Pharmacological Research 220 (2025) 107918



Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs





All roads lead to glutamate: NMDA and AMPA receptors as targets for rapid-acting antidepressants

Florian Freudenberg [a,*,1], Christine Reif-Leonhard [a,2], Gerard R. Dawson [b,3], Ruth M. McKernan [c], Andreas Reif [a,d,4]

[a] Goethe University Frankfurt, University Hospital, Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, Frankfurt, Germany
[b] P1vital LTD, Manor House, Howbery Business Park, Wallingford, UK
[c] SV Health Investors, 71 Kingsway, London WC2B 6ST, UK
[d] Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Theodor-Stern-Kai 7, Frankfurt am Main 60596, Germany

ARTICLE INFO

Keywords:
Rapid acting antidepressants
Major depressive disorder
Unipolar depression
Treatment resistant depression
Ketamine
NMDA
AMPA

ABSTRACT

Treatment-resistant depression (TRD) represents a major clinical challenge. Affecting about 30 % of major depressive disorder (MDD) patients, effective treatments for TRD are urgently needed. While depression research and antidepressant (AD) development have long centred on monoaminergic targets, research over the past 35 years has increasingly explored glutamatergic mechanisms. Here we present an extended discussion on developments in glutamatergic drug discovery, focusing on mechanistic convergence between NMDA and AMPA receptor signalling. Beyond established rapid-acting antidepressants (RAADs), such as (es)ketamine and dextromethorphan/bupropion (AXS-05), we highlight novel therapeutic directions involving esmethadone (REL-1017), nitrous oxide, and positive allosteric modulators (PAMs) of NMDA receptors (e.g. rapastinel, zelquistinel, and apimostinel). Moreover, we discuss forward-looking strategies using AMPA receptor PAMs (e.g. osavampator and tulrampator) and targeting of AMPA receptor-interacting proteins. By integrating recent clinical evidence with molecular and physiological findings, we highlight a convergent mechanism across these compounds. This involves increased AMPA receptor activation, triggering BDNF release and mTOR signalling, promoting synaptic strengthening through enhanced AMPA receptor trafficking and dendritic spine formation. Together, targeting glutamatergic signalling represents a transformative path for TRD treatment with high efficacy by more directly modulating pathologically affected signalling modules. These developments place glutamatergic agents at the forefront of next-generation AD strategies.

1. Introduction

Major depressive disorder (MDD) is a common mental condition and a significant health concern and leading cause of disability worldwide [1]. The predominant mode of action (MoA) of most currently used antidepressants (ADs) is aimed at increasing synaptic levels of monoamines, in particular serotonin, norepinephrine and/or dopamine, and, especially for older ADs, targeting several monoamine receptors [2]. Although many MDD patients benefit from treatment with such "conventional" ADs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), they are ineffective in at least one-third of patients, which qualifies as treatment-resistant depression (TRD) [3]. Therefore, there is an urgent need to develop more effective ADs, especially for TRD cases [4]. This review builds on our recently published article on glutamatergic rapid-acting antidepressants (RAADs) in clinical development [5] and on our ten-year-old review proposing a central role of AMPA receptors in depression [6]. Here, we shift from a compound-centric overview to a

* Correspondence to: Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital, Goethe University Frankfurt, Heinrich-Hoffmann-Str. 10, Frankfurt am Main 60528, Germany.
E-mail address: freudenberg@em.uni-frankfurt.de (F. Freudenberg).
[1] 0000-0003-1438-3850
[2] 0000-0002-7628-8413
[3] 0000-0002-8624-7500
[4] 0000-0002-0992-634X

https://doi.org/10.1016/j.phrs.2025.107918
Received 14 May 2025; Received in revised form 15 August 2025; Accepted 16 August 2025
Available online 19 August 2025
1043-6618/© 2025 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

mechanism-centric synthesis centred on NMDA-AMPA-BDNF-mTOR convergence, extending the discussion to AMPA-targeted strategies and their translational positioning. In doing so, we outline why and how targeting glutamatergic and neuroplastic mechanisms, rather than monoaminergic signalling, has moved into the spotlight for TRD treatment.

While there is no clear consensus definition for TRD, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) define it as a failure to respond to two or more conventional antidepressants prescribed at an adequate dose and duration. Notably, several other definitions for TRD have been proposed and additionally, instead of binary solutions, staging approaches that better embrace the disease trajectories of depression have been put forward. Therefore, TRD is currently best understood not as a distinct biological entity, but as a normative construct with variable definitions. Consistent with this variability, the prevalence of TRD has been estimated to range from 6 % up to 55 % [7]

Despite the substantial number of TRD cases and the delayed onset in AD efficacy of several weeks, the view that deficits of the monoaminergic system are the underlying cause of depression predominated for decades [8,9]. However, over time several other hypotheses for the neurobiological mechanisms underlying MDD have been proposed. For example, a critical involvement of the glutamatergic system in the pathophysiology of depression has been shown as extensively discussed elsewhere (e.g. [5,6,10–14]). Given the important involvement of the glutamatergic system as a mediator of synaptic plasticity [15], the observed glutamatergic changes have been suggested to affect synaptic plasticity in MDD patients, culminating in the formulation of the neuroplasticity hypothesis of depression (e.g. reviewed in [16–19]).

According to this neuroplasticity hypothesis, pathological stimuli such as stress, inflammation, and trauma induce changes in neuronal plasticity at glutamatergic synapses. These molecular and synaptic alterations and their reversal by glutamatergic modulators are summarised in Fig. 1. They mainly involve increased inhibition of presynaptic terminals leading to reduced activation of postsynaptic ionotropic glutamate receptors, specifically N-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. This results in diminished activation of downstream pathways important for synaptic plasticity, in particular reduced brain-derived neurotrophic factor (BDNF)-mediated activation of the mammalian target of rapamycin (mTOR) pathway. This reduction in synaptic plasticity leads to a structural decrease in synaptic contacts, which has been suggested to lead to depression [20]. More recently, deficits in metaplasticity, i.e. the priming of synapses for subsequent plasticity-induced changes, have been emphasized as a cause for deficient neuroplasticity in depression and in AD action [21].

Taken together, the neuroplasticity hypothesis and the concept of deficient metaplasticity convincingly integrate diverse depression risk factors [18,22–25], while also accounting for the delayed efficacy of predominantly monoaminergic conventional ADs [17,20,21,26]. At the heart of these neuroplastic alterations both in depression and following AD treatment are changes in glutamatergic neurotransmission, particularly through NMDA and AMPA receptors.

Because of the central role that these receptors play in the pathophysiology and treatment of MDD, we argue that all roads in MDD therapy ultimately lead to glutamate. We propose that NMDA and AMPA receptor mediated changes in synaptic plasticity, among others by affecting BDNF-mTOR signalling, represent a convergent mechanism underlying AD treatment. Thus, using substances that directly affect NMDA and/or AMPA receptor signalling may lead to more rapid and robust clinical outcomes.

2. Rapid acting antidepressants

The clinical breakthrough of rapid-acting NMDA receptor modulators, most notably ketamine, has pivoted research and clinical developments toward glutamatergic and neuroplasticity-based therapeutics. Preclinical studies in the early 1990s [27–29] and subsequent clinical studies by Berman et al. (2000) [30] and Zarate et al. (2006) [31] demonstrated that subanaesthetic doses of the NMDA receptor antagonist ketamine produced rapid and sustained AD effects with efficacy in TRD patients. While even before the discovery of ketamine's AD action the term RAAD was sporadically used (e.g. [32–36]), it was only broadly applied thereafter. Since then, RAAD has become a functional category significantly guiding drug development pipelines.

RAADs have a rapid onset of action, usually within minutes or hours, often after the first dose, and show high efficacy in TRD patients [37]. However, most studies do not adequately capture the temporal dynamics of RAADs. Often, a baseline measure is compared to a post-administration measurement followed by a later timepoint. When scrutinized on a more granular level, it seems that RAAD administration might follow a seesaw pattern: an initial improvement is followed by relapse, followed by remission after the next administration, until consolidation occurs after five or six administrations [38]. Thus, one might postulate an immediate (i.e. rapid), but short-lasting AD effect, accompanied by a parallel mechanism leading to a more slowly increasing AD effect emerging after several administrations. However, currently too few studies investigate RAAD effects with the granularity required to detect such a pattern and thus do not allow firm conclusions.

As described in our previous review [5] different substance classes of RAADs have been described, which directly or indirectly target the glutamatergic system. In the following, we will discuss the properties of RAADs that modulate the glutamatergic system, particularly focusing on substances targeting NMDA and AMPA receptors. Here we will highlight and discuss the physiological and molecular mechanisms leading to their AD efficacy, particularly in the context of TRD, and will also describe recent clinical developments.

3. NMDA receptor modulators as RAADs

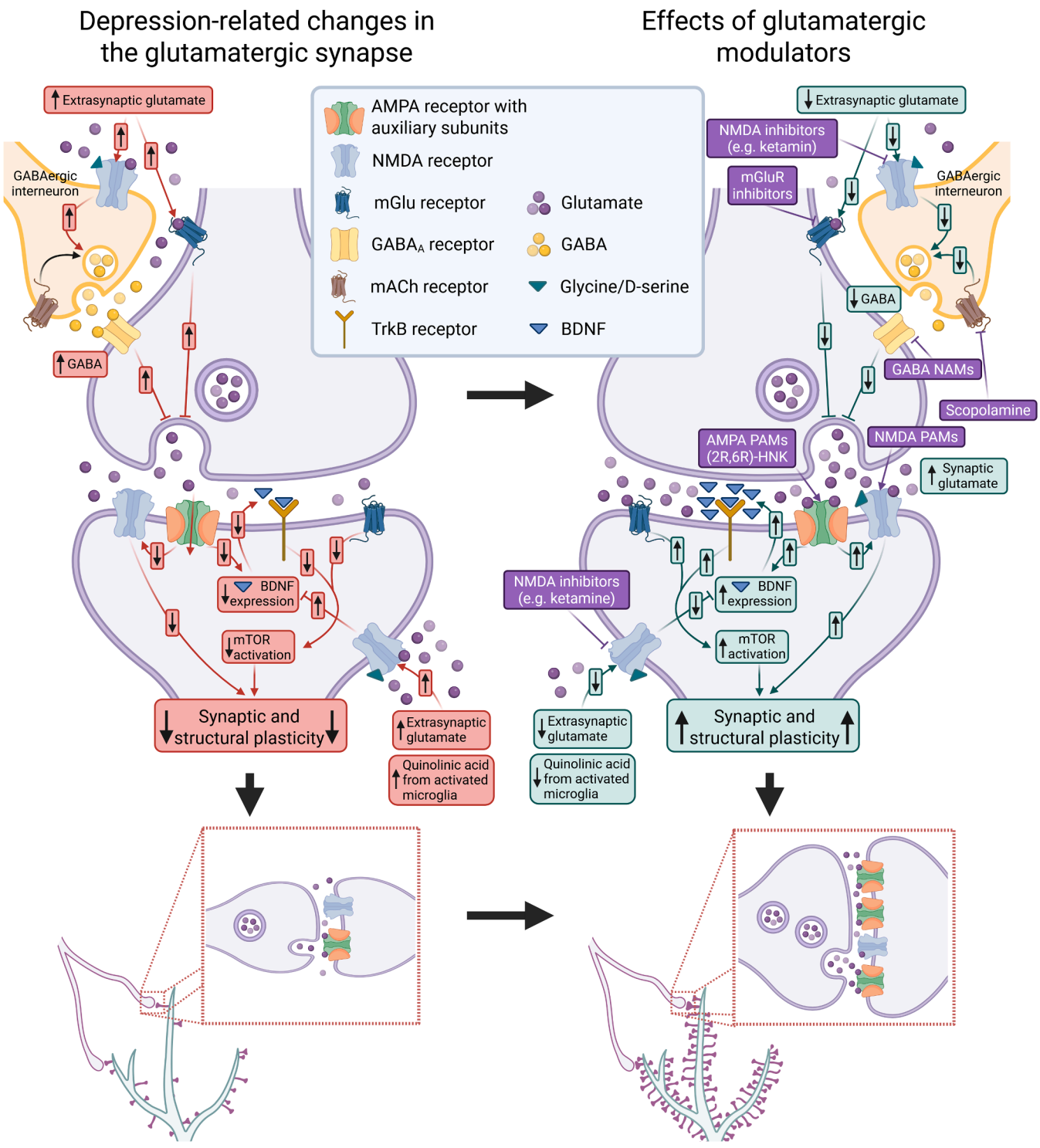
NMDA receptors are tetrameric ionotropic glutamate receptors that are important mediators of neuronal plasticity. The channel pore of NMDA receptors is normally blocked by Mg^{2+} making NMDA receptors synaptic coincidence detectors, i.e. the Mg^{2+}-block is only released at depolarizing potentials and only then will the binding of an agonist lead to channel conductance. Moreover, NMDA receptors conduct Ca^{2+}-ions that can activate downstream synaptic plasticity pathways. Additionally, synaptic plasticity-dependent enhancement of glutamatergic signalling is not only achieved by AMPA, but also NMDA receptor trafficking to the postsynaptic density [39,40].

NMDA receptors have a highly diverse subunit composition that can affect biophysical and pharmacological properties including receptor kinetics and agonist/antagonist binding. Each receptor is composed of two obligatory GluN1 subunits and two subunits of the GluN2 subfamily, of which four different subunits exist, GluN2A, GluN2B, GluN2C, and GluN2D. Alternative incorporation of one of the GluN3 subunits, GluN3A or GluN3B, is possible though comparatively sparse. The agonist glutamate only binds to the GluN2 subunits, while the GluN1 and GluN3 subunits contain a glycine/d-serine binding site. Most NMDA receptors in the early developing brain are GluN1/GluN2B diheteromers. Shortly after birth, GluN2A-containing receptors progressively increase and predominate in the adult forebrain [39–41], though in fact triheteromers, particularly those containing GluN1, GluN2A, and GluN2B, might represent the most abundant receptor species in the adult forebrain [40,42]. Differences in subunit composition between principal neurons and interneurons have been described and have been suggested to differentially contribute to plasticity and disease [43].

As we described previously [5] ketamine's AD properties have been mainly discussed as a result of its preferential inhibition of NMDA receptors localized on GABAergic interneurons [10] leading to disinhibition of the glutamatergic presynaptic terminal. The resulting glutamate release activates postsynaptic AMPA receptors and triggers BDNF-TrkB

stimulation and activation of the mTOR pathway [10,44,45]. Ketamine, via BDNF-TrkB stimulation, has also been shown to activate the ERK pathway [46]. Moreover, ketamine is metabolized to hydroxynorketamine (HNK), which has been suggested to exert AD-like effects by more directly increasing AMPA receptor transmission (see 4.2).

Thus, ketamine does not exert its AD effect simply via NMDA receptor blockade, but importantly also involves other pathways and especially includes enhancement of AMPA receptor transmission. Complicating matters further, opioid activity of ketamine has been linked to its AD properties [47–49]. Whether any of these individual mechanisms themselves can have AD effects, or if they can even be disentangled from each other remains unclear. However, what is clear is that a complex interplay of NMDA and AMPA receptor activity in and around the glutamatergic synapse and their effect on synaptic plasticity are important mediators of the AD effects of ketamine, and likely, also other ADs especially when targeting the glutamate system.



(caption on next page)

Fig. 1. Glutamatergic dysfunction in depression and effects of glutamatergic modulators with rapid-acting antidepressant (RAAD) potential. Left side: Depression-associated alterations at the glutamatergic synapse include increased levels of extrasynaptic glutamate leading to presynaptic activation of metabotropic glutamate (mGlu) receptors and NMDA receptors on GABAergic interneurons projecting on the glutamatergic presynaptic terminal leading to increased GABA release; both mGlu receptor activation and GABA release reduced synaptic glutamate levels. This in turn leads to reduced activation of postsynaptic AMPA, NMDA and mGlu receptors, and consequently reduced activation of downstream plasticity pathway e.g. via brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR) pathway activation. BDNF expression is further inhibited by increased extrasynaptic glutamate (and possibly via inflammatory activation of microglia also quinolinic acid). Longer term, this leads to a reduction of AMPA receptors in the postsynaptic membrane and shrinkage of the postsynaptic spine. **Right side:** Several changes in the glutamatergic synapse are reversed by antidepressant treatment and glutamatergic modulators with RAAD potential directly affect at least some of the aspects. The presynaptic GABA release can be reduced by NMDA receptor inhibitors (e.g. (es)ketamine, dextromethorphan, esmethadone, nitrous oxide), but also by muscarinic inhibitors like scopolamine or GABA receptor negative allosteric modulators (GABA NAMs). The reduced GABA-mediated activation of the presynaptic terminal leads to increased glutamate release. Increased presynaptic glutamate release can also be achieved by inhibition of presynaptically located mGlu receptors. Increases synaptic levels of glutamate can lead to enhanced activation of postsynaptic AMPA and NMDA receptors, which can also be enhanced by the corresponding positive allosteric modulators (PAMs) and AMPA receptor transmission is also enhanced by the ketamine metabolite (2 R,6 R)-hydroxynorketamine (HNK). Increased activation of AMPA, NMDA, and also mGlu receptors, leads to increased BDNF synthesis. BDNF synthesis is also enhanced by NMDA inhibitors acting on extrasynaptic NMDA receptors of the postsynaptic neuron and by reduced extracellular glutamate levels. These effects lead to increased activation of the mTOR and other neural plasticity pathways. Longer term, antidepressant activity leads increased synaptic insertion of AMPA receptors and structural synaptic growth. Created in https://BioRender.com.

