

Genetic variables of the glutamatergic system associated with treatment-resistant depression: A review of the literature

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Abstract

Depression is a common, recurrent mental disorder and one of the leading causes of disability and global burden of disease worldwide. Up to 15%-40% of cases do not respond to diverse pharmacological treatments and, thus, can be defined as treatment-resistant depression (TRD). The development of biomarkers predictive of drug response could guide us towards personalized and earlier treatment. Growing evidence points to the involvement of the glutamatergic system in the pathogenesis of TRD. Specifically, the N-methyl-D-aspartic acid receptor (NMDAR) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

(AMPA), which are targeted by ketamine and esketamine, are proposed as promising pathways. A literature search was performed to identify studies on the genetics of the glutamatergic system in depression, focused on variables related to NMDARs and AMPARs. Our review highlights *GRIN2B*, which encodes the NR2B subunit of NMDAR, as a candidate gene in the pathogenesis of TRD. In addition, several studies have associated genes encoding AMPAR subunits with symptomatic severity and suicidal ideation. These genes encoding glutamatergic receptors could, therefore, be candidate genes for understanding the etiopathogenesis of TRD, as well as for understanding the pharmacodynamic mechanisms and response to ketamine and esketamine treatment.

Key Words: Genetics; N-methyl-D-aspartic acid receptor; α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Treatment-resistant depression; Ketamine; Esketamine

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Core Tip: Depression is a common mental disorder and one of the leading causes of disability worldwide. Up to 15%-40% of cases are considered treatment-resistant depression, which seems to be conditioned by environmental and genetic factors. The glutamatergic system, specifically N-methyl-D-aspartic acid receptor (NMDAR) dysfunction, has been proposed to be involved in the pathogenesis of treatment-resistant depression (TRD). A literature search was performed to identify studies on the genetics of the glutamatergic system in depression, focused on NMDAR and the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor. Our review highlights *GRIN2B*, which encodes the NR2B subunit of NMDAR, as a candidate gene in the pathogenesis of TRD.

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INTRODUCTION

Depression: An overview

Depression is characterized by sustained low mood, anhedonia, psychomotor inhibition and, frequently, somatic alterations that significantly affect an individual's functioning and, as such, poses a social and economic problem, as well as a health problem. It is, according to the World Health Organization, a common, recurrent mental disorder and one of the leading causes of disability and global burden of disease worldwide[1]. Thus, it has been highlighted as one of the priority conditions covered by the Mental Health Gap Action Programme. The 12-mo prevalence of major depressive disorder (MDD) is estimated to be approximately 6%[2], whereas the lifetime risk of depression is between 15% and 18% [3]. Thus, MDD is common, with almost one in five people experiencing one episode at some point in their lifetime. Between 2005 and 2015, the incidence of depression increased by 18.4% worldwide[4]. Regarding gender differences, the lifetime-incidence of a major depressive episode in females has been reported to be twice that of males[5].

Depression significantly affects family, social, and occupational functioning and is, therefore, a health, social and economic problem. A recent review calculated that the direct costs of depression, due to the higher use of healthcare services, may be up to 24,069€ *per patient/year*, depending on the jurisdiction wherein the analyses were performed[6]. Productivity losses, for their part, were estimated to be between 1963€ and 27364€ *per person per year*[6]. It is among the leading causes of loss of disability-adjusted life years, mainly in the age range between 10 and 49 years[7], and is the most frequently identified diagnosis in people who have died by suicide[8]. Thus, in recent years, depression has become a major target of public health policies[9,10] due to the consequences that both depression itself, as well as associated events such as suicide, have on society.

If depression is untreated or inadequately treated, it is associated with higher rates of medical morbidity, lower productivity, decreased life expectancy, higher rates of suicide, and higher rates of functional disability. However, sometimes, despite evidence-based treatment, the patient may not respond favorably to treatment. Even though we have a growing number of therapeutic alternatives available to treat depression, approximately half of patients do not respond, and up to two-thirds do not achieve remission after first-line treatment[11]. In this context, the development of biomarkers

predictive of drug response, which could guide us towards personalized treatment for each patient, is a challenge for the future.

