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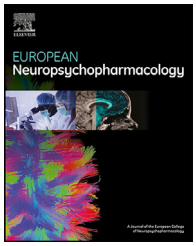

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REVIEW

Ketamine and esketamine for crisis management in patients with depression: Why, whom, and how?

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Abstract
Currently, only a limited number of interventions can rapidly relieve depressive symptomatology in patients with major depressive disorder or bipolar disorder experiencing extreme distress. Such crises, especially when suicide attempt or ideation is involved, are a major risk factor of suicide. Ketamine, a N-methyl-D-aspartate glutamate receptor antagonist, and its enantiomer esketamine rapidly reduce depressive symptoms in depressed patients with current suicidal ideation. Recently, esketamine has been approved for use in patients with depression at risk of suicide and for psychiatric emergency by major medical agencies in the United States and Europe, whereas ketamine is increasingly used off-label. However, there is currently limited guidance on why, when, and how to use these drugs in patients with depression to treat a crisis. In this review article, we provide a succinct overview of the cellular and molecular mechanisms of action of ketamine and esketamine, and of the functional brain changes following their administration. We also summarize the major clinical studies on ketamine and esketamine efficacy in patients experiencing a crisis (generally, suicidal ideation), and propose a profile of patients who can benefit most from such drugs, on the basis of neurobiological and

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clinical observations. Finally, we describe the administration mode, the efficacy and tolerability profiles, the side effect management, possible concomitant treatments and the issue of deprescribing.

1. Introduction

Ketamine, a glutamate receptor antagonist, is a versatile drug used in anaesthesiology, pain management, and most recently, major depressive disorder (MDD). The first ketamine trial in seven patients with MDD (Berman et al., 2000) was followed by studies on ketamine and its S enantiomer esketamine. Most of these studies were carried out in patients who are difficult to treat, or with treatment-resistant depression (TRD) (Phillips et al., 2019a; Popova et al., 2019) due to the risks related to ketamine utilization and its complicated history as a recreational drug. Twenty years later, esketamine has been approved for TRD by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (EMA, 2021; FDA, 2020). Treatment recommendations for the use ketamine and esketamine in TRD have been published earlier (McIntyre et al., 2021).

The first ketamine and esketamine trials in MDD excluded patients with suicidal ideation (SI), a frequent practice in depression trials. However, it was later reported that ketamine might be effective in patients with MDD and SI (Ballard et al., 2014). This was greeted with enthusiasm due to the currently limited repertoire of strategies for providing rapid relief to such patients. Indeed, it generally takes several weeks to observe the clinical response to selective serotonin reuptake inhibitors (SSRI) and serotonin and noradrenaline reuptake inhibitors (SNRI), the first-line treatment options for MDD. Moreover, treatment response is lower in patients with MDD and SI (Lopez-Castroman et al., 2016), further underlining the critical need for novel treatment strategies in such patients.

Therefore, several trials assessed esketamine in patients with MDD and baseline SI, and this led to the FDA approval of esketamine for the treatment of depressive symptoms in adults with MDD and active SI or suicidal behaviour (SB) (FDA, 2020). On the other hand, EMA approved esketamine for MDD and psychiatric emergencies, without specifying them, due to the lack of evidence on esketamine effect on SI (EMA, 2021). However, there is currently neither agreement nor guidance on how to best integrate ketamine and esketamine in the clinical care of patients with MDD and SI, SB, or other psychiatric emergencies. The present review summarizes the theoretical and empirical bases for their use and provide best practice suggestions.

2. Experimental procedures

We performed a narrative review of studies on the use of ketamine and esketamine in individuals with SI. It should be noted that this article is not meant to be an exhaustive review of the literature, which requires smaller scope and systematic approach, and, based on exact subject, have been published earlier (Siegel et al., 2021). To address the study aims, we searched the PubMed, PsycINFO and Google Scholar (first five pages) databases to identify articles in English or French languages published from 1 June 2010 to 1 June 2021 (updated in January 2022) using the broad terms "suicid*" AND "ketamine" OR "esketamine. Then, we carried out several individual searches for each predetermined section of the review by combining either "suicid*" and the following terms: "treatment", "intervention", "emergency" or "ketamine" OR "esketamine" AND "mechanism", "side effects", "tolerability", "efficacy". The first author screened the retrieved articles on the basis of their title and abstract, and then fully read all articles deemed eligible and hand-searched the reference lists of the selected original studies and review articles to identify additional relevant articles. When multiple studies were available on one subject, we selected based on the representability, which was judged based on the following criteria: type and quality of the methodology (good-quality systematic reviews were preferred to randomized controlled trials that were preferred to other type of studies), recency, sample size, impact (impact factor of the journal and number of citations), and preregistration.

2.1. Putative mechanisms of ketamine and esketamine antisuicidal action

SI and SB are complex and multifaceted phenomena that are interlinked with depression but not exclusive to it (Lengvenyte et al., 2021a). Although the mechanisms underlying effects of ketamine and esketamine in patients with MDD and SI are not fully understood and are beyond the scope of the current review, in brief, it seems that in patients with SI or SB, ketamine and esketamine use is justified by its effects on stress, chronic inflammation, and anhedonia-related brain alterations. The main mechanistic models of ketamine and its enantiomer esketamine action agree on rapid synaptogenesis and neural connectivity modulation that might underlie structural and functional changes, such as the white matter structure remodelling observed already at 24 h after ketamine infusion (Sydnor et al., 2020; Zanos et al., 2018). In addition, to the best-described action as non-competitive antagonism of the excitatory ionotropic N-methyl-D-aspartate receptors (NMDAR) which is implicated in the aforementioned neuroplasticity, other systems, including opioid, monoaminergic, muscarinic and cholinergic, have also been implicated and might contribute to its antisuicidal actions (Lengvenyte et al., 2019; Wu et al., 2021).

Individuals with SI and SB have been shown to have some distinct qualities from other depressed patients, such as higher rates of childhood adversity, impaired stress-response system, increased proinflammatory cytokine levels, anhedonia and impaired decision making, as compared to depressed patients without SI and SB history (Alacreu-Crespo et al., 2020; Angelakis et al., 2019; Ducasse et al., 2021; Perrain et al., 2021). Meanwhile, unlike with classical antidepressants, early life adversity and increased peripheral inflammation have been associated with a higher reduction of depressive symptomatology and SI following ketamine administration (O'Brien et al., 2019; Yang et al., 2015). Decreased levels of pro-inflammatory cytokines and anhedonia alleviation following ketamine administration also predict the acute and short-term antidepressant and anti-suicidal response to ketamine (Rodrigues et al., 2020; Zhou et al., 2020). In addition, several evidences suggest that ketamine might restore normal connectivity patterns between lim-

Table 1 Major clinical trials on the efficacy of intranasal esketamine in adults with MDD at imminent risk of suicide.

