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Suicide Has Many Faces, So Does Ketamine: a Narrative Review on Ketamine's Antisuicidal Actions

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Abstract

Purpose of Review Suicidal behaviours are a challenge for a medical system and public health, partly due to the current lack of evidence-based, effective, rapid tools for suicidal crisis management. Ketamine and its enantiomer esketamine have raised hopes regarding this issue in the recent years. However, their efficacy in suicidal behaviours and mechanisms for it remain a topic of debate.

Recent Findings Subanesthetic ketamine doses rapidly, albeit transiently decrease suicidal ideation, with effects emerging within an hour and persisting up to a week. Current evidence points to various and not necessarily exclusive mechanisms for ketamine's antisuicidal action, including effects on neuroplasticity, inflammation, reward system and pain processing.

Summary Ketamine rapidly decreases suicidal ideation, but whether it leads to meaningful clinical outcomes past 1 week is unclear. Multiple putative mechanisms drive ketamine's antisuicidal action. Future studies will have to show long-term ketamine treatment outcomes and further elucidate its mechanisms of action.

Keywords Ketamine · Suicide · Suicidal ideation · Neuronal plasticity · Inflammation · Anhedonia

Introduction

Suicide is globally acknowledged as a major public health problem. The most recent estimate of past-year non-fatal suicidal behaviours (SB) prevalence in adolescents in low- and middle-income countries is striking 17% [1]. Geography aside, unfavourable socioeconomic factors increase suicide risk in the lower income groups in every single country [2], and even in Europe, where the suicide rate is declining, the socioeconomic inequalities in suicide have increased over the past decades [3]. It is clear that the current level of suicide prevention and management is insufficient, and the need for effective, rapid, cost-effective and accessible tools to control suicidal crisis is urgent.

Suicidal behaviour is a common and serious psychiatric emergency. However, no medication has been approved for the treatment of patients at imminent risk for suicide. Antidepressants, prescribed for depression, a major risk factor for SB, reduce long-term suicide risk [4], but delayed therapeutic onset diminishes their value in the face of imminent suicide. Moreover, suicidal ideation (SI) is a predictor to antidepressant non-response [5], and is considered as a rare, but possible antidepressant treatment initiation side effect [6]. Established specific clinical interventions, namely clozapine, lithium, cognitive behavioural therapy and dialectic behavioural therapy, are also limited to the long-term suicide risk reduction [7, 8]. Electroconvulsive therapy, providing fastest relief from SI, still has a pronounced response delay in addition to its low accessibility, frequent adverse events, unclear mechanism of action, high cost and persisting stigma surrounding this procedure [9]. Options for patients that enter the healthcare system with acute SI therefore wrap up to acute crisis management, which mainly relies on safety measures including hospitalization, reducing severe psychological

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distress and addressing visible psychiatric symptoms, with an ultimate goal of keeping the patient alive during the crisis, and creating the treatment plan for tackling the underlying conditions. These interventions lack specificity in their biological targets and predictability in outcomes.

One of the most enigmatic findings in modern psychiatry research is about ketamine, a drug, which has been used in clinical practice as a dissociative anaesthetic for more than half a century. Since its discovery, there has been a great effort to disentangle its complex molecular mechanisms and to find broader clinical applicability. Indeed, a subanesthetic dose of ketamine has demonstrated utility in such clinical situations as pain management [10]. In psychiatry, interest in ketamine was kindled in 2000, when Berman et al. demonstrated its acute antidepressive effect in a crossover randomized placebo-controlled trial (RCT) with seven patients [11]. A compelling accumulation of data followed, showing that a single subanesthetic dose of ketamine exhibits well-replicated, rapid, robust and relatively sustained, yet transient, antidepressant effect even in cases of previous treatment resistance [12–14]. However, ketamine's application in depression treatment is not straightforward, as repetitive doses are required, which is hindered by drug's abuse and dissociative potential. Also, studies show that ketamine encompasses a specific and rapid suppression of suicidal ideation (SI), which is unprecedented in psychiatric practice. In this review, we discuss the recent progress in ketamine research, with a focus on its utility in managing suicidal crisis, and biological basis for that.

