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# Polish standard of treatment with racemic ketamine for patients with depressive disorders developed by a Working Group appointed by the National Consultant in the field of psychiatry

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**Summary**

The Polish standard of treatment with racemic ketamine for patients with depressive disorders was developed by a Working Group appointed by the National Consultant in the field of psychiatry.

Despite the wide range of available medications, as many as one-third of depressed patients do not respond to standard antidepressant treatment, raising the need for an ongoing search for new effective and safe therapies. In recent years, the possible role of overactivity of the glutamatergic system in the etiopathogenesis of depression has again attracted the attention of many experts. The possibility of using substances with a modulating effect on the gluta-

matergic system in the treatment of depressive disorders has been postulated, among others, the long-known anesthetic ketamine, which is a noncompetitive NMDA receptor antagonist. This paper summarizes the results of studies on the efficacy and safety of racemic ketamine (administered intravenously) in the treatment of patients with depressive symptoms in the course of both unipolar and bipolar affective disorder, and, meeting the expectations of many practicing psychiatrists wishing to broaden the range of therapies offered to their patients, presents recommendations on indications, contraindications, precautions and the treatment regimen itself with intravenous ketamine for patients with mood disorders.

**Key words:** racemic ketamine, depressive disorders, bipolar disorder

## Introduction

Depression is a serious medical and social problem. Despite the wide range of available medications, as many as one-third of patients do not respond to standard antidepressant treatment, which raises the need for a continuous search for new effective and safe therapies [1, 2]. In recent years, the possible role of overactivity of the glutamatergic system in the etiopathogenesis of depression has again attracted the attention of many experts [3-5]. The possibility of using substances with a modulating effect on the glutamatergic system in the treatment of depressive disorders has been postulated [6, 7], among others, the long-known anesthetic ketamine, which is a noncompetitive antagonist of NMDA receptors stimulated by L-glutamate [8]. In 2000, Berman and colleagues [9] first described rapid relief of depressive symptoms after just a single subanesthetic intravenous infusion of ketamine. In the following years, this finding was confirmed in a number of studies.

Ketamine administered intravenously in the dose range of 0.5-1.0 mg/kg has shown efficacy in reducing depressive symptoms and suicidal thoughts in both unipolar and bipolar depressed patients [8-12]. Both the *Canadian Network for Mood and Anxiety Treatments* (CANMAT) group recommendations [10] and international expert consensus statements [13, 14] emphasize the significant role of ketamine in the treatment of depressive disorders. However, despite its suggested efficacy in scientific studies, intravenous ketamine is still not registered for the treatment of patients with mood disorders. Ketamine and its racemic forms are a group of drugs opening up a new approach to treatment, based on effects on the glutamatergic system, allowing for a faster effect and bypassing the usual nuisance side effects of classic monoamine-based antidepressants.

Hence, to meet the expectations of many practicing psychiatrists wishing to expand the range of therapies offered to their patients, we present recommendations on indications, contraindications, precautions and the treatment regimen itself of intravenous ketamine for patients with mood disorders.

## Indications and choice of route of administration

Ketamine, along with its racemic forms, esketamine (S-ketamine) and R-ketamine, is available in many formulations, and its bioavailability varies depending on the route of administration. Bioavailability is highest for ketamine administered intravenously, reaching 100%. For intranasally administered esketamine, bioavailability is estimated to be around 30%-50%. Oral administration of ketamine has a fairly low and very unstable bioavailability of 10-20% [13, 15]. The dosing equivalence of intravenously administered ketamine and intranasally administered esketamine has not been definitively established. However, because intravenous racemic ketamine contains an equal molar ratio of S- and R-ketamine (arketamine), it is estimated that 0.5 mg/kg of ketamine approaches the bioavailability of approximately 56 mg of S-ketamine [15].

Ketamine is metabolized mainly by CYP3A4 and CYP2B6 to its main metabolite, norketamine. CYP3A4 demethylates esketamine at a faster rate than R-ketamine, and CYP2B6 metabolizes both isomers with equal efficiency [13, 15]. Drugs that induce cytochrome P450 (CYP)2B6 and CYP3A4 have the potential to decrease ketamine exposure, while drugs that inhibit these enzymes increase it. The elimination half-life is slightly shorter for racemic ketamine (2-4 hours) than for esketamine (5 hours) [13, 16]. Ketamine is a highly lipophilic compound by which it rapidly penetrates tissues, its plasma half-life being about 15 minutes [17, 18].

Note that glutamate-releasing antidepressants can oppose the antidepressant effect of ketamine when given concurrently. In a clinical study, 16 healthy volunteers were initially given lamotrigine (300 mg), followed by intravenous ketamine. It was observed that lamotrigine alleviated ketamine-induced dissociative symptoms [19, 20]. Similarly, lamotrigine has been shown to protect against ketamine-induced psychosis in an animal model [19, 21]. Although animal studies and clinical trials with small samples suggest pharmacodynamic interactions of ketamine not only with lamotrigine, but also with memantine (also an NMDA antagonist), clozapine, haloperidol and risperidone (attenuating effect of risperidone), the clinical significance of these interactions remains to be studied [19, 22]. However, benzodiazepines have repeatedly been shown to shorten the duration of ketamine's antidepressant effect [22]. Most conventional antidepressants can probably be combined with ketamine without compromising efficacy or increasing the burden of side effects [23].