Racemic ketamine, containing both the (S)-enantiomer (esketamine) and the (R)-enantiomer (arketamine), has been validated for its RAAD potential in multiple clinical trials [50,51]. However, it is particularly esketamine that appears to exert the AD properties. Although both enantiomers show AD-like potential in animal models (reviewed in [44]), esketamine has about 4-fold higher affinity for the NMDA receptor than arketamine [45]. Consistently, arketamine lacks clinical AD activity (see NCT05414422), whereas esketamine's AD effect has been repeatedly confirmed [52–54]. Esketamine has been approved by both the FDA and EMA in the form of a nasal spray (Spravato®) in 2019. However, off-label use of the racemic mixture mainly via the i.v. route is still part of clinical practice (e.g. [38]) largely due to regulatory requirements that e.g. require combination treatment of the intranasal formulation with a SSRI/SNRI or lacking approval for bipolar depression.

The most promising candidates and their neurobiological effects are discussed in the following. For a more expansive description about the clinical advancements in NMDA receptor based RAADs you are referred to our recent review on this topic [5].

3.1. Dextromethorphan/bupropion

Dextromethorphan (DXM), an over-the-counter cough suppressant, is a low-affinity NMDA receptor antagonist, agonist of sigma-1 receptors, antagonist of nicotinic receptors, and an inhibitor of norepinephrine and serotonin transporters [55,56]. DXM is rapidly O-demethylated to dextrorphan by hepatic CYP2D6 and eliminated [55] thereby limiting brain exposure. However, supra-therapeutic amounts of DXM have psychoactive effects including psychomotor agitation, hallucinations, and paranoia, the so-called "robo-tripping" named after the DXM-containing cough syrup Robitussin®, [57], suggesting transport to the brain at sufficiently high levels.

To circumvent the rapid metabolization of DXM and increase its bioavailability, this drug has been given together with CYP2D6 inhibitors [56]. In preclinical tests, DXM in combination with CYP2D6 inhibitors, consistently showed AD-like effects [58,59]. In clinical trials a fixed DXM/bupropion combination (AXS-05) improved depressive symptoms within one week compared to bupropione alone [60,61]. AXS-05 received FDA approval for treatment of MDD in adults in 2022 and is marketed in the US under the brand-name Auvelity®. *Axsome Therapeutics* has recently started recruitment for phase 4 post-market surveillance (NCT06223880) but is currently unknown whether they will be seeking approval of AXS-05 for the treatment of MDD in the EU or any other jurisdiction. Given the potential of AXS-05 as a first-in-class oral NMDA antagonist treatment, this is quite unfortunate, and we call upon both pharmaceutical industry as well as regulatory/health technology assessment (HTA) agencies to find a way to make this treatment widely available also outside the US.

As SSRIs also inhibit CYP2D6 [62], one clinical trial (NCT05181527) attempted to give DXM as augmentation in patients with mild to moderate depression that are treated with SSRIs. This study showed greater improvement in MDD patients receiving both DXM and SSRIs when compared to SSRI treatment alone [63]. These findings suggest that a DXM/SSRI combination might be a feasible alternative to treatment with specific CYP2D6 inhibitors, but it would be interesting to see if such an approach will also be efficacious in TRD patients.

While it has not been fully resolved yet, how DXM might exert its AD effects, molecular mechanisms akin to those described for ketamine have been proposed [64]. DXM's AD effects appear to require NMDA receptor inhibition, possibly also involving nitric oxide signalling [65], and depend on AMPA receptor activation [58,66]. DXM has no affinity for AMPA receptors itself [67], and in contrast to ketamine, DXM causes reduced glutamate release [55]. Yet, akin to ketamine, DXM may activate the mTOR pathway, thereby increasing synaptic AMPA receptor levels [64]. While no direct evidence for this hypothesis has been provided yet, DXM treatment has been shown to increase levels of circulating BDNF [63,68] supporting a MoA closely aligned with that of ketamine. Yet, there is still relatively limited information on the specific molecular effects of DXM, and how these are possibly altered by co-treatment with CYP2D6 inhibitors.

Of note, deuterated DXM (AVP-786), i.e. DXM with supposedly enhanced metabolic stability, has been tested as an adjunctive treatment in TRD patients by *Otsuka*. However, according to the 2016 financial report [69] development for MDD treatment was halted after a phase 2 trial (NCT02153502) did not provide sufficient evidence for efficacy. It is interesting to note that while deuterated DXM showed AD-like effects in mice, this was not blocked by pre-treatment with AMPA or sigma-1 receptor inhibitors [70], suggesting a distinct MoA from DXM, which may explain the lack of clinical efficacy.

3.2. Esmethadone

Esmethadone (also written d-methadone or dextromethadone), the (S)-enantiomer of methadone, only has weak affinity for opioid receptors and has neither analgesic effects, nor does it cause physical dependence or withdrawal [71–73]. However, esmethadone is a potent NMDA receptor antagonist, with comparable binding affinity as other NMDA receptor inhibitors like ketamine or memantine [73] and has been tested as a potential novel RAAD [74]. In a double-blind phase 2a randomized controlled trial by *Relmada Therapeutics* (NCT03051256) in MDD patients, esmethadone (REL-1017) treatment for seven days caused rapid improvements in depression scores within 4 days that were sustained for at least two weeks, without exerting psychomimetic effects [75]. Two phase 3 clinical trials by *Relmada Therapeutics* (NCT04855747 and NCT06011577), assessing the efficacy of esmethadone as an adjunctive therapy for MDD however were terminated after *"data monitoring committee (DMC) evaluation of the full dataset"* (see December

2024 press release [76]); public release of the data is currently pending. Thus, until the trial results are published, it remains unclear whether this decision was only due to a strategic realignment or also due to a lack of efficacy. The future of esmethadone's development as a RAAD therefore remains uncertain.

Overall, little is known about esmethadone's downstream molecular effects beyond inhibition of NMDA receptors. In a phase 1 trial from *Relmada Therapeutics* (NCT03637361) treatment with esmethadone in healthy adults resulted in a relatively rapid increase in plasma BDNF within 4 h that was sustained throughout the 10-day treatment; BDNF levels strongly correlated with the plasma levels of esmethadone [77]. Although mTOR levels were not assessed, this increase in BDNF suggests, similar to ketamine's effects, activation of this pathway by esmethadone. In fact, a preclinical study showed that esmethadone treatment increased mTOR phosphorylation and levels of PSD-95, synapsin-1 and GluA1 in the medial prefrontal cortex, but not in the hippocampus of male Sprague-Dawley rats [78]. In the same study, esmethadone also increased mTOR phosphorylation in rat cortical primary neurons; in addition, primary neurons showed higher phosphorylation of ERK1/2 and increased BDNF levels. Moreover, esmethadone enhanced serotonin and NMDA-induced EPSCs and increased the diameter of spine heads in layer V mPFC pyramidal neurons [78]. Taken together, these findings place esmethadone on the same mechanistic continuum as ketamine, i.e. linking NMDA receptor blockade to BDNF-mTOR-driven synaptic remodelling. Yet, further confirmation in larger clinical samples, alongside translational work will be essential to validate and expand these observations.

3.3. Nitrous oxide

Currently primarily discussed for its harmful recreational abuse, particularly in young adults [79], nitrous oxide (N_2O, laughing gas) is being investigated as an RAAD [80]. Nitrous oxide acts as a non-competitive NMDA receptor antagonist [81,82], but has also been shown to inhibit AMPA receptors [83]. Moreover, nitrous oxide exerts opioid action, which has been discussed as an important MoA in the context of AD treatment [48], but also its abuse potential [79].

In a small pilot trial [84] and a couple small phase 2 trials (NCT02139540 and NCT03283670) nitrous oxide inhalation resulted in rapid improvement of depression symptoms within 2 h that persisted for up to two weeks [85,86]. The rapid, but not the sustained AD effects of nitrous oxide were confirmed in a meta-analysis [81]. However, a recently concluded phase 2b trial (NCT03869736), investigated repeated nitrous oxide inhalation over three weeks in 81 TRD patients. The findings from this study again showed rapid improvement of depressive symptoms within 1 h, which were sustained until the end of treatment. Four weeks after termination of nitrous oxide treatment, depression scores in the N_2O group remained lower than in the placebo group, though this effect was not significant [87]. While additional phase 2 clinical trials by the University of Chicago (NCT05357040, NCT05710887) and the University Hospital Tours (NCT06382389) are planned or ongoing, no further advancement into phase 3 has been recorded yet.

Of note, mechanisms beyond NMDA receptor inhibition have been suggested in the AD-like effects of nitrous oxide, particularly its opioid effects [79,81,82]. Moreover, a recent study suggested that nitrous oxide might exert its AD-like effects via rapid activation of prefrontal layer 5 pyramidal neurons by inhibition of SK2 channels [88]. Yet, NMDA antagonism is an important MoA by which nitrous oxide is suggested to exert its AD activity. Importantly, nitrous oxide has been shown to increase BDNF levels [89,90] and to activate its receptor TrkB as well as GSK3β [90]. Moreover, nitrous oxide increases neuronal nitric oxide synthase levels [89,91], suggesting a broader involvement of glutamatergic pathways in its activity.

3.4. NMDA receptor activation

While most researched ADs that target the NMDA receptor exert inhibitory action, some positive modulators of NMDA receptors have been investigated as potential ADs [92–94].

The principal GluN1 subunits of NMDA receptors bind glycine or D-serine in their agonist binding domain [40]. D-cycloserine, a glycine-site agonist, improved depressive symptoms as an adjunctive treatment in a TRD phase 2 trial (NCT00408031) [95] and in bipolar disorder patients in a fixed combination with the antipsychotic lurasidone (NRX-101) (NCT02974010) [96]. Thus, the potential to achieve AD properties with NMDA receptor positive allosteric modulators (NMDA PAMs) remains interesting. In this context the NMDA PAM rapastinel (GLYX-13) showed early efficacy but failed in more advanced trials [93]. Other NMDA PAMs clinically tested for MDD include apimostinel (GATE-202, NRX-1074) with unpublished results from a phase 2 clinical trial (NCT02067793), but unofficial reports suggesting positive outcome. Zelquistinel (GATE-251, AGN-241751) demonstrated preclinical efficacy [97,98], but two initial clinical trials by *Gate Neurosciences* were negative (NCT03586427, NCT03726658); a new phase 2 trial by *Gate Neurosciences* is currently ongoing (NCT06547489). Interestingly, also a new phase 2 trial combining apimostinel with automated cognitive training has recently been launched at the University of Pittsburgh (NCT06400121). These recently initiated trials reflect continued interest in and cautious optimism for the AD potential of NMDA PAMs; perhaps they might have a more important role as cognitive enhancers, with potential use either against cognitive deficits in depression or to augment cognitive-behavioural therapy. However, whether these agents will ultimately fulfil these promises remains to be determined.

Although NMDA PAMs enhance rather than inhibit receptor activity, accumulating evidence shows that they still recruit a neural plasticity cascade comparable to ketamine involving BDNF release, mTOR-activation and AMPA receptor recruitment. This is most likely because most NMDA PAMs appear to mainly enhance postsynaptically located NMDA receptors, while ketamine's AD effect has been assigned to its inhibition of extrasynaptic NMDA receptors, which among others, leads to disinhibition of the presynaptic neuron [94].

In rodent models, both ketamine and rapastinel increased mTOR pathway components (i.e. ERK and p70S6 kinase) and elevated BDNF release and AMPA receptor trafficking; these effects were abolished by AMPA receptor blockade or BDNF inhibition [99–101]. Repeated injection of rapastinel increased phosphorylation of mTOR, ERK, and TrkB, and BDNF and VGF levels in hippocampus and prefrontal cortex [102], while acute administration normalised stress-induced reductions in AKT, mTOR, eEF2 phosphorylation and VGF levels [103]. Zelquistinel produced a comparable signature in mice, raising mTOR phosphorylation together with increased GluA1 and PSD-95 levels [98]. Together these findings suggest that NMDA PAMs can initiate a neuroplasticity programme remarkably similar to that of ketamine thereby explaining comparable mechanisms for their AD action.

3.5. Future directions for NMDA targeted antidepressants

As described, a range of NMDA receptor modulators with diverse structure and site of action have emerged as potential ADs with rapid action (Fig. 2). With ketamine as the principal RAAD and having taken centre stage as a critical drug in emergency and TRD treatment it remains to be seen if drugs with comparable MoA will be successfully applied in the future. While ketamine and nitrous oxide can cause psychotropic effects necessitating supervised administration, dextromethorphan/bupropion and esmethadone have shown milder side-effect profiles without psychomimetic effects, potentially enabling use outside clinical settings.

Given that the development of esmethadone is on hold and that dextromethorphan/bupropion formulations, for now, are US-only, further development of ADs with activity at the NMDA receptor that

have a favourable side-effect profile will be required. However, many substances, like the NMDA receptor antagonists memantine [104] or lanicemine [105] were not effective and are not further pursued as ADs. Most GluN2B NAMs have also failed to pass beyond early development [5], with the exception of BI 1569912, developed by *Boehringer Ingelheim*, which showed AD properties in a small clinical trial (NCT04937829) studying patients not adequately responding to a SSRI/SNRI [106]. Importantly, the drug can be given orally, it has no dissociative effect, and its effect has a rapid onset, yet is lasting for days. Larger studies are however needed to confirm these promising data. In fact, two phase 2 trials by *Boehringer Ingelheim* assessing the use of BI 1569912 as adjunctive therapy (NCT06280235) or as monotherapy (NCT06558344) have been completed, but no data have been published yet.

Across these agents, a common mechanistic denominator emerges: transient NMDA modulation sparks an immediate AMPA-receptor-dependent glutamatergic burst, BDNF release, and downstream mTOR activation, collectively driving rapid and sustained synaptic potentiation. This provides a natural segue to the second part of this review, examining the role of AMPA receptors in depression and their potential as therapeutic targets.

4. AMPA receptors in depression

AMPA receptors are a class of ionotropic glutamate receptor ion channels that mediate fast excitatory synaptic transmission and are critical for synaptic plasticity and learning and memory. AMPA receptors are assembled from the four subunits GluA1 to -A4 (encoded by the *Gria1* to *Gria4* genes). Most of the receptors are GluA1/A2 or GluA2/A3 heterodimers (80 % and 16 % respectively) [107]. The GluA1/A2-containing receptors are trafficked into synapses to mediate their plasticity-dependent strengthening; GluA2/A3 assemblies replace existing AMPA receptors to stabilize and maintain synaptic signalling [108]. AMPA receptors lacking the GluA2 subunit (mostly GluA1 homomers) are highly Ca^{2+}-permeable and are important mediators of synaptic plasticity [109]. GluA4 subunits are primarily expressed in interneurons.

Ten years ago, we published a review article hypothesizing that AMPA receptors might be centrally involved in the development and pathophysiology of MDD [6]. This hypothesis was based on diverse evidence, including (i) changes in AMPA receptor gene expression in postmortem samples from MDD patients, (ii) changes in the expression of AMPA receptor genes and proteins after stress induction in rodents, (iii) behavioural findings in knockout mice, (iv) the dependency of AMPA receptor activation in AD treatment (including using ketamine), (v) the AD-like properties of positive allosteric modulators of AMPA receptors (AMPA PAMs) in rodents. In the decade since, further evidence has strengthened the case for a central involvement of AMPA receptors in depression, as detailed below.

4.1. NMDA-targeting antidepressants are dependent on AMPA receptors

As extensively summarized over the last decade, by us [5,6] and others [44,45,110–113] the AD effects of ketamine heavily involve AMPA receptor function. Specifically, ketamine indirectly leads to synaptic glutamate release, particularly on pyramidal neurons of the prefrontal cortex, activating AMPA receptors, which in turn induces BDNF-release, subsequently leading to activation of the mTOR pathway. These processes culminate in the postsynaptic enrichment of GluA1-containing AMPA receptors together with PSD-95, leading to neuroplastic changes that underlie the rapid and sustained AD response [44,45].