Author (country), years	Sample size (active/control), mean age,% women	Dosing, comparator	Outcome	Comment
Canuso et al. (US), 2018	68 (31/34), 35.9 years, 65.2%	84 mg twice/week, vs bitter placebo	Greater reduction in MADRS score in esketamine group at 4 and 24 h †, but not at 25 days. Significant SI reduction in esketamine group.	Phase II trial.
Fu et al. (international), 2020	226 (114/112), 39.3 years, 60.6%	84 mg twice/week, vs bitter placebo	Greater reduction in MADRS score in esketamine group at 4, and 24 h†, and up to day 25. No difference in SI.	Phase III trial.
Ionescu et al. (international), 2021	230 (115/115), 40.8 years, 59.9%	84 mg twice/week, vs bitter placebo	Greater reduction in MADRS score in esketamine group at 24 h†, and up to day 25. No difference in SI.	Phase III trial.

Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale (Montgomery and Asberg, 1979); MDD, Major depressive disorder; SI, Suicidal ideation.
†Primary outcome.

bic regions and higher-order cognitive networks, enhancing the top-down regulation (Dai et al., 2020; Gärtner et al., 2019).

3. Clinical studies on esketamine and ketamine efficacy in patients with depression and acute si or SB

3.1. Esketamine

Three trials – one phase II and two phase III - assessed the antidepressant efficacy of twice weekly fixed-dose intranasal esketamine 84 mg, added to the comprehensive standard-of-care, including initiation or optimization of antidepressant treatment (+/- augmentation with a second antidepressant, antipsychotic or mood stabilizer) or hospitalization, in patients with MDD and active SI with intent to die (Table. 1) (C.M. Canuso et al., 2018; Fu et al., 2020; Ionescu et al., 2020). The first dose was administered in the Emergency Department (ED) or after admission to an impatient unit – strategy generally used in patients with severe suicidal crisis. All three trials reported that esketamine outperforms a bitter intranasal placebo for depressive symptom reduction at 24 h post-administration. Conversely, the SI reduction observed in the phase II trial (C.M. Canuso et al., 2018) was not replicated in the two larger identical phase III trials (ASPIRE-I and ASPIRE-II) (Fu et al., 2020; Ionescu et al., 2020). Further post-hoc analyses that combined both double-blind randomized placebo-controlled phase III trials including 456 patients in total, further strengthened these findings, confirming that esketamine plus comprehensive standard of care rapidly reduced depressive symptoms in patients with MDD and active SI with intent to die. Notably, the effect was larger in patients with a history of SA (Canuso et al., 2021) – a group of patients whose symptoms tend to respond less to classic antidepressants (Lopez-Castroman et al., 2016).

While ASPIRE trials failed to show changes in SI resulting in a rather unexpected indication for depression in patients with MDD and current SI, several considerations should be taken into account. First, the primary outcome was depression symptomatology, and the study was not powered to measure SI. Second, all patients had active SI and two thirds of patients had prior history of SA, reflecting a very severe and possibly very particular patient population (Lopez-Castroman et al., 2016; Nobile et al., 2021). Third, three quarters of patients were using benzodiazepines – molecules that have been demonstrated to undermine the efficacy of ketamine (Andrashko et al., 2020). Fourth, given the risks when conducting research with patients with active SI and limited past experiences (patients with SI are historically excluded from antidepressant trials), all patients received extensive care, which included major factors of confusion – frequent and extensive contact with the healthcare professionals, introduction or adaptation of antidepressant medication and augmentation strategies, possibility to receive psychotherapy and, if needed, hospitalization (Olié et al., 2020). Interpersonal aspect is key in suicide pathophysiology (Chu et al., 2017). Indeed, maintaining connectedness with healthcare specialists after a suicidal crisis one of the best-replicated suicide prevention strategy (Doupnik et al., 2020), and outperforming it clinical trial settings might prove extremely difficult. Furthermore, SI tend to fluctuate heavily in a large proportion of patients (Kleiman et al., 2017), and catching them might prove to both be extremely difficult and not the best proxy for future risk of SI and SB. Indeed, SI decreased drastically in both groups, and remained so during the four weeks of double-blind phase (Fu et al., 2020; Ionescu et al., 2020). Furthermore, authors used a newly developed scale to measure SI and suicide risk (Suicide Ideation and behavior Assessment Tool (SIBAT) (Alphs et al., 2020)), which, while innovative and targeted at rapid SI changes, is not extensively used and is yet to prove its usefulness in research and clinical practice.

While esketamine is currently approved only for adults, but an ongoing study is assessing its effect in adolescents with MDD at imminent risk of suicide (Trials.Gov NCT03185819).

3.2. Ketamine

Unlike esketamine, ketamine is not an officially approved treatment option in psychiatry. However, it is widely used in many countries, and is the only putatively accessible option in low-resource countries. While the existing studies were not as rigorous as esketamine trials that underwent scrutiny to get the approval by medical agencies, they suggest that ketamine might provide benefit in some patients with SI. While there are no direct head-to-head comparisons of ketamine and esketamine, several systematic reviews and meta-analyses reported SI reduction after ketamine administration (Bahji et al., 2021; Lengvenyte et al., 2021b; Siegel et al., 2021; Witt et al., 2020), which was also reported to be comparable or even more significant as compared to the reduction following esketamine administration (Bahji et al., 2021; Siegel et al., 2021). To date, five relatively small randomized controlled trials evaluated the efficacy of a single dose of ketamine (40 mg intranasal, or 0.2-0.5 mg/kg intravenous) for SI reduction in patients with clinically significant SI with and without an established psychiatric diagnosis (Burger et al., 2016; Y. Domany et al., 2019; Domany and McCullumsmith, 2021; M.F. Grunebaum et al., 2018; Murrough et al., 2015). They all found lower SI scores in the ketamine group from few hours up to two days after ketamine administration, although the timeframe was heterogenous. Furthermore, a study in patients with TRD that performed an analysis with a subset of patients with baseline SI found that this antisuicidal effect was short-lasting, and recurrence of SI was extensive in patients that received either ketamine or placebo (Feeney et al., 2021). Only two studies reported reduction of the depressive symptomatology: the first one in adults who presented to the ED with SI irrespective of diagnosis (Domany and McCullumsmith, 2021), and the second one in patients with TRD and clinically significant SI (M.F. Grunebaum et al., 2018). See Table 2 for summary.

