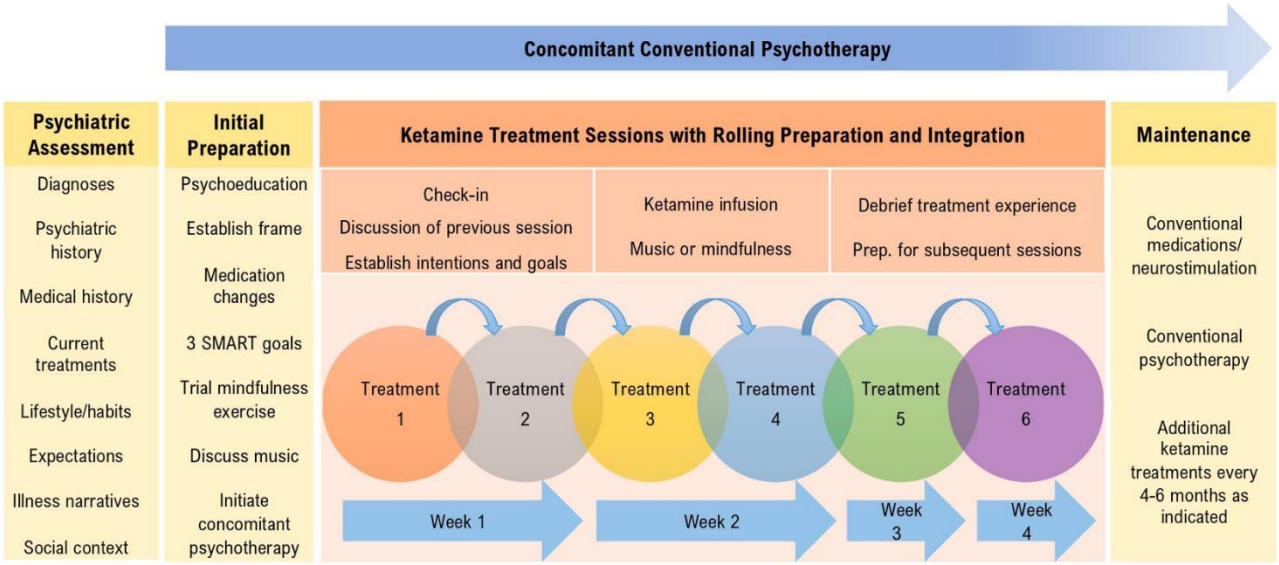
Ketamine-assisted psychotherapy distinguishes itself from ketamine infusion with basic psychological support, although this distinction is not always clearly defined.[15] In ketamine-assisted psychotherapy, patients are prepared for the experience using psychoeducation and psychotherapeutic tools that promote flexibility and acceptance.[15,39-42] Different psychotherapeutic frameworks can be used, such as the general change mechanisms model (further described by Wolff et al.)[40] or EMBARK model (described by Brennan et al.)[42]. The use of a structured model of psychotherapeutic change during preparation, dosing sessions and integration can be beneficial.[42] During the dosing sessions, the interaction between a patient and the psychotherapist is generally limited compared to other forms of psychotherapy.[40] The music played during the session plays an important role in mediating the therapeutic effect.[44] Some psychotherapeutic interventions might be warranted during the experience and patients can be reminded of tools that have been discussed during the preparation sessions.[42] Following the dosing sessions (or inbetween multiple dosing sessions) integration sessions are used to further allow the psychotherapeutic effects to sink in. Those integration sessions (at least in part) take place during the period of enhanced neuroplasticity, which should optimize the synergistic effects of the biomedical

and psychotherapeutic effects of ketamine-assisted psychotherapy.[27]

