

Rapid-acting antidepressants targeting modulation of the glutamatergic system: clinical and preclinical evidence and mechanisms

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ABSTRACT

Major depressive disorder (MDD) is a devastating mental illness that affects approximately 20% of the world's population. It is a major disease that leads to disability and suicide, causing a severe burden among communities. Currently available medications for treating MDD target the monoaminergic systems. The most prescribed medications include selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors. However, these medications have serious drawbacks, such as a delayed onset requiring weeks or months to reach efficacy and drug resistance, as one-third of patients are unresponsive to the medications. Therefore, it is imperative to develop novel therapies with rapid action, high efficacy and few adverse effects. The discovery of the rapid antidepressant effect of ketamine has triggered tremendous enthusiasm for studying new antidepressants that target the glutamatergic system in the central nervous system. Many agents that directly or indirectly modulate the glutamatergic system have been shown to provide rapid and lasting antidepressant action. Among these agents, ketamine, an antagonist of metabotropic glutamate 2/3 receptors, and scopolamine, an unspecific muscarinic acetylcholine receptor antagonist, have been extensively studied. In this review, we discuss the clinical and preclinical evidence supporting the antidepressant efficacy of these agents and the current understanding of the underlying mechanisms.

INTRODUCTION

Major depressive disorder (MDD) is a worldwide devastating mental disorder characterised by a low mood, reduced interest and impaired cognitive functions.¹ It has a lifetime prevalence of up to 20% of the world's population, affecting both sexes and most ages, and is one of the leading causes of disability.² Currently available medications mainly target the monoaminergic systems, such as selective serotonin and norepinephrine reuptake inhibitors. However, they have significant drawbacks, including slow onset and drug resistance.³ Current antidepressants were discovered in the 1960s, and there had been no breakthroughs in

finding mechanistically different antidepressants until the recent discovery of ketamine's rapid antidepressant action.⁴⁻⁶ Ketamine is an N-methyl D-aspartate receptor (NMDA) antagonist that exerts rapid and long-lasting antidepressant effects in patients with MDD and treatment-resistant depression (TRD). The antidepressant action of ketamine is believed to be achieved by modulating the glutamatergic system.⁶ Following ketamine, many other agents that directly or indirectly modulate glutamate synapses have been found to have rapid antidepressant efficacy in clinical and preclinical studies. Other extensively studied agents include antagonists of metabotropic glutamate 2/3 receptors (mGluR2/3) and scopolamine, a non-specific muscarinic acetylcholine receptor (mAChR) antagonist.^{3 7 8} To date, clinical trials have provided strong evidence supporting the efficacy and safety of ketamine in the treatment of MDD, TRD, bipolar depression, post-traumatic stress disorder (PTSD) and suicidal ideations.^{9 10} Clinical trials also support the efficacy of scopolamine in treating depression and bipolar depression; however, the effectiveness of scopolamine in TRD is still under study.¹¹ Clinical studies on the efficacy of mGluR2/3 antagonists in depression are still in the early phase, and few outcomes have been published. The mechanisms underlying the rapid antidepressant actions of these agents have been extensively studied in animal models of depression. It is generally agreed that ketamine, mGluR2/3 antagonists and scopolamine share a convergent mechanism: enhanced glutamatergic activity which activates brain-derived neurotrophic factor (BDNF) and the mammalian target of rapamycin complex-1 (mTORC1) signalling system, leading to neurogenesis.^{12 13} In this article, we review the clinical and preclinical evidence of the antidepressant efficacy of



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ketamine, mGluR2/3 antagonists, and scopolamine and the underlying mechanisms.

RAPID ANTIDEPRESSANT ACTION OF KETAMINE

Ketamine is a non-competitive antagonist of NMDA receptors.¹⁴ The antidepressant effects of NMDA receptor antagonists have been reported for the first time in preclinical studies. It was found that competitive and non-competitive antagonists and partial agonists of NMDA receptors had antidepressant effects in a stress animal model, similar to clinically used antidepressants.¹⁵ Subsequently, it was found that a single anaesthetic dose of ketamine (160mg/kg) significantly reduced immobility in the forced swim test in a rat model of depression.¹⁶ The first placebo-controlled, double-blinded clinical trial of ketamine in the treatment of depression was conducted on seven subjects with MDD. It was found that a single intravenous subanaesthetic dose of ketamine (0.5mg/kg, 40min infusion) significantly improved depressive symptoms within 72 hours.^{4,6} Another placebo-controlled, double-blind crossover study showed that a single intravenous dose of ketamine (0.5mg/kg) induced rapid antidepressant effects that occurred as early as 2 hours after infusion and lasted a week.⁵ Since these pioneering studies, the antidepressant efficacy of ketamine has been generally replicated and demonstrated in clinical trials with TRD, bipolar disorder, suicidal ideation, PTSD and adolescent depression.