Beside the long-term efficacy, the ideal dosing regimen is still discussed, and the aim of an undergoing trial is to establish the efficacy of 90 mg intranasal racemic ketamine in adults with MDD at imminent risk of suicide (Trial.Gov NCT04669665).

Notably, bipolar disorder is associated with frequent and debilitating SI and SB. While esketamine was not investigated in patients with BD, three studies evaluated ketamine efficacy in BD (Diazgranados et al., 2010; Grunebaum et al., 2017; Zarate et al., 2012) (Table 3). However, only one of them included patients with significant baseline SI, and found a non-significant difference in SI and depressive symptomatology reduction between ketamine and midazolam (Grunebaum et al., 2017). The other two studies, of which the second was the replication of the first one, reported a swift reduction in depressive symptomatology following ketamine administration, compared with the inactive placebo (Diazgranados et al., 2010; Zarate et al., 2012). Only the second, larger study also found a significantly higher reduction in SI from 40 min to 3 days after ketamine administration (Zarate et al., 2012). It should be noted that a meta-analysis found higher antidepressant response rates in patients with BD than with MDD, and numerically higher improvement in SI after ketamine administration, as compared to placebo (Bahji et al., 2021).

Finally, data from real-world settings support ketamine effect on depressive symptom severity and SI (McIntyre et al., 2020). Several ongoing trials (Trial.Gov NCT04669665, NCT01944293, NCT04099771) on ketamine efficacy in patients with SI will hopefully elucidate the extent and duration of ketamine antidepressant and possibly, anti-suicidal effects in this patient group.

3.3. To whom? A patient in the emergency department

Mood disorders complicated by SI are common amongst patients presenting to the ED. In the US, esketamine is indicated for patients with MDD and active SI, while the EMA indication for MDD and psychiatric emergencies leaves more room for interpretation. Nevertheless, clinicians are faced with patients in crisis, often with a mixture of depressive symptoms, SI or SB, and frequently also with agitation, anxiety, or intoxication. Therefore, they must rapidly decide whether, when and how to prescribe (es)-ketamine and any other additional treatment(s)/care.

First, it should be established whether there is a psychiatric emergency. SI and SB should be assessed in all people arriving at the ED for emotional or behavioural problems because approximately 10% of all ED patients have or have recently experienced SI or SB, but many do not disclose this unless asked (Betz and Boudreaux, 2016). amongst the suicide risk screening tools, the self-reported Columbia-Suicide Severity Rating Suicidal Ideation (C-SSRS SI) subscale (Posner et al., 2011) is a valid tool to rapidly assess SI. Moreover, the presence of mood disorders should be investigated in all patients with SI or SB. SI and SB are neither sufficient nor necessary for the diagnosis of MDD, but have the strongest association with the global clinical severity of depression (Zimmerman et al., 2018). Appropriate validated depression screening tools include, but are not limited to:

1. Patient Health Questionnaire 9 (Kroenke et al., 2001), a brief, reliable self-rated screening instrument that can be used in ED.
2. Beck Depression Inventory Short Form (BDI-SF) (A. A. Beck et al., 1974), a tool tailored to detect moderate to severe depressive episodes and changes in depression severity, but might capture physical illness effects, if concomitant.
3. Quick Inventory of Depressive Symptoms-Self Rated 16 (QIDS-SR16) or Clinician Rated (QIDS-C) (Rush et al., 2003), a valid, Diagnostic and Statistical Manual IV criteria-based tool to measure the severity of nine major symptom domains.
4. Maudsley 3-item Visual Analogue Scale (VAS) (Moulton et al., 2020), a simple instrument that measures low mood, SI and anhedonia changes.
5. Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), the ten-item gold-standard clinician-rated scale to measure depressive symptomatology severity, focusing on core mood symptoms.
6. A structured version of the Hamilton Depression Rating Scale (Hamilton, 1960), a widely used scale focused on somatic symptoms. Despite its demonstrated reliability, it is criticized for poor psychometric properties.

Table 2 Major clinical studies on ketamine efficacy in patients with SI.

Author (country), years	Participants	Sample size (active/control), mean age,% women	Dosage, comparator	Outcome	Comment
Burger et al., 2016	Soldiers admissible to ED for depression and SI	41 (20/21), 21–43, 30%	0.2 mg/kg vs saline, single	Significant reduction in SI† and hopelessness with ketamine, but not saline.	Pilot study; only 10 patients analysed.
Domany et al., 2019	Adults at ED with clinically significant SI and depression	18 (9/9), 35.44, 44.4%	0.2 mg/kg vs midazolam, single	Lower MADRS-SI† with ketamine at 90–180 min. No significant reduction in BSS†.	Pilot study; 5-minute technique.
Domany and Cummum-smith, 2021	Adults at ED with clinically significant SI	30 (15/15), 35.44, 81.8%	40 mg intra-nasal vs saline, single	Lower MADRS-SI† and MADRS scores in ketamine group at 4 h. More patients without SI in ketamine group at 4 h. No significant difference in BSS score reduction.	Proof-of-concept. Patients with any clinical diagnosis. No group by time interaction in the linear mixed model.
Feeney et al., 2021	Adults with TRD	56 (40/16), 45.75, 50%	0.1, 0.5 or 1 mg/kg vs midazolam, single	Lower MADRS-SI score from day 1 to day 30 in ketamine group, with weakening effect from day 3†.	This trial was in TRD, and current analysis focused on patients with baseline SI
Murrough et al., 2015	Adults with mood/ anxiety disorder and clinically significant SI	24 (12/12), 42.4 (13.3), 66.7%	0.5 mg/kg vs midazolam, single	Lower BSS† with ketamine at 48, but not 24 h; MADRS-SI: lower in ketamine 24 h; MADRS and QIDS: no difference.	Pilot study
Grunebaum et al., 2018	Adults with TRD and clinically significant SI	80 (40/40), 39.6, 60.0%	0.5 mg/kg vs midazolam, single	Day 1: greater reduction in SSI† and the Profile of Mood States depression subscale with ketamine.	Anti-suicidal effect partly independent of antidepressant effect.

