

REVIEW

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Esketamine: the first glutamatergic drug for the management of treatment-resistant depression

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Summary

Intranasal esketamine has been recently approved by both the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treatment-resistant depression in adults and will be soon clinically available also in Italy. Esketamine is the (S) enantiomer of ketamine, a non-competitive N-Methyl-D-aspartate (NMDA) glutamate receptor antagonist, introduced in clinics as anesthetic and analgesic since over 50 years ago. Due to its dissociative properties and abuse/misuse potential, ketamine is also widespread used at high dose as recreational drug.

Accumulating clinical studies demonstrated that the off-label use of low-dose ketamine infusion in severe depressed treatment-resistant patients produces a rapid and sustained antidepressant effect, with only transient and mild dissociative side effects. Although short/medium-long efficacy and safety of repeated intranasal esketamine has been demonstrated in well-powered clinical studies, few is still known about the cellular/molecular mechanisms underlying its nonpareil antidepressant effect. Therefore, if on one hand long-term benefit/risk assessment with careful monitoring of cognition and behavior are still missing, the in-depth study of fast antidepressant effect, together with the search of alternative drugs acting on the same targets, are required.

Overall, despite the limitations and some skepticism of part of the scientific community, esketamine can be considered the first drug approved as rapid-acting antidepressant, with a new mechanism of action implying the direct modulation of glutamate transmission and neuroplasticity.

Introduction

Depressive disorders are highly invalidating psychiatric diseases, characterized by low remission rate and high percentage of treatment resistant subjects (1). After more than half a century of studies, compelling evidence implies that long-term changes in brain areas and circuits mediating complex cognitive and emotional behaviors represent the biological underpinnings of depression (2-4). Changes in

the levels and clearance of glutamate, the main excitatory neurotransmitter in the brain, and its metabolites were found in corticolimbic areas of depressed patients, while neuroimaging and histopathological studies showed morphological and functional alterations in these same areas (5,6).

On the other hand, preclinical studies on stress-based animal models of depression showed that stress potently affects glutamate synaptic transmission and plasticity and induces consistent dendritic

remodeling and synaptic spines reduction in corresponding brain areas (4,7).

The beginning of 2020 saw the sad loss of two pioneer neuroscientists who studied how changes in brain function and structure is related with the etiopathogenesis of neuropsychiatric diseases.

Bruce McEwen (passed away in January) has been a world leader in the study on how stress hormones reshape neural circuits and brain structures (4,7-9). He coined the concept of “allostatic load”, referring to sustained and progressive changes accumulated in the brain of susceptible individuals, after overwhelming or prolonged stress exposure, resulting in a substantial pathogenic deviation from the original brain functioning. Stress is indeed commonly acknowledged as the major predisposing and triggering factor for depression, which is in turn considered the most common stress-related disorder (3,4,10). Emotional trauma (including grief, social rejection, physical or sexual abuse), major life changes (such as bereavement, health condition, childbirth, financial difficulties, natural disasters, war) and adversities in childhood or adolescence (including maltreatment, neglect or bullying) are widely associated with the exacerbation of mental disorders (3,4).

Ronald S Duman, who left us in February, was known for his valuable work on synaptic dysfunctions associated with the neurobiology of depression (3,11), and in the last years also for his landmark studies on the molecular mechanisms underlying the rapid antidepressant effect of ketamine (12,13). He is one of the main founders of the hypothesis according which depression is caused by disruption of homeostatic mechanisms that control synaptic plasticity, resulting in destabilization and loss of synaptic connections in mood and emotion circuitry (11). A number of molecular effectors and players has been suggested to be involved in the synaptic loss and dysfunction associated with depression, being the Brain-Derived Neurotrophic Factor (BDNF), and downstream signaling pathways, one of the most frequently cited and widely recognized for its role in modulating neurotrophic

mechanisms (12). Accordingly, oppositely to the effects of stress and depression, chronic antidepressants were consistently reported to produce a slow increase in neurotrophic factor expression and to enhance synaptic plasticity (14,15). Duman’s lab was also the first showing that the rapid antidepressant actions of ketamine are associated with fast induction of synaptogenesis in rodents and reversal of the atrophy caused by chronic stress (16,17).

Altogether, these pieces of evidence contribute to support the idea that antidepressant effect is dependent on restoring altered synaptic plasticity (3,10,12).

Racemic ketamine in the treatment of depression

Ketamine is a racemic dissociative anesthetic, non-competitive antagonist at the phencyclidine site on the N-Methyl-D-aspartate (NMDA) glutamate receptor, used for surgical procedures both in humans and in veterinary medicine, since 1960s (**figure 1**). It is also a drug of abuse, inducing at high dose and after chronic use cognitive and memory impairments as well as psychotic symptoms and neurotoxicity (18).