As also described in the sections above, this mechanism is not unique to ketamine as similar MoAs have also been described for other NMDA

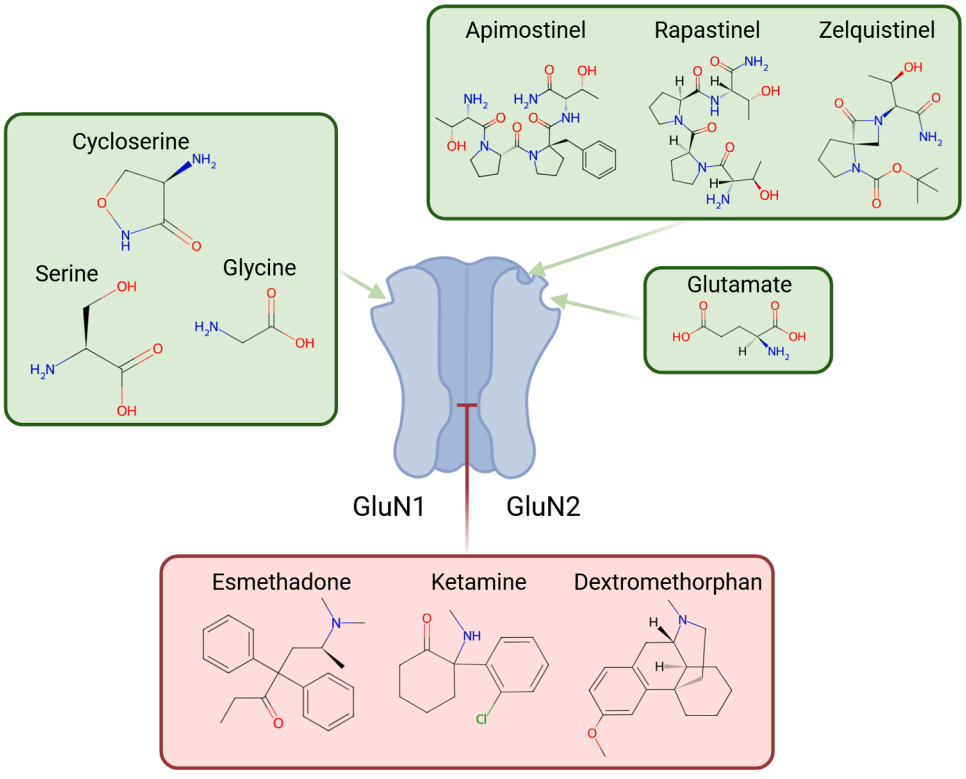


Fig. 2. Schematic overview of NMDA receptor agonists and antagonists. The chemical structure of NMDA receptor agonists (i.e. glutamate, glycine, and D-serine) and substances with rapid acting antidepressant (RAAD) potential are shown (all chemical structures were obtained from ChEMBL via https://www.ebi.ac.uk/chembl/). The green shading indicates agonists and positive allosteric modulators, and their binding sites are shown by green arrows. Red shading indicates antagonists with their binding sites shown by red arrows. Created in https://BioRender.com.

receptor targeting substances with AD potential. Like ketamine, DXM [58,63,66,68], rapastinel [99,101,102], esmethadone [77,78], nitrous oxide [89,90], and zelquistinel [98] were shown to require AMPA receptor activation and/or enhance BDNF-mTOR signalling, leading to GluA1 and PSD-95 insertion.

Collectively, these findings indicate that AMPA receptors and AMPA receptor-dependent synaptic plasticity are required, though not necessarily sufficient, for the rapid and sustained actions of NMDA-modulating ADs. Future pharmacological strategies may thus capitalise on this AMPA receptor-dependent cascade in the development of novel ADs.

4.2. Increased AMPA receptor transmission by ketamine metabolites

As described above, different theories exist about how ketamine exerts its rapid AD effects. Most of these revolve around direct or indirect disinhibition of the glutamatergic synapses via inhibition of extrasynaptic NMDA receptors. However, it has been suggested that the ketamine metabolite (2 R,6 R)-HNK exerts rapid and sustained AD-like effects in mice, without requiring NMDA receptor inhibition. Instead, (2 R,6 R)-HNK leads to and requires activation of AMPA receptors [114], though this was debated by some studies [115,116]. Moreover, (2 R,6 R)-HNK treatment increased synaptic levels of GluA1 and GluA2, as well as BDNF [114]. This study further expanded the diverse MoA of ketamine from indirect involvement of AMPA receptor activity to more direct enhancement of AMPA receptor transmission. The AD-like effects of (2 R,6 R)-HNK were confirmed in later studies [117,118], ultimately leading to clinical trials studying (2 R,6 R)-HNK as an AD in TRD:

Despite solid preclinical evidence for the AD-like activity of (2 R,6 R)-HNK the clinical data are rather conflicting. A phase 1 study in 74 healthy participants (NCT04711005) showed that (2 R,6 R)-HNK was well tolerated [119]. However, a clinical trial in TRD patients treated with ketamine showed that higher plasma levels of HNK were associated with weaker AD efficacy [120]; similar results have been reported in patients with suicidal depression [121]. Thus, while promising, current evidence for a clinical benefit by HNK is not convincing but also has not been directly tested yet. At the end of last year, a phase 2 trial in TRD patients treated with different dosages of (2 R,6 R)-HNK has started and is currently in the recruitment stage (NCT06511908). Further development of (2 R,6 R)-HNK for AD treatment will strongly depend on a positive outcome of this study.

Whether the AD properties of ketamine are mainly driven by direct (2 R,6 R)-HNK-mediated enhancement of AMPA receptors or via NMDA receptor inhibition is still a matter of debate. There is strong support of (2 R,6 R)-HNK's ability to affect synaptic plasticity and metaplasticity [26] and to exert AD effects at least in preclinical studies [114,117,118]. However, some studies indicate that (2 R,6 R)-HNK may not have sufficient AD activity at concentrations observed after ketamine administration [115]. Moreover, (2 R,6 R)-HNK might also inhibit NMDA receptors [116]. Thus, further systematic analyses regarding the contribution of ketamine metabolites during AD treatment with ketamine will be needed. Importantly, regardless of whether ketamine's RAAD effects are primarily mediated by (2 R,6 R)-HNK, the metabolite itself remains as an interesting compound under investigation as a potential standalone AD.

4.3. Antidepressant potential of AMPA PAMs

AMPA PAMs including AMPAkines, enhance AMPA receptor ion channel conductance by increasing the agonist binding affinity, reduce desensitization and prolong channel opening time and/or by stabilizing ligand binding [122–126]. Importantly, because AMPA PAMs are not direct receptor ligands, meaning they do not directly lead to receptor channel opening, they preserve the native spatial and temporal fidelity of synaptic AMPA receptor signalling and function [127].

AMPA PAMs have long been hypothesized to have AD-like potential (e.g. reviewed in [123–129]) and several preclinical studies have reinforced this hypothesis with a range of AMPA PAMs showing AD-like efficacy in animal models (see e.g. [130–134]). Mechanistically, treatment with AMPA PAMs has been shown to increase BDNF mRNA and protein levels in different rodent *in vitro* and *in vivo* models [133, 135–145] consequently leading to increased mTOR phosphorylation [143,144,146]. Thus, it appears conceivable that AMPA PAMs may be able to exert AD-like effects through enhancement of synaptic plasticity via BDNF signalling. In fact, treatment with AMPA PAMs has been shown to enhance hippocampal long-term potentiation [138,147] and this effect was reversed by scavenging and effectively blocking BDNF [138]. Structurally, AMPA PAM treatment increased the number and length of dendrites as well as the soma size [146]. In addition, AMPA PAMs appear to refine synapses by reducing the density of spines and the number of synaptic contacts but increasing dendritic spine size [147]. Notably, spine enlargement has also been linked to the AD effects of ketamine and other RAADs; however, in contrast to AMPA PAMs, ketamine was also shown to increase spine density [20], suggesting a differential regulation in spine dynamics. If these lead to similar effects with regard to synaptic scaling remain to be determined.

In addition to its involvement in synaptic plasticity, elevated BDNF has also been linked to neuroprotective mechanisms in mood disorders [148]. In this context, treatment with AMPA PAMs has been shown to enhance cell proliferation and survival [149,150] and the neuroprotective effects of AMPA PAMs were shown to be reversed by scavenging BDNF [139].

Ampakines and other AMPA PAMs have been extensively studied preclinically, in relation to a number of different disorders. However, only few clinical studies have been performed using these drugs, and most of them were not targeting MDD [127]. Although AMPA-PAMs have had an inconsistent history in clinical development, some evidence for their clinical efficacy has been published. Early AMPA PAMs appear to be well tolerated clinically [151–154] however a narrow therapeutic index between efficacy and proconvulsant activity has been observed for multiple compounds until recently [155].

The first Ampakine that went into an MDD-related clinical trial was Org 26576 (MK-8777). In a small phase 1b study (NCT00610649) oral administration twice daily for 28 days of either 100 or 400 mg Org 26576 vs. placebo in 10 MDD patients per group resulted in numerically greater non-significant improvement in Montgomery Asberg Depression Rating Scale (MADRS) scores [154]. Of note, treatment with Org 26576 resulted in significant improvements in executive functioning and processing speed. Interestingly, while this drug was overall well-tolerated, the maximum tolerable dose in MDD patients was twice that of healthy volunteers [153], which might indirectly support the notion that MDD patients might benefit from AMPA receptor enhancement.

Another phase 2 clinical trial (NCT00113022) using the AMPA PAM farampator (Org 24448) in MDD patients was terminated prematurely after recruitment of only 9 participants *"due to concerns about adverse events in separate study"*. In fact, a clinical trial in 16 healthy elderly volunteers (60–75 years of age) farampator was linked to a range of side-effects including headache, somnolence, and nausea [156].

A relatively recently completed phase 2 randomized controlled trial by *Neurocrine Biosciences* (NCT05203341) investigated the safety and efficacy of the AMPA PAM osavampator (TAK-653, NBI-1065845). In preclinical models, osavampator was able to exert AD-like effects, including among others elevated BDNF levels and mTOR phosphorylation [144]. Unfortunately, the results of the clinical trial have so far only been released in a press release. According to this press release, when compared to placebo, osavampator orally once a day significantly improved the MADRS score after 28 days (primary outcome) and 56 days (secondary outcome) of treatment [157]. Another secondary outcome, MADRS score at day 7, was not mentioned in the press release, making it unclear whether osavampator would strictly qualify as a RAAD. Yet, the results from this trial are the most promising indication that at least some AMPA PAMs might exert AD properties.

Osavampator appears to be distinct from other AMPA PAMs, by more potently enhancing AMPA receptor-mediated synaptic responses when compared to another AMPA PAM (LY451646). Unlike many other AMPA PAMs, osavampator enhanced AMPA-induced Ca^{2+} influx and synaptic currents, in the absence of virtually any agonistic effect [145]. Thus, this drug does not activate AMPA receptors that have no glutamate bound, reducing the possibility of unspecific low-level tonic AMPA receptor activation. Two phase 3 clinical trials with osavampator as adjunctive treatment in TRD patients were initiated in January and March 2025 respectively by *Neurocrine Biosciences* (NCT06786624, NCT06911112).

Another phase 2 trial (NCT02805439) by *Servier* in 414 MDD patients using the AMPA PAM tulrampator (S-47445, CX-1632) as an adjunctive treatment to ongoing SSRI treatment was negative: the findings are published on the *Servier* website [158]. Thus, the results of the ongoing osavampator trials are highly anticipated and may determine the future fate of AMPA PAM development as stand-alone or adjunctive rapid-acting treatments for TRD, although a further AMPA-PAM, DT-101 has recently entered clinical trials for MDD from a UK Biotech company, *Draig Therapeutics,* as noted on their website (draigtherapeutics.com).

While AMPA PAMs represent a promising class for AD compounds by enhancing synaptic plasticity, with solid preclinical evidence, their clinical development has so far been limited. Overall, AMPA PAMs have not yet significantly advanced as potential ADs in particular compared to NMDA receptor modulators, even though these also lead to enhanced AMPA receptor activation. In this context, an important consideration is their potential for substantial side effects that already lead to premature termination of clinical trials (see the farampator trial described above). Among those, an increased risk for seizures has been shown for high-impact AMPA PAMs, possibly due to some agonistic activity of these compounds [128]. Thus, adequate dosing and the development of low-impact AMPA PAMs that lack agonist activity, like osavampator [145], will be essential to possibly fulfil their AD potential. Moreover, in contrast to NMDA receptor modulators, AMPA PAMs may lead to a broader induction of associated molecular and physiological pathways and networks, though this has not been systematically investigated yet. In this context, a more promising potential might be provided by the development of AMPA PAMs selective for AMPA receptors bound to specific interacting proteins, but these have not yet been developed (also see 4.4). Together, the development and clinical testing of safe but effective AMPA-PAM, lacking dissociative effects but mimicking (es) ketamine's long term AD effect, is still ahead of us, but represents a worthwhile endeavour.

4.4. AMPA receptor interacting proteins

AMPA receptors are stabilized and regulated by numerous proteins adding further functional diversity; among these proteins are 4.1 N, SAP97, Shank3, NSF, GRIP1, and PICK1, all of which have been shown to contribute to AMPA receptor mediated synaptic plasticity mechanisms [159,160]. Consequently, these interactions have been suggested to contribute to brain disorders [159,161]. However, despite the importance of synaptic plasticity in depression, no clear clinical evidence for an involvement of these proteins in MDD exists.

Further diversity of AMPA receptors is achieved via auxiliary subunits. To this date at least five different classes of AMPA receptor auxiliary subunits have been characterized: (i) The transmembrane AMPA receptor proteins (TARPs) γ-2, −3, −4, −5, −7, and −8 (encoded by *CACNG2, 3, 4, 5, 7,* and *8*), (ii) the cornichon homologue proteins CNIH2 and CNIH3, (iii) the cysteine-knot AMPA receptor modulating proteins (CKAMPs, also called Shisa proteins), CKAMP39, 44, 52, and 59 (encoded by *SHISA8, 9, 6, and 7* respectively), (iv) the synapse differentiation induced genes (SynDIG) 1 and 4 (encoded by *SYNDIG1* and *PRRT1* respectively), and (v) and germline-specific gene 1-like (GSG1L) [159,162–164].

AMPA receptor auxiliary subunits impact AMPA receptors in many ways. Like NMDA receptors, AMPA receptors are linked to the PSD scaffold via DLG MAGUKs [165]. However, unlike NMDA receptors, AMPA receptors interact with DLG MAGUKs via their auxiliary subunits, except for GluA1 which is able to directly interact with SAP97 [166,167] and even Shank3 [168]. Thus, almost all auxiliary subunits affect synaptic localization of AMPA receptors. Additionally, auxiliary subunits affect AMPA receptor trafficking, ligand affinity, and signalling dynamics including conductance, deactivation and desensitization rate, and recovery [162,164].

Given their critical involvement in AMPA receptor function, AMPA auxiliary subunits have been suggested to be involved in neurological and mental disorders [159,162,169]. However, surprisingly little is known about their potential contribution to these conditions. Mice globally lacking TARP γ-8 have about 85 % loss of hippocampal AMPA receptors [170] and show a range of behavioural deficits including hyperactivity, impulsivity, increased anxiety, and cognitive deficits [171–173]. Moreover, mice with ventral hippocampus-specific knockdown of TARP γ-8 show a depression-like phenotype [174].

In addition, stress and stress resilience in mice exposed to chronic mild stress seem to be affected by TARP γ-8 by increasing the synaptic localization of GluA1-containing AMPA receptors [175]. Moreover, chronic social defeat in mice caused a reduction in TARP γ-8 levels and depression-related behavioural deficits in chronically defeated mice were reversed by ventral hippocampal overexpression of TARP γ-8 [174]. Inhibition of TARP γ-8 associated AMPA receptor complexes using JNJ-55511118 was shown to disrupt the AD-like effects of TARP γ-8 overexpression and stress-resilience in mice [174,175].

These findings suggest a potential involvement of TARP γ-8 in depression. However, they are limited to preclinical data and thus far no involvement of *CACNG8*/TARP γ-8 in clinical samples was shown. In fact, in a phenome-wide association analysis of 228 *CACNG6*, 126 *CACNG7*, and 137 *CACNG8* SNPs across different mental disorder cohorts only showed significant association for rs12610534 at *CACNG6* for the MDD cohort, but none for the investigated *CACNG7* or *CACNG8* SNPs [173]. Thus, research into potential involvement of TARPs in depression and their potential as treatment targets are still in the early stages.