TREATMENT-RESISTANT DEPRESSION

Although there is no consensus on the definition of treatment-resistant depression (TRD), it is a useful concept to characterize a group of patients with MDD that do not respond to traditional monoaminergic antidepressants. The European Medicines Agency considers TRD to be that which has not responded to two antidepressants of different classes, prescribed at adequate doses (within a therapeutic range), for the appropriate time (> 6 wk) and ensuring correct adherence to the protocol[12,13]. Some authors add that potentiation strategies, such as lithium, neuroleptic drugs, or electroconvulsive therapy, also need to have been used.

According to the well-known Sequenced Treatment Alternatives to Relieve Depression study, one-third of patients with depression could be classified as TRD, as they do not respond to two different antidepressant treatments[11]. Along the same lines, other works have described that 15%-40% of patients with MDD do not respond to multiple pharmacological treatments[14].

Patients with MDD are more likely to make attempts and/or complete suicide, as well as to experience more frequent relapses and hospitalizations, and to have a worse overall prognosis. In other words, they form a subgroup of depressive patients characterized by clinical severity and higher health and social costs[15].

Resistance to treatment seems to be conditioned by genetic and environmental factors[16]. The underlying genetic factors of individuals cannot be modified, but genetic information could be used to predict response and tailor treatments to the idiosyncrasies of each patient. Emerging evidence has shown that genetic variations associated with antidepressant responses appear to cluster in families, supporting the importance of these variations in the underlying mechanism of depression, especially in TRD[17].

Identifying biomarkers that can predict the antidepressant response could be helpful in designing the initial treatment, decreasing the need for trial-and-error testing, and also avoiding suffering and possible chronicity. Single nucleotide polymorphisms (SNPs) have been suggested to be a decisive factor in the antidepressant response; numerous genetic polymorphisms have been described as possible risk factors for MDD and TRD[18-21].

GENETICS OF DEPRESSION

Albeit a clinically heterogeneous pathology, there is consistent evidence, based on twin and adoption studies, that there is a heritability of 29%-49% in MDD (reviewed in[22]). Research has also been performed to identify more genetically homogeneous groups of MDD, indicating that clinical severity, the need for certain therapeutic strategies, recurrent episodes, and postpartum depression show differences in heritability[23,24].

It is a polygenic disease caused by the combined effect of polymorphisms, common to the general population, in different genes[25]. The genetics of depression has been studied for years *via* a candidate gene approach, mainly focusing the study on genes involved in the serotonergic, noradrenergic, and dopaminergic pathways, targets of the usual treatments[26-28]. A recent literature review of 18 candidate genes showed that most of the studies performed lacked sufficient statistical power and, thus, questioned previous depression candidate gene findings[29]. More recent work has begun to focus on the glutamatergic pathway as a candidate in the study of genetic factors involved in depression[30].

In recent years, genome-wide association studies (GWAS) have proliferated in an attempt to identify genes involved in various pathologies, including depression. A recent GWAS identified 102 independent variants, 269 genes, and 15 gene-sets associated with depression, including both genes and gene pathways associated with synaptic structure and neurotransmission, providing further evidence of the importance of prefrontal brain regions. A previous GWAS implicated voltage-gated calcium channels, the D2 dopamine receptor and, interestingly, glutamate receptors[31]. The authors stated that all humans carry a lesser or greater number of genetic risk factors for MDD.

Along this line, many authors have investigated the interaction between genetics and environment in the pathogenesis of depression. Recent reviews concluded that various genetic polymorphisms in the serotonergic system moderate the association between adverse childhood experiences and depression [32], and that early-life stress produces transcriptomic changes that are moderated by the female sex[33].

Finally, postmortem studies have also been conducted to investigate differential gene expression in human brains. *GluR* gene expression in the dorsolateral prefrontal cortex has been studied in small postmortem cohorts of MDD subjects and controls, with inconclusive results to date[34,35]. Nonetheless, the data seemed to indicate a fundamental dysfunction of the glutamatergic system in the frontal cortex in MDD[36].