Findings From Clinical Ketamine Studies

The evidence for ketamine's antisuicidal properties is less solid than for its antidepressive effects. Yet, it seems convincing. Meta-analysis in MDD patients that used SI as a secondary outcome reported reduced suicidality for 3 days after ketamine treatment [14]. A later meta-analysis that used single-arm data from five clinical trials with 99 patients focused specifically on SI, and found a substantial benefit from as early as 40-min post-treatment [15]. However, several limitations, such as no comparator group, small pooled sample size and no information on outcomes for specific scales, as well the later retraction of one of the included studies (authors did not report drastic changes in their findings after data re-evaluation), impede conclusions. To date, the most convincing evidence comes from a meta-analysis published in 2018, which used individual patient-level data of 167 adults with major depressive disorder (MDD), bipolar depression or posttraumatic stress disorder, and SI from 10 RCTs. Single intravenous infusion of ketamine was associated with rapid effect within a few hours and a significant reduction of SI that lasted up to 7 days both in terms of clinician-administered and self-report outcome measures, and was superior to the comparator (either saline or midazolam) with moderate-to-large effect size. Notably, this effect was partially independent of depressive symptomatology [16••]. While this meta-analysis is valuable and timely, it still has several caveats. The sample size was still small, follow-up period too short and the measurement of SI often involved a single item on depression severity rating scales. Most included studies consisted of patients with treatment-resistant mood disorders, and several trials expressly excluded patients at serious suicidal risk, while involving patients with mild SI, resulting in a patient population that does not necessarily reflect the picture of individuals that come to the emergency department in suicidal crisis.

Several studies that emerged in recent years reinforced the confidence in ketamine's efficacy in reducing SI. In a small pilot RCT in depressed bipolar patients with SI, there was a tendency for ketamine to reduce SI, albeit not statistically significant (the study was underpowered) [17]. In a larger RCT, 80 inpatients with MDD and SI were given a single infusion of 0.5 mg/kg ketamine in adjunction to continuous antidepressant treatment. Ketamine was associated with a significantly higher reduction of SI measured at 4- and 24-h post-infusion than midazolam, with a medium-to-large effect size at 24 h. The effect was sustained for up to 6 weeks, although assessments in a double-blind controlled fashion were made only up to 1 day. Notably, this association was partially independent of depressive symptomatology [18••]. Findings from recent open-label studies support this line of evidence. In a study with ten patients, decrease in SI after a rapid ketamine infusion was observed among the entire study sample invariably of antidepressant response [19]. Similar results came from another research group that studied the effects of six ketamine infusions within 12 days. Two subsequent studies with depressed patients showed that ketamine was able to rapidly reduce SI at least partly independently from depressive symptomatology [20, 21]. Ketamine's rapid effect on SI is further supported by a small RCT from the emergency department [22]. However, in a recent outpatient trial, with various subanesthetic doses of ketamine in patients with treatment-resistant depression (TRD), where SI was not a primary outcome, any dose of ketamine was not superior to midazolam in regard to SI, and two patients that spontaneously reported SI were in the ketamine group [13].

Findings From Esketamine Studies

Clinical development of ketamine treatment faces many obstacles, mostly since its patent is long expired, and it is a generic medication, therefore receives limited attention from pharmaceutical companies. One of a few successful research paths that stemmed from an analysis of ketamine's biological targets is the development of the ketamine's enantiomer (S)-ketamine nasal spray. Trials reported rapid antidepressant

effect in patients with TRD in adjunction to oral antidepressants with a favourable tolerability profile [23, 24], resulting in its approval by the Food and Drug Administration for treatment of TRD in March 2019. In a recent multicentre proof-of-concept RCT, 68 depressed patients at imminent risk of suicide were given fixed dose (84 mg) of esketamine or placebo for 4 weeks, in addition to standard-of-care treatment. Authors found an association with ketamine's administration and a rapid, as within hours, SI reduction on a depression rating scale, with a moderate-to-large effect size. However, the advantage over placebo disappeared within 24 h. Besides, the clinician global judgement of suicide risk showed no difference to placebo at any time point [25••]. Notably, participants in this study were severely depressed and suicidal. Vigilance remains needed, and results from multiple ongoing or recently finished trials in patients at imminent risk of suicide (NCT03039192, NCT03097133) or hospitalized due to acute suicide risk (NCT02133001, NCT02299440) will likely help to come to more reliable conclusions.