While so far three inhibitors of TARP γ-8 associated AMPA receptors have been identified (i.e., LY3130481 (CERC-611), JNJ-55511118, JNJ-61432059), no PAMs specific to TARP carrying AMPA receptors have been found or pursued. If such a type of substance would be effective at all remains to be determined. However, one of the attractive aspects AMPA modulators specific to specific TARPs is the brain region specific distribution of TARPs that would largely restrict the effects of these modulators to these brain regions. For example, TARP γ-2 and γ-3 are predominantly expressed in cerebellar granular cells and TARP γ-8 in hippocampal and cortical neurons [162]. The US-based biotech company *Rapport Therapeutics* has initiated clinical development of a NAM that targets TARP γ-8 containing AMPA receptors for bipolar disorder (see Rapport Therapeutics Pipeline and Programs [176]), but the rationale for its investigation in depression is equally compelling. To the best of our knowledge, this is the first compound selectively targeting AMPA receptor-associated proteins to enter clinical development for affective disorders. Although currently investigated for bipolar depression, this approach appears highly promising.

Even less evidence exists for other AMPA auxiliary subunits in depression. The strongest link so far was found for CKAMP44 and CKAM52 (encoded by *SHISA9* and *SHISA6* respectively). Both *SHISA9* and *SHISA6* were significantly associated with MDD in the most recent genome-wide association analysis by the Psychiatric Genomics Consortium [177]. However, no further dedicated investigations into the role of CKAMP44/*SHISA9* in depression have been made. Increased *Shisa6* was found in nucleus accumbens D1-medium spiny neurons after chronic social defeat in susceptible, but not in resilient mice. Moreover, social interaction-deficits induced by chronic social defeat were reduced by *Shisa6* downregulation and enhanced by *Shisa6* overexpression

[178]. These findings suggest that CKAMP52 (Shisa6) might be an important mediator of stress susceptibility and may be an attractive drug target [178], though no specific CKAMP inhibitors have been identified thus far.

Taken together, auxiliary and scaffolding partners control discrete aspects of AMPA receptor gating, trafficking, and synaptic anchoring. Because each interaction regulates a narrowly defined function often in a relatively region-specific manner, pharmacologically enhancing or dampening these interactions may fine-tune AMPA receptor signalling without the broad excitatory surge produced by direct AMPA PAMs. Possibly, such precision may yield rapid AD benefits while minimising risks of excitotoxicity, seizure liability, or other side-effects, making modulators of AMPA receptor interactions a potentially attractive next-generation strategy for MDD/TRD.

5. Complementary approaches for the development of RAADs

Several approaches for RAADs that do not directly target the glutamatergic system have been proposed and many of those have been tested in clinical trials. Three classes of substances studied as potential RAADs are also interesting in the context of this review as these employ somewhat complementary mechanisms to NMDA or AMPA receptor related substances. Among others these include metabotropic glutamate (mGlu) receptor antagonists (5.1), negative allosteric modulators (NAMs) of $GABA_A$ receptor (GABA NAMs) (5.2), and muscarinic acetylcholine antagonists (5.3), though other substances (e.g. psychedelics) might also be of relevance, though their description would exceed the scope of this review.

5.1. Metabotropic glutamate receptor antagonists

In addition to binding to ionotropic glutamate receptors, glutamate is a ligand for mGlu receptors, a class of G-protein coupled receptors. In several preclinical studies NAMs of mGlu5 have shown AD-like potential, but they were largely unsuccessful in clinical trials [179]. On the other hand, enhanced mGluR5 signalling has been suggested to exert AD-like effects via mTOR activation increasing synaptic AMPA receptor levels and activity [180]. Interestingly mGlu5 has also been suggested to be involved in the AD effects of ketamine, possibly by enhancing diffusion of extrasynaptic mGlu5 to the synaptic membrane. However, evidence for this hypothesis is overall limited and partially inconsistent [179,181].

In preclinical studies antagonists of mGlu2/3 receptors have shown AD-like effects that were both rapid and long-lasting and therefore have been compared to the AD-like effects of ketamine. In fact, the AD-like effects of mGlu2/3 receptor antagonists have been shown to involve AMPA receptor activation and BDNF/TrkB signalling [182]. While in clinical trials, adjunctive treatment with the mGlu2/3 NAM decoglurant was negative in TRD patients [183], a phase 2 trial using the orthosteric antagonist TS-161 in TRD patients (NCT04821271) has been terminated prematurely due to low recruitment. The available data show no clear improvement TS-161 vs placebo treated patients, which is not surprising, given the low sample size (TS-161, $n = 10$ vs placebo, $n = 9$). Therefore, it remains interesting to see if the promising potential of mGlu2/3 antagonists can hold up in exerting AD effects that are akin to ketamine, in particular considering that TS-161, in contrast to ketamine, has only mild side effects [182].

5.2. $GABA_A$ receptor negative allosteric modulators

Since ketamine is proposed to have its effects by acting at GABAergic interneurons to disinhibit the release of glutamate from primary output neurons the same effect can also be achieved by GABA NAMs. In this context, particular GABA NAMs targeting receptors containing the α5 subunit have been investigated [110]. For example, the Danish biotech company *Saniona* has an α5-selective GABA NAM (SAN2465) which they plan to develop for MDD [184]. Other α5-GABA NAMs, such as *Basmisanil* from Roche, which has AD-like effects in mice [185], have been in clinical trials in multiple indications, though not for MDD/TRD. To date the only observed clinical effect of a α5-GABA NAM is in cognitive improvement in an experimental medicine study [186].

5.3. Muscarinic acetylcholine antagonists

Another target that has received increasing interest over the years for the development of RAADs are the muscarinic acetylcholine receptors. In the particular the nonselective muscarinic antagonist scopolamine has been shown to produce rapid and sustained AD-like effects in preclinical studies and initial clinical trials [187]. A meta-analysis across four clinical trials incorporating 103 patients, significant AD effects of scopolamine were found after three days of treatment; in the same analysis, no AD effects of scopolamine could be found 25 days after 3 days of treatment, but this only incorporated one study [188]. Of interest, also in the context of this review, scopolamine has been shown to induce a rapid AMPA receptor-mediated glutamate surge in the prefrontal cortex, which leads to increased BDNF levels and activation of the mTOR pathway [187].

6. Conclusions and outlook

As outlined above, a plethora of pre-clinical evidence suggests an involvement of the glutamatergic system in depression. An overview of the current clinical development landscape of NMDA and AMPA receptor modulators is provided in Fig. 3. In line with this, there are already two compounds available which target the NMDA receptor and are efficacious in depression and especially TRD, aiming at patients where the monoamine system might not have a role. However, these drugs also work in general MDD – although, as for conventional ADs, not in every patient. This calls for precision psychiatry approaches, i.e., identifying and developing predictive markers that indicate patients in which glutamatergic treatments might be most effective. These may include biomarkers such as PET imaging of glutamatergic function or assessment of peripheral or central molecular markers like GluA1 expression levels. Importantly, these approaches should also consider sex/gender and developmental aspects, which may influence efficacy and side-effect profiles of RAADs. Until recently, such theranostic markers were not needed as only monoaminergic treatments were available; with the advent of many more and fundamentally different MoAs, such markers could be instrumental in the matchmaking of patient and drug, thereby significantly shortening the time until the right treatment is found. However, hitherto no such marker has been identified despite multiple attempts.

With the advent of further glutamatergic depression treatments, of which we consider the most promising GluN2B NAMs and AMPA PAMs, this issue becomes even more relevant: as such new therapies will come along with a substantially higher price tag than the standard of care: treatment with SSRI and SNRI incurs a daily cost of less than one Euro [189]), and considering the prevalence of depression, it will be crucial to identify the right patients as precisely as possible, not to overburden the healthcare system. For example, MDD cases that are more inflammatory in origin might not be as efficiently treated using glutamatergic compounds. However, at least some of ketamine's therapeutic effects have been linked to anti-inflammatory mechanisms [190], though it remains unclear, whether this effect also extends to other glutamatergic modulators that are explored as RAADs.

As is the case for monoaminergic ADs, the remission rate for esketamine is around 30–50 [50,53,54] and it seems unlikely that this will be different for any other glutamatergic compound. While the underlying reason is unclear to this date, pharmacokinetic issues seem less likely, as esketamine is administered i.v. or intranasally, thereby bypassing hepatic metabolism. Heterogeneity of depression is an obvious possibility; meaning that not every patient diagnosed with MDD will have a deficit

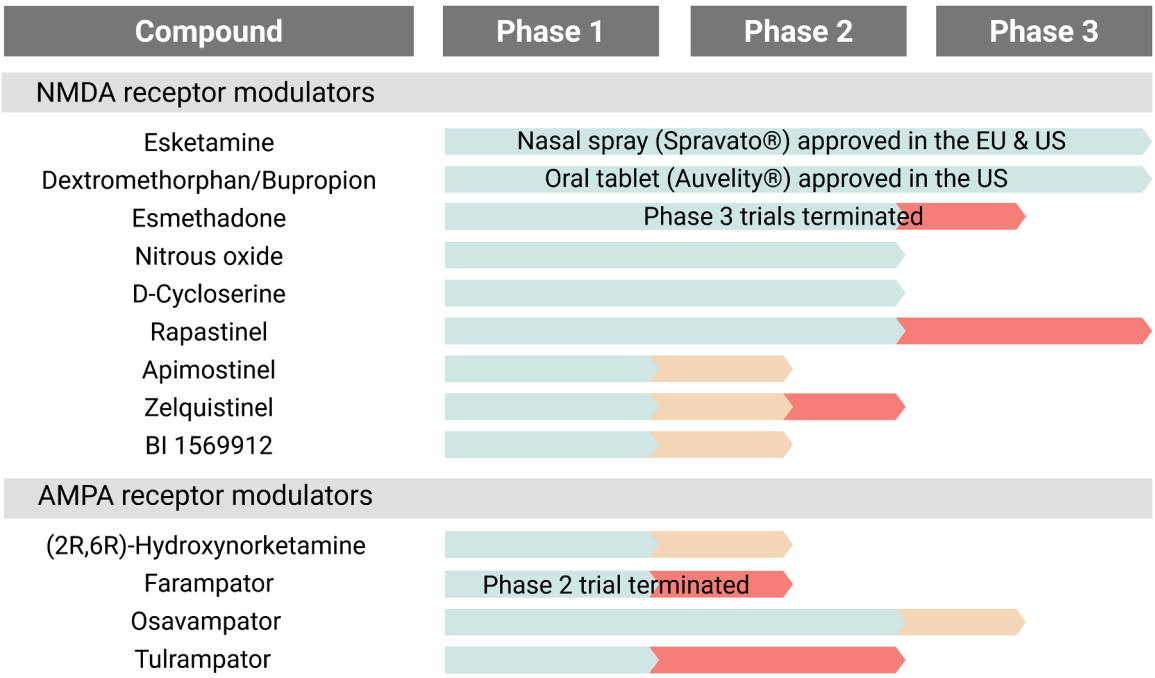


Fig. 3. Clinical development status of glutamatergic rapid-acting antidepressants (RAADs). Overview of NMDA and AMPA receptor modulators with previous or ongoing clinical investigations as RAADs. Compounds are grouped by primary target and the latest known stage in clinical development (phase 1–3) is indicated. Green indicated successful passage of the clinical phase (i.e. positive data available). Yellow indicated ongoing trials or trials where data have not yet been published. Red indicated failed clinical trials or trials that were prematurely terminated and further development has halted. Of the indicated substances approval has only been obtained for intranasal esketamine (Spravato®, EU and US) and dextromethorphan/bupropion (Auvelity®; US only). Created in https://BioRender.com.

in NMDA/AMPA/BDNF-induced neuronal/synaptic plasticity. Alternatively, or in addition, plasticity induced by glutamatergic compounds might only be effective in the presence of further internal or external stimuli. The latter possibility has the potential for direct clinical application, however, to our best knowledge this has not yet been studied in greater detail. Thus, many open questions remain regarding patient selection and optimal timing and sequencing of glutamatergic treatments.

In summary, glutamatergic treatments will become an integral part of MDD/TRD treatment. There are only few studies investigating how AD treatments should be modified upon non-response, the largest to date still being the more than 20-year-old STAR*D study [191,192]. AD switching and combination strategies were limited by the fact that they all target the monoamine systems, thus all focusing on the same mechanisms. Now that glutamatergic treatments are available, combining them with existing therapies or switching to such medications offers new treatment perspectives. To assess where and how such treatments should be positioned in the treatment algorithm, new sequential treatment studies (also including e.g. repetitive Transcranial Magnetic Stimulation or Vagus Nerve Stimulation) should be initiated to inform guidelines and clinical practice. In this context, practicalities such as route of administration have to be considered as well. For instance, intranasal esketamine requires a period of monitoring which is a barrier for widespread use especially in primary care settings. As a consequence, further refinement regarding the precise targets of glutamatergic treatments, so that therapies become even less burdensome yet still rapid-acting, should prompt research to intensify efforts especially in translating preclinical evidence to the patient.

In addition to human resources needed for the administration, cost of the medication as such could impede their usage; especially considering the low cost of SSRI therapy. However, medical costs must be contrasted against the cost of illness, e.g. loss of productivity, sickness leave, early retirement etc. Only such a holistic approach will reveal whether new treatments are cost-effective or not. In this regard, recent studies showing that intranasal esketamine is superior to quetiapine not only regarding clinical scales, but also with respect to functional outcomes [193] and quality of life (unpublished data currently under review) are highly promising. After years of stagnation in AD development, the approval of Spravato® and Auvelity®, together with a rich pipeline, therefore spark hope for new breakthroughs in depression treatment including for TRD patients.

Author contributions

FF and AR developed the overall concept of this manuscript and CRL, GRD, and RMM contributed further concepts and ideas. FF and AR wrote the original draft and CRL, GRD, and RMM reviewed and edited the manuscript.

CRediT authorship contribution statement

Florian Freudenberg: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Data curation, Conceptualization. **Gerard R Dawson:** Writing – review & editing, Conceptualization. **Christine Reif-Leonhard:** Writing – review & editing, Conceptualization. **Andreas Reif:** Writing – review & editing, Writing – original draft, Validation, Project administration, Conceptualization. **Ruth M McKernan:** Writing – review & editing, Conceptualization.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to improve phrasing and structure of some sentences/paragraphs

of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of Competing Interest

FF has nothing to declare. CRL received speaker's and consultant honoraria from Janssen, LivaNova and Das Fortbildungskolleg. GRD is founder and significant shareholder in P1vital LTD that provides services and consultancy to the Pharma industry. RMM is an Operating Partner at SV Health Investors, a trustee for Alzheimers Research UK and a Board member/Founder of Cumulus Neuroscience, and AstronauTx and interim CEO of Draig Therapeutics. AR has received honoraria for lectures and/or advisory boards from Janssen, Boehringer Ingelheim, Compass, GH Research, SAGE/Biogen, LivaNova, Medice, Shire/Takeda, Newron, MSD, AbbVie, cyclerion. Also, he has received research grants from Medice and Janssen. AR has been involved in the ESCAPE-TRD trial (NCT04338321) that contributed to the approval for reimbursement of Spravato® treatment in TRD patients.

References

[1] W. Marx, B.W.J.H. Penninx, M. Solmi, T.A. Furukawa, J. Firth, A.F. Carvalho, M. Berk, Major depressive disorder, Nat. Rev. Dis. Prim. 1 (9) (2023) 1–21, https://doi.org/10.1038/s41572-023-00454-1.

[2] G.S. Malhi, J.J. Mann, Depression, Lancet 392 (2018) 2299–2312, https://doi.org/10.1016/S0140-6736(18)31948-2.

[3] D. Voineskos, Z.J. Daskalakis, D.M. Blumberger, Management of treatment-resistant depression: challenges and strategies, Neuropsychiatr. Dis. Treat. 16 (2020) 221–234, https://doi.org/10.2147/NDT.S198774.

[4] G.I. Papakostas, D.F. Ionescu, Towards new mechanisms: an update on therapeutics for treatment-resistant major depressive disorder, Mol. Psychiatry 10 (20) (2015) 1142–1150, https://doi.org/10.1038/mp.2015.92.

[5] F. Freudenberg, C. Reif-Leonhard, A. Reif, Advancing past ketamine: emerging glutamatergic compounds for the treatment of depression, Eur. Arch. Psychiatry Clin. Neurosci. (2024), https://doi.org/10.1007/s00406-024-01875-z.

[6] F. Freudenberg, T. Celikel, A. Reif, The role of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in depression: central mediators of pathophysiology and antidepressant activity, Neurosci. Biobehav. Rev. 52 (2015) 193–206, https://doi.org/10.1016/j.neubiorev.2015.03.005.