THE GLUTAMATERGIC SYSTEM AND TRD

The neurotransmitter systems most studied in the etiopathogenesis of depression have been the serotonergic, noradrenergic, and dopaminergic systems, which are targeted by the most commonly used antidepressant drugs. However, another system involved is the glutamatergic system. Glutamate exerts its action *via* ionotropic receptors [N-methyl-D-aspartic acid receptor (NMDAR), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), and 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine kainate receptors (KAR)] and metabotropic receptors. In the last two decades, the glutamatergic system, specifically NMDAR dysfunction, has been shown to be involved in the pathogenesis of TRD[37]. In particular, NMDAR antagonism has been highlighted, marking it a target of numerous drugs indicated for TRD[38], such as ketamine and esketamine[39,40].

Intravenous ketamine and intranasal esketamine, rather than inhibiting, activate glutamate release [41], resulting in a rapid antidepressant effect, a prompt disappearance of suicidal ideation[42,43], and a reduction of anhedonic symptoms[44]. This emerging hypothesis suggests that NMDAR antagonism in GABAergic interneurons (the mechanism of action of ketamine and esketamine) leads to glutamate release[45]. Regarding this gamma-amino butyric acid (GABA)-glutamate neurotransmitter system, animal and human studies have described that intravenous ketamine administration reduces GABA concentration in several brain areas, such as the frontal cortex[45-47].

Treatment with ketamine and esketamine has proven particularly useful in cases of TRD[48], thus their mechanism of action in glutamatergic pathways, being the major difference with respect to usual antidepressant treatments, is an interesting starting point for understanding the etiopathogenesis of TRD.

Central glutamatergic activity is measured at the peripheral level *via* plasma levels of glutamate (pGlu) and GABA (pGABA). pGlu and pGABA levels have been described to significantly correlate with cerebrospinal fluid glutamate levels[49,50], indicating that, although the plasma levels assessed derive from both the brain and the periphery, the plasma levels of these amino acids reflect brain concentrations[51]. Previous studies reported altered levels of pGlu in blood, cerebrospinal fluid, and prefrontal, frontal, and occipital cortical areas of patients with depression compared with healthy volunteers[52-55].

In relation to GABA, as a neurotransmitter system closely related to the glutamatergic, a recent meta-analysis indicated a decrease in pGABA levels in patients with depression compared with healthy controls, although the heterogeneity was significant[56].

All these findings indicate that alterations in the glutamatergic system may play a key role in the development of TRD. Therefore, it has been proposed that genes involved in glutamatergic transmission could be candidate genes to explain the neurobiological basis of TRD, *i.e.*, genetic risk factors for the development of depression, especially TRD[55,57].

GENETIC VARIABLES OF THE GLUTAMATERGIC SYSTEM ASSOCIATED WITH TRD

Literature search

A literature search was performed to identify studies regarding the genetics of the glutamatergic system in depression. A total of 118 articles, published up to October 15, 2021, were retrieved from the PubMed and Reference Citation Analysis (<https://www.referencecitationanalysis.com/>) databases using broad search terms in order to identify as many potentially eligible studies as possible: [(NMDA receptor OR AMPA receptor) AND gene* AND depression]. An age filter was added: "Adults: 19+ years". Studies were included according to three criteria: (1) They investigated the influence of genetics/epigenetics on glutamate receptors in depression; (2) They were systematic reviews, meta-analyses, narrative reviews, or original research studies; and (3) They were written in English or Spanish. The reference lists of the selected studies and reviews were also checked to identify additional relevant articles using a snowballing approach. Finally, 46 papers were included in the review.

This is not a systematic review, but a narrative one; it summarizes the findings described in the selected reports and, in this way, provides an overview of the subject. The main results are summarized in Table 1.

NMDA receptor

NMDAR, indicated as a therapeutic target in TRD[58], consists of four subunits (Figure 1). Two of them must be the NR1 subunit, mandatory for the receptor to be functional, while the other two subunits can be any of the four NR2 subunits (NR2A-D), or two NR3[59]. The NR2A-D subunits bind glutamate[60]. These subunits are encoded by the *GRIN1*, *GRIN2A-D*, and *GRIN3* genes[61,62].