Strength of Current Evidence and Related Risks

For now, it is hard to say if the initial promise of ketamine will translate to marked changes in clinical practice. In addition to the unclear mode of action, there is uncertainty regarding the evidence from clinical trials. Variety of methods used to evaluate SI, possible inability to catch rapid SI change and potential influence of repeated questioning on the validity of responses, different or lack of control group limit the strength of existing evidence. Moreover, current evidence is mostly based on patients with severe mood disorders, but in a suicidal crisis, quick clinical decisions are required, even in the absence of a diagnosis. Questions regarding ketamine use in patients using other drugs altering glutamatergic neurotransmission, such as benzodiazepines, and any acutely intoxicated patients or those with psychotic disorders remain open. In a number of studies, patients were washed out from their previous psychotropic medications, and medication naïve patients are rare in psychiatric practice. Moreover, functional unblinding in studies remains a problem, as it is easy to distinguish ketamine even from midazolam. Current trials support ketamine's favourable safety profile and efficacy in reducing SI up to 1 week [16••, 26]. However, future studies will have to demonstrate long-term outcomes of ketamine use in acute suicidal crisis management, knowing that SI has a low predictive value for suicide [27], and the ultimate goal of antisuicidal interventions is reducing suicide rates, and not only transient relief from SI.

Antisuicidal Action

Despite accumulating evidence showing the specific antisuicidal effect of ketamine, the underlying neurobiology is poorly understood. Evidence from research, mostly based on animal depression models, point to several putative mechanisms that we will further discuss regarding suicidal ideation (see Fig. 1). A full review of ketamine's complex pharmacological properties is beyond the scope of this paper, and an interested reader is referred to reviews on ketamine and related drugs pharmacological qualities [28•, 29•].

Ketamine-Induced Neuroplasticity

While ketamine has multiple biological targets, prevailing theories of its molecular mechanism stem from its high-affinity inhibition of the N-methyl-D-aspartate receptors (NMDARs). Disinhibition theory claims that ketamine blocks NMDARs on tonic firing γ-aminobutyric acid (GABA) interneurons in the prefrontal cortex (PFC), resulting in glutamate surge from pyramidal neurons [29•]. Glutamate, in turn, activates postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which trigger mammalian target of rapamycin (mTOR)-dependent protein synthesis and structural plasticity in medial PFC and hippocampus at least partly via brain-derived neurotrophic factor (BDNF). A second hypothesis claims that ketamine directly inhibits postsynaptic NMDARs on pyramidal neurons elicited by the spontaneous release of glutamate, preventing the phosphorylation of eukaryotic elongation factor 2 (eEF2), which results in rapid BDNF translation [30]. The third theory includes ketamine action on extra-synaptic NMDARs that are tonically activated by ambient glutamate, and subsequent disinhibition of the mechanistic target of rapamycin (mTOR) [28•]. Rodent studies with ketamine metabolites [31], enantiomers [32] and ketamine itself [33••] demonstrated that ketamine might also target neuroplasticity in NMDA-independent manner. Aforementioned theories converge on activation of neuroplasticity cascades via the activation of BDNF and mTOR pathways [29•]. BDNF is a major brain neurotrophic factor, and it activates intracellular signalling cascades. One of them is mTOR, which regulates synaptic protein synthesis, and its rapid increase in the medial PFC following the ketamine administration results in local structural plasticity [29•]. Carriers of defective BDNF alleles exhibit a diminished antisuicidal response to ketamine [34]. Intact BDNF system is also critical for sleep regulation [35], and antisuicidal response to ketamine has been linked to normalized sleep [36•]. Meanwhile, mTOR alterations have been specifically associated with suicide attempts [37], and pre-administration of its selective inhibitor blocks actions of ketamine [38].