The first report showing the antidepressant effect of a single low-dose infusion of racemic ketamine is dated 2000, when Berman and coworkers published evidence of rapid onset (within hours) and long-lasting (up to one week) effect in nine medication-free depressed patients (19) (**figure 1**). Since then, a high number of clinical studies has followed, largely confirming an antidepressant effect of one single sub-anesthetic dose of ketamine in treatment-resistant unipolar and bipolar depressed patients, emerging 2-4 hours after treatment (with a substantial mood improvement at 24 hours), and lasting from a few days to more than 2 weeks (20-22). Notably, it was also shown that ketamine directly targets anhedonia, helplessness and suicidality, rather than inducing a nonspecific mood elevating effect and clinical benefits appear in approximately 50% to 80% of the patients (23). Recent studies showed that ketamine infusions every 2–3 days over a two-

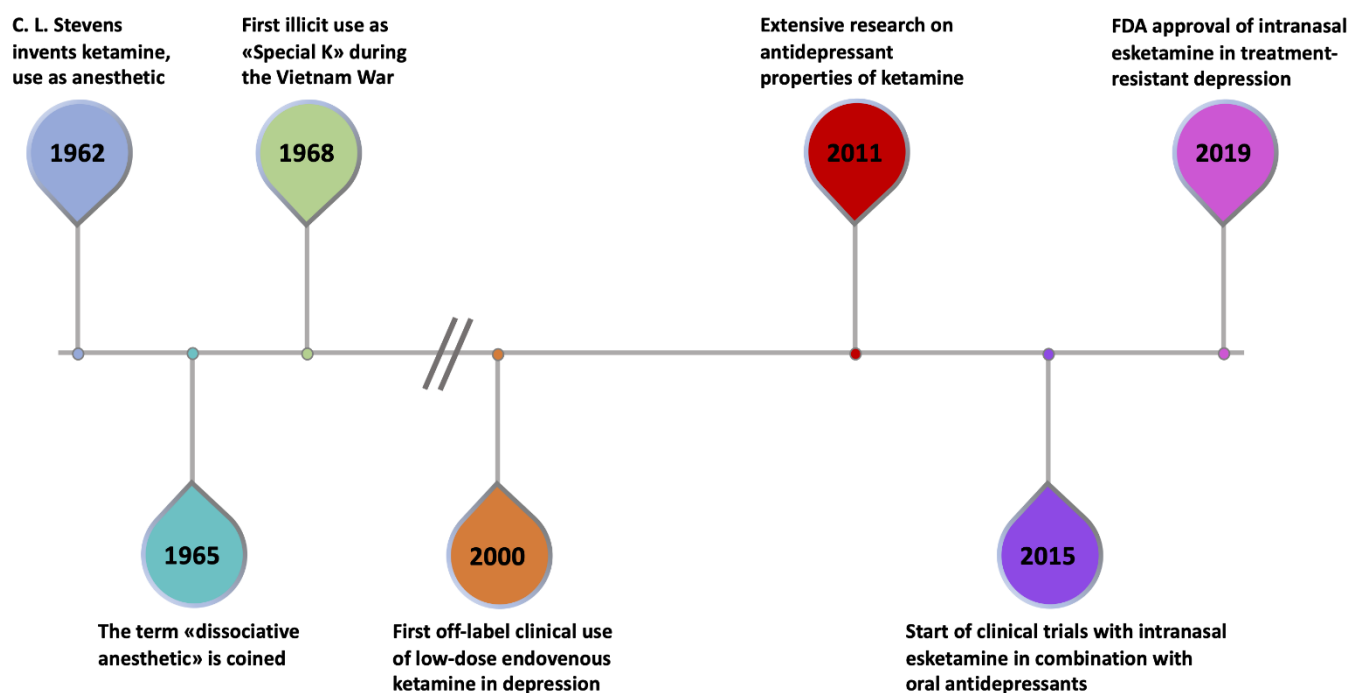
week period maintains the antidepressant response, increases the percentage of responding patients, and lengthens the duration of antidepressant response after treatment cessation (24,25). Although generally well-tolerated at subanesthetic antidepressant doses, ketamine is associated with significant transient side effects, including dissociative symptoms, blurred vision, drowsiness, tachycardia, hypertension, increased irritability, anxiety, dizziness, nausea and vomiting. Ketamine also has potential abuse liability by patients with substance use disorders (26). It is however important to notice that, despite the high number of studies, the safety and efficacy of single or repeated injections of racemic ketamine in treatment-resistant depression have yet not been fully investigated in large and well-powered clinical studies, which are required to obtain more clear and

unconfrontable results (27). The reason of the lack of systematic studies is that racemic ketamine has never been under clinical development as antidepressant, but is just used off-label in cases of severe depression. Indeed, ketamine dissociative side effects, risk of cognitive impairments after chronic use and abuse potential strongly limit the wide use of the drug, and rise some skepticism in the scientific community.