[7] R.S. McIntyre, M. Alsuwaidan, B.T. Baune, M. Berk, K. Demyttenaere, J. F. Goldberg, P. Gorwood, R. Ho, S. Kasper, S.H. Kennedy, J. Ly-Uson, R. B. Mansur, R.H. McAllister-Williams, J.W. Murrough, C.B. Nemeroff, A. A. Nierenberg, J.D. Rosenblat, G. Sanacora, A.F. Schatzberg, R. Shelton, S. M. Stahl, M.H. Trivedi, E. Vieta, M. Vinberg, N. Williams, A.H. Young, M. Maj, Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions, World Psychiatry 22 (2023) 394–412, https://doi.org/10.1002/WPS.21120.

[8] R.M.A. Hirschfeld, History and evolution of the monoamine hypothesis of depression, J. Clin. Psychiatry 61 (2000) 8272. ⟨https://www.psychiatrist.com/jcp/history-evolution-monoamine-hypothesis-depression⟩. accessed April 27, 2024.

[9] F. Lopez-Munoz, C. Alamo, Monoaminergic neurotransmission: the history of the discovery of antidepressants from 1950s until today, Curr. Pharm. Des. 15 (2009) 1563–1586, https://doi.org/10.2174/138161209788168001.

[10] R.S. Duman, G. Sanacora, J.H. Krystal, Altered connectivity in depression: GABA and glutamate neurotransmitter deficits and reversal by novel treatments, Neuron 102 (2019) 75–90, https://doi.org/10.1016/J.NEURON.2019.03.013.

[11] L. Musazzi, G. Treccani, A. Mallei, M. Popoli, The action of antidepressants on the glutamate system: regulation of glutamate release and glutamate receptors, Biol. Psychiatry 73 (2013) 1180–1188, https://doi.org/10.1016/J.BIOPSYCH.2012.11.009.

[12] S. Moriguchi, A. Takamiya, Y. Noda, N. Horita, M. Wada, S. Tsugawa, E. Plitman, Y. Sano, R. Tarumi, M. ElSalhy, N. Katayama, K. Ogyu, T. Miyazaki, T. Kishimoto, A. Graff-Guerrero, J.H. Meyer, D.M. Blumberger, Z.J. Daskalakis, M. Mimura, S. Nakajima, Glutamatergic neurometabolite levels in major depressive disorder: a systematic review and meta-analysis of proton magnetic resonance spectroscopy studies, Mol. Psychiatry 24 (2019) 952–964, https://doi.org/10.1038/S41380-018-0252-9.

[13] K. Tokita, T. Yamaji, K. Hashimoto, Roles of glutamate signaling in preclinical and/or mechanistic models of depression, Pharm. Biochem. Behav. 100 (2011) 688–704, https://doi.org/10.1016/j.pbb.2011.04.016.

[14] C. Yüksel, D. Öngür, Magnetic resonance spectroscopy studies of glutamate-related abnormalities in mood disorders, Biol. Psychiatry 68 (2010) 785–794, https://doi.org/10.1016/j.biopsych.2010.06.016.

[15] G.L. Collingridge, W.C. Abraham, Glutamate receptors and synaptic plasticity: the impact of evans and watkins, Neuropharmacology 206 (2022), https://doi.org/10.1016/J.NEUROPHARM.2021.108922.

[16] G. Racagni, M. Popoli, Cellular and molecular mechanisms in the long-term action of antidepressants, Dialog. Clin. Neurosci. 10 (2008) 385–400, https://doi.org/10.31887/DCNS.2008.10.4/GRACAGNI.

[17] C.J. Harmer, R.S. Duman, P.J. Cowen, How do antidepressants work? New perspectives for refining future treatment approaches, Lancet Psychiatry 4 (2017) 409–418, https://doi.org/10.1016/S2215-0366(17)30015-9.

[18] C. Pittenger, R.S. Duman, Stress, depression, and neuroplasticity: a convergence of mechanisms, Neuropsychopharmacology 33 (2008) 88–109, https://doi.org/10.1038/sj.npp.1301574.

[19] R.S. Duman, G.K. Aghajanian, G. Sanacora, J.H. Krystal, Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants, Nat. Med. (2016) 238–249, https://doi.org/10.1038/nm.4050.

[20] C. Liao, A.N. Dua, C. Wojtasiewicz, C. Liston, A.C. Kwan, Structural neural plasticity evoked by rapid-acting antidepressant interventions, Nat. Rev. Neurosci. (2024), https://doi.org/10.1038/s41583-024-00876-0.

[21] L.R. Vose, P.K. Stanton, Synaptic plasticity, metaplasticity and depression, Curr. Neuropharmacol. 15 (2017) 71–86, https://doi.org/10.2174/1570159X14666160202121111.

[22] G. Sanacora, Z. Yan, M. Popoli, The stressed synapse 2.0: pathophysiological mechanisms in stress-related neuropsychiatric disorders, Nat. Rev. Neurosci. 23 (2022) 86–103, https://doi.org/10.1038/s41583-021-00540-x.

[23] E. Beurel, M. Toups, C.B. Nemeroff, The bidirectional relationship of depression and inflammation: double trouble, Neuron 107 (2020) 234–256, https://doi.org/10.1016/j.neuron.2020.06.002.

[24] E. Haroon, A.H. Miller, Inflammation effects on brain glutamate in depression: mechanistic considerations and treatment implications, curr top, Behav. Neurosci. 31 (2017), https://doi.org/10.1007/7854_2016_40.

[25] R. Troubat, P. Barone, S. Leman, T. Desmidt, A. Cressant, B. Atanasova, B. Brizard, W. El Hage, A. Surget, C. Belzung, V. Camus, Neuroinflammation and depression: a review, Eur. J. Neurosci. 53 (2021) 151–171, https://doi.org/10.1111/ejn.14720.

[26] K.A. Brown, T.D. Gould, Targeting metaplasticity mechanisms to promote sustained antidepressant actions, Mol. Psychiatry (2024) 1114–1127, https://doi.org/10.1038/s41380-023-02397-1.

[27] R. Trullas, P. Skolnick, Functional antagonists at the NMDA receptor complex exhibit antidepressant actions, Eur. J. Pharmacol. 185 (1990) 1–10, https://doi.org/10.1016/0014-2999(90)90204-J.

[28] P. Skolnick, Antidepressants for the new millennium, 1999. ⟨www.elsevier.nlrlocaterejphar⟩.

[29] P. Skolnick, R.T. Layer, P. Popik, G. Nowak, I.A. Paul, R. Trullas, Adaptation of N-methyl-D-aspartate (NMDA) receptors following antidepressant treatment: implications for the pharmacotherapy of depression, Pharmacopsychiatry 29 (1996) 23–26, https://doi.org/10.1055/s-2007-979537.

[30] R.M. Berman, A. Cappiello, A. Anand, D.A. Oren, G.R. Heninger, D.S. Charney, J. H. Krystal, Antidepressant effects of ketamine in depressed patients, Biol. Psychiatry 47 (2000) 351–354, https://doi.org/10.1016/S0006-3223(99)00230-9.

[31] C.A. Zarate, J.B. Singh, P.J. Carlson, N.E. Brutsche, R. Ameli, D.A. Luckenbaugh, D.S. Charney, H.K. Manji, A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression, Arch. Gen. Psychiatry 63 (2006) 856, https://doi.org/10.1001/archpsyc.63.8.856.

[32] H.S. Feldmann, H.C.B. Denber, Long-term study of fluvoxamine: a new rapid-acting antidepressant, Int. Pharmacopysch. 17 (1982) 114–122, https://doi.org/10.1159/000468564.

[33] R. Sarges, H.R. Howard, R.G. Browne, L.A. Lebel, P.A. Seymour, B.K. Koe, 4-Amino[1,2,4]triazolo[4,3-a]quinoxalines. a novel class of potent adenosine receptor antagonists and potential rapid-onset antidepressants, J. Med. Chem. 33 (1990) 2240–2254, https://doi.org/10.1021/JM00170A031.

[34] L. Cervo, R. Samanin, Potential antidepressant properties of 8-hydroxy-2-(di-n-propylamino)tetralin, a selective serotonin1A receptor agonist, Eur. J. Pharmacol. 144 (1987) 223–229, https://doi.org/10.1016/0014-2999(87)90523-1.

[35] S.M. Stahl, Regulation of neurotransmitter receptors by desipramine and other antidepressant drugs: the neurotransmitter receptor hypothesis of antidepressant action, J. Clin. Psychiatry 45 (1984) 37–45. ⟨http://www.ncbi.nlm.nih.gov/pubmed/6090439⟩.

[36] R. Cancro, Experience with a new rapid-acting antidepressant: amoxapine, Adv. Biochem Psychopharmacol. 32 (1982) 121–124. ⟨http://www.ncbi.nlm.nih.gov/pubmed/7090890⟩.

[37] J.M. Witkin, A.E. Martin, L.K. Golani, N.Z. Xu, J.L. Smith, Rapid-acting antidepressants, Adv. Pharm. 86 (2019) 47–96, https://doi.org/10.1016/BS.APHA.2019.03.002.

[38] C. Reif-Leonhard, S.N. Millard, D. Ferdowssian, A. Finlayson, M. Aichholzer, J. Repple, M. Stäblein, S.E. Thanarajah, X. Wang, G.R. Dawson, A. Reif, A. Malik, Effects of repeated intravenous esketamine administration on affective biases, World J. Biol. Psychiatry 26 (2025) 60–73, https://doi.org/10.1080/15622975.2024.2441304.

[39] N.G. Glasgow, B. Siegler Retchless, J.W. Johnson, Molecular bases of NMDA receptor subtype-dependent properties, J. Physiol. 593 (2015) 83–95, https://doi.org/10.1113/JPHYSIOL.2014.273763.

[40] P. Paoletti, C. Bellone, Q. Zhou, NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease, Nat. Rev. Neurosci. 14 (2013) 383–400, https://doi.org/10.1038/NRN3504.

[41] E. Lang, A.S. Mallien, A.N. Vasilescu, D. Hefter, A. Luoni, M.A. Riva, S. Borgwardt, R. Sprengel, U.E. Lang, P. Gass, D. Inta, Molecular and cellular dissection of NMDA receptor subtypes as antidepressant targets, Neurosci.