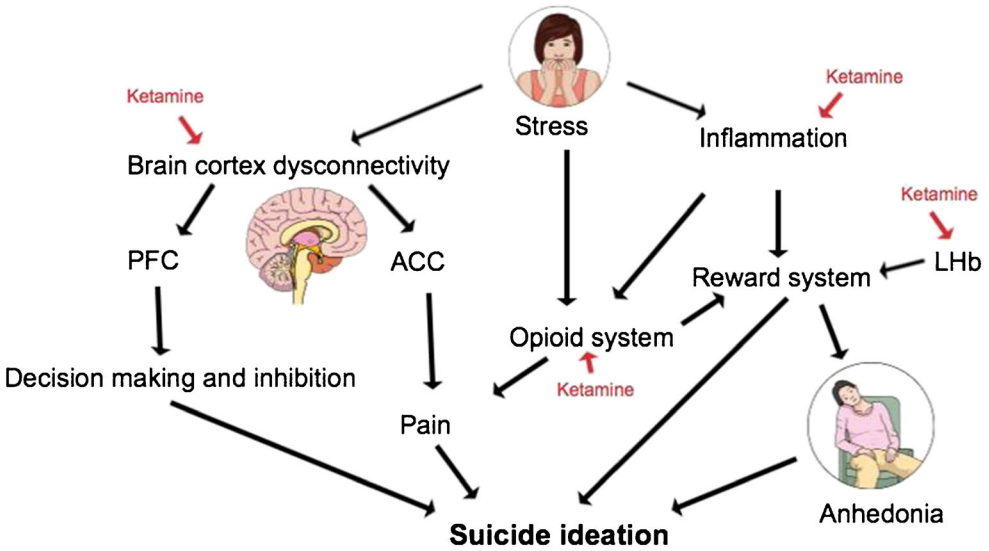

Fig. 1 Major hypotheses regarding ketamine's antisuicidal actions. (1) Increasing neuroplasticity reverses stress-induced dysconnectivity in brain cortex areas, such as prefrontal cortex (PFC), responsible for decision-making and inhibition and anterior cingulate cortex (ACC), involved in pain processing. (2) Addressing stress-induced inflammation via inhibition of quinolinic acid binding to N-methyl-D-aspartate (NMDA) receptors and restoring prefrontal cortex and mesolimbic reward system functioning; (3) Modulation of opioid system leads to relief of pain and restores reward processing. (4) Inhibition of overactive lateral habenula (LHb) restores reward processing and decreases anhedonia

Increased synaptogenesis is proposed to underlie neuroplasticity and sustained effects of ketamine [28•, 29•]. Both preclinical and clinical studies show that ketamine induces the overall network reconfiguration of disrupted prefrontal connectivity, restoring metabolic homeostasis [39]. Response to ketamine treatment is related to changes in brain circuits related to affective processing, such as the subgenual anterior cingulate cortex (ACC), PFC, hippocampus and infralimbic cortex [40••]. Abnormalities in these areas, especially PFC and ACC, have been consistently reported in patients with a history of SB/ SI [41]. Therefore, ketamine's antisuicidal action might be related to its ability to rapidly restore impaired brain connectivity.

Patients with Stress-Responsive SI Pattern–Responders?

Several studies reported that patients with a longstanding, chronic history of SI have weaker ketamine antisuicidal response [25••, 42••, 43]. In addition to higher severity, it could be explained by the existence of different SI patterns. Patients displaying persistent SI are less stress-responsive, more depressed, have lower serotonin levels and better cognitive control, allowing them to plan and execute suicide. Meanwhile, in the stress-responsive pattern, which is associated with early-life adversity via impulsivity and HPA axis dysregulation, SI is not as chronic and often follows stressful life events [44, 45]. Early-life adversity increases the risk of suicide throughout diagnostic categories [46] and is associated with epigenetic modification of genes involved in stress response, cognitive processes and neuronal plasticity [47]. While suicide is associated with brain grey matter volume changes, studies show impairments in dorsolateral PFC and ACC only in suicide descendants with early-life adversity history [48, 49]. In addition, in a postmortem brain study, authors found a link between suicide and lower BDNF levels in ACC only when considered concerning early-life adversity [50]. Given ketamine's extensive effects on the plasticity of aforementioned regions, its normalizing effect on the HPA axis [51] and high non-response rates in chronic SI, it is plausible that ketamine may be particularly useful in patients with stress-responsive SI pattern.

Not that Different From Other Psychedelics?

Considering these vast connectivity changes induced by ketamine, it is worth to note that ketamine is also an atypical psychedelic. It is unclear whether the psychotomimetic effects of ketamine are related to its therapeutic effects. Interestingly, a longitudinal cohort-based study from Canada demonstrated that naturalistic psychedelic drug use was independently associated with reduced suicidality [52]. The therapeutic effect of psychedelics has mainly been attributed to their ability to reduce the activity of the default mode network (DMN), which is most active when the person is not involved in specific tasks [53]. It seems that ketamine might not be that different from other psychedelics, as it also interferes with the DMN connectivity [54], transiently normalizing it in depressed patients,

possibly attenuating pathologically increased self-focus [55•]. It also helps the posterior ACC to regain variable responsiveness to negative stimuli [56]. While DMN role in ketamine antisuicidal response is not yet clear, its changes were reported to correlate to pain relief in neuropathic patients [57], and sham stimulation of its part has been associated with decreased SI independently from depression [58]. Hub nodes that were found only in suicide attempters were also found to belong mostly to the DMN regions [59].