Ketamine dosing regimens for treatment-resistant depression often focus on maximizing ketamine's bioavailability and limiting its first-pass metabolism, based on the assumption that ketamine's parent molecule is most important in the treatment of depression. However, it is important to note that ketamine's metabolites (including (2R,6R)-hydroxynorketamine-R-HNK) appear to play an important role in its antidepressant effects [18].

Although intranasal application of esketamine is a non-invasive, effective and fairly simple method, it can be associated with quite a bit of variability in the bioavailability of the drug between administrations. It should also be borne in mind that there

are a number of contraindications to intranasal application of the drug, i.e., frequent nosebleeds, nasal trauma, ulcers in the nasal cavity.

A large meta-analysis conducted by Bahji and colleagues [24], considering 24 clinical trials and representing a total of as many as 1,877 participants, showed that intravenously administered racemic ketamine, compared to intranasally applied esketamine, had higher overall response rates (Response Rate – RR = 3.01 vs. RR = 1.38) and remission rates (RR = 3.70 vs. RR = 1.47), as well as lower dropout rates (RR = 0.76 vs. RR = 1.37) [24]. No difference was shown in the context of evaluating the efficacy of racemic ketamine use between patients with treatment-resistant depression (TRD) and those with non-treatment-resistant depression (non-TRD) or depression in the course of bipolar disorder [24], indicating the validity of intravenous ketamine use in both uni- and bipolar depression.

Although intranasal esketamine in combination with SSRI/SNRI drugs is registered (FDA, EMA, National Health Service drug program) for the treatment of treatment-resistant depression (TRD) and has more long-term studies on larger numbers of participants, the evidence base to date would suggest recommending intravenous ketamine for treatment-resistant depressive disorders, as it is intravenous ketamine that has study-documented efficacy in treating depression in bipolar disorder (BD) [24]. Indeed, it is important to remember that bipolar features are an important risk factor for TRD.

The risk of manic or hypomanic syndrome symptoms following treatment with intravenous infusions of racemic ketamine of patients with a depressive episode in the course of BD is estimated to be low [18]. A review by Jawad et al. [25] found that only 2 studies (out of 10 analyzed) reported manic/hypomanic symptoms following ketamine infusions in patients with bipolar disorder. Diazgranados et al. [26] reported one patient in the ketamine group and one patient in the control group (intravenous saline) who developed manic symptoms after infusion out of 18 patients included in the study. Moreover, the actual study by Fancy et al. [27] described three patients (out of 66) with BD who developed hypomania after their third or fourth ketamine infusion. All of these patients were taking antidepressants concurrently with intravenous ketamine treatment [27], including bupropion, used in bipolar depression, as an antidepressant with lower phase-change potential [28]. It is therefore suggested to be cautious in patients with BD – using mood stabilizers and, if possible, discontinuing antidepressants before starting treatment with IV ketamine [18, 26]. Also, the profile of observed adverse events seems to be different in patients with bipolar depression, where dissociative symptoms are more frequently observed [29, 30].

The global safety and tolerability profile of intravenous ketamine in bipolar depression is good and, with optimized normothymic treatment, can be recommended for treatment in a general psychiatric unit [30, 31].

Particular caution in planning treatment with intravenous ketamine infusions for bipolar depression is necessary when there is a co-occurrence of cluster B personality disorder, where few reports indicate the possibility of developing or exacerbating

behavioral disorders while maintaining antidepressant effects. In such a situation, the benefits and risks of treatment should be weighed [32].

The use of intravenous ketamine in the treatment of bipolar depression appears to have a special role in the short-term and dynamic reduction of the severity of depressive symptoms, allowing further safe treatment to be planned outside the setting of a general psychiatric ward. In view of the frequently observed persistence of the course of bipolar depression, often complicated by suicidality, the approach of using intravenous ketamine infusions as a 'down-staging' strategy seems to be a valuable option for the practicing psychiatrist [33]. It has also been postulated that ketamine has a unique mechanism of action in bipolar depression relative to symptoms of anhedonia, an effect that occurs independently of the global antidepressant response [34].

Table 1 summarizes studies on the effectiveness of ketamine both as a stand-alone treatment (monotherapy) and in combination with other treatments [9, 26, 29, 32, 34-51].

Currently, racemic ketamine (like esketamine) is recommended as an adjunct treatment to existing pharmacotherapy [13, 18, 52].

## Dose

Studies on the use of i.v. ketamine in the dose range of 0.1 to 1.0 mg/kg of body weight suggest that higher doses (i.e., 0.5-1.0 mg/kg) are more effective compared to lower doses (i.e., 0.1-0.2 mg/kg) [45, 53]. However, the use of ketamine i.v. in the range of 0.5-1.0 mg/kg can be recommended. Doses below 0.5 mg/kg are subtherapeutic, and doses exceeding 1.0 mg/kg do not accumulate antidepressant effects [13], while causing a higher incidence of adverse events. However, it should be noted that some adverse events associated with ketamine treatment (e.g., increased blood pressure) are dose-dependent [54]. Experience with intravenous ketamine administration in adults with treatment-resistant depression (TRD) also indicates that higher doses of intravenous ketamine are associated with higher rates of treatment-related adverse events (e.g., dissociation) compared with lower doses (i.e., 0.75 mg/kg and 0.5 mg/kg, respectively) [55].