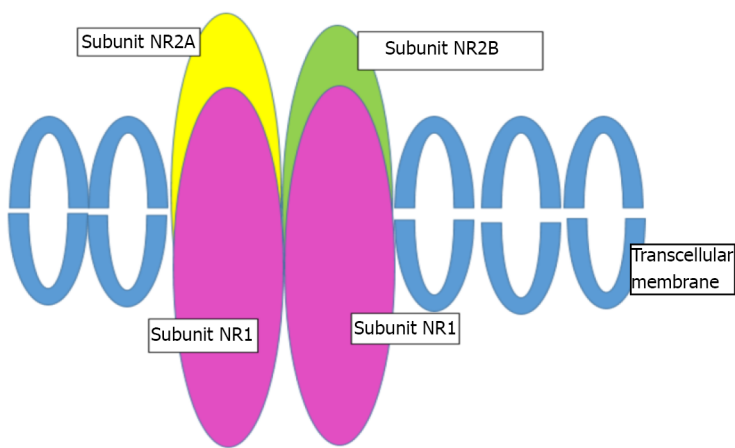
NR2B subunit: The *GRIN2B* gene

Associations between the functionality of these subunits and depression or response to antidepressant molecules were mostly found with the NR2B subunit. This is encoded by the *GRIN2B* gene, which is located on chromosome 12p12 and consists of 13 exons. Three potentially functional SNPs have been

Table 1 Summary of studies on main candidate genes of the glutamatergic system related to depression

Receptor	Gene	Marker	Ref.	Result
NMDA	GRIN2A	rs16966731	Chen <i>et al</i> [79], 2021	T allele associated with antidepressant effect of ketamine
		rs1805502	Zhang <i>et al</i> [69], 2014	G allele associated with TRD
	GRIN2B	rs890	Arnold <i>et al</i> [70], 2009	GT haplotype increased risk of TRD
		rs890	Zhang <i>et al</i> [69], 2014	C allele associated with TRD
		rs890	Arnold <i>et al</i> [70], 2009	
		rs2268115	Sokolowski <i>et al</i> [72], 2013	Associated with suicide attempts
	rs220557	Sokolowski <i>et al</i> [72], 2013	Associated with suicide attempts	
AMPA	GRIA2	rs4302506	Chiesa <i>et al</i> [91], 2012	C allele associated with a lower age of onset in MDD
		rs4400397	Chiesa <i>et al</i> [91], 2012	C allele associated with a lower age of onset in MDD
	GRIA3	rs4825476	Laje and McMahon[17], 2007	G allele associated with suicidal ideation
Kainate	GRIK4	rs1954787	Horstmann <i>et al</i> [94], 2010	CC haplotype associated with response to antidepressants
			Serretti <i>et al</i> [95], 2012	No significant associations
		rs12800734	Horstmann <i>et al</i> [94], 2010	GG haplotype associated with response to antidepressants
			Serretti <i>et al</i> [95], 2012	No significant associations

NMDA: N-methyl-D-aspartic acid; AMPA: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; TRD: Treatment-resistant depression; MDD: Major depressive disorder; T: Thymine; G: Guanine; C: Cytosine.



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Figure 1 Structure of the N-methyl-D-aspartic acid receptor, which consists of four subunits [NR1, and either two of the four NR2 subunits (NR2A-D) or two NR3].

identified in this gene, all located in the 3'-untranslated region (UTR) that governs gene expression: rs1805502 (A to G), rs1806201 (T to C), and rs890 (A to C). They may contribute to the regulation of *GRIN2B* gene expression and influence glutamate release activity in the brain.

Ketamine users have also been reported to have a higher frequency of the rs1806201 TT genotype and a lower frequency of the CC genotype than controls, suggesting that this polymorphism may play a role in ketamine abuse[63]. Clinical trials report the superior therapeutic efficacy of NMDAR NR2B subunit antagonists over conventional antidepressants in patients with TRD[64,65].

Different GWAS have revealed a relationship between SNPs in the *GRIN2B* gene and depression[38, 66,67]. *In vivo* studies evaluating glutamatergic activity at the brain level have shown that carriers of the rs1805502 G, rs1806201 T, or rs890 C allele have decreased glutamate concentrations in the anterior cingulate cortex. These alleles have been related to several psychiatric disorders[68-70], suggesting that they be a risk factor (genetic predictor) for TRD[69] in MDD patients. Recently, in a preclinical study in

transgenic mice with selective mutations in the NR2B subunit in GABAergic interneurons, deletion of NR2B was found to block the antidepressant action of ketamine[71].