Approximately one-third of patients with depression respond inadequately to conventional medications and are diagnosed with TRD.³ TRD was defined as failure to respond to at least two antidepressant medications of different classes.^{17,18} Many clinical trials have demonstrated the efficacy of ketamine for the treatment of TRD. An early clinical study with a few subjects showed that a single dose of ketamine significantly improved depressive symptoms in 71% of patients with TRD after 1 day, and 35% achieved response after 1 week.⁵ A subsequent study with a relatively large number of patients with TRD confirmed the rapid-onset antidepressant efficacy of a single dose of ketamine.¹⁹ Although a single dose of ketamine is effective, the effect may be transient. Therefore, repeated doses of ketamine were tested. It was found that multiple doses of ketamine, such as six doses in 2 weeks, had a cumulative effect lasting more than 3 months in some patients, and ketamine at multiple doses was safe and well tolerated.¹⁹⁻²⁴

Ketamine has also been shown to be effective in the treatment of bipolar depression. A randomised, placebo-controlled, double-blind, crossover add-on study showed that a single dose of ketamine (0.5mg/kg) improved depressive symptoms as early as 40min after the infusion, lasting 3 days in patients with bipolar TRD.²⁵ More than 50% of patients responded to a single dose or multiple doses (six doses) of ketamine. These doses of ketamine were well tolerated.²⁶ Adolescent depression is common and associated with significant morbidity and suicide. A double-blind, randomised, placebo-controlled clinical trial found that intravenous ketamine in adolescents with TRD significantly improved

symptoms and was well tolerated.²⁷ In patients with PTSD, a single dose and repeated doses of ketamine have also been shown to improve depressive symptoms.²⁸⁻³⁰

In depressive patients with suicidal ideation, ketamine has also been shown to reduce suicidal ideations rapidly.³¹ In an open-label study of a single infusion, ketamine (0.5mg/kg) decreased suicidal ideation within 40min, and the effect remained for 4 hours. Other depressive symptoms and anxiety also significantly improved.³² In a randomised, double-blind, placebo-controlled study, a single dose of ketamine (0.2mg/kg) reduced suicidal ideation 90min after ketamine infusion in 88% of patients.³³ Two infusions of ketamine over 2 days showed long-term improvements in suicidal patients.³⁴ Thus, ketamine shows a rapid and persistent benefit for patients with suicidal behaviour.

Ketamine is a racemic mixture comprising equal parts of (R)-ketamine (or arketamine) and (S)-ketamine (or esketamine).³⁵ Clinical trials have found that the intravenous infusion of ketamine exerts a rapid antidepressant effect.^{36,37} The antidepressant effects lasted for several days or weeks. In preclinical studies, (R)-ketamine has been shown to be more effective than (S)-ketamine, but its effect has not been established in clinical trials.^{35,38} Randomised double-blind clinical trials have revealed the effectiveness of the intranasal form of (S)-ketamine in TRD and suicidal ideations.³⁹ The antidepressant effect of intranasal ketamine was significant and rapid, and the effect persisted for more than 2 months when applied biweekly.^{36,39} The Food and Drug Administration approved the intranasal administration of (S)-ketamine in 2019 for TRD in adults. However, due to possible adverse effects such as dissociation, sedation, cognitive impairments and addiction, the use of ketamine is limited under certain conditions.^{20,36}

ANTAGONISTS OF GROUP II METABOTROPIC GLUTAMATE RECEPTORS (MGLURS)

Glutamate receptors mediate excitatory synaptic transmission in the central nervous system and are divided into two subtypes: ionotropic receptors and mGluRs.⁴⁰ Ionotropic receptors are ion channels that mediate synaptic transmission, whereas mGluRs regulate synaptic transmission and plasticity by interacting with G proteins. mGluRs contain eight subtypes classified into three groups according to their coupled G proteins and functions.⁴¹ Group II mGluRs, including mGluR2/3, have been implicated in depression due to their antidepressant effects. The expression of mGluR2/3 was found to be significantly increased in the prefrontal cortex (PFC) of patients with depression. The same has been observed in animal models of depression, indicating the possible role of mGluR2/3 in depression.⁴²