In most current practices of ketamine administration for psychiatric illnesses, ketamine is given repeatedly during a longer period and most often it is not combined with a specific tailor-made psychotherapeutic approach. The Montreal model (described by Garel et al.)[27] provides an integrative approach of short-term, intensive psychotherapy, augmented with multiple ketamine infusions and changes in lifestyle and psychotropic medications. The intensive treatment phase of ketamine-assisted psychotherapy is seen as a 'window of opporunity' to induce long-lasting changes in psychiatric symptoms and general well-being.[27] The use of a structured model is beneficial and can be helpful in managing expectations, especially given the media attention that has been given to the efficacy of ketamine and psychedelics.[27]

Rather than splitting the treatment into distinct phases of preparation, dosing sessions and integration, the Montreal model uses a 'rolling model' of preparation, dosing and integration. Within the period of treatment, experiences from one dosing session are used to prepare for another dosing session, as illustrated in Figure 2.

Figure 2: Overview of the Montreal model of ketamine-assisted psychotherapy (by Garel et al.)[27] with 'rolling' phases of preparation, dosing and integration.



Opportunities

The administration of subanesthetic doses of ketamine has been described as one of psychiatry's biggest pharmacological breakthroughs in decades.[3,7-9,27] It's rapid and robust onset of action, effectiveness in the treatment of treatment-resistant depression and favourable safety profile make it a unique treatment option for depression.[3,8]

To date, most studies that evaluate the effect of ketamine for psychiatric illnesses have focussed on the biomedical model, rather than the psychedelic model of effect.[19,27] However, the addition of psychotherapy could further expand and sustain the therapeutic effects of ketamine.[19] The ketamine-induced state of neuroplasticity provides opportunities to increase the effectiveness of psychotherapeutic interventions.

Ketamine-assisted psychotherapy could be embedded in several psychotherapeutic frameworks. The use of evidence-based, trans-diagnostic models that promote psychological flexibility could be particularly useful.[15,39-42] Psychotherapeutic frameworks should be flexible enough to individualize treatment for each patient.[42] When psychotherapeutic effects

are measured on different dimensions of change, future studies can assess which components of therapy are predictive of which effects.[40]

As of yet, ketamine is the only psychedelic drug with a market authorisation. Research with other psychedelic compounds is increasing and both 3,4-methylenedioxymethamphatamine (MDMA) and psilocybin have been granted 'breakthrough therapy designation' by the United States Food and Drug Administration (FDA).[11,33,43,45-47] The implementation of ketamine-assisted psychotherapy can therefore be seen as a test-case for other forms of psychedelic-assisted psychotherapy.[11]

Challenges

The induction of an expanded state of consciousness is often associated with an increased suggestibility, lowering of personal boundaries and an overall vulnerable state of the patient. This state of mind increases the potential for harm and therefore creates unique and novel requirements for ethical sensitivity of the therapist.[42,48]

Another challenge in the introduction of ketamine-assisted psychotherapy is how to include (sub)cultural considerations. Different (sub)cultural groups might benefit from different approaches in the therapeutic framework, therapeutic setting and cultural sensitivity of the therapist.[42,49] Higher educated, white patients and therapists are overrepresented in the clinical trials on psychedelics to date.[42,49]

Ketamine-assisted psychotherapy is an intensive form of treatment. Treatment sessions last longer than other forms of psychotherapy and in some protocols two therapists are present. This results in higher costs of treatment. Reimbursement by insurance policies is generally not designed for these intense forms of therapy. This argument would be even more relevant for other forms of psychedelic-assisted psychotherapy, as other psychedelic agents have a much longer duration of action.[27] Another challenge is that research on the optimal form of psychotherapy is generally not of interest to the pharmaceutical industry and funding is therefore more difficult to acquire.[15]

Conclusions

Ketamine is a dissociative anesthetic drug with unique pharmacological and psychological properties. The dissociative state that is induced by subanesthetic doses of ketamine should not be seen as an unwanted side-effect, but can be utilized in ketamine-assisted psychotherapy as a cathalyst for change.