Studies have shown that the appropriate dose of intravenous ketamine for depression should be 0.5 mg per kilogram of body weight, administered slowly over a 40-minute infusion. In addition, for safety reasons in people with a high BMI, dosing based on calculated ideal body weight is suggested. One clinical suggestion would therefore be to limit the initial intravenous dose of ketamine to 50 mg in the first infusion, with cautious dose increases (based on clinical response and tolerability) with subsequent infusions to a maximum dose of 100 mg [56].

## Maintaining the antidepressant effect

One potential strategy for prolonging the duration of ketamine's antidepressant effect is to use its repeated infusions [41, 48, 52, 57]. In a study by Phillips and colleagues (2019) [48], 41 patients suffering from drug-resistant unipolar depression, while taking standard antidepressants, received a single, randomized, double-blind crossover infusion of ketamine or midazolam (an active placebo control), followed by six open-ended infusions of ketamine over two weeks. The researchers found that the antidepressant effect of repeated infusions was cumulative, and the severity of depressive symptoms decreased after each infusion. The 23 participants with a 50% decrease in MADRS score (classified as remission) received four additional weekly infusions to maintain the antidepressant effect [48]. Another double-blind, randomized, placebo-controlled study of ketamine administered intravenously twice a week and three times a week for four weeks similarly demonstrated the efficacy of repeated infusions in maintaining the antidepressant effect; no significant difference was observed between the different dosing frequencies [41].

A large meta-analysis published in the journal Lancet Psychiatry in the second half of 2022 considered 18 open-label studies, case series and case reports on maintenance intravenous ketamine treatment (a total of 222 patients with unipolar depression, bipolar depression or treatment-resistant schizoaffective disorder). The duration of intravenous maintenance treatment ranged from 4 weeks to as long as 5 years. Treatment frequency ranged from once daily to once every 12 weeks. Of the 76 patients who had an initial response to treatment, 55 (72%) showed a sustained response within the first 6 months. No difference in efficacy was observed when comparing the results of studies involving both unipolar and bipolar depressed patients. There is evidence even for the sustained therapeutic potential of intravenous maintenance treatment one year after the initial response to treatment [58].

Currently, intravenous ketamine is most often recommended in a regimen of 2 to 3 times a week for a period of 3 weeks. After this period, the doctor determines the response to treatment and the appropriateness of continuing treatment with ketamine (maintenance phase). In the maintenance phase, the frequency of infusions should be once a week to once every 4 weeks, and the goal is to extend the interval between infusions to as long as possible (usually monthly) if remission of depressive symptoms persists. This should be individualized based on patient response, tolerance and preference/availability. The duration of total treatment should not exceed 1 year [58, 59] (Fig. 1).

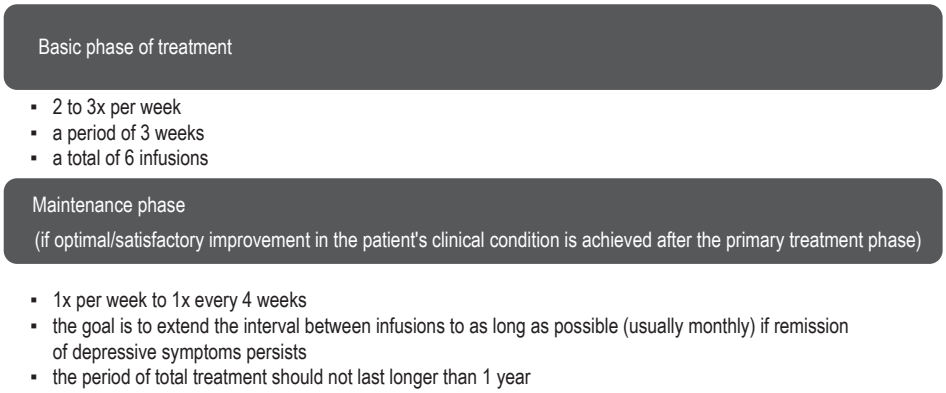


Figure 1. **Suggested treatment regimen with racemic ketamine ***

*Scheme should be individualized based on patient response, tolerance, and preference/availability.

## Safety and precautions

Although reports on the repeated use of ketamine in patients with chronic pain or recreational users have indicated that it carries risks of urologic toxicity, hepatotoxicity, cognitive deficits and dependence, studies on the use of ketamine in depressed patients have shown that the most common adverse effects of ketamine are generally transient, mild and self-limiting, which are related to the drug's metabolism and pharmacokinetics. They include dissociation, nausea, headache, elevated heart rate and blood pressure [60]. A possible explanation for this discrepancy is the relatively low doses and better-controlled conditions in most depression treatment programs. Second, in many studies, exclusion criteria for ketamine treatment included substance use disorders and unstable medical conditions, likely limiting the risk of increased or uncontrolled use with these potential side effects. Third, current data may be too limited or the follow-up time too short [58].