The rapid antidepressant effect of mGluR2/3 antagonists has mainly been found in animal studies.⁴³ It was first shown that the intraperitoneal injection of (1R, 2R, 3R, 5R and 6R)-2-amino-3-(3,4-dichlorobenzoyloxy)-6-fluorobicyclo(3.1.0)hexane-2,6-dicarboxylic acid (MGS0039, 3mg/kg) or (2S)-2-amino-2-((1S,2S)-2-carboxycycloprop-1-yl)-3-(xanth-9-yl) propanoic acid (LY341495, 1mg/kg), two

potent mGluR2/3 antagonists, significantly decreased the immobility time of forced swim and tail suspension tests in rats. Since then, many preclinical studies have shown that mGluR2/3 antagonists have rapid antidepressant effects in various animal models, including learnt helplessness⁴⁴ and olfactory bulb enucleation.⁴⁵ Similar to ketamine, mGluR2/3 antagonists are also effective in models of depression in which conventional antidepressants are ineffective.⁴⁶ MGS0039 or LY341495 reversed depressive behaviours caused by chronic corticosterone administration in mice and rats, whereas traditional antidepressants did not affect this type of depression model.⁴⁶ Moreover, in chronic unpredictable stress and chronic social frustration models, a single dose of a mGluR2/3 antagonist could have a rapid antidepressant effect lasting for more than 1 week.^{47,48}

In contrast to ketamine, studies have found that mGluR2/3 antagonists might not have adverse effects similar to ketamine.^{49–51} mGluR2/3 antagonists can protect cognitive function. It has been shown that intraperitoneal administration of the mGluR2/3 antagonist MGS0039 enhanced social recognition memory^{52–54} and had anxiolytic effects in the conditional fear stress model and Vogel conflict drinking test.^{44,55} These results indicate that mGluR2/3 antagonists are promising therapeutics for depression, with fewer adverse effects than ketamine. However, clinical studies on the efficacy of mGluR2/3 antagonists in depression are still in the early phase and few outcomes have been published.⁴³

SCOPOLAMINE: A MACHR ANTAGONIST

Hypersensitivity of the cholinergic system has been proposed to mediate the pathogenesis of depression.⁵⁶ This notion was supported by early findings that cholinesterase inhibitors, such as physostigmine, led to or aggravated depressive symptoms in healthy people and depressive patients.⁵⁷ Thus, antagonism of the cholinergic system has been proposed to exert antidepressant effects. Scopolamine is a non-selective antagonist of mAChRs that has been shown to exert a rapid antidepressant effect.^{58,59} The first clinical trial to study the effects of scopolamine in patients with depression was conducted in 1991.⁶⁰ Intramuscular injection of scopolamine (0.4 mg, three doses) was found to exert a small but significant antidepressant effect 24 hours after the injection. Subsequently, several well-designed double-blind placebo-controlled trials have been conducted. Intravenous infusions of scopolamine at three doses (4.0 µg/kg, 15 min per dose) with 3–4 day intervals between doses resulted in significant reductions in depressive symptoms.⁷ Patients with depression and bipolar disorder were included in the trial. The antidepressant action of scopolamine was later replicated in a second double-blind placebo-controlled trial conducted by the same group of patients with purely unipolar depressive patients. It has also been found that scopolamine exerts an antidepressant effect with greater efficacy in women.⁶¹ However, the antidepressant action of scopolamine has not been replicated in some clinical studies, and it remains unclear whether scopolamine exerts comparable antidepressant effects in patients with bipolar disorder.^{11,59,62} A clinical

trial is ongoing in patients with only bipolar disorder.⁶³ Clinical trials are also needed to investigate the antidepressant effects of scopolamine in TRD.

MECHANISMS UNDERLYING RAPID ANTIDEPRESSANTS

Ketamine, mGluR2/3 antagonists and scopolamine have been shown to share a common mechanism for their rapid antidepressant actions: the activation of BDNF–mTORC1 signalling cascades leading to neurogenesis.^{13,64} It was also agreed that these new antidepressants initially enhance α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor activity in pyramidal neurons in the PFC and hippocampus, which increases the production and release of BDNF. BDNF subsequently activates the BDNF–mTORC1 signalling pathway, leading to neurogenesis and restoration of neuronal circuitries.^{13,65,66}

Increased activity of AMPA receptors

An increase in glutamate concentration in the PFC and the subsequent increase in AMPA receptor activity play crucial roles in the rapid antidepressant action of ketamine, scopolamine and mGluR2/3 antagonists.^{12,13} Considerable evidence has been reported to support the idea that enhanced AMPA receptor activity mediates the initial action of these antidepressants. Systemic administration or microinjection of the AMPA receptor antagonist 2,3-dioxo-6-nitro-7-sulfamoyl-benzo(f)quinoxaline into the medial PFC blocked the antidepressant effects of all these agents.⁶⁷