The clinical development of esketamine

In March 2019, the US Food and Drug Administration (FDA) approved a nasal spray formulation of the S-enantiomer of ketamine (esketamine) for the treatment of resistant depression in association with antidepressant drugs, in adults (**figure 1**).

Figure 1. Timeline of ketamine pharmacological development.



In December 2019, the same therapeutic indication received a positive feedback also by the European Medicine Agency (EMA) for approval and licensing in European countries.

The documents submitted to regulatory agencies for approval mainly rely on four randomized, double-blind, multicenter Phase III clinical trials (28-31), three of which were short-term placebo-controlled efficacy trials conducted in participants suffering from treatment-resistant depression (28,30,31). The success of esketamine compared to racemic ketamine essentially depends on the route of administration (intranasal spray vs. intravenous infusion) and that clinical evidence on esketamine, having been designed in a rational way to demonstrate the real effectiveness of the drug (with the final aim to be presented to health authorities), is highly structured and gives more information about the effectiveness and safety of the drug.

Esketamine is a more potent antagonist at the phenylcyclidine site on the NMDA receptor compared to the R- enantiomer, and exerts an anesthetic potency two to four times greater than R-ketamine, with less psychotomimetic effects (18). Thus, esketamine was chosen for the clinical development as antidepressant in virtue of its greater affinity for the NMDA receptor. TRANSFORM-1 was the first Phase III trial aimed at assessing the safety and efficacy of intranasal esketamine given twice weekly in patients with treatment resistant depression, combined with a newly initiated oral antidepressant (30). The study lasted 4 weeks and involved a total of 346 adult patients and 2 doses of esketamine (56 mg and 84 mg). The results showed rapid therapeutic response by day 2 in both treatment arms as compared to the control arm, although at the end of the study the antidepressant effect was statistically significant only in esketamine 56 mg group.

In TRANSFORM-2 227 patients under treatment with oral antidepressant were randomized into two groups and were given flexible dosing of intranasal esketamine (56 mg or 84 mg twice weekly) in one

group and intranasal placebo twice weekly in the other, for 4 weeks (31). Here highly significant antidepressant effect was reported at the end of the 4 weeks.

The FDA approval of intranasal esketamine was mainly based on the findings of this study.

TRANSFORM-3 was the only trial till date having enrolled elderly patients (≥ 65 years of age) (Ochs-28,32). Again, patients were randomized in placebo and esketamine groups and the treatment was administered twice week, in adjunction to oral antidepressants, for a total of 4 weeks. No significant antidepressant effect was seen on day 28, however, in the subgroup analysis performed for the 65–74 years age group, a significant change in Montgomery–Asberg Depression Rating Scale score was noted between esketamine and placebo groups.

The fourth clinical study (SUSTAIN-1) involving 297 patients was focused on the maintenance effect of intranasal esketamine or the ability of the drug to prevent relapses, up to 92 weeks (29). Esketamine was shown to reduce the risk of relapse by 50% in patients who had initially achieved stable remission and by 70% in those who had initially achieved a stable response.

A second long-term study (SUSTAIN-2), primarily focused on treatment emergent adverse events, has been started (33). The main aim was to avert the danger of long-term cognitive and memory impairments. 90% patients had adverse events through the period of 56 weeks out of whom 17% presented with renal and urinary tract symptoms. Dizziness, headache, feeling of dissociation, somnolence and viral upper respiratory tract infections were among the common adverse effects.

Proposed mechanisms of action

Extensive research efforts have been focused on the study of cellular mechanisms underlying the rapid and long-lasting antidepressant effect of ketamine, although the high majority of preclinical reports

used only racemic ketamine. The full description of all the proposed mechanisms is out from the scope of the present review (for comprehensive recent reviews on this topic, please see 34-36), however, one striking effect of acute ketamine in rodents, reported for raceme and both enantiomers, is the ability to rapidly (within 24 hours of administration) restore dendritic arborization and synaptic spine density reduced by chronic stress, an effect observed with traditional antidepressants only after several weeks of treatment (16,17,37-40). This effect coincides with the peak of acute ketamine antidepressant effects in animal models (24 hours) and is considered essential for its therapeutic action. However, the cellular mechanisms driving this effect have not yet been fully elucidated.