Feifel and colleagues [61], in their study of a sample of 6630 patients receiving repeated (but not necessarily maintenance) parenteral administration of ketamine for the treatment of depression, indicated that only 0.7% of patients experienced adverse effects that required discontinuation of ketamine. The most common cause was psychological discomfort during treatment. Other adverse events were extremely rare (such as bladder dysfunction (0.1%), cognitive decline (0.03%) and psychotic symptoms (0.03%). Among the 20 published reports of repeated parenteral ketamine treatment, the rate of significant adverse events resulting in treatment discontinuation was low (1.2%). The data suggest that long-term treatment of depression with ketamine is quite safe [61].

Although treatment with intravenous ketamine appears to be generally well tolerated and safe, due precautions must be taken.

It is not recommended to administer ketamine to patients [62, 63]:

- who are addicted to ketamine (6C4D.1 and 2 according to ICD-11 criteria);
- who are addicted to benzodiazepines (F13 according to ICD-10);
- who are taking benzodiazepines up to 72 hours before ketamine administration;
- who are addicted to alcohol or other substances (except nicotine) in the past six months;
- whose medical condition prevents them from taking ketamine;
- actually taking any of the following contraindicated medications: ketoconazole, voriconazole, itraconazole, fluconazole, erythromycin, telithromycin, clarithromycin, saquinavir, nefazodone, diltiazem, verapamil, theophylline;
- with a confirmed diagnosis of dementia;
- with a history of schizophrenia or schizoaffective disorder;
- with active eating disorders: anorexia nervosa or bulimia nervosa in the past 12 months;
- pregnant or unable to confirm the use of adequate contraception during the study;
- breastfeeding.

According to the Summary of Product Characteristics, ketamine is contraindicated in people who have an increase in blood pressure (current uncontrolled hypertension – systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 90 mm Hg) and in patients in whom an increase in blood pressure would pose a serious risk, in patients with eclampsia or preeclampsia, severe coronary artery disease or other severe myocardial disease, cerebrovascular incident or traumatic brain injury, or in cases of hypersensitivity to the active substance [63]. The presence of psychotic symptoms is also a contraindication to ketamine treatment [18], despite its good safety and tolerability profile [63, 64].

Although ketamine-induced cystitis (KIC) is a known complication of recreational ketamine use, only one case of its occurrence in a patient treated with ketamine for depression has been reported. However, regular screening for urinary symptoms is recommended for all patients treated with ketamine [64, 65].

Ketamine should be used with extreme caution in patients with cirrhosis or other types of liver dysfunction (it may be metabolized more slowly in such patients), with increased intraocular pressure (e.g., glaucoma), porphyria, a history of epilepsy, and respiratory tract infection (ketamine increases the cough reflex, which can cause laryngospasm). Above all, however, attention should be paid to the aforementioned risks associated with increased blood pressure [62].

Before starting treatment with ketamine, a package of laboratory tests is recommended: peripheral blood count, CRP, AST, ALT, creatinine level, urea level, ionogram, glucose level, TSH, urine drug test (toxicology), general urine test, betaHCG (for women of childbearing age), electrocardiogram (ECG) and internal medicine and

anesthesiology consultation. Assessment of blood pressure, pulse rate and saturation (according to the chart) is advisable [63-67]. It is important to remember to obtain the patient's informed written consent before starting treatment (consent template with patient information attached).

### Procedure for administration of racemic ketamine by intravenous route – scheme

(T – is the time of the start of the infusion)

**T-2 days or earlier:** Urine drug screens and pregnancy tests are taken.

Patient may not eat in the 6-hour period before ketamine administration, may drink clear liquids up to 2 hours before ketamine administration (clear liquid i.e., water, clear glucose solutions).

**T-60 min:** Establishment of intravenous route by a nurse or other qualified professional. Carry out: examination of vital signs (blood pressure, heart rate, respiratory rate and saturation), CADSS examination (for dissociative state) – as baseline measurements.

**T-0:** Provided that vital signs are acceptable and urine drug test and pregnancy tests are negative. Administer ketamine at a dose of 0.5 mg/kg by intravenous infusion using an infusion pump over 40 minutes. For patients with a body mass index >30 kg/m$^2$ to increase the safety profile, it is suggested to calculate the dose based on the patient's due weight rather than actual body weight, although studies in this area are inconclusive [68].

**T-0 to +40 min:** Monitor for sedation, dissociation and other possible adverse events.

**T+10 min, 20 min, 30 min and 40 min**: Vital parameters (as above, in 10 min increments).

When blood pressure is 20% higher than patient's baseline or reaches 160 systolic or 100 diastolic – slow down or stop ketamine supply. Additional criteria for stopping may include, but are not limited to, symptoms of sudden hypertension, the presence of shortness of breath, pallor, cyanosis, chest/jaw/shoulder pain, psychomotor agitation, and the patient's desire to complete the procedure.

To treat anxiety or unpleasant dissociative states usually intravenous lorazepam is administered (as needed, monitoring sedation).

**T+80 min:** Vital signs and check for cessation of sedation, dissociation and other possible side effects. A tool can be used to monitor the occurrence of side effects: Ketamine Side Effect Tool (KSET) [61, 66].