Biobehav Rev. 84 (2018) 352–358, https://doi.org/10.1016/J.NEUBIOREV.2017.08.012.
[42] D. Stroebel, M. Casado, P. Paoletti, Triheteromeric NMDA receptors: from structure to synaptic physiology, Curr. Opin. Physiol. 2 (2018) 1–12, https://doi.org/10.1016/j.cophys.2017.12.004.
[43] S.A. Booker, D.J.A. Wyllie, NMDA receptor function in inhibitory neurons, Neuropharmacology 196 (2021) 108609, https://doi.org/10.1016/J.NEUROPHARM.2021.108609.
[44] P. Zanos, T.D. Gould, Mechanisms of ketamine action as an antidepressant, Mol. Psychiatry 23 (2018) 801–811, https://doi.org/10.1038/MP.2017.255.
[45] J.-W. Kim, K. Suzuki, E.T. Kavalali, L.M. Monteggia, Ketamine: mechanisms and relevance to treatment of depression, Annu Rev. Med. 75 (2024) 129–143, https://doi.org/10.1146/annurev-med-051322-120608.
[46] Z.Z. Ma, N.J. Guzikowski, J.-W. Kim, E.T. Kavalali, L.M. Monteggia, Enhanced ERK activity extends ketamine's antidepressant effects by augmenting synaptic plasticity, Science 388 (2025) 646–655, https://doi.org/10.1126/SCIENCE.ABB6748.
[47] N.R. Williams, B.D. Heifets, C. Blasey, K. Sudheimer, J. Pannu, H. Pankow, J. Hawkins, J. Birnbaum, D.M. Lyons, C.I. Rodriguez, A.F. Schatzberg, Attenuation of antidepressant effects of ketamine by opioid receptor antagonism, Am. J. Psychiatry 175 (2018) 1205–1215, https://doi.org/10.1176/APPI.AJP.2018.18020138.
[48] M.A. Gillman, Opioid properties of nitrous oxide and ketamine contribute to their antidepressant actions, Int. J. Neuropsychopharmacol. 24 (2021) 892, https://doi.org/10.1093/IJNP/PYAB045.
[49] M.E. Klein, J. Chandra, S. Sheriff, R. Malinow, Opioid system is necessary but not sufficient for antidepressive actions of ketamine in rodents, Proc. Natl. Acad. Sci. USA 117 (2020) 2656–2662, https://doi.org/10.1073/PNAS.1916570117/SUPPL_FILE/PNAS.1916570117.SAPP.PDF.
[50] A. Bahji, C.A. Zarate, G.H. Vazquez, Efficacy and safety of racemic ketamine and esketamine for depression: a systematic review and meta-analysis, Expert Opin. Drug Saf. 21 (2022) 853–866, https://doi.org/10.1080/14740338.2022.2047928.
[51] Y. Alnefeesi, D. Chen-Li, E. Krane, M.Y. Jawad, N.B. Rodrigues, F. Ceban, J.D. Di Vincenzo, S. Meshkat, R.C.M. Ho, H. Gill, K.M. Teopiz, B. Cao, Y. Lee, R. S. McIntyre, J.D. Rosenblat, Real-world effectiveness of ketamine in treatment-resistant depression: a systematic review & meta-analysis, J. Psychiatr. Res. 151 (2022) 693–709, https://doi.org/10.1016/j.jpsychires.2022.04.037.
[52] S. Oraee, M. Alinejadfard, H. Golsorkh, M. Sadeghian, M. Fanaei, R. Centis, L. D'Ambrosio, G. Sotgiu, H. Goudarzi, G.B. Migliori, M.J. Nasiri, Intranasal esketamine for patients with major depressive disorder: a systematic review and meta-analysis, J. Psychiatr. Res. 180 (2024) 371–379, https://doi.org/10.1016/j.jpsychires.2024.11.010.
[53] K.N. Fountoulakis, A. Saitis, A.F. Schatzberg, Esketamine treatment for depression in adults: a PRISMA systematic review and Meta-Analysis, Am. J. Psychiatry 182 (2025) 259–275, https://doi.org/10.1176/appi.ajp.20240515.
[54] A. Reif, I. Bitter, J. Buyze, K. Cebulla, R. Frey, D.-J. Fu, T. Ito, Y. Kambarov, P.-M. Llorca, A.J. Oliveira-Maia, T. Messer, S. Mulhern-Haughey, B. Rive, C. von Holt, A.H. Young, Y. Godinov, Esketamine nasal spray versus quetiapine for treatment-resistant depression, N. Engl. J. Med. 389 (2023) 1298–1309, https://doi.org/10.1056/NEJMOA2304145.
[55] L. Nguyen, K.L. Thomas, B.P. Lucke-Wold, J.Z. Cavendish, M.S. Crowe, R. R. Matsumoto, Dextromethorphan: an update on its utility for neurological and neuropsychiatric disorders, Pharm. Ther. 159 (2016) 1–22, https://doi.org/10.1016/j.pharmthera.2016.01.016.
[56] A. Majeed, J. Xiong, K.M. Teopiz, J. Ng, R. Ho, J.D. Rosenblat, L. Phan, B. Cao, R. S. McIntyre, Efficacy of dextromethorphan for the treatment of depression: a systematic review of preclinical and clinical trials, Expert Opin. Emerg. Drugs 26 (2021) 63–74, https://doi.org/10.1080/14728214.2021.1898588.
[57] C.N. Stanciu, T.M. Penders, E.M. Rouse, Recreational use of dextromethorphan, "Robotripping"—A brief review, Am. J. Addict. 25 (2016) 374–377, https://doi.org/10.1111/ajad.12389.
[58] L. Nguyen, R.R. Matsumoto, Involvement of AMPA receptors in the antidepressant-like effects of dextromethorphan in mice, Behav. Brain Res. 295 (2015) 26–34, https://doi.org/10.1016/j.bbr.2015.03.024.
[59] L. Nguyen, M.J. Robson, J.R. Healy, A.L. Scandinaro, R.R. Matsumoto, Involvement of sigma-1 receptors in the antidepressant-like effects of dextromethorphan, PLoS One 9 (2014), https://doi.org/10.1371/JOURNAL.PONE.0089985.
[60] H. Tabuteau, A. Jones, A. Anderson, M. Jacobson, D.V. Iosifescu, Effect of AXS-05 (Dextromethorphan-Bupropion) in major depressive disorder: a randomized Double-Blind controlled trial, Am. J. Psychiatry 179 (2022) 490–499, https://doi.org/10.1176/APPI.AJP.21080800.
[61] D.V. Iosifescu, A. Jones, C. O'Gorman, C. Streicher, S. Feliz, M. Fava, H. Tabuteau, Efficacy and safety of AXS-05 (Dextromethorphan-Bupropion) in patients with major depressive disorder: a phase 3 randomized clinical trial (GEMINI, J. Clin. Psychiatry 83 (2022), https://doi.org/10.4088/JCP.21M14345.
[62] H. Crewe, M. Lennard, G. Tucker, F. Woods, R. Haddock, The effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes, Br. J. Clin. Pharmacol. 34 (1992) 262–265, https://doi.org/10.1111/J.1365-2125.1992.TB04134.X.
[63] S. Maji, A. Mishra, D. Mohapatra, B.R. Mishra, M. Jena, A. Srinivasan, R. Maiti, Early augmentation therapy with dextromethorphan in mild to moderate major depressive disorder: a group sequential, response adaptive randomized controlled trial, Psychiatry Res. 342 (2024), https://doi.org/10.1016/j.psychres.2024.116257.
[64] E.C. Lauterbach, An extension of hypotheses regarding rapid-acting, treatment-refractory, and conventional antidepressant activity of dextromethorphan and dextrorphan, Med. Hypotheses 78 (2012) 693–702, https://doi.org/10.1016/j.mehy.2012.02.012.
[65] E. Sakhaee, S. Ostadhadi, M.I. Khan, F. Yousefi, A. Norouzi-Javidan, R. Akbarian, M. Chamanara, S. Zolfaghari, A.R. Dehpour, The role of NMDA receptor and nitric oxide/cyclic guanosine monophosphate pathway in the antidepressant-like effect of dextromethorphan in mice forced swimming test and tail suspension test, Biomed. Pharmacother. 85 (2017) 627–634, https://doi.org/10.1016/j.biopha.2016.11.073.
[66] L. Nguyen, B.P. Lucke-Wold, A.F. Logsdon, A.L. Scandinaro, J.D. Huber, R. R. Matsumoto, Behavioral and biochemical effects of ketamine and dextromethorphan relative to its antidepressant-like effects in Swiss webster mice, Neuroreport 27 (2016) 1004–1011, https://doi.org/10.1097/WNR.0000000000000646.
[67] L.L. Werling, A. Keller, J.G. Frank, S.J. Nuwayhid, A comparison of the binding profiles of dextromethorphan, memantine, fluoxetine and amitriptyline: treatment of involuntary emotional expression disorder, Exp. Neurol. 207 (2007) 248–257, https://doi.org/10.1016/j.expneurol.2007.06.013.
[68] S.Y. Lee, T.Y. Wang, S.L. Chen, Y.H. Chang, P.S. Chen, S.Y. Huang, N.S. Tzeng, L. J. Wang, I.H. Lee, K.C. Chen, Y.K. Yang, J.S. Hong, R.B. Lu, Combination of dextromethorphan and memantine in treating bipolar spectrum disorder: a 12-week double-blind randomized clinical trial, Int J. Bipolar Disord. 8 (2020), https://doi.org/10.1186/s40345-019-0174-8.
[69] Otsuka Holdings Company Limited, Consolidated Financial Results for the Fiscal Year Ended December 31, 2016, 2017. ⟨https://ssl4.eir-parts.net/doc/4578/ir_material_for_fiscal_ym2/101965/00.pdf⟩ (accessed April 20, 2025).
[70] L. Nguyen, A.L. Scandinaro, R.R. Matsumoto, Deuterated (d6)-dextromethorphan elicits antidepressant-like effects in mice, Pharmacol. Biochem. Behav. 161 (2017) 30–37, https://doi.org/10.1016/j.pbb.2017.09.005.
[71] K. Lemberg, V.K. Kontinen, K. Viljakka, I. Kylänlahti, J. Yli-Kauhaluoma, E. Kalso, Morphine, oxycodone, methadone and its enantiomers in different models of nociception in the rat, Anesth. Analg. 102 (2006) 1768–1774, https://doi.org/10.1213/01.ane.0000205751.88422.41.
[72] J. Henningfield, D. Gauvin, F. Bifari, R. Fant, M. Shram, A. Buchhalter, J. Ashworth, R. Lanier, M. Pappagallo, C. Inturrisi, F. Folli, S. Traversa, P. L. Manfredi, REL-1017 (esmethadone; D-methadone) does not cause reinforcing effect, physical dependence and withdrawal signs in sprague dawley rats, Sci. Rep. 12 (2022), https://doi.org/10.1038/S41598-022-15055-3.
[73] G. Bernstein, K. Davis, C. Mills, L. Wang, M. McDonnell, J. Oldenhof, C. Inturrisi, P.L. Manfredi, O.V. Vitolo, Characterization of the safety and pharmacokinetic profile of d -Methadone, a novel n -Methyl- d -Aspartate receptor antagonist in healthy, Opioid-Naive subjects: results of two phase 1 studies, J. Clin. Psychopharmacol. 39 (2019) 226–237, https://doi.org/10.1097/JCP.0000000000001035.
[74] M. Fava, S.M. Stahl, S. De Martin, A. Mattarei, E. Bettini, S. Comai, A. Alimonti, F. Bifari, L. Pani, F. Folli, C. Guidetti, A. Furlan, J. Sgrignani, P. Locatelli, A. Cavalli, C. O'Gorman, S. Traversa, C.E. Inturrisi, M. Pappagallo, P.L. Manfredi, Esmethadone-HCl (REL-1017): a promising rapid antidepressant, Eur. Arch. Psychiatry Clin. Neurosci. 273 (2023) 1463–1476, https://doi.org/10.1007/S00406-023-01571-4.
[75] M. Fava, S. Stahl, L. Pani, S. De Martin, M. Pappagallo, C. Guidetti, A. Alimonti, E. Bettini, R.M. Mangano, T. Wessel, M. de Somer, J. Caron, O.V. Vitolo, G. R. DiGuglielmo, A. Gilbert, H. Mehta, M. Kearney, A. Mattarei, M. Gentilucci, F. Folli, S. Traversa, C.E. Inturrisi, P.L. Manfredi, REL-1017 (Esmethadone) as adjunctive treatment in patients with major depressive disorder: a phase 2a randomized Double-Blind trial, Am. J. Psychiatry 179 (2022) 122–131, https://doi.org/10.1176/appi.ajp.2021.21020197.
[76] Relmada Therapeutics, Relmada Therapeutics to Discontinue the Reliance II and Relight Phase 3 Studies of REL-1017, 2024. ⟨https://www.relmada.com/for-investors/news/detail/307/relmada-therapeutics-to-discontinue-the-reliance-ii-and⟩ (accessed April 10, 2025).
[77] S. De Martin, D. Gabbia, F. Folli, F. Bifari, P. Fiorina, N. Ferri, S. Stahl, C. E. Inturrisi, M. Pappagallo, S. Traversa, P.L. Manfredi, REL-1017 (Esmethadone) increases circulating BDNF levels in healthy subjects of a phase 1 clinical study, Front. Pharmacol. 12 (2021) 671859, https://doi.org/10.3389/FPHAR.2021.671859/BIBTEX.
[78] M.V. Fogaça, K. Fukumoto, T. Franklin, R.J. Liu, C.H. Duman, O.V. Vitolo, R. S. Duman, N-Methyl-D-aspartate receptor antagonist d-methadone produces rapid, mTORC1-dependent antidepressant effects, Neuropsychopharmacology 44 (2019) 2230–2238, https://doi.org/10.1038/S41386-019-0501-X.
[79] S.A. Zaloum, D. Mair, A. Paris, L.J. Smith, M. Patyjewicz, B.L. Onen, A.J. Noyce, Tackling the growing burden of nitrous oxide-induced public health harms, Lancet Public Health 10 (2025) e257–e263, https://doi.org/10.1016/S2468-2667(24)00298-6.
[80] H. Liu, J. Kerzner, I. Demchenko, D.N. Wijeysundera, S.H. Kennedy, K.S. Ladha, V. Bhat, Nitrous oxide for the treatment of psychiatric disorders: a systematic review of the clinical trial landscape, Acta Psychiatr. Scand. 146 (2022) 126–138, https://doi.org/10.1111/ACPS.13432.
[81] G. Kronenberg, G. Schoretsanitis, E. Seifritz, S. Olbrich, The boon and bane of nitrous oxide, Eur. Arch. Psychiatry Clin. Neurosci. (2024), https://doi.org/10.1007/S00406-024-01801-3.
[82] V. Lew, E. McKay, M. Maze, Past, present, and future of nitrous oxide, Br. Med. Bull. 125 (2018) 103–119, https://doi.org/10.1093/BMB/LDX050.
[83] S. Mennerick, V. Jevtovic-Todorovic, S.M. Todorovic, W. Shen, J.W. Olney, C. F. Zorumski, Effect of nitrous oxide on excitatory and inhibitory synaptic

transmission in hippocampal cultures, J. Neurosci. 18 (1998) 9716–9726, https://doi.org/10.1523/JNEUROSCI.18-23-09716.1998.
[84] M.C. Guimarães, T.M. Guimarães, J.E. Hallak, J. Abrão, J.P. Machado-De-sousa, Nitrous oxide as an adjunctive therapy in major depressive disorder: a randomized controlled double-blind pilot trial, Braz. J. Psychiatry 43 (2021) 484, https://doi.org/10.1590/1516-4446-2020-1543.
[85] P. Nagele, A. Duma, M. Kopec, M.A. Gebara, A. Parsoei, M. Walker, A. Janski, V. N. Panagopoulos, P. Cristancho, J.P. Miller, C.F. Zorumski, C.R. Conway, Nitrous oxide for treatment-resistant major depression: a proof-of-concept trial, Biol. Psychiatry 78 (2015) 10–18, https://doi.org/10.1016/J.BIOPSYCH.2014.11.016.
[86] P. Nagele, B.J. Palanca, B. Gott, F. Brown, L. Barnes, T. Nguyen, W. Xiong, N. C. Salloum, G.D. Espejo, C.N. Lessov-Schlaggar, N. Jain, W.W.L. Cheng, H. Komen, B. Yee, J.D. Bolzenius, A. Janski, R. Gibbons, C.F. Zorumski, C. R. Conway, A phase 2 trial of inhaled nitrous oxide for treatment-resistant major depression, Sci. Transl. Med. 13 (2021), https://doi.org/10.1126/SCITRANSLMED.ABE1376.
[87] P.S. Myles, J. Kulkarni, J. Kasza, S. Wallace, C. Deng, A. Turbić, V. Aykanat, C. R. Conway, F. Brown, R. Lee, R.D. Gibbons, P. Nagele, Antidepressant effects of nitrous oxide in major depressive disorder: a phase 2b randomized clinical trial, Biol. Psychiatry Glob. Open Sci. 0 (2025) 100504, https://doi.org/10.1016/j.bpsgos.2025.100504.
[88] J. Cichon, T.T. Joseph, X. Lu, A.Z. Wasilczuk, M.B. Kelz, S.J. Mennerick, C. F. Zorumski, P. Nagele, Nitrous oxide activates layer 5 prefrontal neurons via SK2 channel inhibition for antidepressant effect, Nat. Commun. 16 (2025) 2999, https://doi.org/10.1038/s41467-025-57951-y.
[89] W. Liu, Q. Li, B. Ye, H. Cao, F. Shen, Z. Xu, W. Du, F. Guo, J. Liu, T. Li, B. Zhang, Z. Liu, Repeated nitrous oxide exposure exerts Antidepressant-Like effects through neuronal nitric oxide synthase activation in the medial prefrontal cortex, Front. Psychiatry 11 (2020), https://doi.org/10.3389/FPSYT.2020.00837/PDF.
[90] S. Kohtala, W. Theilmann, M. Rosenholm, L. Penna, G. Karabulut, S. Uusitalo, K. Järventausta, A. Yli-Hankala, I. Yalcin, N. Matsui, H.K. Wigren, T. Rantamäki, Cortical excitability and activation of TrkB signaling during rebound slow oscillations are critical for rapid antidepressant responses, Mol. Neurobiol. 56 (2019) 4163–4174, https://doi.org/10.1007/S12035-018-1364-6/FIGURES/6.
[91] D. Cattano, S. Valleggi, A. Abramo, F. Forfori, M. Maze, F. Giunta, Nitrous Oxide Discretely Up-regulates nNOS and p53 in Neonatal Rat Brain, 2010.
[92] J.E. Donello, P. Banerjee, Y.-X. Li, Y.-X. Guo, T. Yoshitake, X.-L. Zhang, O. Miry, J. Kehr, P.K. Stanton, A.L. Gross, J.S. Burgdorf, R.A. Kroes, J.R. Moskal, Positive N-Methyl-D-Aspartate receptor modulation by rapastinel promotes rapid and sustained Antidepressant-Like effects, Int. J. Neuropsychopharmacol. 22 (2019) 247–259, https://doi.org/10.1093/ijnp/pyy101.
[93] T. Kato, R.S. Duman, Rapastinel, a novel glutamatergic agent with ketamine-like antidepressant actions: convergent mechanisms, Pharm. Biochem. Behav. 188 (2020), https://doi.org/10.1016/J.PBB.2019.172827.
[94] J.E. Donello, R.S. McIntyre, D.B. Pickel, S.M. Stahl, Demystifying the antidepressant mechanism of action of stinels, a novel class of neuroplastogens: positive allosteric modulators of the NMDA receptor, Pharmaceuticals 18 (2025) 157, https://doi.org/10.3390/ph18020157.
[95] U. Heresco-Levy, G. Gelfin, B. Bloch, R. Levin, S. Edelman, D.C. Javitt, I. Kremer, A randomized add-on trial of high-dose D-cycloserine for treatment-resistant depression, Int J. Neuropsychopharmacol. 16 (2013) 501–506, https://doi.org/10.1017/S1461145712000910.
[96] A. Nierenberg, P. Lavin, D.C. Javitt, R. Shelton, M.T. Sapko, S. Mathew, R. E. Besthof, J.C. Javitt, NRX-101 (D-cycloserine plus lurasidone) vs. Lurasidone for the maintenance of initial stabilization after ketamine in patients with severe bipolar depression with acute suicidal ideation and behavior: a randomized prospective phase 2 trial, Int. J. Bipolar Disord. 11 (2023), https://doi.org/10.1186/s40345-023-00308-5.
[97] J.S. Burgdorf, X.L. Zhang, P.K. Stanton, J.R. Moskal, J.E. Donello, Zelquistinel is an orally bioavailable novel NMDA receptor allosteric modulator that exhibits rapid and sustained Antidepressant-Like effects, Int. J. Neuropsychopharmacol. 25 (2022) 979–991, https://doi.org/10.1093/IJNP/PYAC043.
[98] S. Pothula, R.J. Liu, M. Wu, A.N. Sliby, M.R. Picciotto, P. Banerjee, R.S. Duman, Positive modulation of NMDA receptors by AGN-241751 exerts rapid antidepressant-like effects via excitatory neurons, Neuropsychopharmacology 46 (2021) 799–808, https://doi.org/10.1038/S41386-020-00882-7.
[99] A.E. Lepack, E. Bang, B. Lee, J.M. Dwyer, R.S. Duman, Fast-acting antidepressants rapidly stimulate ERK signaling and BDNF release in primary neuronal cultures, Neuropharmacology 111 (2016) 242–252, https://doi.org/10.1016/j.neuropharm.2016.09.011.
[100] T. Kato, M.V. Fogaça, S. Deyama, X.Y. Li, K. Fukumoto, R.S. Duman, BDNF release and signaling are required for the antidepressant actions of GLYX-13, Mol. Psychiatry 23 (2018) 2007–2017, https://doi.org/10.1038/MP.2017.220.
[101] J. Burgdorf, X.L. Zhang, K.L. Nicholson, R.L. Balster, J. David Leander, P. K. Stanton, A.L. Gross, R.A. Kroes, J.R. Moskal, GLYX-13, a NMDA receptor glycine-site functional partial agonist, induces antidepressant-like effects without ketamine-like side effects, Neuropsychopharmacology 38 (2013) 729–742, https://doi.org/10.1038/NPP.2012.246.
[102] M. Shen, D. Lv, X. Liu, C. Wang, ERK/mTOR signaling May underlying the antidepressant actions of rapastinel in mice, Transl. Psychiatry 12 (2022), https://doi.org/10.1038/S41398-022-02290-5.
[103] Y. Lu, C. Wang, Z. Xue, C. Li, J. Zhang, X. Zhao, A. Liu, Q. Wang, W. Zhou, PI3K/AKT/mTOR signaling-mediated neuropeptide VGF in the hippocampus of mice is involved in the rapid onset antidepressant-like effects of GLYX-13, Int. J. Neuropsychopharmacol. 18 (2014) 1–12, https://doi.org/10.1093/IJNP/PYU110.
[104] T. Kishi, S. Matsunaga, N. Iwata, A meta-analysis of memantine for depression, J. Alzheimer'S. Dis. 57 (2017) 113–121, https://doi.org/10.3233/JAD-161251.
[105] G. Sanacora, M.R. Johnson, A. Khan, S.D. Atkinson, R.R. Riesenberg, J. P. Schronen, M.A. Burke, J.M. Zajecka, L. Barra, H.L. Su, J.A. Posener, K.H. Bui, M.C. Quirk, T.M. Piser, S.J. Mathew, S. Pathak, Adjunctive lanicemine (AZD6765) in patients with major depressive disorder and history of inadequate response to antidepressants: a randomized, Placebo-Controlled study, Neuropsychopharmacology 42 (2017) 844–853, https://doi.org/10.1038/NPP.2016.224.
[106] Roger S. McIntyre, Gerard Sanacora, David P. Walling, Elan A. Cohen, Shishuka Malhotra, Holger Rosenbrock, Manuela Schmitz, Andreas Scholz, Sigurd D. Suessmuth, Franco De Crescenzo, ACNP 63rd Annual Meeting: Poster Abstracts P1-P304: P219. Efficacy and Safety of a Single Administration of the NMDA Subunit 2B-Selective Negative Allosteric Modulator, BI 1569912, in People Living With Major Depressive Disorder: A Phase IB Randomized Controlled Trial, Neuropsychopharmacology 49 (2024) 65–235, https://doi.org/10.1038/s41386-024-02011-0.
[107] W. Lu, Y. Shi, A.C. Jackson, K. Bjorgan, M.J. During, R. Sprengel, P.H. Seeburg, R. A. Nicoll, Subunit composition of synaptic AMPA receptors revealed by a single-cell genetic approach, Neuron 62 (2009) 254–268, https://doi.org/10.1016/J.NEURON.2009.02.027.
[108] S.-H. Shi, Y. Hayashi, J.A. Esteban, R. Malinow, Subunit-specific rules governing AMPA receptor trafficking to synapses in hippocampal pyramidal neurons, Cell 105 (2001) 331–343, https://doi.org/10.1016/S0092-8674(01)00321-X.
[109] Y. Ge, Y.T. Wang, GluA1-homomeric AMPA receptor in synaptic plasticity and neurological diseases, Neuropharmacology 197 (2021), https://doi.org/10.1016/j.neuropharm.2021.108708.
[110] P. Zanos, S.M. Thompson, R.S. Duman, C.A. Zarate, T.D. Gould, Convergent mechanisms underlying rapid antidepressant action, CNS Drugs 32 (2018) 197–227, https://doi.org/10.1007/S40263-018-0492-X.
[111] M. Park, M.J. Niciu, C.A. Zarate, Novel glutamatergic treatments for severe mood disorders, Curr. Behav. Neurosci. Rep. 2 (2015) 198–208, https://doi.org/10.1007/S40473-015-0050-5.
[112] M.J.Y. Kang, E. Hawken, G.H. Vazquez, The mechanisms behind rapid antidepressant effects of ketamine: a systematic review with a focus on molecular neuroplasticity, Front. Psychiatry 13 (2022) 860882, https://doi.org/10.3389/FPSYT.2022.860882/XML/NLM.
[113] A. Suzuki, H. Hara, H. Kimura, Role of the AMPA receptor in antidepressant effects of ketamine and potential of AMPA receptor potentiators as a novel antidepressant, Neuropharmacology 222 (2023), https://doi.org/10.1016/J.NEUROPHARM.2022.109308.
[114] P. Zanos, R. Moaddel, P.J. Morris, P. Georgiou, J. Fischell, G.I. Elmer, M. Alkondon, P. Yuan, H.J. Pribut, N.S. Singh, K.S.S. Dossou, Y. Fang, X.P. Huang, C.L. Mayo, I.W. Wainer, E.X. Albuquerque, S.M. Thompson, C.J. Thomas, C. A. Zarate, T.D. Gould, NMDAR inhibition-independent antidepressant actions of ketamine metabolites, Nature 533 (2016) 481–486, https://doi.org/10.1038/NATURE17998.
[115] C.L. Shaffer, J.K. Dutra, W.C. Tseng, M.L. Weber, L.J. Bogart, K. Hales, J. Pang, D. Volfson, C.W. am Ende, M.E. Green, D.L. Buhl, Pharmacological evaluation of clinically relevant concentrations of (2R,6R)-hydroxynorketamine, Neuropharmacology 153 (2019) 73–81, https://doi.org/10.1016/j.neuropharm.2019.04.019.
[116] K. Suzuki, E. Nosyreva, K.W. Hunt, E.T. Kavalali, L.M. Monteggia, Effects of a ketamine metabolite on synaptic NMDAR function, Nature 546 (7659) (2017) E1–E3, https://doi.org/10.1038/nature22084.
[117] T.H. Pham, C. Defaix, X. Xu, S.X. Deng, N. Fabresse, J.C. Alvarez, D.W. Landry, R. A. Brachman, C.A. Denny, A.M. Gardier, Common neurotransmission recruited in (R,S)-Ketamine and (2R,6R)-Hydroxynorketamine-Induced sustained Antidepressant-like effects, Biol. Psychiatry 84 (2018) e3–e6, https://doi.org/10.1016/J.BIOPSYCH.2017.10.020.
[118] E.W. Lumsden, T.A. Troppoli, S.J. Myers, P. Zanos, Y. Aracava, J. Kehr, J. Lovett, S. Kim, F.H. Wang, S. Schmidt, C.E. Jenne, P. Yuan, P.J. Morris, C.J. Thomas, C. A. Zarate, R. Moaddel, S.F. Traynelis, E.F.R. Pereira, S.M. Thompson, E. X. Albuquerque, T.D. Gould, Antidepressant-relevant concentrations of the ketamine metabolite (2 R,6 R)-hydroxynorketamine do not block NMDA receptor function, Proc. Natl. Acad. Sci. USA 116 (2019) 5160–5169, https://doi.org/10.1073/PNAS.1816071116.
[119] S.M. Raja, J.T. Guptill, M. Mack, M. Peterson, S. Byard, R. Twieg, L. Jordan, N. Rich, R. Castledine, S. Bourne, M. Wilmshurst, S. Oxendine, S.G.C. Avula, H. Zuleta, P. Quigley, S. Lawson, S.J. McQuaker, R. Ahmadkhaniha, L. G. Appelbaum, K. Kowalski, C.T. Barksdale, B.T. Gufford, A. Awan, A.R. Sancho, M.C. Moore, K. Berrada, G.B. Cogan, J. DeLaRosa, J. Radcliffe, M. Pao, M. Kennedy, Q. Lawrence, L. Goldfeder, L. Amanfo, P. Zanos, J.R. Gilbert, P. J. Morris, R. Moaddel, T.D. Gould, C.A. Zarate, C.J. Thomas, A. Phase, 1 assessment of the safety, tolerability, pharmacokinetics and pharmacodynamics of (2R,6R)-Hydroxynorketamine in healthy volunteers, Clin. Pharmacol. Ther. 116 (2024), https://doi.org/10.1002/CPT.3391.
[120] C.A. Farmer, J.R. Gilbert, R. Moaddel, J. George, L. Adeojo, J. Lovett, A. C. Nugent, B. Kadriu, P. Yuan, T.D. Gould, L.T. Park, C.A. Zarate, Ketamine metabolites, clinical response, and gamma power in a randomized, placebo-controlled, crossover trial for treatment-resistant major depression, 2020 45:8 45, Neuropsychopharmacology (2020) 1398–1404, https://doi.org/10.1038/s41386-020-0663-6.
[121] M.F. Grunebaum, H.C. Galfalvy, T.H. Choo, M.S. Parris, A.K. Burke, R.F. Suckow, T.B. Cooper, J.J. Mann, Ketamine metabolite pilot study in a suicidal depression