Augmenting psychotherapy with drug-induced states of expanded consciousness might lead to a revolution in psychiatric healthcare. However, working with patients in such a sensitive, vulnerable state requires high standards of care and ethical practice. Studies evaluating the effectiveness of ketamine-assisted psychotherapy should focus not only on reduction of psychiatric symptoms, but also on general well-being and quality of life.

Conflicts of Interest Statement:

The author has no conflicts of interest to declare.

Funding Statement:

None

Acknowledgement Statement:

Figure 1 was created by Frans Hessels and was previously used in an article in iAM (www.prelum.nl/iam/) by Daniël Kleinloog.

References:

1. Domino EF. Taming the ketamine tiger. *Anesthesiology*. 2010;113(3):678-684. doi: 10.1097/ALN.0b013e3181ed09a2

2. Domino EF, Chodoff P, Corssen G. Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. *Clin Pharmacol Ther*. 1965;6 (3):279-291. doi: 10.1002/cpt196563279

3. Kohtala S. Ketamine – 50 years in use: from anesthesia to rapid antidepressant effects and neurobioloical mechanisms. *Pharmacol Rep*. 2021; 73(2):323-345. doi: 10.1007/s43440-021-00232-4

4. Barrett W, Buxhoeveden M, Dhillon S. Ketamine: a versitale tool for anesthesia and analgesia. *Curr Opin Anaesthesiol*. 2020;33(5):633-638. doi: 10.1097/ACO.0000000000000916

5. Gao M, Rejaei D, Liu H. Ketamine use in current clinical practice. *Acta Pharmacol Sin*. 2016; 37(7):865-872. doi: 10.1038/aps.2016.5

6. Zanos P, Moaddel R, Morris PJ, et al. Ketamine and ketamine metabolite pharmacology: insights into therapeutic mechanisms. *Pharmacol Rev*. 2018;70:621-660. doi: 10.1124/pr.117.015198

7. Duman RS. The dazzling promise of ketamine. *Cerebrum*. 2018:cer-04-18.

8. Krystal JH, Kaye AP, Jefferson S. Ketamine and the neurobiology of depression: toward next-generation rapid-acting antidepressant treatments. *Proc Natl Acad Sci U S A*. 2023;120(49):e2305772120. doi: 10.1073/pnas.2305772120

9. Jelen LA, Young AH, Stone JM. Ketamine: a tale of two enantiomers. *J Psychopharmacol*. 2021;35(2):109-123. doi: 10.1177/0269881120959644

10. Vollenweider FX, Leenders KL, Øye I, Hell D, Angst J. Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). *Eur Neuropsychopharmacol*. 1997;7(1):25-38. doi: 10.1016/s0924-977x(96)00042-9

11. Dore J, Turnipseed B, Dwyer S, et al. Ketamine assisted psychotherapy (KAP): patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *J Psychoactive Drugs*. 2019;51(2): 189-198. doi: 10.1080/02791072.2019.1587556

12. Wang X, Lin C, Lan L, Liu J. Perioperative intravenous S-ketamine for acute postoperative pain in adults: a systematic review and meta-analysis. *J Clin Anesth*. 2021;68:110071. doi: 10.1016/j.jclinane.2020.110071

13. Yang Y, Maher DP, Cohen SP. Emerging concepts on the use of ketamine for chronic pain. *Expert Rev Clin Pharmacol*. 2020;13(2):135-146. doi: 10.1080/17512433.2020.1717947

14. Brinck ECV, Tiippana E, Heesen M, et al. Perioperative intravenous ketamine for acute postoperative pain in adults. *Cochrane Database Syst Rev*. 2018;12(12):CD012033. doi:10.1002/14651858.CD012033.pub4

15. Mathai DS, Mora V, Garcia-Romeu A. Toward synergies of ketamine and psychotherapy. *Front Psychol*. 2022;13:868103. doi: 10.3389/fpsyg.2022.868103