Abbreviations: BSS, Beck Scale for Suicidal Ideation, self-report (Beck et al., 1988); ED, Emergency Department; MADRS, Montgomery-Åsberg Depression Rating Scale (Montgomery and Asberg, 1979); QIDS, Quick Inventory of Depressive Symptoms (Rush et al., 2003) ; MDD, Major depressive disorder; SI, Suicidal ideation; SSI, Beck Scale for Suicidal Ideation, clinician-rated (Beck et al., 1979); TRD, Treatment resistant depression.
†Primary outcome.

Table 3 Major clinical studies on ketamine efficacy in bipolar depression.

Author (country), years	Participants	Sample size (active/control), mean age,% women	Dosage, comparator	Outcome	Comment
Grunebaum et al., 2017	Adults with BD, depression, and clinically significant SI	16 (7/9), 41.2, 62.5%	0.5 mg/kg vs midazolam, single	Not significantly greater reduction in SSI† and MADRS with ketamine at day 1.	Pilot study
Diazgranados et al., 2010	Adults with TRD BD, not at serious risk of suicide	9, 47.9, 66.7%	0.5 mg/kg vs placebo, single	Significant reduction in MADRS† within 40 min to 3 days.	Pilot study
Zarate et al., 2012	Adults with TRD BD, variable baseline SI	15, 46.7, 53.5%	0.5 mg/kg vs placebo, single	Significant reduction in MADRS† and MADRS-SI within 40 min to 3 days.	Replication study of the study by Diazgranados et al. Baseline SI was not an inclusion criterion.

Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale (Montgomery and Asberg, 1979); SI, Suicidal Ideation; SSI, Beck Scale for Suicidal Ideation, clinician-rated (Beck et al., 1979); †Primary outcome.

In patients with long-lasting depression despite the current treatment, a treatment resistance questionnaire, such as the Maudsley Staging Method for Treatment-Resistant Depression (Fekadu et al., 2009), should be used to establish whether TRD management must be started.

Alcohol misuse is associated with suicide reattempt within one year after the initial ED visit for a suicidal crisis (Arias et al., 2016). Paradoxically, such patients tend to be taken less seriously in the ED. Suicide risk and depression should be evaluated in all patients presenting for intoxication-related symptoms. Moreover, in all patients with psychiatric crisis the presence of acute intoxication should be always investigated by blood, breath, or urine testing because many people attempt suicide while intoxicated.

3.4. To whom not? Absolute contra-indications

1. Ketamine and esketamine induce a transitory activation of the sympathetic nervous system. This is generally mild and well-tolerated, but even moderate changes can be dangerous in some patient populations. Specifically, (es)-ketamine should not be administered to patients with underlying conditions that can worsen with blood pressure elevation, including unstable angina, aortic dissection, history of intracerebral haemorrhage, uncontrolled arterial hypertension, recent myocardial infarction, and history of aneurysms and arteriovenous malformations;
2. Prior hypersensitivity to ketamine, esketamine and their excipients;
3. Paediatric patients, due to lack of studies.

3.5. To whom might, but with precautions? Relative contra-indications and special concerns

1. In patients with elevated baseline blood pressure (>140/90 mmHg (Mancia et al., 2014)), risk-benefit ratio should be evaluated, and blood pressure should be corrected before (es-)ketamine administration if it is decided that benefit outweighs risks.
2. The risk-benefit ratio during pregnancy and breastfeeding should be discussed. The toxicity in humans is unknown, but preclinical models show deleterious effects on the nervous system development upon neonatal exposure (Zhang et al., 2020).
3. Severe hepatic and renal insufficiency: ketamine is metabolized by liver and excreted by kidneys. Prolonged effects on hepatic or renal function have not been reported when used at sub-anaesthetic doses, but evidences concerning its long-term use are limited, and ketamine has not been studied in patients with severely impaired liver or kidney function (Cohen et al., 2018).
4. Active alcohol intoxication and withdrawal: ketamine is safe in alcohol intoxication and withdrawal (Hopper et al., 2015; Wong et al., 2015). However, additive sedation should be considered, and it is advisable to wait until the end of the acute intoxication.
5. Use of other central nervous system depressants (e.g. benzodiazepines, antipsychotics, opioids): the decision should be taken for each individual patient in relation to the magnitude of the pre-existing sedation.
6. Substance use disorder, abuse or misuse: in psychiatry, ketamine is mostly known as an illegal substance, associated with rave culture. This contributed to the general suggestion that it should be contraindicated in individuals with substance use disorders (Cohen et al., 2018). However, a sub-anaesthetic dose might actually be beneficial, because preliminary studies showed that a single ketamine infusion, integrated with behavioural treatment, reduces alcohol and cocaine use (Dakwar et al., 2020; E. 2019). Ketamine is contraindicated in patients with ketamine abuse history.
7. History of primary psychotic disorder and current psychosis: a single infusion of subanaesthetic dose of ketamine does not exacerbate psychosis, and markedly improves depressive symptoms in patients with depres-

sion and history of psychosis (Pennybaker et al., 2017). On the basis of the theoretical risk of psychosis exacerbation, ketamine should be avoided until psychosis resolution in patients with active symptoms. The risk-benefit ratio should be individually discussed in patients with psychosis history.

8. Factors that might exacerbate sympathomimetic side effects: patients with pheochromocytoma and uncontrolled hyperthyroidism might experience more severe cardiovascular effects and anxiety. In patients taking psychostimulants or monoamine oxidase inhibitors, blood pressure should be monitored closely. For the same reason, stimulants, including caffeine, should be avoided before administration.
9. Weak relative contraindications: low level of evidence suggest increased risk in patients with elevated intracranial and intraocular pressure, brain tumour and traumatic brain injury, acute globe injury and glaucoma (Cohen et al., 2015; Drayna et al., 2012).
10. Age: current data does not support long-term safety differences, as demonstrated by age-stratified long-term safety analysis of esketamine trials in TRD (Ochs-Ross et al., 2021). However, when working with extremely ill populations, general precaution should always be taken, esketamine, like many antidepressants, has a boxed warning for increased risk of SI in young adults, and older patients (>65 years of age or with ageing-accelerating comorbidities, such as obesity and diabetes) should be carefully monitored due to the theoretical risk of occult coronary disease.
11. Lack of capacity to consent.

3.6. Concomitant treatment(s)

Due to its short-term efficacy, (es-)ketamine should be combined with traditional antidepressant agents (SSRI or SNRI). This approach does not seem to affect the safety of the concomitantly used standard antidepressants (Andrade, 2017). Moreover, a study in a rat model of depressive behaviour found that combining ketamine with traditional antidepressants accelerates neuroplasticity events and increases the antidepressant efficacy in reducing stress-induced anxiety (Melo et al., 2015).