trial, J. Psychiatr. Res. 117 (2019) 129–134, https://doi.org/10.1016/J.JPSYCHIRES.2019.08.005.
[122] A.C. Arai, M. Kessler, Pharmacology of Ampakine Modulators: From AMPA Receptors to Synapses and Behavior, 2007.
[123] A. Alt, J. Witkin, D. Bleakman, AMPA receptor potentiators as novel antidepressants, Curr. Pharm. Des. 11 (2005) 1511–1527, https://doi.org/10.2174/1381612053764814.
[124] A. Alt, E.S. Nisenbaum, D. Bleakman, J.M. Witkin, A role for AMPA receptors in mood disorders, Biochem Pharmacol. 71 (2006) 1273–1288, https://doi.org/10.1016/j.bcp.2005.12.022.
[125] D. Bleakman, A. Alt, J.M. Witkin, AMPA receptors in the therapeutic management of depression, CNS Neurol. Disord. Drug Targets 6 (2008) 117–126, https://doi.org/10.2174/187152707780363258.
[126] M.J. O'Neill, D. Bleakman, D.M. Zimmerman, E.S. Nisenbaum, AMPA receptor potentiators for the treatment of CNS disorders, Curr. Drug Targets CNS Neurol. Disord. 3 (2004) 181–194, https://doi.org/10.2174/1568007043337508.
[127] B. Kadriu, L. Musazzi, J.N. Johnston, L.E. Kalynchuk, H.J. Caruncho, M. Popoli, C. A. Zarate, Positive AMPA receptor modulation in the treatment of neuropsychiatric disorders: a long and winding road, Drug Discov. Today 26 (2021) 2816–2838, https://doi.org/10.1016/j.drudis.2021.07.027.
[128] D.P. Radin, A. Lippa, S. Rana, D.D. Fuller, J.L. Smith, R. Cerne, J.M. Witkin, Amplification of the therapeutic potential of AMPA receptor potentiators from the nootropic era to today, Pharm. Biochem. Behav. 248 (2025) 173967, https://doi.org/10.1016/j.pbb.2025.173967.
[129] B. Pirotte, P. Francotte, E. Goffin, P. De Tullio, AMPA receptor positive allosteric modulators: a patent review, Expert Opin. Ther. Pat. 23 (2013) 615–628, https://doi.org/10.1517/13543776.2013.770840.
[130] J.C. Quirk, E.S. Nisenbaum, LY404187: a novel positive allosteric modulator of AMPA receptors, CNS Drug Rev. 8 (2002) 255–282, https://doi.org/10.1111/J.1527-3458.2002.TB00228.X.
[131] X. Li, J.P. Tizzano, K. Griffey, M. Clay, T. Lindstrom, P. Skolnick, Antidepressant-like Actions of an AMPA Receptor Potentiator (LY392098), 2001. ⟨www.elsevier.com/locate/neuropharm⟩.
[132] H. Yao, D. Zhang, H. Yu, H. Shen, X. Lan, H. Liu, X. Chen, X. Wu, G. Zhang, X. Wang, AMPAkine CX516 alleviated chronic ethanol exposure-induced neurodegeneration and depressive-like behavior in mice, Toxicol. Appl. Pharmacol. 439 (2022), https://doi.org/10.1016/j.taap.2022.115924.
[133] M. Gordillo-Salas, R. Pascual-Antón, J. Ren, J. Greer, A. Adell, Antidepressant-Like effects of CX717, a positive allosteric modulator of AMPA receptors, Mol. Neurobiol. 57 (2020) 3498–3507, https://doi.org/10.1007/s12035-020-01954-x.
[134] R.J. Knapp, R. Goldenberg, C. Shuck, A. Cecil, J. Watkins, C. Miller, G. Crites, E. Malatynska, Antidepressant activity of memory-enhancing drugs in the reduction of submissive behavior model, Eur. J. Pharmacol. 440 (2002) 27–35, https://doi.org/10.1016/s0014-2999(02)01338-9.
[135] D.P. Radin, S. Johnson, R. Purcell, A.S. Lippa, Effects of chronic systemic low-impact ampakine treatment on neurotrophin expression in rat brain, Biomed. Pharmacother. 105 (2018) 540–544, https://doi.org/10.1016/j.biopha.2018.06.008.
[136] M.L. Woolley, K.A. Waters, J.E. Gartlon, L.P. Lacroix, C. Jennings, F. Shaughnessy, A. Ong, D.J. Pemberton, M.H. Harries, E. Southam, D.N.C. Jones, L.A. Dawson, Evaluation of the pro-cognitive effects of the AMPA receptor positive modulator, 5-(1-piperidinylcarbonyl)-2,1,3-benzoxadiazole (CX691), in the rat, Psychopharmacology 202 (2009) 343–354, https://doi.org/10.1007/S00213-008-1325-2/FIGURES/6.
[137] J.C. Lauterborn, E. Pineda, L.Y. Chen, E.A. Ramirez, G. Lynch, C.M. Gall, Ampakines cause sustained increases in brain-derived neurotrophic factor signaling at excitatory synapses without changes in AMPA receptor subunit expression, Neuroscience 159 (2009) 283–295, https://doi.org/10.1016/J.NEUROSCIENCE.2008.12.018/ASSET/5A2BCD85-F166-4DEF-B6D9-757551589B4F/MAIN.ASSETS/GR7.JPG.
[138] C.S. Rex, J.C. Lauterborn, C.Y. Lin, E.A. Kramár, G.A. Rogers, C.M. Gall, G. Lynch, Restoration of long-term potentiation in middle-aged hippocampus after induction of brain-derived neurotrophic factor, J. Neurophysiol. 96 (2006) 677–685, https://doi.org/10.1152/JN.00336.2006/ASSET/IMAGES/LARGE/Z9K0080675990006.JPEG.
[139] H. Jourdi, L. Hamo, T. Oka, A. Seegan, M. Baudry, BDNF mediates the neuroprotective effects of positive AMPA receptor modulators against MPP+-induced toxicity in cultured hippocampal and mesencephalic slices, Neuropharmacology 56 (2009) 876–885, https://doi.org/10.1016/j.neuropharm.2009.01.015.
[140] F. Fumagalli, F. Calabrese, A. Luoni, M. Shahid, G. Racagni, M.A. Riva, The AMPA receptor potentiator org 26576 modulates stress-induced transcription of BDNF isoforms in rat hippocampus, Pharm. Res. 65 (2012) 176–181, https://doi.org/10.1016/j.phrs.2011.10.004.
[141] B. Legutko, X. Li, P. Skolnick, Regulation of BDNF Expression in Primary Neuron Culture by LY392098, a Novel AMPA receptor potentiator, 2001. ⟨www.elsevier.com/locate/neuropharm⟩.
[142] A. Kunugi, Y. Tajima, H. Kuno, S. Sogabe, H. Kimura, HBT1, a novel ampa receptor potentiator with lower agonistic effect, avoided bell-shaped response in in vitro BDNF productions, J. Pharmacol. Exp. Ther. 364 (2018) 377–389, https://doi.org/10.1124/jpet.117.245050.
[143] A. Suzuki, K. Murakami, Y. Tajima, H. Hara, A. Kunugi, H. Kimura, TAK-137, an AMPA receptor potentiator with little agonistic effect, produces antidepressant-like effect without causing psychotomimetic effects in rats, Pharm. Biochem. Behav. 183 (2019) 80–86, https://doi.org/10.1016/j.pbb.2019.06.004.
[144] H. Hara, A. Suzuki, A. Kunugi, Y. Tajima, R. Yamada, H. Kimura, TAK-653, an AMPA receptor potentiator with minimal agonistic activity, produces an antidepressant-like effect with a favorable safety profile in rats, Pharm. Biochem. Behav. 211 (2021), https://doi.org/10.1016/J.PBB.2021.173289.
[145] A. Suzuki, A. Kunugi, Y. Tajima, N. Suzuki, M. Suzuki, M. Toyofuku, H. Kuno, S. Sogabe, Y. Kosugi, Y. Awasaki, T. Kaku, H. Kimura, Strictly regulated agonist-dependent activation of AMPA-R is the key characteristic of TAK-653 for robust synaptic responses and cognitive improvement, Sci. Rep. 1 (11) (2021) 1–15, https://doi.org/10.1038/s41598-021-93888-0.
[146] L. Cavalleri, E. Merlo Pich, M.J. Millan, C. Chiamulera, T. Kunath, P.F. Spano, G. Collo, Ketamine enhances structural plasticity in mouse mesencephalic and human iPSC-derived dopaminergic neurons via AMPAR-driven BDNF and mTOR signaling, Mol. Psychiatry 23 (2018) 812–823, https://doi.org/10.1038/mp.2017.241.
[147] P.K.Y. Chang, G.A. Prenosil, D. Verbich, R. Gill, R.A. Mckinney, Prolonged ampakine exposure prunes dendritic spines and increases presynaptic release probability for enhanced long-term potentiation in the hippocampus, Eur. J. Neurosci. 40 (2014) 2766–2776, https://doi.org/10.1111/ejn.12638.
[148] K. Hashimoto, E. Shimizu, M. Iyo, Critical role of brain-derived neurotrophic factor in mood disorders, Brain Res. Rev. 45 (2004) 104–114, https://doi.org/10.1016/j.brainresrev.2004.02.003.
[149] X.W. Su, X.Y. Li, M. Banasr, J.W. Ook Koo, M. Shahid, B. Henry, R.S. Duman, Chronic treatment with AMPA receptor potentiator org 26576 increases neuronal cell proliferation and survival in adult rodent hippocampus, Psychopharmacology 206 (2009) 215–222, https://doi.org/10.1007/S00213-009-1598-0/FIGURES/5.
[150] F. Bai, M. Bergeron, D.L. Nelson, Chronic AMPA receptor potentiator (LY451646) treatment increases cell proliferation in adult rat hippocampus, Neuropharmacology 44 (2003) 1013–1021, https://doi.org/10.1016/S0028-3908(03)00104-7.
[151] D.P. Radin, R. Cerne, J.L. Smith, J.M. Witkin, A. Lippa, Safety, tolerability and pharmacokinetic profile of the low-impact ampakine CX717 in young healthy Male subjects and elderly healthy Male and female subjects, Eur. J. Pharmacol. 993 (2025) 177317, https://doi.org/10.1016/j.ejphar.2025.177317.
[152] D.P. Radin, R. Cerne, J.M. Witkin, A. Lippa, Safety, tolerability, and pharmacokinetic profile of the Low-Impact ampakine CX1739 in young healthy volunteers, Clin. Pharm. Drug Dev. (2024), https://doi.org/10.1002/cpdd.1475.
[153] K.R. Nations, R. Bursi, P. Dogterom, L. Ereshefsky, L. Gertsik, T. Mant, J. Schipper, Maximum tolerated dose evaluation of the AMPA modulator org 26576 in healthy volunteers and depressed patients: a summary and method analysis of bridging research in support of phase II dose selection, Drugs R. D. 12 (2012) 127–139, https://doi.org/10.2165/11634360-000000000-00000.
[154] K.R. Nations, P. Dogterom, R. Bursi, J. Schipper, S. Greenwald, D. Zraket, L. Gertsik, J. Johnstone, A. Lee, Y. Pande, G. Ruigt, L. Ereshefsky, Examination of org 26576, an AMPA receptor positive allosteric modulator, in patients diagnosed with major depressive disorder: an exploratory, randomized, double-blind, placebo-controlled trial, J. Psychopharmacol. 26 (2012) 1525–1539, https://doi.org/10.1177/0269881112458728.
[155] S.E. Ward, M.H. Harries, L. Aldegheri, A.M. Bradford, E. Ballini, L. Dawson, L. Lacroix, J. Pardoe, K. Starr, A. Weil, K. Waters, J.R. Atack, M. Woolley, Pharmacological characterisation of MDI-222, a novel AMPA receptor positive allosteric modulator with an improved safety profile, J. Psychopharmacol. 34 (2020) 93–102, https://doi.org/10.1177/0269881119872198.
[156] E. Wezenberg, R. Jan Verkes, G.S.F. Ruigt, W. Hulstijn, B.G.C. Sabbe, Acute effects of the ampakine farampator on memory and information processing in healthy elderly volunteers, Neuropsychopharmacology (2006) 1272–1283, https://doi.org/10.1038/sj.npp.1301257.
[157] Neurocrine Biosciences, Neurocrine Biosciences Reports Positive Phase 2 Data for NBI-1065845 in Adults with Major Depressive Disorder SAVITRI TM Study Met Primary Endpoint with Statistically Significant Reduction in Montgomery Åsberg Depression Rating Scale (MADRS) Total Score at Day 28 Met Key Secondary Endpoints, Including Statistically Significant Reduction in MADRS Score at Day 56 NBI-1065845 Was Generally Well-Tolerated, 2024. ⟨https://www.prnewswire.com/news-releases/neurocrine-biosciences-reports-positive-phase-2-data⟩-.
[158] Servier, Efficacy and safety of S 47445 Versus Placebo as Adjunctive Treatment of Major Depressive Disorder in Patients with an Inadequate Response to Antidepressant therapy. A randomised, double-blind, placebo controlled international, multicentre study. - Servier Clinical Trials, (2018). ⟨https://clinicaltrials.servier.com/trial/efficacy-and-safety-of-s-47445-versus-placebo-as-adjunctive-treatment-of-major-depressive-disorder-in-patients-with-an-inadequate-response-to-antidepressant-therapy-a-randomised-double-blind-placeb/⟩ (accessed April 7, 2025).
[159] D. Bissen, F. Foss, A. Acker-Palmer, AMPA receptors and their minions: auxiliary proteins in AMPA receptor trafficking, Cell. Mol. Life Sci. 11 (76) (2019) 2133–2169, https://doi.org/10.1007/S00018-019-03068-7.
[160] R. Sprengel, Role of AMPA receptors in synaptic plasticity, Cell Tissue Res. 326 (2006) 447–455, https://doi.org/10.1007/s00441-006-0275-4.
[161] J.G. He, H.Y. Zhou, F. Wang, J.G. Chen, Dysfunction of glutamatergic synaptic transmission in depression: focus on AMPA receptor trafficking, Biol. Psychiatry Glob. Open Sci. 3 (2022) 187–196, https://doi.org/10.1016/J.BPSGOS.2022.02.007.
[162] E. Jacobi, J. Von Engelhardt, I. Forsythe, J.-C.B. Béique, Modulation of information processing by AMPA receptor auxiliary subunits, J. Physiol. 599 (2021) 471–483, https://doi.org/10.1113/JP276698.
[163] A. Kamalova, T. Nakagawa, I. Forsythe, J. Sjöström, A. Kamalova, T. Nakagawa, J. Physiol, AMPA receptor structure and auxiliary subunits, J. Physiol. 599 (2021) 453–469, https://doi.org/10.1113/JP278701.