16. Jelen LA, Stone JM. Ketamine for depression. *Int Rev Psychiatry*. 2021;33(3):207-228. doi: 10.1080/09540261.2020.1854194

17. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000;47(4):351-354. doi: 10.1016/s0006-3223(99)00230-9

18. Zarate Jr CA, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006;63(8):856-864. doi: 10.1001/archpsyc.63.8.856

19. Krystal JH, Kavalali ET, Monteggia LM. Ketamine and rapid antidepressant action: new treatments and novel synaptic signaling

mechanisms. *Neuropsychopharmacology*. 2024;49 (1):41-50. doi: 10.1038/s41386-023-01629-w

20. Lai R, Katalinic N, Glue P, et al. Pilot dose-response trial of i.v. ketamine in treatment-resistant depression. *World J Biol Psychiatry*. 2014;15:579-584. doi: 10.3109/15622975.2014.922697

21. Loo CK, Gálvez V, O'Keefe E, et al. Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. *Acta Psychiatr Scand*. 2016;134:48-56. doi: 10.111/acps.12572

22. Xu Y, Hackett M, Carter G, et al. Effects of low-dose and very low-dose ketamine among patients with major depression: a systematic review and meta-analysis. *Int J Neuropsychopharmacol*. 2016;19:1-15. doi: 10.1093/ijnp/pyv124

23. McGirr A, Berlim MT, Bond DJ, Fleck MP, Yathan LN, Lam RW. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. *Psychol Med*. 2015;45(4):693-704.
doi: 10.1017/S0033291714001603

24. McIntyre RS, Carvalho IP, Lui LMW, et al. The effect of intravenous, intranasal, and oral ketamine in mood disorders: meta-analysis. *J Affect Disord*. 2020;276:576-584.
doi: 10.1016/j.jad.2020.06.050

25. McIntyre RS, Rosenblat JD, Nemeroff CB, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. *Am J Psychiatry*. 2021;178(5):383-399.
doi: 10.1176/appi.ajp.2020.20081251

26. Alnefeesi Y, Chen-Li D, Krane E, et al. Real-world effectiveness of ketamine in treatment-resistant depression: a systematic review & meta-analysis. *J Psychatr Res*. 2022;151:693-709. doi: 10.1016/j.jpsychires.2022.04.037

27. Garel N, Drury J, Thibault Lévesque J, et al. The Montreal model: an integrative biomedical-psychedelic approach to ketamine for severe treatment-resistant depression. *Front Psychiatry*. 2023;14:1268832. doi: 10.3389/fpsyt.2023.1268832

28. Anand A, Mathew SJ, Sanacora G, et al. Ketamine versus ECT for nonpsychotic treatment-resistant major depression. *N Engl J Med*. 2023; 388(25):2315-2325. doi: 10.1056/NEJMoa2302399

29. European monitoring centre for drugs and drug addiction (EMDDA). European drug report 2024: trends and developments. www.emcdda.europa.eu, accessed on June 16th, 2024. doi: 10.2810/91693

30. Trimbos Institute. National Drug Monitor 2024. www.nationaledrugmonitor.nl, accessed on June 16th, 2024.

31. Short B, Fong J, Galvez V, Shelker W, Loo CK. Side-effects associated with ketamine use in depression: a systematic review. *Lancet Psychiatry*. 2018;5(1):65-78.
doi: 10.1016/S2215-0366(17)30272-9

32. Duman RS, Aghajanian GK, Sanacora G, Krystal JH. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med*. 2016;22(3):238-249. doi: 10.1038/nm.4050

33. Johnston JN, Kadriu B, Allen J, Gilbert JR, Henter ID, Zarate Jr CA. Ketamine and serotonergic psychedelics: an update on the mechanisms and biosignatures underlying rapid-acting antidepressant treatment. *Neuropharmacology*. 2023;226:109422. doi: 10.1016/j.neuropharm.2023.109422