Patients in crisis frequently are treated with benzodiazepines or antipsychotics for symptom management. Concomitant benzodiazepine treatment at higher doses interferes with ketamine antidepressant effect (24 h of observation) (Andrashko et al., 2020). Mechanistically, benzodiazepines act as allosteric GABA-A receptor agonists on GABAergic neurons, possibly antagonizing ketamine effect on GABAergic interneurons. They also decrease ketamine psychotomimetic effects (MacPherson et al., 2008). Some studies suggest that the intensity of psychotomimetic and dissociative symptoms during ketamine infusion is linked to its antidepressant effect; however, this claim was not confirmed in subsequent ketamine and esketamine trials (Ballard and Zarate, 2020; Chen et al., 2022). Meanwhile, data from esketamine trials in MDD with SI showed higher rates of sedation in benzodiazepine users versus non-users, but no difference in antidepressant effect (Diekamp et al., 2021).

Anti-glutamatergic anticonvulsive drugs (e.g. lamotrigine) also attenuate ketamine acute neuropsychiatric effects (Deakin et al., 2008) and its action on brain functions that might explain its antidepressant effects (Abdallah et al., 2017). Similarly, antipsychotic drugs counteract ketamine effects on hippocampus and dissociation, and might undermine its effects on depression (Rame et al., 2017).

Based on this data and good clinical practice, chronic benzodiazepine, anticonvulsant or antipsychotic regimens should not be stopped/modified when starting (es-)ketamine because acute withdrawal might be dangerous and undermine the treatment effects. However, they should also not be initiated and dose should not be increased at ketamine or esketamine treatment start.

3.7. How to: initial screening and drug administration

Concerning ketamine risk profile, the physical evaluation should include an assessment of cardiovascular and kidney symptoms (e.g. interstitial cystitis symptoms) (Sirinian et al., 2005). Besides routine blood counts, baseline physical measures should include blood pressure, urine screening for psychoactive substances, urine proteinuria and haematuria, and if clinically indicated, pregnancy test and electrocardiography.

After the initial evaluation, patients should be informed about the possible side effects, with a special focus on common transitory psychotomimetic effects that are not dangerous. The first experience of altered consciousness might be daunting, especially when a patient is undergoing a psychological crisis, and general reassurance might help to alleviate the treatment-related anxiety.

Patients should receive ketamine by a qualified nurse or self-administer intranasal esketamine under the direct supervision of a healthcare provider. Due to the risk of nausea solid food and liquids should be avoided at least 2 h and 30 min, respectively, before the drug administration. Then, patients are monitored for at least 120 min in a low-stimulation environment that may help to mitigate the unpleasant emergence of dissociative phenomena and psychotomimetic side effects. Patient-selected or clinician-proposed music might be used to alleviate the distress related to dissociative phenomena (Greenway et al., 2021).

Patients can self-administer esketamine in medically-supervised healthcare settings. Each nasal-spray device contains 28 mg of esketamine delivered in two sprays (one to each nostril). A typical dosing regimen is 84 mg (three devices, administered at 5-minute interval) twice per week for four weeks, and possible treatment prolongation after benefit evaluation. If poorly tolerated, the dose can be reduced to 56 mg. It should be noted that the intranasal delivery of esketamine may pose problems for some patients with nasal cavity problems. Patients with previous failure to administer the drug, or severe nasal malformation/infection might not benefit from esketamine. Patients are invited to blow their nose and to put the head in a semi-reclined position to administer the drug. In the US, esketamine is available only through a Risk Evaluation and Mitigation Strategy programme, in which the drug is sold to certified medical

offices for specific patients who are enroled in a registry (FDA, 2020).

Ketamine is not approved for mental disorders and SI. Therefore, the proposed regimens are tentative. Currently, ketamine must be administered by a licensed medical professional. While the optimal dose is not established, the most commonly used regimen in depression trials is 0.5 mg/kg of body weight infused over 40 min. For patients in crisis, a single 0.5 mg/kg dose is generally proposed. This dose outperformed 0.2 mg/kg in reducing depressive symptomatology in TRD (Su et al., 2017). A dose-response relationship has been observed in depressed adults with ketamine doses ranging from 0.1 to 0.5 mg/kg, and the highest dose led to the highest reduction of depressive symptoms (Milak et al., 2020). In obese patients, the dosage might be calculated according to the ideal body weight because these patients are more likely to experience cardiovascular side effects (Wan et al., 2015). Moreover, a single intranasal administration of 40 mg ketamine reduced SI in ED patients in one trial (Domany and McCullumsmith, 2021), and an 80 mg dose is under investigation (NCT04669665).

3.8. Pharmacokinetics: special concerns

Ketamine is metabolized extensively in the body by CYP2B6- and CYP3A4-mediated N-demethylation to norketamine that is converted to other metabolites (Zanos et al., 2018). Multiple drugs and also grapefruit juice interact with these enzymes. Meanwhile, intranasal esketamine is absorbed directly through the vascular system of the nasal cavity, and is not metabolized in liver. Esketamine reaches the maximum plasma concentration within 10–15 min after administration (Fanta et al., 2015). Ketamine enantiomers and metabolites are secreted in the urine (Cohen et al., 2018).

Older adults have decreased hepatic blood flow, resulting in higher maximum concentrations of ketamine and norketamine (Perez-Ruixo et al., 2020). Higher drug concentrations have also been reported in non-Japanese and Japanese Asians. Non-Japanese Asian ancestry has been related to slower elimination than in non-Asians, and Japanese origin has been linked to a significantly higher nasal absorption (Perez-Ruixo et al., 2020). However, there is currently no evidence that these age- or race-related differences correspond to efficacy and safety changes at sub-anaesthetic doses. For precaution, in patients older than 65 years or of Asian origin, the starting dose should be halved, with further dose changes in function of the treatment response and side effects.

3.9. Prediction of the treatment response

Currently, there is no well-established predictor of the response to ketamine or esketamine. However, some traits and states are emerging as putative predictors. Generally, longer duration of the current episode, higher degree of treatment resistance, and chronic history of SI and SB predict worse response (Ballard et al., 2018; Ana C. Ana C. Lucchese et al., 2021; Niciu et al., 2014). Studies reported that high body mass index predicts ketamine response (Chen et al., 2020), but this was later challenged (Dale et al., 2020). One study reported that lower baseline level of adiponectin, which improves insulin sensitivity and has potent anti-inflammatory effects, predicts ketamine antidepressant efficacy (Machado-Vieira et al., 2017). Moreover, patients with positive family history of alcohol use disorder respond better to ketamine used as antidepressant (Rong et al., 2018).