**T+120 min:** Vital signs, CADSS and assessment of readiness to leave the room for procedures (consider the modified Aldrete method).

Centers treating patients with mood disorders with intravenous ketamine should have appropriate equipment (infusion pump, cardiac monitor, anesthesia station) and access to anesthesia care in preparation for and during the procedure. The patient

should remain under medical supervision for a minimum of 2 hours after the end of the infusion.

Before discharge, the patient must return to a stable medical (including mental) state. Due to the psychotomimetic and cognitive effects of ketamine, patients must leave the treatment room accompanied by another person with standard instructions not to drive or operate equipment or heavy machinery for the rest of the day.

## Summary

To the present, racemic ketamine by intravenous infusion has yet to receive a positive opinion from the U.S. Food and Drug Agency (FDA) or the European Medicines Agency (EMA) for use in psychiatric patients, although numerous studies emphasize its legitimacy in patients diagnosed with a depressive episode in the course of both recurrent depressive disorder and bipolar affective disorder. They point to its rapid effect in reducing the severity of suicidal thoughts. It should be noted that research efforts are also underway to develop other drugs that interact with ionotropic and metobotropic receptors for glutamate [69].

Table 1. **Summary of studies on the use of racemic ketamine in depression**

| Study | Study group | Intervention | Results |
|---|---|---|---|
| Berman et al. 2000 [9] | Depression N = 9 | Monotherapy with racemic ketamine i.v. 0.5 mg/kg vs. placebo | Those with depression showed significant improvement in depressive symptoms within 72 hours after ketamine infusion, but not placebo (i.e., mean 25-point Hamilton Depression Scale scores decreased by 14 +/ – SD 10 points compared to 0 +/ – 12 points during active treatment and placebo, respectively). |
| Kudoh et al. 2002 [35] | Depression N = 70 | Racemic ketamine i.v. (1 mg/kg) administered during anesthesia (propofol, fentanyl) for surgery 1 mg/kg i.v. vs. anesthesia with propofol and fentanyl alone | The HDRS score in the group of patients who received ketamine 1 day after surgery was significantly ($p < 0.05$) lower than in the group of patients who did not receive it. |

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| Zarate et al. 2006 [36] | TRD depression N = 18 | After a 2-week drug-free period, racemic ketamine i.v. (0.5 mg/kg) vs. placebo | Those receiving ketamine showed a significant improvement in depression compared to those receiving placebo within 110 minutes after injection, which remained significant throughout the following week. The effect size for the drug difference was very large (d = 1.46 [95% confidence interval [CI], 0.91-2.01]) after 24 hours and moderate to large (d = 0.68 [95% CI, 0.13-1.23]) after 1 week. Of the 17 patients treated with ketamine, 71% met response criteria and 29% met remission criteria the day after ketamine infusion. Thirty-five percent of patients maintained their response for at least 1 week. |
| Diazgranados et al. 2010 [26] | TRD BD N = 9 | Patients maintained on therapeutic levels of lithium or valproate received an intravenous infusion of racemic ketamine (0.5 mg/kg) vs. placebo | Significant improvement within 40 minutes in the ketamine group compared with placebo (d = 0.52, 95% CI, 0.28-0.76); this improvement remained significant through Day 3. The effect size of the drug difference was greatest on Day 2 (d = 0.80, 95% CI, 0.55-1.04). 71% of patients responded to ketamine and 6% to placebo. One participant receiving ketamine and one receiving placebo developed manic symptoms. Ketamine was generally well tolerated; the most common adverse effect was dissociative symptoms, only at the 40-minute point. |
| Zarate et al. 2012 [37] | TRD BD N = 15 | Patients maintained on therapeutic levels of lithium or valproate received an intravenous infusion of racemic ketamine (0.5 mg/kg) vs. placebo | At the 40-minute time point, depressive symptoms, as well as suicidal thoughts, improved significantly in those receiving ketamine compared to placebo (d = 0.89, 95% CI = 0.61-1.16 and 0.98, 95% CI = 0.64-1.33, respectively); these improvements remained significant through Day 3. 79% of subjects responded to ketamine and 0% to placebo. The most common adverse effect was dissociative symptoms, which occurred only at the 40-minute time point. |