Inflammation and Suicide

Suicidal behaviour has been strongly and independently linked to inflammation [60]. Inflammatory cytokines are upregulated in suicidal patients and suicide victims [61], and SB risk is increased in such inflammatory conditions as infections [62] and traumatic brain injury [63]. When inflammation exceeds the normal range, occurs during critical developmental periods or on a background of chronic stress, it leads to synaptic damage, entailing longstanding maladaptive neurobiological changes [64]. One of the inflammation-related processes might be of particular relevance for ketamine actions. Chronic excess of pro-inflammatory cytokines continuously upregulates the expression of the indoleamine 2,3-dioxygenase, which metabolizes tryptophan via the kynurenine pathway in disadvantage of serotonin synthesis. Activated immune cells convert kynurenine into quinolinic acid. The latter, in addition to contributing to the perpetuation of inflammatory processes, dysregulates glutamate signalling via NMDA agonism, resulting in synaptic dysfunction [65]. Indeed, suicidal behaviours have been linked to elevated levels of quinolinic acid [66], and SI has been associated with microglial activation in depressed patients [67]. Longitudinal studies suggest sustained dysregulation of the tryptophan-kynurenine pathway for at least 2 years after suicide attempts [68]. Beneficial ketamine effects could be due to its competing action with quinolinic acid on NMDAR. Indeed, it reversed depressive symptomatology caused by a pro-inflammatory agent and associated with quinolinic acid, while not altering sickness behaviour and inflammatory processes in rodent study [69]. Increased level of kynurenic pathway products and changes in their balance have been linked to ketamine antidepressant response [70•].

Anhedonia and Suicide

Convergent lines of evidence link inflammation, anhedonia and SI. Firstly, all of them are linked to conventional antidepressants non-response [5, 71, 72]. Secondly, inflammation has been associated with both SI [61] and anhedonia [73•], while the latter is on itself linked to SI [74]. Ketamine rapidly and independently from depression symptoms change improves anhedonia in depressed patients [75••]. Anhedonia, defined as the reduced ability to feel pleasure, is related to stress-induced dysregulation of mesolimbic dopaminergic reward circuitry, and possibly acts as a mediator between chronic stress exposure and suicidal crisis [76]. One of the possible pathways is via inflammation. In response to stress, inflammation disrupts mesolimbic reward functioning by interfering with dopamine synthesis, or via oxidative stress [77•]. A recent rodent study demonstrated that chronic social stress leads to peripheral inflammation, immune activation in and reduced the functioning of the mesolimbic dopaminergic pathway, resulting in reduced reward-directed behaviours [78]. In humans, systemic inflammation predicted glutamate levels in the basal ganglia, which in turn predicted anhedonia [79]. Inflammation appears to make the less rewarding stimuli less attractive and increases the averseness of negative stimuli compared with positive stimuli [80].

Ketamine has been proposed to preferentially affect dopaminergic circuits and networks subserving positive valence systems [81], and increases neural activation in reward-processing areas [40••], which may subserve its antisuicidal properties. It both attenuates anhedonic behaviours induced by chronic unpredictable stress and revert the stress-induced synaptic deficits in animal models [82]. In a recent study with marmoset monkeys, over-activation of subgenual anterior ACC was followed by increased metabolic activity in several brain regions, including dorsal ACC, and caused transient anhedonic behaviours, that were reversed within 1 day after ketamine administration [83••]. In accordance, studies with depressive human subjects linked anti-anhedonic effects of ketamine to activation in the dorsal ACC [84].

Lateral Habenula and Reward

An alternative line of evidence on how ketamine might decrease anhedonia and SI comes from its actions in a small midbrain structure lateral habenula (LHb). It has rich reciprocal connectivity with forebrain and midbrain, and modulates the midbrain monoaminergic pathways, playing the pivotal role in reward and punishment processing [85]. Aberrant activity of the LHb is associated with such symptoms as helplessness, anhedonia and excessive negative focus [86]. Studies suggest that the LHb is implicated in the connection between stress and mental disorders, as maternal deprivation increased LHb intrinsic excitability and bursting activity in mice while linking it to depressive-like symptoms [87, 88]. A single injection of ketamine reversed stress-induced LHb neuronal dysfunction and the behavioural response [88]. Besides, higher connectivity between the left habenula and several brain areas has been linked to the history of SB independently from depressive symptomatology in humans [89]. A recent