In addition, unlike what observed with traditional antidepressants, the response to ketamine is higher (Ionescu et al., 2014; Liu et al., 2019) or similar in patients with high baseline anxiety (Wang et al., 2019) or anxiety disorder as comorbidity (Ana C Ana C. Lucchese et al., 2021). Higher baseline insomnia also predicts better antidepressant response to ketamine (Liu et al., 2020). Finally, higher baseline anhedonia might not only predict better antidepressant response, but its reduction might contribute to ketamine antidepressant and anti-suicidal efficacy (Rodrigues et al., 2020).

Results are conflicting about the influence of sex in ketamine response, with some studies showing better antidepressant response in men, but not others (Freeman et al., 2019). Men seem to experience significantly more depersonalization and amnestic symptoms than women after ketamine administration, a phenomenon that decreases with age and might be related to delayed brain maturation in men compared with women (Derntl et al., 2019).

Finally, data on the role of dissociation in ketamine antidepressant effects are contradictory. Although in some studies dissociation has been linked to better response (Mathai et al., 2020), dissociation and the antidepressant effects might be two co-occurring phenomena, and dissociation might not be necessary for reducing depressive symptoms (Ballard and Zarate, 2020). Early response, demonstrated by the rapid reduction of anhedonia and depression symptoms, predicts further antidepressant effect (Murrough et al., 2015; Zhou et al., 2020). Conversely, treatment-emergent anxiety is associated with poorer response (Aust et al., 2019).

3.10. Clinical efficacy: what to measure

Rapid modifications and possibly high placebo effect hinder our ability to detect meaningful clinical changes. The following non-exhaustive list includes some validated depressive symptomatology assessment tools that might be used for treatment response monitoring:

1. QIDS-SR16 (Rush et al., 2003), a scale that measures a range of mood and somatic depression symptoms and is responsive to clinical changes in depressed patients.
2. Maudsley 3-item VAS (Moulton et al., 2020), a short and simple instrument for the quick assessment of core depressive symptoms, including SI.
3. MADRS (Montgomery and Asberg, 1979), a tool that is particularly sensitive to treatment changes, and can therefore be used to measure treatment response.
4. BDI-SF (A. A. Beck et al., 1974), a tool for long-term outcome evaluation, but is less sensitive to rapid changes.

SI can be partly evaluated with specific items from depression measurement tools. The MADRS suicidal ideation item score (from 0 to 6) is sensitive to SI changes, and has

been used in ketamine trials (Ballard et al., 2015). However, in suicidal patients, a more extensive SB assessment might be preferred with a tool from the following list:

1. Sheehan-Suicidality Tracking Scale (Preti et al., 2013), a concise, sensitive 8-item scale to monitor SI changes in response to treatment.
2. Beck Scale for Suicidal Ideation, self-report (Beck et al., 1988) or clinician-rated (Beck et al., 1979), a validated and widely used scale that can measure baseline SI and the long-term changes in response to treatment. It is less useful for measuring the immediate effects because it conflates trait and state factors and because the first five questions assess the approach towards death and largely determine the overall score.
3. C-SSRS SI (Posner et al., 2011), a brief tool that focuses on the past week and has been successfully used in ketamine efficacy evaluation (Ionescu et al., 2019).

Other symptom evaluation tools might be used to thoroughly assess the clinical efficacy. As it has been reported that changes in anhedonia play an important role in ketamine response (Delfino et al., 2021; Rodrigues et al., 2020), this symptom category can be measured separately with a specific tool, such as the widely used 14-item Snaith-Hamilton Pleasure Scale that assesses baseline impairment and acute changes (Snaith et al., 1995), and the Dimensional Anhedonia Rating Scale (Rizvi et al., 2015) that is considered to have high sensitivity and validity, but is not yet available in many languages. Crisis-related symptom changes can be measured with the Beck Hopelessness Scale (Beck et al., 1974b)() that assesses attitudes towards the future and could be used to identify the suicide risk and observe treatment-emerging changes in cognitions regarding the self and future. To complement the depression measurement with the Maudsley 3-item VAS (Moulton et al., 2020), patient-experienced psychological pain can be measured with a psychological pain VAS (Olié et al., 2010). Changes in rumination can be measured with the Ruminative Response Scale (Treynor et al., 2003) that is responsive to ketamine administration (Vidal et al., 2020).

3.11. Safety concerns

In general, sub-anaesthetic doses of ketamine and esketamine are relatively safe (Short et al., 2018). The incidence and severity of side effects following ketamine and esketamine administration are dose-dependant, and those observed at the sub-anaesthetic doses used in psychiatry are transient and self-limiting, generally fully resolving within two hours (Acevedo-Diaz et al., 2020). Although no extensive direct comparison has been made, esketamine and ketamine in subanesthetic doses have been described to have a similar side effect profile in indirect comparisons (Ceban et al., 2021; Vankawala et al., 2021). Currently, there is no widely used tool to monitor side effects. A ketamine side effects tool (KSET) is under evaluation, and should soon become available (Short et al., 2020). It includes patient evaluation at selection, baseline, immediate, and delayed after-treatment phases. Meanwhile, esketamine (Spravato ®) has the ongoing Risk Evaluation and Mitigation Strategy (REMS) to mitigate potential risks of serious adverse outcomes associated with sedation, dissociation, and misuse/abuse. This requires the drug to be administered in a healthcare setting, and for patients to be monitored for resolution of sedation, dissociation and changes in vital signs for at least two hours.

3.11.1. Acute psychiatric side effects: monitoring and management

Dizziness is the most common (one third of patients) side effect, followed by short-lasting psychotomimetic effects (generally experienced as dissociation, perceptual disturbances, feeling weird or strange, including depersonalization and derealization) (Canuso et al., 2021; Ceban et al., 2021; Sapkota et al., 2021; Short et al., 2018). Dissociative symptoms can be measured with a simplified Clinician Administered Dissociative Symptom Scale (CADSS-6) (Rodrigues et al., 2020), a tool, that is sensitive to dissociation experienced by patients receiving ketamine. Alternatively, the depersonalization subscale of the Clinician-Administered Dissociative States Scale (CADSS) can be used. It should be noted that dissociation severity decreases with the subsequent administrations (McIntyre et al., 2020).