These *GRIN2B* gene polymorphisms have been described both as risk variables for MDD and predictors of TRD. An association was reported between the GT haplotype (rs1805502-rs890) and increased TRD risk compared with controls, as well as between the rs1805502 G allele and TRD (compared with non-resistant depression)[69].

A GWAS-based study reported a significant association between *GRIN2B* and suicide attempts, as well as a gene-environment relationship with a history of physical abuse in childhood and adolescence, which also increases the risk of suicide[72]. Indeed, they found that *GRIN2B* and *ODC1* (encoding ornithine decarboxylase, a rate-limiting enzyme of the polyamine synthesis pathway) seem to be associated with severe suicide attempts, as well as with serious physical assault in childhood and adolescence[73,74], which in turn increases the risk of suicide attempts, thereby configuring a gene-by-environment interaction.

Finally, human postmortem studies found *GRIN2B* expression to be higher in suicidal MDD patients, compared with non-suicidal MDD patients[36], and in the locus coeruleus of depressed individuals[75]. It is therefore postulated that *GRIN2B* mRNA level may be a biomarker of suicide; indeed, *GRIN2B* genetic polymorphisms in MDD have been reported to predict treatment resistance, suicide attempts, and reasoning ability[72].

Based on the data described, *GRIN2B* is considered a promising candidate gene for MDD susceptibility, and more specifically for TRD, supporting the contention that TRD can be classified as a specific subtype of MDD[69].

Other NMDAR subunits: *GRIN1*, *GRIN2A*, *C*, and *D*, and *GRIN3*

Regarding other NMDAR subunits, postmortem studies in rodents using depression models have observed that chronic stress, besides increasing NR2B subunit mRNA, also increases NR1 and NR2A in several brain regions[76,77]. Postmortem studies in humans reported higher expression levels of *GRIN1* and *GRIN2A* in the brains of depressed patients than in controls, and of *GRIN2B* in suicidal compared with non-suicidal MDD patients[36,78]. Likewise, the *GRIN2A* rs16966731 polymorphism (T to C, intron area) has been associated with the rapid and persistent antidepressant effect of ketamine[79]. Chandley *et al*[75] also reported altered expression of the *GRIN2C* gene at the locus coeruleus in depressed patients [75]. Finally, one paper reported that women with MDD had higher expression levels of all the NMDAR subunit genes; the only one not reaching statistical significance was *GRIN3A*[36].

From a gene-environment interaction perspective, an epigenetic study showed that *GRIN1* methylation was a significant predictor of depression in a sample of abused children[80]. In one study, *GRIN2A* hypermethylation in the hippocampus and prefrontal cortex in postmortem studies was related to overexpression of the GluN2A subunit[81,82]. Interestingly, maternal separation increases the expression of this subunit in the hippocampus of adult rats, but not of subunit 2B. Numerous rat stress models have evaluated *GRIN1A*, *GRIN2B*, and *GRIN2A* with results similar to those described above [77,83,84].

AMPA receptor: The *GRIA2* and *GRIA3* genes

AMPA receptors are transmembrane ionotropic glutamatergic receptors and the main receptors mediating rapid synaptic neurotransmission in the brain. They consist of four subunits (GluR1-4) encoded by four genes (*GRIA1-4*)[85] (Figure 2). Evidence also suggests that the antidepressant mechanism of action of ketamine and esketamine involves the activation of AMPARs, with a subsequent increase in brain-derived neurotrophic factor levels (usually reduced in patients with depression)[45], as has been observed in rodent models[86]. Therefore, AMPARs have been proposed to play a key role in the antidepressant effect associated with ketamine[87].

Ketamine and its enantiomer, esketamine, lead to the disinhibition of glutamatergic neurons that modulate AMPARs by antagonizing the NMDAR of GABAergic interneurons[45,88]. In addition, ketamine metabolites such as hydroxynorketamine seem to exert their antidepressant effect *via* AMPAR activation[84,89].

In mouse models reproducing depression and stress, increased expression of AMPARs has been observed[76,90]. Postmortem studies described increased *GRIA2-4* expression in the prefrontal cortex of MDD patients *vs* controls[36], and of *GRIA3* in suicidal *vs* non-suicidal patients with MDD. As regards the *GRIA2* gene, several authors have observed an association between carriers of the C allele (rs4302506; C to T, located in the coding exon) and carriers of the T allele (rs4400397; C to T, 3'-UTR), and a lower age of MDD onset[91]. Also, the G allele (rs4825476; G to A, intron 3) of the *GRIA3A* gene has been associated with suicidal ideation in patients with major depression treated with monoaminergic antidepressants[17]. The AMPAR subunits GluA2-4 had significantly higher expression in female MDD patients[36].