Enhanced BDNF production and release

BDNF is a growth factor that regulates neuronal growth, synaptogenesis and synaptic plasticity⁶⁸ and also plays an important role in the pathophysiology of depression and treatment.⁶⁹ Conventional antidepressants and electroconvulsive therapy enhance BDNF and tropomyosin receptor kinase B (TrkB) mRNA expression in the hippocampus and cortical regions.^{70,71} Deletion of BDNF in the hippocampal dentate gyrus region reduced the antidepressant action.⁷² It was found that the expression level of BDNF decreased in the brain of depressed patients.^{73,74} The direct injection of BDNF into the hippocampus resulted in an antidepressant effect.⁷⁵ Infusion of BDNF antibodies into the medial PFC blocks the antidepressant effect.⁷⁶ Patients with depression carrying Met/Met, showing a deficit in BDNF production and release, did not respond to ketamine.^{77,78} Similarly, the rapid antidepressant action of scopolamine was attenuated in BDNF Val/Met knock-in mice and prevented by the infusion of an anti-BDNF antibody into the medial PFC.⁷⁹ The mGluR2/3 antagonists LY341495 and MGS0039 also require the activation of BDNF signalling pathways for their rapid antidepressant actions.⁴⁷

BDNF–mTORC1 signalling pathways

BDNF binds to its primary receptor, TrkB, to activate several signalling pathways.⁶⁸ It enhances the activity of AMPA receptors by increasing AMPA receptor translation and surface expression.⁸⁰ Subsequent activation of

the phosphatidylinositol 3-kinase and mitogen-activated protein kinase signalling pathways leads to the activation of mTORC1, which facilitates phosphorylation of the synaptic p70S6 kinase and suppression of 4E binding proteins, resulting in the synthesis of proteins related to synaptogenesis and dendrite spine growth.¹³ Preclinical studies have shown that ketamine, mGluR2/3 antagonists and scopolamine all increase phospho-mTOR, phospho-p70S6 kinase in the hippocampus and medial PFC of rodents.⁸¹ Pretreatment with the selective mTORC1 inhibitor rapamycin prevented the antidepressant actions.¹³ Thus, the mTORC1 signalling pathway is an integral molecular mechanism underlying the antidepressant action.

Disinhibition hypothesis

While ketamine, mGluR2/3 antagonists and scopolamine act on different receptors, they all activate the glutamatergic system and BDNF–mTORC1 signalling pathways, which are believed to underlie their antidepressant action.¹³ The initial mechanisms that increase glutamatergic activity and BDNF production are poorly understood. One hypothesis is the disinhibition of pyramidal neurons, which is proposed to be caused by the inhibition of GABAergic interneurons.^{82–83} Silencing GABAergic interneurons in the PFC has been reported to induce a rapid antidepressant effect.⁸⁴ The antidepressant effect of ketamine requires the NMDA receptor subunit GluN2B in GABAergic interneurons but not in the pyramidal neurons in the PFC since the knockdown of these receptors in the interneurons blocks the ketamine's effect.⁸⁵ Ketamine and scopolamine have been reported to inhibit pyramidal neurons by reducing the inhibitory input into the pyramidal cells.⁸⁶ Furthermore, the antidepressant action of scopolamine was shown to depend on the inhibition of GABAergic interneurons and muscarinic receptors in the GABAergic neurons since the activation of GABAergic interneurons or knockdown of M1 receptors in the interneurons in the PFC blocked the antidepressant effect.^{82–84}

Another theory is that ketamine blocks the spontaneous NMDA receptor activity of pyramidal neurons in the resting state, which inactivates eukaryotic elongation factor two kinase, leading to the disinhibition of the BDNF synthesis.^{87–88} The antidepressant effect of ketamine has also been reported to be independent of the blockage of NMDA receptors. (2R, 6R)-Hydroxynorketamine is a metabolite of ketamine, which is found to exert a rapid antidepressant action but does not block the NMDA receptors, and requires the activation of AMPA receptors, BDNF and mTORC1 signalling pathways.⁸⁹

Interaction with serotonin (5-HT) and the dopamine system

Recent studies have indicated that the serotonergic system may play a critical role in the rapid antidepressant action of ketamine and mGluR2/3 antagonists.^{90–91} It was found that ketamine increased extracellular serotonin concentration in the medial PFC, which is mediated by the AMPA receptor activity in serotonergic neurons in the dorsal raphe nucleus (DRN).⁹² Similar to ketamine, mGluR2/3 antagonists also require the activation of 5-HT neurons in the DRN.⁶⁷

Furthermore, 5-HT1a receptors were found to mediate the effects of both ketamine and mGluR2/3 antagonists.^{93–94} The activity of dopamine neurons in the ventral tegmental area may also play a role in the rapid antidepressant action.⁴⁹ Therefore, multiple systems and signalling pathways might be involved in the mechanisms underlying the antidepressant action.