To mitigate psychiatric side effects, patients should be informed and reassured that most side effects, notably dissociation, are transient and inherent to the administered drug. However, in patients with intolerable psychiatric side effects, a medical professional should be available to start pharmacological management, if necessary. Psychotomimetic and anxiety side effects that emerge shortly after ketamine administration can be significantly reduced or eliminated with benzodiazepines or antipsychotics that alleviate the excessive stimulation of cortico-limbic neurons (Giannini et al., 2000; MacPherson et al., 2008). For emergency purposes, a small dose of a benzodiazepine (single dose, for instance up to 10 mg of diazepam) or antipsychotic drug (e.g. up to 5 mg of haloperidol) can be administered. Moreover, dissociative and psychotomimetic effects are dose-related, and dose reduction can help to mitigate these side effects in future administrations (Cooper et al., 2017).

Other reported psychiatric side effects include transient anxiety, mild agitation, irritability, euphoria, delusions, panic attacks, and apathy (Short et al., 2018). In addition, deleterious effects on attention, working memory and executive function have been reported to disappear within one day (Davis et al., 2021). Patients should be informed that they may feel tired on administration day, and should not drive, sign documents, or care for vulnerable individuals. To avoid excessive sedation, alcohol should also be avoided on administration day.

3.11.2. Acute somatic side effects: monitoring and management

Due to sympathetic activation, ketamine and esketamine frequently induce a mild, dose-dependant and self-limiting asymptomatic blood pressure elevation (10–15 mmHg above the baseline values) and increases the heart rate by 5 beats/min on average. These effects normalize within two hours and are observed after each administration (Vankawala et al., 2021). Other cardiovascular side effects include transitory palpitations and chest pain or pressure, blood pressure drop, and arrhythmia (Short et al., 2018).

Given the increased risk of transient cardiovascular changes, monitoring should be put in place, with blood pressure and heart rate measurement before and at 40 min after the drug administration, and then until values are back to normal. If clinically indicated (hypertension, past hypertensive response to ketamine, > 55 years of age), blood pressure should be measured more frequently, ideally every 15-20 min. Generally, blood pressure increase generally starts immediately after administration, peaks at 30-60 min, and resolves within 2-4 h (Liebe et al., 2017). However, if it remains elevated, acute blood pressure management should be delivered, based on local guidelines. Finally, while severe side effects are unlikely, as a general precaution and in accordance with previous recommendations (Sanacora et al., 2017), haemodynamic (electrocardiogram, blood pressure) and respiratory monitoring (end-tidal carbon dioxide and oxygen saturation), as well as an on-site clinician who can manage emergency situations, such as respiratory depression, should be available during ketamine, while esketamine administration requires only the latter.

Headache, numbness, sedation and drowsiness, faintness, vertigo, blurred vision, dry mouth, body temperature changes, hypaesthesia and nausea also have been reported as common side effects of both ketamine and esketamine (Acevedo-Diaz et al., 2020; Canuso et al., 2021; Ceban et al., 2021; Short et al., 2018). These side effects are largely transient, and disappear within four hours post-administration. If needed, they can also be managed symptomatically.

3.11.3. Long-term side effects: what to expect and best practices

Due to its history of street use, ketamine is considered as a drug of abuse. When used in larger doses recreationally, ketamine is recognised to have withdrawal effects, such as dysphoria, fatigue, poor appetite, and anxiety (Chen et al., 2014). Furthermore, ketamine and esketamine side effects (dissociation, relaxation) may be sought after for abuse. Pharmacovigilance database analysis regarding esketamine has also identified reports on tolerance, withdrawal syndrome, drug dependence and misuse (Baudot et al., 2021). However, the abuse potential of sub-anaesthetic doses of ketamine and esketamine have never been systematically demonstrated, and ketamine might actually be beneficial in individuals with substance use disorder (Dakwar et al., 2020). In support, repeated low-dose ketamine does not increase the abuse potential of ketamine-seeking behaviour in rats (Wright et al., 2019). Although ketamine and esketamine use in the clinic seems unlikely to cause addiction in most patients, clinical precaution requires careful monitoring of any signs of misuse and abuse behaviours, including drug-seeking behaviours, and treatment should be promptly stopped if such tendencies are detected. In case of esketamine, such concern is partly addressed via implementation of the REMS program, as the patient takes the medication in supervised environment. However, it does not prevent patients from looking for ketamine or esketamine illegally outside healthcare settings, and such risk should be evaluated.

Another concern related to ketamine use is its possible urogenital toxicity, as suggested by the observation of cystitis, dysuria, urinary urgency, haematuria, and male erectile dysfunction in chronic ketamine abusers (Popova et al., 2019; Yang et al., 2018). While systemic evidence regarding urogenital toxicity of subanesthetic doses of ketamine and esketamine (Ng et al., 2021), some authors have pointed to high rate of bladder effects reporting in esketamine trials (Horowitz and Moncrieff, 2021). Until better evidence, the appearance of genitourinary symptoms during treatment should be actively investigated, and treatment discontinuation considered upon their emergence.

Studies in rodents and in long-term ketamine abusers have highlighted cognitive function impairment. Currently, there is no evidence that the controlled administration of sub-anaesthetic doses of ketamine or esketamine for depression treatment causes long-term cognitive impairment; however, studies often do not report long-term side effects (Short et al., 2018). Therefore, clinicians should monitor cognitive function alterations in case of prolonged treatment regimens.

Finally, despite esketamine being used an antisuicidal agent, "treatment emergent" SI and SB have also been reported in long-term TRD trials that included patients without baseline SI, notably, with 15% of patients reported new-onset SI during the 48-week maintenance phase in the long-term open-label safety assessment (SUSTAIN-2) (Wajs et al., 2020). In addition, first-year post-marketing surveillance since esketamine approval by the FDA showed a 24-fold increased risk of spontaneous reports of SI emergence and 6-fold increased risk for suicide for esketamine compared with other medications (Gastaldon et al., 2021). While these observations might represent increased vigilance given to this novel substance and events associated with other older substances are underreported, it also underlines the need for continuous suicide risk assessment and, when needed, implementation of other evidence-based interventions targeted at suicide risk reduction.

3.12. After. Considerations on when to stop and approaches to extend the efficacy of ketamine and esketamine

The major unresolved question is how long should ketamine and esketamine be used for this indication and when and how it is safe to stop them. There are virtually no long-term data on long-term outcomes of ketamine and esketamine use in patients with MDD and SI. In the TRD (which is a different indication and a poor proxy – yet, the only one in which esketamine has been studied long-term), one long-term trial (SUSTAIN-I) showed negative results after exclusion of the outlier centre (Turner, 2019). In another (SUSTAIN-II) open-label trial, which focused on relapse prevention, authors reported that half of patients relapsed in the first four weeks after ketamine cessation. While the study reported no withdrawal symptoms associated with esketamine, some authors have expressed concern, as withdrawal symptoms, reported with physician withdrawal checklist largely overlap with the items of depression measures, such as insomnia, depression, fatigue, and lack of appetite (Horowitz and Moncrieff, 2021).