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| Sos et al. 2013 [38] | Depression N = 30 | Racemic ketamine (0.5 mg/kg b.w.) vs. placebo | Greater psychotomimetic symptom severity, as measured by the BPRS, during ketamine administration correlated with an easing of mood ratings over the following week, with a maximum on day seven. Ketamine was superior to placebo at all visits (days 1, 4 and 7) as assessed by the MADRS with effect sizes (Cohen's d) of 0.62, 0.57 and 0.44, respectively. |
| Murrough et al. 2013 [39] | TRD depression N = 72 | Monotherapy with racemic ketamine i.v. (0.5 mg/kg i.v.) vs. midazolam | The ketamine-treated group had a greater improvement in MADRS score than the midazolam-treated group 24 hours after treatment. After adjusting for baseline and site, the MADRS score was lower in the ketamine group than in the midazolam group by 7.95 points (95% CI: 3.20 to 12.71). The probability of response after 24 hours was higher for ketamine than for midazolam (odds ratio: 2.18; 95% CI: 1.21 to 4.14), with response rates of 64% and 28%, respectively. |
| Hu et al. 2016 [40] | TRD depression N = 27 | Racemic ketamine i.v. (0.5 mg/kg i.v.) + escitalopram vs. escitalopram + placebo | After 4 weeks, more patients treated with escitalopram + ketamine than those treated with escitalopram + placebo experienced response (92.3% v. 57.1%, p = 0.04) and remission (76.9% v. 14.3%, p = 0.001), with significantly shorter time to response (hazard ratio [HR] = 0.04, 95% CI: 0.01-0.22, p < 0.001) and remission (HR = 0.11, 95% CI: 0.02-0.63, p = 0.01). Compared with escitalopram + placebo, escitalopram + ketamine was associated with significantly lower MADRS scores from 2 hours to 2 weeks (peak = 3 days-2 weeks; effect size [ES] = 1.08-1.18), QIDS-SR scores from 2 hours to 2 weeks (maximum ES = 1.27), and QIDS-SR suicidality from 2 to 72 hours (maximum ES = 2.24). Only YMRS scores increased significantly with ketamine augmentation (1 and 2 h), with no significant increase in BPRS or CADSS. |

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| Singh et al. 2016 [41] | TRD depression N = 67 | Racemic ketamine i.v. (0.5 mg/kg i.v.) vs. placebo (two dosing regimens 2 or 3 times a week for 4 weeks) | In the twice-weekly dose groups, the mean change in MADRS score on Day 15 was – 18.4 (SD = 12.0) for ketamine and – 5.7 (SD = 10.2) for placebo; in the three-times-weekly dose groups, it was – 17.7 (SD = 7.3) for ketamine and – 3.1 (SD = 5.7) for placebo. Similar observations were noted for ketamine during the open-label phase (twice weekly, – 12.2 [SD = 12.8] on Day 4; three times weekly, – 14.0 [SD = 12.5] on Day 5). Both regimens were generally well tolerated. Headache, anxiety, dissociation, nausea and dizziness were the most common (≥20%) treatment-related adverse events. Dissociative symptoms were transient and resolved with repeated dosing. |
| Li et al. 2016 [42] | TRD depression N = 64 | Racemic ketamine i.v. (0.2 mg/kg b.w.) vs. racemic ketamine i.v. (0.5 mg/kg b.w.) vs. placebo | The rapid antidepressant effect of ketamine was associated with facilitated glutamatergic neurotransmission in PFC (Positron emission tomography F-FDG). |
| Grunebaum et al. 2017 [43] | Depression BD N = 16 | Racemic ketamine i.v. (0.5 mg/kg i.v.) vs. midazolam (0.02 mg/kg i.v.). Current pharmacotherapy was maintained. | The mean reduction in SSI after ketamine infusion was almost 6 points greater than after midazolam, although this was not statistically significant (estimate = 5.84, SE = 3.01, t = 1.94, P = 0.074, 95% CI: 0.65 to 12.31). The number needed to treat for response (SSI <4 and at least 50% below baseline) was 2.2, and for remission (SSI = 0) was 3.2. The strongest neurocognitive correlation was between memory improvement in the selective recall test (SRT) and reduction in SSI score on day 1 after ketamine (ρ = – 0.89, P = 0.007). A decrease in serum brain-derived neurotrophic factor (BDNF) before and after infusion correlated with a decrease in SSI from baseline to day 1 after ketamine (n = 5, ρ = 0.90, P = 0.037), but not with midazolam (P = 0.087). SSI – Scale for Suicidal Ideation |

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| Rybakowski et al. 2017 [44] | TRD BD N = 53 | Racemic ketamine (0.5 mg/kg body weight) | Thirteen men and 40 women participated in the study. All received at least one first- or second-generation normothymic drug. After a single infusion of ketamine, improvement after 7 days (Hamilton scale reduction of ≥ 50%) was found in 27 patients (51%), more often in men (77%) than women (43%). There was no correlation with type of bipolar disorder, age of onset, length of depression, family history of affective disorder or alcoholism, alcohol abuse, or type of normothymic treatment used. |
| Su et al. 2017 [45] | TRD depression N = 95 | Racemic ketamine i.v. (0.2 mg/kg b.w.) vs. racemic ketamine i.v. (0.5 mg/kg b.w.) vs. placebo | This study showed a significant dose-dependent effect of ketamine on Hamilton Depression Rating Scale (HAMD) scores. Response analysis (>50% reduction from baseline in HAMD on at least 2 days between days 2 and 5) also showed a significant dose-dependent effect (placebo: 12.5%, ketamine 0.2 mg/kg: 39.1%; ketamine 0.5 mg/kg: 45.8%). BDNF genotypes were included. |
| Grunebaum et al. 2018 [46] | TRD depression N = 80 | Racemic ketamine i.v. (0.5 mg/kg i.v.) vs. midazolam | The addition of intravenous ketamine to antidepressant treatment showed a clinically significant reduction in suicidal thoughts in depressed patients within 24 hours compared to midazolam, partly independent of the antidepressant effect. |
| Fava et al. 2018 [47] | TRD depression N = 99 | A single intravenous dose of ketamine 0.1 mg/kg, b.w. (N = 18) vs. a single ketamine dose of 0.2 mg/kg b.w. (N = 20) vs. a single ketamine dose of 0.5 mg/kg b.w. (N = 22) vs. a single dose of ketamine 1.0 mg/kg b.w. (N = 20) vs. a single dose of midazolam 0.045 mg/kg (active placebo) (n = 19) | Greater dissociative symptoms and transient increases in blood pressure at higher doses. The results suggest that there is evidence for the efficacy of 0.5 mg/kg and 1.0 mg/kg subanesthetic doses of intravenous ketamine and no clear or consistent evidence for clinically significant efficacy of lower doses of intravenous ketamine. |