SUMMARY

The discovery of the rapid antidepressant action of ketamine is a significant step toward the development of novel antidepressants. Since then, great attention has been paid to the glutamatergic system, as it is believed to probably mediate depression and antidepressant processes and be a new target in developing new antidepressants that will have fewer drawbacks than the current antidepressants. Ketamine, a mGluR2/3 antagonist, and scopolamine have been extensively studied as novel rapid antidepressants. These studies have shed significant light on the cellular and molecular mechanisms underlying depression and antidepressant actions. It is now generally believed that BDNF–mTORC1-neurogenesis is possibly a common signalling pathway shared by different antidepressants. The intranasal form of (S)-ketamine has been approved for clinical use in the treatment of TRD. Our understanding of the underlying mechanisms of rapid antidepressant action has advanced substantially, and as a result, more new targets will be revealed to develop rapid, efficacious antidepressants. Further clinical trials are ongoing to investigate the possible extended use of ketamine. Clinical trials are being conducted for scopolamine, mGluR2/3 antagonists and other agents.

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REFERENCES

- Otte C, Gold SM, Penninx BW, *et al*. Major depressive disorder. *Nat Rev Dis Primers* 2016;2:16065.
- Kessler RC, Bromet EJ. The epidemiology of depression across cultures. *Annu Rev Public Health* 2013;34:119–38.
- Machado-Vieira R, Henter ID, Zarate CA. New targets for rapid antidepressant action. *Prog Neurobiol* 2017;152:21–37.
- Berman RM, Cappiello A, Anand A, *et al*. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 2000;47:351–4.