There is no robust data on prescription duration of ketamine and esketamine. Results from esketamine ASPIRE tri-

als showed that stopping esketamine after four weeks of active treatment was relatively safe, and there were no apparent patterns suggestive of rebound during the next two months when adequate care was continued (Canuso et al., 2021; Fu et al., 2020; Ionescu et al., 2020). We suggest that the one-month timeframe should be used to implement other evidence-based suicide risk management strategies, such as safety planning, care coordination, and brief contact interventions (Doupnik et al., 2020). In addition, following the response to the acute-phase treatment, psychotherapy should be considered in all patients because it might allow leveraging (es-)ketamine-induced neuroplasticity. For instance, it has been shown that cognitive behavioural therapy strengthens ketamine antidepressant efficacy and might sustain the initial antidepressant effect after initial treatment with ketamine in TRD (Wilkinson et al., 2017), and is effective in patients with SI (Riblet et al., 2017).

As with all antidepressants, a large portion of patients will not respond to treatment with esketamine or ketamine. While there is limited data on esketamine and ketamine response rates in patients with MDD and SI when they failed to respond initially, treatment effect should generally be seen in two weeks, and patients that did not respond in first two weeks have been excluded from maintenance phase in ketamine trial in TRD and SI (Phillips et al., 2019b).

Due to the limited duration of ketamine and esketamine efficacy, treatment must always be combined with an antidepressant (SSRI or SNRI) (EMA, 2021; FDA, 2020), based on symptoms, response, side effects history, and comorbidity. This is in line with the observed synergistic effect between ketamine and SSRI on brain plasticity and symptom improvement in a rat model of stress-induced anxiety (Melo et al., 2015). The prescribed antidepressant should not be obligatorily changed if it is effective and the crisis is due to well-defined circumstances or treatment compliance failure that was not related to tolerability issues. Furthermore, ketamine or esketamine treatment is also not a contraindication for other augmentation strategies that were widely used in esketamine trials (Canuso et al., 2021). For instance, the mood stabilizer lithium potentiates the antidepressant-like effects and ameliorates oxidative stress induced by acute ketamine in a rodent model of stress (Chiu et al., 2015). Conversely, a small human trial did not confirm the benefit of lithium for depressive symptomatology after acute ketamine treatment (Costi et al., 2019). Therefore, the choice of lithium or other mood stabilizers should be based on previously established guidelines, and on the fact that lithium augmentation and monotherapy remain one of the best evidence-based strategies to reduce long-term suicide risk in patients with mood disorders (Del Matto et al., 2020).

While studies observed rapid changes in depressive symptomatology and SI, there are no studies for esketamine use as a "one-shot" intervention to tackle suicidal crisis, hindering the use of this molecule in such situations. Meanwhile, several studies have shown that ketamine can be safely and effectively used in such cases, providing a bridge to implementing longer-term strategies, such as hospitalization and introduction of other molecules (Y. Domany et al., 2019; Domany and McCullumsmith, 2021). While such option needs more studies and is currently off-label, most of vastly used interventions in suicidal crisis (e.g. admission to inpatient unit or sedation with antipsychotics or benzodiazepines) suffer from the same drawbacks. When combined with implementation of other suicide prevention strategies, it is a viable option with better evidence in suicidal crisis if local guidelines and legislator practices permit.

3.13. Limitations and research directions

The present review and the treatment propositions are based on limited clinical evidence on ketamine or esketamine use in psychiatric emergency, and practices might change in response to the evolving knowledge on these molecules. Moreover, we did not discuss several risks related to ketamine and esketamine use, particularly (but not limited to) the diagnostic drift (when patients are overdiagnosed with MDD or the expansion of what is considered psychiatric emergency), the transient mood response followed by a crash, the often-inadequate psychological support that results in limited beneficial effects of the increased neuroplasticity, and the theoretical induction of mood instability. Well-conducted studies with reasonable sample sizes are needed to validate the observed effects, to measure the role of symptom fluctuation in patients in crisis, placebo effects, long-term outcomes, and costs for the healthcare systems. Such studies should also help to define the best approaches to enhance treatment effects, including different psychotherapy types and pharmacological treatments that might enhance or diminish the observed efficacy.

Furthermore, significant cost considerations exist, both esketamine and ketamine treatment regiments being extremely resource-intensive compared to more traditional approaches in psychiatry, and the added cost of esketamine. Analysis in the United States has found a modest estimated impact of esketamine introduction in the treatment of patients with MDD and SI, with per-member-per-month cost of 0.10 cents (Voelker et al., 2022). While these treatment options are free for users in some countries, individuals can pay for their treatment as an off-label option, and financial burden should be included in the risk-benefit ratio discussion.

Despite these challenges, ketamine and esketamine have opened a window into new mode of action in treatment of patients with MDD and, possibly, suicidal crisis. While the current indication of esketamine is MDD and SI, initial evidence with ketamine suggests possible utility in patients with BD and SI, as well as suicidal crisis without any mental disorders (Domany and McCullumsmith, 2021; Zarate et al., 2012). In addition, dynamic research is now taking place exploring the possible use of other rapid-acting antidepressants in patients with SI. Several initial trials have demonstrated that glutamatergic agents, such as nitrous oxide, might be effective in rapidly reducing SI (Henter et al., 2021; Nagele et al., 2021). However, caution must be taken as initially promising findings with another glutamatergic agent rapastinel were not confirmed in phase three trials. Another line of research is serotoninergic psychedelics, that have been initially shown to rapidly reduce depressive symptomatology in patients with MDD and cancer (Carhart-Harris et al., 2021; Ross et al., 2021), and are proposed

to tackle suicide pathophysiology (Strumila et al., 2021). These medications, just like ketamine and esketamine will have to go through scrutiny regarding safety and efficacy considerations.

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PC and AL conceived the idea. AL managed the literature searches, information synthesis and wrote the first draft of the manuscript. PC, RS and EO revised the manuscript and gave advise on multiple changes. All authors contributed to and have approved the final manuscript.

Conflict of Interest

EO, PC and AL have received have consulted for Janssen-Cilag company. These consultations are not related to the current work. RS declares no conflicts of interest.

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