34. Olsen DE. The subjective effects of psychedelics may not be necessary for their enduring therapeutic effects. *ACS Pharmacol Transl Sci*. 2021;4:563-567. doi: 10.1021/acsptsci.0c00192

35. Wolfson P, Vaid G. Ketamine-assisted psychotherapy, psychedelic methodologies, and the impregnable value of the subjective – a new and evolving approach. *Front Psychiatry*. 2024; 15:1209419. doi: 10.3389/fpsyt.2024.1209419

36. Sos P, Klirova M, Novak T, Kohutova B, Horacek J, Palenicek T. Relationship of ketamine's

antidepressant and psychotomimetic effects in unipolar depression. *Neuro Endocrinol Lett.* 2013; 34(4):287-93.

37. Luckenbaugh DA, Niciu MJ, Ionescu DF, et al. Do the dissociative side effects of ketamine mediate its antidepressant effects? *J Affect Disord.* 2014;159:56-61. doi: 10.1016/j.jad.2014.02.017

38. Lii TR, Smith AE, Flohr JR, et al. Randomized trial of ketamine masked by surgial anesthesia in patients with depression. *Nat Ment Health.* 2023;1 (11):876-886. doi: 10.1038/s44220-023-00140-x

39. Wolff M, Evens R, Mertens LJ, et al. Learning to let go: a cognitive-behavioral model of how psychedelic therapy promotes acceptance. *Front Psychiatry.* 2020;11:5. doi: 10.3389/fpsyt.2020.00005

40. Wolf M, Evens R, Mertens LJ, et al. Measuring psychotherapeutic processes in the context of psychedelic experiences: validation of the general change mechanisms questionnaire (GCMW). *J Psychopharmacol.* 2024;38(5):432-457. doi: 10.1177/02698811241249698

41. Gründer G, Brand M, Mertens LJ et al. Treatment with psychedelics is psychotherapy: beyond reductionism. *Lancet Psychiatry.* 2024;11 (3):231-236. doi: 10.1016/S2215-0366(23)00363-2

42. Brennan W, Belser AB. Models of psychedelic-assisted psychotherapy: a contemporary assessment and an introduction to EMBARK, a transdiagnostic trans-drug model. *Front Psychol.* 2022;13:866018. doi:10.3389/fpsyg.2022.866018

43. Reiff CM, Richman EE, Nemeroff CB, et al. Psychedelics and psychedelic-assisted psychotherapy. *Am J Psychiatry.* 2020;177(5):391-410. doi: 10.1176/appi.ajp.2019.19010035

44. Kaelen M, Giribaldi B, Raine J, et al. The hidden therapist: evidence for a central role of music in psychedelic therapy. *Psychopharmacology (Berl).* 2018;235(2):505-519. doi: 10.1007/s00213-017-4820-5

45. Mitchell JM, Bogenschutz M, Lilienstein A, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med.* 2021;27(6):1025-1033. doi: 10.1038/s41591-021-01336-3

46. Fonseka LN, Woo BK. Therapeutic role of psilocybin and 3,4-methylenedioxymethamphetamine in trauma: a literature review. *World J Psychiatry.* 2023;13(5):182-190. doi: 10.5498/wjp.v13.i5.182

47. Goodwin GM, Aaronson ST, Alvarez O, et al. Single-dose psilocybin for a treatment-resistant episode of major depression. *N Engl J Med.* 2022;387(18):1637-1648. doi: 10.1056/NEJMoa2206443

48. Evans J, Robinson OC, Ketzitzidou Argyri E, et al. Extended difficulties following the use of psychedelic drugs: a mixed methods study. *PloS One.* 2023;18(10):e0293349. doi: 10.1371/journal.pone.0293349

49. Graziosi M, Singh M, Nayak SM, Yaden DB. Acute subjective effects of psychedelics within and beyond WEIRD contexts. *J Psychoactive Drugs.* 2023;55(5):558-569. doi: 10.1080/02791072.2023.2255274