- 5 Zarate CA, Singh JB, Carlson PJ, *et al.* A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 2006;63:856–64.
- 6 Krystal JH, Abdallah CG, Sanacora G, *et al.* Ketamine: a paradigm shift for depression research and treatment. *Neuron* 2019;101:774–8.
- 7 Furey ML, Drevets WC. Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. *Arch Gen Psychiatry* 2006;63:1121–9.
- 8 Chaki S, Koike H, Fukumoto K. Targeting of metabotropic glutamate receptors for the development of novel antidepressants. *Chron Stress* 2019;3:247054701983771.
- 9 Krystal JH, Sanacora G, Duman RS. Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond. *Biol Psychiatry* 2013;73:1133–41.
- 10 Krystal JH, Charney DS, Duman RS. A new rapid-acting antidepressant. *Cell* 2020;181:7.
- 11 Drevets WC, Bhattacharya A, Furey ML. The antidepressant efficacy of the muscarinic antagonist scopolamine: past findings and future directions. *Adv Pharmacol* 2020;89:357–86.
- 12 Wohleb ES, Gerhard D, Thomas A, *et al.* Molecular and cellular mechanisms of rapid-acting antidepressants ketamine and scopolamine. *Curr Neuropharmacol* 2017;15:11–20.
- 13 Zanos P, Thompson SM, Duman RS, *et al.* Convergent mechanisms underlying rapid antidepressant action. *CNS Drugs* 2018;32:197–227.
- 14 Zarate CA, Machado-Vieira R. Potential pathways involved in the rapid antidepressant effects of nitrous oxide. *Biol Psychiatry* 2015;78:2–4.
- 15 Trullas R, Skolnick P. Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. *Eur J Pharmacol* 1990;185:1–10.
- 16 Yilmaz A, Schulz D, Aksoy A, *et al.* Prolonged effect of an anesthetic dose of ketamine on behavioral despair. *Pharmacol Biochem Behav* 2002;71:341–4.
- 17 Gaynes BN, Lux L, Gartlehner G, *et al.* Defining treatment-resistant depression. *Depress Anxiety* 2020;37:134–45.
- 18 Rybak YE, Lai KSP, Ramasubbu R, *et al.* Treatment-resistant major depressive disorder: Canadian expert consensus on definition and assessment. *Depress Anxiety* 2021;38:456–67.
- 19 Murrough JW, Perez AM, Pillemer S, *et al.* Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry* 2013;74:250–6.
- 20 Wan L-B, Levitch CF, Perez AM, *et al.* Ketamine safety and tolerability in clinical trials for treatment-resistant depression. *J Clin Psychiatry* 2015;76:247–52.
- 21 aan het Rot M, Collins KA, Murrough JW, *et al.* Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry* 2010;67:139–45.
- 22 Phillips JL, Norris S, Talbot J, *et al.* Single, repeated, and maintenance ketamine infusions for treatment-resistant depression: a randomized controlled trial. *Am J Psychiatry* 2019;176:401–9.
- 23 Covvey JR, Crawford AN, Lowe DK. Intravenous ketamine for treatment-resistant major depressive disorder. *Ann Pharmacother* 2012;46:117–23.
- 24 Shiroma PR, Thuras P, Wels J, *et al.* A proof-of-concept study of subanesthetic intravenous ketamine combined with prolonged exposure therapy among veterans with posttraumatic stress disorder. *J Clin Psychiatry* 2020;81:20113406.
- 25 Diazgranados N, Ibrahim L, Brutsche NE, *et al.* A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry* 2010;67:793–802.
- 26 Bahji A, Zarate CA, Vazquez GH. Ketamine for bipolar depression: a systematic review. *Int J Neuropsychopharmacol* 2021;24:535–41.
- 27 Dwyer JB, Landeros-Weisenberger A, Johnson JA, *et al.* Efficacy of intravenous ketamine in adolescent treatment-resistant depression: a randomized midazolam-controlled trial. *Am J Psychiatry* 2021;178:352–62.
- 28 Feder A, Parides MK, Murrough JW, *et al.* Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder. *JAMA Psychiatry* 2014;71:681–8.
- 29 Feder A, Costi S, Rutter SB, *et al.* A randomized controlled trial of repeated ketamine administration for chronic posttraumatic stress disorder. *Am J Psychiatry* 2021;178:193–202.
- 30 Albott CS, Lim KO, Forbes MK, *et al.* Efficacy, safety, and durability of repeated ketamine infusions for comorbid posttraumatic stress disorder and treatment-resistant depression. *J Clin Psychiatry* 2018;79:17m11634.
- 31 Wilkinson ST, Ballard ED, Bloch MH, *et al.* The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *Am J Psychiatry* 2018;175:150–8.