Other glutamatergic receptors associated with treatment response

Animal studies have suggested that ionotropic glutamate receptors play a role in the action of antidepressant drugs[92,93]. Another widely investigated gene is *GRIK4*, which encodes subunit 4 of the ionotropic glutamate KAR. Here, an association was observed between the rs1954787 polymorphism

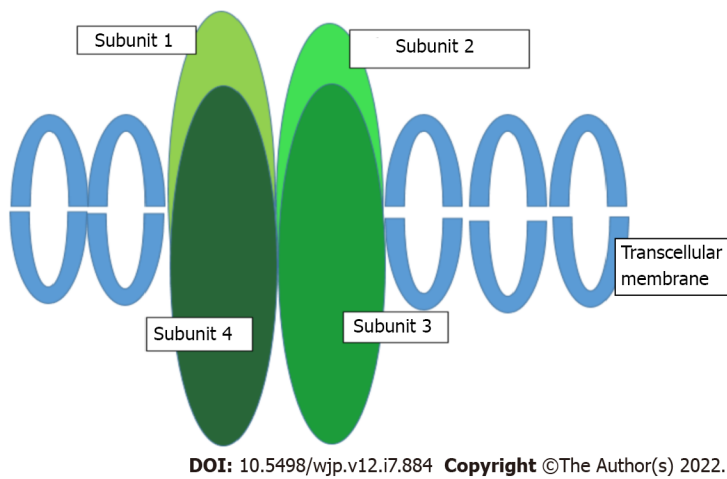


Figure 2 Structure of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, which consists of four subunits (GluR1-4).

and antidepressant response[94]; however, the *GRIK4* polymorphism with the highest predictive value for treatment outcome was rs12800734. Nonetheless, these findings have not been replicated in other studies, probably due to design differences[95]. Existing data also revealed increased expression of the KAR subunits, GluK1 and GluK2. In addition, the strongest predictor of suicide was *GRIK3* (GluK3) expression in both sexes[36]. KARs appear to regulate L-glutamate release by functioning as facilitatory or inhibitory autoreceptors during repetitive synaptic activation. The KAR activity may contribute to excitotoxic cell death; however, the role of these receptors in the dorsolateral prefrontal cortex of MDD subjects remains to be elucidated. Genetic variation in *GRIK3* has been associated with recurrent MDD [36].

In addition to ionotropic glutamatergic receptors, metabotropic receptors have also been involved in the genesis of MDD. Increased expression of *GRIN1*, *GRIN2A-D*, *GRIA2-4*, *GRIK1-2*, *GRM1*, *GRM4*, *GRM5*, and *GRM7* has been observed in female MDD patients. In contrast, *GRM5* expression was lower in male MDD patients relative to male controls. When suicidal MDD patients were compared with non-suicidal patients, *GRIN2B*, *GRIK3*, and *GRM2* were expressed at higher levels in suicidal patients[36]. Recent studies showed that mGluR4 regulation is altered in male suicidal individuals, leading to higher expression of mGluR. Higher expression levels of the mGluR2 encoding gene, *GRM2*, were also detected; *GRM2* has been proposed as a biomarker of suicide[36].

Repeated stress in male rats has been reported to be associated with lower expression of AMPARs and NMDARs, and, also, with a lower activity of these receptors. In contrast, in female rats exposed to stress, the expression of AMPARs and NMDARs was normalized *via* the activation of estrogen receptors, resulting in a neuroprotective and procognitive effect[96]. The authors proposed that, in female patients, estrogenic activity may lead to a differential response to ketamine; it should be noted that two-thirds of MDD patients are women.

Finally, there is downregulation of metabotropic receptors in mice reproducing models of depression, especially in the mGlu2 subunit, which is completely restored by ketamine administration[97].