[164] E. Díaz, Beyond the AMPA receptor: diverse roles of SynDIG/PRRT brain-specific transmembrane proteins at excitatory synapses, Curr. Opin. Pharmacol. 58 (2021) 76–82, https://doi.org/10.1016/J.COPH.2021.03.011.
[165] J. Zhu, Y. Shang, M. Zhang, Mechanistic basis of MAGUK-organized complexes in synaptic development and signalling, Nat. Rev. Neurosci. (2016) 209–223, https://doi.org/10.1038/nrn.2016.18.
[166] A.S. Leonard, M.A. Davare, M. Horne, C.C. Garner, J.W. Hell, SAP97 is associated with the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor GluR1 subunit, J. Biol. Chem. 273 (1998) 19518. ⟨http://www.jbc.org/content/273/31/19518.short⟩.
[167] C. Cai, S.K. Coleman, K. Niemi, K. Keinänen, Selective binding of synapse-associated protein 97 to GluR-A alpha-amino-5-hydroxy-3-methyl-4-isoxazole propionate receptor subunit is determined by a novel sequence motif, J. Biol. Chem. 277 (2002) 31484–31490, https://doi.org/10.1074/jbc.M204354200.
[168] S. Uchino, H. Wada, S. Honda, Y. Nakamura, Y. Ondo, T. Uchiyama, M. Tsutsumi, E. Suzuki, T. Hirasawa, S. Kohsaka, Direct interaction of post-synaptic density-95/Dlg/ZO-1 domain-containing synaptic molecule Shank3 with GluR1 alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor, J. Neurochem. 97 (2006) 1203–1214, https://doi.org/10.1111/j.1471-4159.2006.03831.x.
[169] M. Qneibi, S. Bdir, M. Bdair, S.A. Aldwaik, M. Heeh, D. Sandouka, T. Idais, Exploring the role of AMPA receptor auxiliary proteins in synaptic functions and diseases, FEBS J. (2024), https://doi.org/10.1111/FEBS.17287.
[170] N. Rouach, K. Byrd, R.S. Petralia, G.M. Elias, H. Adesnik, S. Tomita, S. Karimzadegan, C. Kealey, D.S. Bredt, R.A. Nicoll, TARP γ-8 controls hippocampal AMPA receptor number, distribution and synaptic plasticity, Nat. Neurosci. (2005) 1525–1533, https://doi.org/10.1038/nn1551.
[171] X.-L. Sun, J. Cui, H. Bai, W. Zhang, W.-J. Bai, Aniracetam ameliorates attention deficit hyperactivity disorder behavior in adolescent mice, ENeuro 12 (2025), https://doi.org/10.1523/ENEURO.0578-24.2025.
[172] J. Park, A.E. Chávez, Y.S. Mineur, M. Morimoto-Tomita, S. Lutzu, K.S. Kim, M. R. Picciotto, P.E. Castillo, S. Tomita, CaMKII phosphorylation of TARPγ-8 is a mediator of LTP and learning and memory, Neuron 92 (2016) 75–83, https://doi.org/10.1016/J.NEURON.2016.09.002.
[173] W.J. Bai, X.G. Luo, B.H. Jin, K.S. Zhu, W.Y. Guo, X.Q. Zhu, X. Qin, Z.X. Yang, J. J. Zhao, S.R. Chen, R. Wang, J. Hao, F. Wang, Y.S. Shi, D.Z. Kong, W. Zhang, Deficiency of transmembrane AMPA receptor regulatory protein γ-8 leads to attention-deficit hyperactivity disorder-like behavior in mice, Zool. Res. 43 (2022) 851–870, https://doi.org/10.24272/J.ISSN.2095-8137.2022.122.
[174] S.G. Xue, J.G. He, L.L. Lu, S.J. Song, M.M. Chen, F. Wang, J.G. Chen, Enhanced TARP-γ8-PSD-95 coupling in excitatory neurons contributes to the rapid antidepressant-like action of ketamine in Male mice, Nat. Commun. 14 (2023), https://doi.org/10.1038/S41467-023-42780-8.
[175] Y. Sakai, H. Li, H. Inaba, Y. Funayama, E. Ishimori, A. Kawatake-Kuno, H. Yamagata, T. Seki, T. Hobara, S. Nakagawa, Y. Watanabe, S. Tomita, T. Murai, S. Uchida, Gene-environment interactions mediate stress susceptibility and resilience through the CaMKIIβ/TARPγ-8/AMPAR pathway, IScience 24 (2021), https://doi.org/10.1016/J.ISCI.2021.102504.
[176] Rapport Therapeutics, Pipeline and Programs, (n.d.). ⟨https://www.rapportrx.com/pipeline/⟩ (accessed April 28, 2025).
[177] Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. Electronic address: andrew.mcintosh@ed.ac.uk, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Trans-ancestry genome-wide study of depression identifies 697 associations implicating cell types and pharmacotherapies., Cell 188 (2025) 640-652.e9. https://doi.org/10.1016/J.CELL.2024.12.002/ASSET/C50942E3-CE73-4D14-A8F5-9D9A99BD689A/MAIN.ASSETS/FIGS1.JPG.
[178] H.D. Kim, J. Wei, T. Call, N.T. Quintus, A.J. Summers, S. Carotenuto, R. Johnson, X. Ma, C. Xu, J.G. Park, S. Qiu, D. Ferguson, Shisa6 mediates cell-type specific regulation of depression in the nucleus accumbens, Mol. Psychiatry 26 (2021) 7316–7327, https://doi.org/10.1038/S41380-021-01217-8.
[179] S.A. Barnes, D.J. Sheffler, S. Semenova, N.D.P. Cosford, A. Bespalov, Metabotropic glutamate receptor 5 as a target for the treatment of depression and smoking: robust preclinical data but inconclusive clinical efficacy, Biol. Psychiatry 83 (2018) 955–962, https://doi.org/10.1016/j.biopsych.2018.03.001.
[180] A. Holz, F. Mülsch, M.K. Schwarz, M. Hollmann, M.D. Döbrössy, V.A. Coenen, M. Bartos, C. Normann, K. Biber, D. van Calker, T. Serchov, Enhanced mGlu5 signaling in excitatory neurons promotes rapid antidepressant effects via AMPA receptor activation, Neuron 104 (2019), https://doi.org/10.1016/J.NEURON.2019.07.011.
[181] O.S.A. Elmeseiny, H.K. Müller, A molecular perspective on mGluR5 regulation in the antidepressant effect of ketamine, Pharm. Res 200 (2024), https://doi.org/10.1016/J.PHRS.2024.107081.
[182] S. Chaki, M. Watanabe, mGlu2/3 receptor antagonists for depression: overview of underlying mechanisms and clinical development, Eur. Arch. Psychiatry Clin. Neurosci. 273 (2023) 1451–1462, https://doi.org/10.1007/S00406-023-01561-6.
[183] D. Umbricht, M. Niggli, P. Sanwald-Ducray, D. Deptula, R. Moore, W. Grünbauer, L. Boak, P. Fontoura, Randomized, Double-Blind, Placebo-Controlled trial of the mGlu2/3 negative allosteric modulator decoglurant in partially refractory major depressive disorder, J. Clin. Psychiatry 81 (2020), https://doi.org/10.4088/JCP.18M12470.
[184] Saniona, S.A.N.2465, (n.d.). ⟨https://saniona.com/pipeline/san2465/⟩ (accessed April 26, 2025).
[185] F. Daher, N.A. Villalobos, M. Hanley, J.R. Atack, M.O. Popa, M.V. Fogaça, Basmisanil, an α5-GABAAR negative allosteric modulator, produces rapid and sustained antidepressant-like responses in Male mice, Neurosci. Lett. 833 (2024), https://doi.org/10.1016/j.neulet.2024.137828.
[186] D.J. Nutt, M. Besson, S.J. Wilson, G.R. Dawson, A.R. Lingford-Hughes, Blockade of alcohol's amnestic activity in humans by an α5 subtype benzodiazepine receptor inverse agonist, Neuropharmacology 53 (2007) 810–820, https://doi.org/10.1016/j.neuropharm.2007.08.008.
[187] E.S. Wohleb, D. Gerhard, A. Thomas, R.S. Duman, Molecular and cellular mechanisms of Rapid-Acting antidepressants ketamine and scopolamine, Curr. Neuropharmacol. 15 (2017) 11–20, https://doi.org/10.2174/1570159X14666160309114.
[188] S. Vaidya, A.A. Guerin, L.C. Walker, A.J. Lawrence, Clinical effectiveness of muscarinic Receptor-Targeted interventions in neuropsychiatric disorders: a systematic review, 2022 36:11 36, CNS Drugs (2022) 1171–1206, https://doi.org/10.1007/S40263-022-00964-8.
[189] W.-D. Ludwig, B. Mühlbauer Roland Seifert Hrsg, Arzneiverordnungs-Report 2023, Springer Berlin Heidelberg, Berlin, Heidelberg, 2023. https://doi.org/10.1007/978-3-662-68371-2.
[190] J.N. Johnston, M.S. Greenwald, I.D. Henter, C. Kraus, A. Mkrtchian, N.G. Clark, L. T. Park, P. Gold, C.A. Zarate, B. Kadriu, Inflammation, stress and depression: an exploration of ketamine's therapeutic profile, Drug Discov. Today 28 (2023), https://doi.org/10.1016/j.drudis.2023.103518.
[191] A.J. Rush, M.H. Trivedi, S.R. Wisniewski, J.W. Stewart, A.A. Nierenberg, M. E. Thase, L. Ritz, M.M. Biggs, D. Warden, J.F. Luther, K. Shores-Wilson, G. Niederehe, M. Fava, Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression, N. Engl. J. Med. 354 (2006) 1231–1242, https://doi.org/10.1056/NEJMOA052963.
[192] M.H. Trivedi, M. Fava, S.R. Wisniewski, M.E. Thase, F. Quitkin, D. Warden, L. Ritz, A.A. Nierenberg, B.D. Lebowitz, M.M. Biggs, J.F. Luther, K. Shores-Wilson, A.J. Rush, Medication augmentation after the failure of SSRIs for depression, N. Engl. J. Med. 354 (2006) 1243–1252, https://doi.org/10.1056/NEJMOA052964.
[193] E. Vieta, N. Ahmed, C. Arango, A.J. Cleare, K. Demyttenaere, M. Dold, T. Ito, Y. Kambarov, S. Krüger, P.M. Llorca, R.S. McIntyre, G. Sani, C. von Holt, B. Rive, Improvements in functioning and workplace productivity with esketamine nasal spray versus quetiapine extended release in patients with treatment resistant depression: findings from a 32-week randomised, open-label, rater-blinded phase IIIb study, Eur. Neuropsychopharmacol. 93 (2025) 29–39, https://doi.org/10.1016/J.EURONEURO.2024.12.013.