Since the antidepressant action of ketamine has been linked to NMDA receptor antagonism, and esketamine has a 3-4 higher affinity for this receptor than (R)-ketamine (18), it is generally accepted that the same mechanisms drive the pharmacological effects of both racemic ketamine and esketamine. NMDA receptor-dependent mechanisms are forced to pass through receptor antagonism, which is expected to block excitatory glutamatergic neurotransmission. However, it was shown that acute ketamine conversely increases overall activity, at least in the prefrontal cortex. Thus, it was formulated the so called "disinhibition hypothesis", confirmed in animal models, which postulates that ketamine preferentially blocks NMDA receptors on GABAergic interneurons in the prefrontal cortex, thus increasing the firing of pyramidal neurons (13,23,26). Moreover, there is also evidence arguing a direct effect of ketamine on gamma amino butyric acid (GABA)ergic interneurons, leading to the suppression of inhibitory activity. The disinhibition of glutamatergic transmission was shown to induce a glutamate burst, which increases α -amino-3-hydroxy-methyl-4-isoxazole propionic acid (AMPA) receptor mediated excitatory transmission, in turn promoting the release of BDNF at synapses, and a fast and transient activation of mammalian target of rapamycin complex (mTORC) signaling (34). This

was shown to increase the local expression of synaptic proteins, consistently with the rapid formation of new spines observed after ketamine treatment (16,37).

Via a different, though not necessarily alternative mechanism, ketamine has also been shown to induce rapid BDNF synthesis in the hippocampus (34,41). Indeed, under physiological conditions, NMDA receptor-dependent activation of the eucariotic Elongation Factor 2 Kinase (eEF2K) results in inactivation (phosphorylation) of eEF2 leading to the blockade of the elongation phase of protein synthesis and thus inhibition of protein translation. It was proposed that a single sub-anesthetic dose of ketamine, via inhibition of spontaneous synaptic NMDAR-mediated glutamatergic neurotransmission, decreases activation of eEF2K resulting in eEF2 dephosphorylation and a subsequent disinhibition of protein translation.

In particular, in vivo eEF2 dephosphorylation was shown to de-suppress BDNF protein translation, which was hypothesized to mediate the long-term effects of ketamine via the induction of synaptic plasticity.

Involvement of GABA receptors in ketamine mechanistic pathways for neurogenesis has also been suggested (42).

Additionally, esketamine directed serine phosphorylation of glycogen synthetase kinase (GSK) activates wingless related integration site (Wnt)-signaling and inhibits neuronal apoptosis. Other intriguing mechanisms include the involvement of opioid receptors, blockade of hyperpolarisation-activated cyclic nucleotide gated (HCN) channels, enhancement of vascular endothelial growth factor (VEGF) action and the role of the gut-brain (34-36).

Future perspectives and open questions

Although much is still to be discovered about the cellular pathways activated by ketamine, the excitement over ketamine among depression researchers and clinicians depends on the fact that ketamine is the first drug with a new mechanism of action to

treat depression in more than half a century. The introduction of esketamine represents a real revolution in the treatment of depression and give more hope to patients and trust in new, better and faster therapies for the control of the disease. Unfortunately, because of the risk of sedative and dissociative effects, together with the potential for abuse and misuse of the drug, ketamine remains a “non-ideal” drug for the large-scale treatment of depressive disorders. Long-term effects of esketamine on cognition and possible physical dependence need to be carefully monitored in future prospective studies. Nevertheless, the interest on this drug remains high because it has the nonpareil potential to be used as a tool to understand the mechanisms underlying the fast antidepressant action, and to develop a new class of antidepressants directly targeting the glutamatergic transmission. In this context, an improved understanding of the synaptic and circuit mechanisms underlying ketamine efficacy in pre-clinical models will be required for the identification of cellular targets responsible for its antidepressant effect, and for the development of new molecules with similar therapeutic properties but safer profiles.

A huge number of other molecules, directly targeted at the glutamate synapse, have been tested (or are under study) for their potential antidepressant action.

Considering that NMDA receptor inhibition is acknowledged as the most likely antidepressant mechanism of ketamine, several alternative NMDA receptor antagonists have been studied for antidepressant efficacy, including memantine, lanicemine, selective antagonists of the GluN2B subunit and a functional NMDA receptor partial agonist (GLYX-13, rapastinel). However, none of them showed antidepressant efficacy and safety comparable to ketamine (as a recent review, see 43), suggesting that NMDA receptor modulation could not be sufficient to induce fast and long-lasting antidepressant effects.

AMPA receptor activation was also involved in the antidepressant effect of ketamine (and HNK in animal models) (26,36) and, consistently, AMPA receptor positive allosteric modulators are under pre-clinical evaluation as putative antidepressants.

Finally, numerous studies indicated that metabotropic glutamate (mGlu) receptors may also be involved in the development of a rapid antidepressant effect. Potential antidepressant-like effects of several mGlu receptor ligands, including mGlu5 antagonists, mGlu2/3 antagonists or mGlu7 agonists, have been studied both at preclinical and clinical level, although without obtaining unambiguous results (at least, until now), and more studies are required to understand the potential of mGlu modulation in therapy (44).

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