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|---|---|---|---|
| Phillips et al. 2019 [48] | TRD depression N = 41 | Racemic ketamine i.v. (0.5 mg/kg i.v.) vs. midazolam | Compared with midazolam, a single infusion of ketamine produced a significantly greater reduction in depressive symptoms at the primary efficacy endpoint (24 hours after infusion). 59% of participants met response criteria after multiple infusions, with a median of three infusions required before a response was achieved. Participants reported no further changes in MADRS scores during weekly maintenance infusions. |
| Ionescu et al. 2019 [49] | TRD depression N = 26 | 6 infusions of ketamine (0.5 mg/kg over 45 minutes) vs. saline placebo for three weeks | During the infusion phase, there were no differences in the severity of depression or suicidal thoughts between placebo and ketamine ($p = 0.47$ and $p = 0.32$, respectively). At the end of the infusion phase, two patients in the ketamine group and one in the placebo group met criteria for depression remission. At three-month follow-up, two patients in each group met criteria for depression remission. |
| Correia-Melo et al. 2020 [50] | TRD depression N = 63 | Racemic ketamine i.v. (0.5 mg/kg, b.w.) vs. esketamine i.n. (0.25 mg/kg, b.w.). | Esketamine was no worse than ketamine in terms of TRD 24 hours after infusion. Both therapies were effective, safe and well tolerated. |
| Włodarczyk et al. 2021 [29] | TRD: MDD = 35 BD = 14 | Racemic ketamine (0.5 mg/kg b.w.) – 8 administrations over a 4-week period | Higher incidence of disordered events (dissociation, psychomimetic symptoms) in the bipolar depression group. Good safety and tolerability profile. Apparent antidepressant effect. |
| Wilkowska et al. 2021 [30] | TRD BD N = 13 | Racemic ketamine (0.5 mg/kg b.w.) – 7 administrations over a 4-week period | Good safety and tolerability profile. Apparent antidepressant effect (response in 61.5%; remission in 46.2%) |

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|---|---|---|---|
| Ekstrand et al. 2022 [51] | Depression<br>N = 186 | Racemic ketamine i.v. (0.5 mg/kg b.w.) vs. electroconvulsive therapy (ECT) | Among patients receiving ECT, 63% achieved remission compared to 46% receiving ketamine infusions (p = 0.026; difference 95% CI: 2%, 30%). Both ketamine and ECT required a median of 6 treatment sessions to induce remission. Serious and long-term side effects, including cases of persistent amnesia, were more common with ECT, while treatment-related side effects led to more treatment dropouts in the ketamine group. Among patients in remission, 70% and 63%, with a median of 57 and 61 days in remission, relapsed within 12 months in the ketamine and ECT groups, respectively (p = 0.52). |
| Gałuszko-Węgielnik et al. 2023 [63] | TRD – psychotic symptoms<br>MDD = 17<br>BD = 18 | Racemic ketamine (0.5 mg/kg b.w.) – 8 administrations over a 4-week period | Good safety and tolerability profile. Visible antidepressant effect. |
| Wilkowska et al. 2024 [34] | TRD<br>BD = 22 | Racemic ketamine (0.5 mg/kg b.w.) – 8 administrations over a 4-week period | Good safety and tolerability profile. Visible antidepressant effect and anti-anhedonic effect. |

N – number; p – statistical significance; SD – standard deviation; CI – confidence interval; SE – standard error; d – average deviation; HR – risk ratio; HDRS – Hamilton Depression Rating Scale; MADRS – Montgomery-Åsberg Depression Rating Scale; BPRS – Brief Psychiatric Rating Scale; QIDS – Quick Inventory of Depressive Symptomatology; SSI – Scale for Suicidal Ideation; YMRS – Young Rating Scale for Mania; CADSS – The Clinician-Administered Dissociative States Scale; PFC – prefrontal cortex; TRD – Treatment-resistant depression; MDD – Major depressive disorder (unipolar); BD – Bipolar disorder.