- 32 DiazGranados N, Ibrahim LA, Brutsche NE, *et al.* Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry* 2010;71:1605–11.
- 33 Domany Y, Shelton RC, McCullumsmith CB. Ketamine for acute suicidal ideation. An emergency department intervention: a randomized, double-blind, placebo-controlled, proof-of-concept trial. *Depress Anxiety* 2020;37:224–33.
- 34 Abbar M, Demattei C, El-Hage W, *et al.* Ketamine for the acute treatment of severe suicidal ideation: double blind, randomised placebo controlled trial. *BMJ* 2022;376:e067194.
- 35 Hashimoto K. Molecular mechanisms of the rapid-acting and long-lasting antidepressant actions of (R)-ketamine. *Biochem Pharmacol* 2020;177:113935.
- 36 Daly EJ, Singh JB, Fedgchin M, *et al.* Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry* 2018;75:139–48.
- 37 Bozymski KM, Crouse EL, Titus-Lay EN, *et al.* Esketamine: a novel option for treatment-resistant depression. *Ann Pharmacother* 2020;54:567–76.
- 38 Yang C, Shirayama Y, Zhang J-c, *et al.* R-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. *Transl Psychiatry* 2015;5:e632.
- 39 Canuso CM, Singh JB, Fedgchin M, *et al.* Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. *Am J Psychiatry* 2018;175:620–30.
- 40 Reiner A, Levitz J. Glutamatergic signaling in the central nervous system: ionotropic and metabotropic receptors in concert. *Neuron* 2018;98:1080–98.
- 41 Niswender CM, Conn PJ. Metabotropic glutamate receptors: physiology, pharmacology, and disease. *Annu Rev Pharmacol Toxicol* 2010;50:295–322.
- 42 Feyissa AM, Woolverton WL, Miguel-Hidalgo JJ, *et al.* Elevated level of metabotropic glutamate receptor 2/3 in the prefrontal cortex in major depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2010;34:279–83.
- 43 Chaki S. mGlu2/3 receptor antagonists as novel antidepressants. *Trends Pharmacol Sci* 2017;38:569–80.
- 44 Yoshimizu T, Shimazaki T, Ito A, *et al.* An mGluR2/3 antagonist, MGS0039, exerts antidepressant and anxiolytic effects in behavioral models in rats. *Psychopharmacology* 2006;186:587–93.
- 45 Patucha-Poniewiera A, Wierońska JM, Brański P, *et al.* On the mechanism of the antidepressant-like action of group II mGlu receptor antagonist, MGS0039. *Psychopharmacology* 2010;212:523–35.
- 46 Koike H, Iijima M, Chaki S. Effects of ketamine and LY341495 on the depressive-like behavior of repeated corticosterone-injected rats. *Pharmacol Biochem Behav* 2013;107:20–3.
- 47 Dong C, Zhang J-C, Yao W, *et al.* Rapid and sustained antidepressant action of the mGlu2/3 receptor antagonist MGS0039 in the social defeat stress model: comparison with ketamine. *Int J Neuropsychopharmacol* 2017;20:228–36.
- 48 Dwyer JM, Lepack AE, Duman RS. mGluR2/3 blockade produces rapid and long-lasting reversal of anhedonia caused by chronic stress exposure. *J Mol Psychiatry* 2013;1:15.
- 49 Witkin JM, Monn JA, Schoepp DD, *et al.* The rapidly acting antidepressant ketamine and the mGlu2/3 receptor antagonist LY341495 rapidly engage dopaminergic mood circuits. *J Pharmacol Exp Ther* 2016;358:71–82.
- 50 Witkin JM. mGlu2/3 receptor antagonism: a mechanism to induce rapid antidepressant effects without ketamine-associated side-effects. *Pharmacol Biochem Behav* 2020;190:172854.
- 51 Witkin JM, Monn JA, Li J, *et al.* Preclinical predictors that the orthosteric mGlu2/3 receptor antagonist LY3020371 will not engender ketamine-associated neurotoxic, motor, cognitive, subjective, or abuse-liability-related effects. *Pharmacol Biochem Behav* 2017;155:43–55.
- 52 Shimazaki T, Kaku A, Chaki S. Blockade of the metabotropic glutamate 2/3 receptors enhances social memory via the AMPA receptor in rats. *Eur J Pharmacol* 2007;575:94–7.
- 53 Goeldner C, Ballard TM, Knoflach F, *et al.* Cognitive impairment in major depression and the mGlu2 receptor as a therapeutic target. *Neuropharmacology* 2013;64:337–46.
- 54 Dogra S, Conn PJ. Targeting metabotropic glutamate receptors for the treatment of depression and other stress-related disorders. *Neuropharmacology* 2021;196:108687.
- 55 Stachowicz K, Wierońska J, Domin H, *et al.* Anxiolytic-like activity of mgs0039, a selective group II mGlu receptor antagonist, is serotonin- and GABA-dependent. *Pharmacological Reports* 2011;63:880–7.