study with two rodent stress models linked enhanced LHb neuronal bursting with inhibition of ventral tegmental dopamine neurons, dorsal raphe serotonin neurons and behavioural depression and anhedonia, while ketamine-induced anti-anhedonic actions were associated with rapid silencing of the NMDAR-dependent burst firing of LHb neurons [90••]. A consistent finding in rodent studies is that ketamine administration elicits acute dopamine release in cortex, striatum and nucleus accumbens [91••]. Taken together, ketamine seems to disinhibit dopaminergic reward centres and increase the activity of the reward-seeking circuitry by blocking the activity of LHb neurons.

Ketamine and Psychological Pain

Ketamine has multiple binding sites other than NMDA, and directly, as well as indirectly, affects monoaminergic, cholinergic, opioid, GABAergic and cannabinoid neurotransmitter systems, further contributing to ketamine antisuicidal properties [28•, 29•, 92]. Among those, the role of the opioid system has recently caught the attention of the scientific community, partly because increased suicide rates were linked to the current opioid crisis [93]. The endogenous opioid system participates in pain processing [94], and its involvement in ketamine analgesia has been demonstrated by rodent and genetic studies [95]. Adverse experience, such as childhood abuse, has been shown to result in epigenetic modulation of the opioid system [96], which, in turn, profoundly affects cortical pain matrix during situations of social exclusion or social adversity [97]. Moreover, the opioid system is involved in reward, pleasure-seeking and decision-making, systems, highly impaired in suicide [98]. Buprenorphine, a μ-opioid receptor partial agonist and a κ-opioid receptor antagonist, has been associated with decreased SI in depressed patients [99] and has been associated with dampened response to psychosocial stress [100]. Recently, the opioid hypothesis of ketamine was tested in a small crossover RCT in patients with TRD. Interim analysis of seven patients demonstrated that pretreatment with 50 mg of oral naltrexone, a μ-opioid antagonist, 45 min before the ketamine infusion, profoundly attenuated ketamine's antidepressant effect [101••]. Contradictory results emerged from followed data of 5 patients with MDD and alcohol use disorder, showing that naltrexone did not interfere with ketamine antidepressant effects [102]. However, participants in this study received injectable naltrexone 2–6 days before ketamine infusion. Therefore, the μ-receptor blockade could have been negligible compared with that in the first study. It is known that blood concentration may be essential for naltrexone efficacy in alcohol dependency [103], so naltrexone could have better blocked opioid receptors in the first study. Both studies prevent any meaningful conclusions because of the small study sample sizes, and there is no closure yet concerning opioid system involvement in ketamine's actions.

Despite unclear ketamine interaction with the opioid system, subanesthetic doses of ketamine are effective in an array of pain syndromes, including those difficult to treat with opioids [10]. It has been proposed that ketamine alters conscious pain perception. Rodent and human studies show that a single sub-anaesthetic dose of ketamine selectively improves the affective component of pain [104, 105•]. It alters the perceived salience of different categories of stimuli, possibly leading to decreased affective discrimination of sensorial information [106•]. The anti-aversive property of ketamine was mediated by suppression of the hyperactivity of neurons in the ACC, which is well known to regulate pain affect [105•]. These findings are particularly relevant to the suicide field, as suicidality is strongly associated with psychological pain [107]. The neural network underlying the psychological pain vastly overlaps with that related to the affective processing of physical pain, including the insula, PFC, ACC, amygdala and thalamus, with a particular role of the ACC [108]. It should be noted that reward processing, discussed earlier, is highly implicated in pain circuity [109].

Conclusion

In conclusion, subanesthetic doses of ketamine have been shown to elicit at least partly specific, rapid, albeit transient relief from SI, with effects emerging within an hour and persisting up to a week. For now, it seems that a sensible approach could be ketamine use in suicidal crisis management in adjunct to other treatment to rapidly relieve SI. The myriad of ketamine's molecular and cellular mechanisms results in vast applicability possibilities, but also in an uncertainty on how the drug works. Current evidence supports an array of effects concerning neuroplasticity, inflammation, award and opioid systems, but need further clarifications.

Compliance with Ethical Standards

Conflict of Interest Aiste Lengvenyte declares no potential conflicts of interest.

Emilie Olié has received personal fees from Janssen Cilag and Otsuka.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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