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## Supplementary material

Procedure Card
Informed Consent
Stamp of the unit/department

### PROCEDURE CARD

### TREATMENT WITH INTRAVENOUS INFUSIONS OF KETAMINE

**Infusion number:**
**Date:**
Referring physician (psychiatrist):
**Patient Data:**
Name:
PESEL:
Main Register No.:
Diagnosis:
Body weight: kg
Height: cm
BMI=
**Baseline parameters:**
**RR: HR: SpO2:**
Data of the anesthesiologist performing the procedure:
Ketamine dose*:
Start time of infusion (T)*: Time of end of infusion (T+40 min)*:

| Time | RR | HR | SpO2 | Side effects (+ use of additional drugs)* |
|---|---|---|---|---|
| T+10 min | | | | |
| T+20 min | | | | |
| T+30 min | | | | |
| T+40 min (after the infusion is complete) | | | | |
| T+80 min (40 min after the infusion is complete) | | | | |
| T+120 min (80 min after the infusion is complete) | | | | |
| T+160 min (2 hours after the infusion is complete) | | | | |

Time of completion of patient monitoring*:
Nurse supervising the patient:
* is filled out by the anesthesiologist

**Information for the Patient regarding treatment with intravenous ketamine infusions**

This form provides information on the use of intravenous infusions of ketamine to treat depressive disorders. Ketamine has been used as an anesthetic for years. The use of ketamine in lower, so-called "subanesthetic" doses to treat depression is a new, off-label use. It is usually used when other treatments have proved ineffective. Although ketamine is not formally registered for this indication, there are now many studies showing that it can be an effective and rapid treatment option for depression in both unipolar and bipolar affective disorder. Benefits can occur after just one treatment, although an initial course of several treatments is usually required for a stronger response. If improvement in the reduction of depressive symptoms is achieved after the initial course of ketamine therapy, the patient may receive further maintenance treatment. During the course of ketamine infusions, it is recommended that existing pharmacotherapy (with both antidepressants and mood stabilizers) and psychotherapy be continued, as ketamine therapy works best when it is part of an integrated treatment program. Participation is voluntary, and refusal and withdrawal of consent to participate in the study, without giving a reason, is possible at any time with no consequences.

Qualification process: Before starting treatment with intravenous ketamine, a psychiatrist will assess the indications and contraindications for its use, evaluate the severity of depressive symptoms, and order: a set of laboratory tests (including betaHCG and urine drug testing), electrocardiogram, measurement of blood pressure, heart rate, height and weight (to assess BMI). Each patient will be consulted with an internal medicine physician for a thorough evaluation of the clinical condition.

Important: The patient must not eat during the 6-hour period before undergoing ketamine infusion. The patient may drink clear liquids up to 2 hours before ketamine administration (clear liquids, i.e., water, clear glucose solutions, but not coffee, tea, juices, milk).

Procedure: One hour before the start of the infusion, a nurse or other qualified professional will insert a peripheral intravenous route (venflon) into the patient. He will also perform the following tests: measurement of blood pressure, pulse rate, saturation, CADSS scale test (for dissociative state) – as baseline measurements. Immediately before the procedure, the patient will be consulted by an anesthesiologist.

Provided that vital signs are within normal limits and the urine drug test and pregnancy tests are negative, the patient will receive ketamine at a dose of 0.5 mg/kg body weight by intravenous infusion using an infusion pump over 40 minutes. For patients with a body mass index >30 kg/m2, it is suggested that the dose be calculated based on the patient's due weight rather than actual body weight.

During the entire 40-minute infusion, the patient will remain under the care of an anesthesiologist. He will be monitored for sedation, dissociation and other possible adverse events. Every 10 minutes, vital signs (blood pressure, heart rate, saturation) will be assessed.

Common side effects, risk of occurrence greater than 1% and less than 10%:

- hallucinations;
- vivid dreams and nightmares;
- nausea and vomiting;
- increased salivation;
- dizziness;
- blurred vision;
- increased heart rate and blood pressure during infusion;
- depersonalization/derealization during infusion;
- change in motor skills.

These symptoms subside when the infusion is discontinued. If they are severe, another drug, such as a sedative, may be used to alleviate them.

Uncommon side effects, risk greater than 0.1% and less than 1%, also include: rash, double vision, pain and redness at the injection site, increased intraocular pressure, violent arm movements resembling seizures

The patient will remain under medical supervision for a minimum of 2 hours after the ketamine infusion ends. The patient must return to a stable medical condition (including mental status) before discharge. Due to the psychotomimetic and cognitive effects of ketamine, patients must leave the treatment room accompanied by another person with standard instructions not to drive or operate equipment or heavy machinery for the rest of the day.

Currently, intravenous ketamine is most often recommended in a regimen of 2 to 3 times a week for a period of 3 weeks. After this period, the doctor determines the response to treatment and the appropriateness of continuing treatment with ketamine (maintenance phase). In the maintenance phase, the frequency of infusions should be once a week to once every 4 weeks, and the goal is to extend the interval between infusions to as long as possible (usually monthly) if remission of depressive symptoms persists. This should be individualized based on patient response, tolerance and preference/availability. The duration of total treatment should not exceed 1 year.

## PATIENT INFORMED CONSENT FORM FOR TREATMENT WITH INTRAVENOUS KETAMINE INFUSIONS

I (name)..... certify that I have received and read the patient information. The investigator(s) have provided me with comprehensive answers to my questions. I am sufficiently informed.

YES NO

I have been informed that the treatment of depressive disorders with intravenous ketamine infusions is an "off-label" treatment, i.e., outside the drug's registration indications, but in accordance with current medical knowledge and standards issued by the National Consultant in Psychiatry.

YES NO

I conscientiously and voluntarily consent to treatment with intravenous ketamine infusions and know that I can withdraw my consent at any time without affecting the medical care I will need.

YES NO

Signatures: Date