- 56 Dulawa SC, Janowsky DS. Cholinergic regulation of mood: from basic and clinical studies to emerging therapeutics. *Mol Psychiatry* 2019;24:694–709.
- 57 Janowsky DS, el-Yousef MK, Davis JM, et al. A cholinergic-adrenergic hypothesis of mania and depression. *Lancet* 1972;2:632–5.
- 58 Brown DA. Muscarinic acetylcholine receptors (mAChRs) in the nervous system: some functions and mechanisms. *J Mol Neurosci* 2010;41:340–6.
- 59 Drevets WC, Zarate CA, Furey ML. Antidepressant effects of the muscarinic cholinergic receptor antagonist scopolamine: a review. *Biol Psychiatry* 2013;73:1156–63.
- 60 Gillin JC, Sutton L, Ruiz C, et al. The effects of scopolamine on sleep and mood in depressed patients with a history of alcoholism and a normal comparison group. *Biol Psychiatry* 1991;30:157–69.
- 61 Furey ML, Khanna A, Hoffman EM, et al. Scopolamine produces larger antidepressant and anti-anxiety effects in women than in men. *Neuropsychopharmacology* 2010;35:2479–88.
- 62 Park L, Furey M, Nugent AC, et al. Neurophysiological changes associated with antidepressant response to ketamine not observed in a negative trial of scopolamine in major depressive disorder. *Int J Neuropsychopharmacol* 2019;22:10–18.
- 63 Miravalles C, Kane R, McMahon E, et al. Efficacy and safety of scopolamine compared to placebo in individuals with bipolar disorder who are experiencing a depressive episode (SCOPE-BD): study protocol for a randomised double-blind placebo-controlled trial. *Trials* 2022;23:339.
- 64 Henter ID, Park LT, Zarate CA. Novel glutamatergic modulators for the treatment of mood disorders: current status. *CNS Drugs* 2021;35:527–43.
- 65 Li N, Lee B, Liu R-J, et al. mTOR-Dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* 2010;329:959–64.
- 66 Deyama S, Duman RS. Neurotrophic mechanisms underlying the rapid and sustained antidepressant actions of ketamine. *Pharmacol Biochem Behav* 2020;188:172837.
- 67 Fukumoto K, Iijima M, Chaki S. The antidepressant effects of an mGlu2/3 receptor antagonist and ketamine require AMPA receptor stimulation in the mPFC and subsequent activation of the 5-HT neurons in the DRN. *Neuropsychopharmacology* 2016;41:1046–56.
- 68 Park H, Poo M-ming, Poo MM. Neurotrophin regulation of neural circuit development and function. *Nat Rev Neurosci* 2013;14:7–23.
- 69 Björkholm C, Monteggia LM. BDNF - a key transducer of antidepressant effects. *Neuropharmacology* 2016;102:72–9.
- 70 Nibuya M, Morinobu S, Duman RS. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *The Journal of Neuroscience* 1995;15:7539–47.
- 71 Nibuya M, Nestler EJ, Duman RS. Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. *The Journal of Neuroscience* 1996;16:2365–72.
- 72 Adachi M, Barrot M, Autry AE, et al. Selective loss of brain-derived neurotrophic factor in the dentate gyrus attenuates antidepressant efficacy. *Biol Psychiatry* 2008;63:642–9.
- 73 Duman RS, Aghajanian GK, Sanacora G, et al. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med* 2016;22:238–49.
- 74 Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. *Science* 2012;338:68–72.
- 75 Shirayama Y, Chen AC-H, Nakagawa S, et al. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. *The Journal of Neuroscience* 2002;22:3251–61.
- 76 Lepack AE, Fuchikami M, Dwyer JM, et al. Bdnf release is required for the behavioral actions of ketamine. *Int J Neuropsychopharmacol* 2014;18:pyu033.
- 77 Chen Z-Y, Jing D, Bath KG, et al. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science* 2006;314:140–3.
- 78 Egan MF, Kojima M, Callicott JH, et al. The BDNF Val66Met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 2003;112:257–69.
- 79 Ghosal S, Bang E, Yue W, et al. Activity-dependent brain-derived neurotrophic factor release is required for the rapid antidepressant actions of scopolamine. *Biol Psychiatry* 2018;83:29–37.
- 80 Caldeira MV, Melo CV, Pereira DB, et al. Brain-derived neurotrophic factor regulates the expression and synaptic delivery of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor subunits in hippocampal neurons. *J Biol Chem* 2007;282:12619–28.
- 81 Voleti B, Navarria A, Liu R-J, et al. Scopolamine rapidly increases mammalian target of rapamycin complex 1 signaling, synaptogenesis, and antidepressant behavioral responses. *Biol Psychiatry* 2013;74:742–9.
- 82 Wohleb ES, Wu M, Gerhard DM, et al. Gaba interneurons mediate the rapid antidepressant-like effects of scopolamine. *J Clin Invest* 2016;126:2482–94.
- 83 Miller OH, Moran JT, Hall BJ. Two cellular hypotheses explaining the initiation of ketamine's antidepressant actions: direct inhibition and disinhibition. *Neuropharmacology* 2016;100:17–26.
- 84 Fogaça MV, Wu M, Li C, et al. Inhibition of GABA interneurons in the mPFC is sufficient and necessary for rapid antidepressant responses. *Mol Psychiatry* 2021;26:3277–91.
- 85 Gerhard DM, Pothula S, Liu R-J, et al. Gaba interneurons are the cellular trigger for ketamine's rapid antidepressant actions. *J Clin Invest* 2020;130:1336–49.
- 86 Widman AJ, McMahon LL. Disinhibition of CA1 pyramidal cells by low-dose ketamine and other antagonists with rapid antidepressant efficacy. *Proc Natl Acad Sci U S A* 2018;115:E3007–16.
- 87 Suzuki K, Monteggia LM. The role of eEF2 kinase in the rapid antidepressant actions of ketamine. *Adv Pharmacol* 2020;89:79–99.
- 88 Autry AE, Adachi M, Nosyreva E, et al. Nmda receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature* 2011;475:91–5.
- 89 Zanos P, Moaddel R, Morris PJ, et al. Nmdar inhibition-independent antidepressant actions of ketamine metabolites. *Nature* 2016;533:481–6.
- 90 Chaki S, Fukumoto K. Role of serotonergic system in the antidepressant actions of mGlu2/3 receptor antagonists: similarity to ketamine. *Int J Mol Sci* 2019;20:1270.
- 91 Gigliucci V, O'Dowd G, Casey S, et al. Ketamine elicits sustained antidepressant-like activity via a serotonin-dependent mechanism. *Psychopharmacology* 2013;228:157–66.
- 92 Nishitani N, Nagayasu K, Asaoka N, et al. Raphe AMPA receptors and nicotinic acetylcholine receptors mediate ketamine-induced serotonin release in the rat prefrontal cortex. *Int J Neuropsychopharmacol* 2014;17:1321–6.
- 93 Fukumoto K, Iijima M, Funakoshi T, et al. 5-Ht1A receptor stimulation in the medial prefrontal cortex mediates the antidepressant effects of mGlu2/3 receptor antagonist in mice. *Neuropharmacology* 2018;137:96–103.
- 94 Fukumoto K, Iijima M, Chaki S. Serotonin-1A receptor stimulation mediates effects of a metabotropic glutamate 2/3 receptor antagonist, 2S-2-amino-2-(1S,2S-2-carboxycycloprop-1-yl)-3-(xanth-9-yl) propanoic acid (LY341495), and an N-methyl-D-aspartate receptor antagonist, ketamine, in the novelty-suppressed feeding test. *Psychopharmacology* 2014;231:2291–8.



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