LIMITATIONS AND STRENGTHS

The main limitation of this review is the scarcity and heterogeneity of the literature available on the topic. Few studies have employed similar methodology and, thus, there is limited replication of the described findings. Due to the small number of studies, all research conducted in humans and animals has been included in the review, although the extrapolation of the results, in this case, is limited. As we have noted, this is a narrative review, and limitations inherent to this type of review should also be mentioned: Study selection, data extraction, and synthesis were not protocol-based and, thus, could be prone to bias.

Nonetheless, it should also be noted that this is the first review, to our knowledge, of this specific topic, making it possible to summarize the current state of the art, highlighting the need to advance research in this field.

CONCLUSION

Patients with TRD often experience long periods of therapeutic trials with different antidepressant

medications, resulting in a worse outcome, a delay in symptomatic remission, and an increased risk of fatal events, such as suicide. Therefore, the management of TRD with appropriate therapy could be facilitated by the identification of biological markers of TRD, which could guide treatment choice from the outset.

Although the serotonergic, noradrenergic, and dopaminergic pathways were those historically studied, more recent work indicates the involvement of the glutamatergic pathway. This proposal is consistent with new therapeutic strategies in TRD, such as ketamine and esketamine, which act mainly on glutamatergic receptors.

Our review highlights *GRIN2B*, which encodes the NR2B subunit of NMDAR, as a candidate gene in the pathogenesis of TRD. In addition, several studies have associated genes encoding AMPAR subunits with symptomatic severity and suicidal ideation. These genes encoding glutamatergic receptors could, therefore, be candidate genes for understanding the etiopathogenesis of TRD, as well as for understanding the pharmacodynamic mechanisms and response to ketamine and esketamine treatment. However, further empirical work is required to replicate the observed associations and to confirm the involvement of these genes in the pathogenesis of TRD.

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FOOTNOTES

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REFERENCES

- 1 **World Health Organization.** Depression. [cited 10 January 2022]. Available from: <https://www.who.int/news-room/fact-sheets/detail/depression>
- 2 **Kessler RC, Bromet EJ.** The epidemiology of depression across cultures. *Annu Rev Public Health* 2013; **34**: 119-138 [PMID: [23514317](https://pubmed.ncbi.nlm.nih.gov/23514317/) DOI: [10.1146/annurev-publhealth-031912-114409](https://doi.org/10.1146/annurev-publhealth-031912-114409)]
- 3 **Bromet E, Andrade LH, Hwang I, Sampson NA, Alonso J, de Girolamo G, de Graaf R, Demyttenaere K, Hu C, Iwata N, Karam AN, Kaur J, Kostyuchenko S, Lépine JP, Levinson D, Matschinger H, Mora ME, Browne MO, Posada-Villa J, Viana MC, Williams DR, Kessler RC.** Cross-national epidemiology of DSM-IV major depressive episode. *BMC Med* 2011; **9**: 90 [PMID: [21791035](https://pubmed.ncbi.nlm.nih.gov/21791035/) DOI: [10.1186/1741-7015-9-90](https://doi.org/10.1186/1741-7015-9-90)]
- 4 **GBD 2015 Disease and Injury Incidence and Prevalence Collaborators.** Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388**: 1545-1602 [PMID: [27733282](https://pubmed.ncbi.nlm.nih.gov/27733282/) DOI: [10.1016/S0140-6736\(16\)31678-6](https://doi.org/10.1016/S0140-6736(16)31678-6)]
- 5 **Gabilondo A, Rojas-Farreras S, Vilagut G, Haro JM, Fernández A, Pinto-Meza A, Alonso J.** Epidemiology of major

- depressive episode in a southern European country: results from the ESEMeD-Spain project. *J Affect Disord* 2010; **120**: 76-85 [PMID: 19428121 DOI: 10.1016/j.jad.2009.04.016]
- 6 Coretti S, Rumi F, Cicchetti A. The Social Cost of Major Depression: A Systematic Review. *Rev Eur Stud* 2019; **11**: 73
 - 7 Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, Abbasi-Kangevari M, Abbastabar H, Abd-Allah F, Abdelalim A, Abdollahi M, Abdollahpour I, Abolhassani H, Aboyans V, Abrams EM, Abreu LG, Abrigo MRM, Abu-Raddad LJ, Abushouk AI, Acebedo A, Ackerman IN, Adabi M, Adamu AA, Adebayo OM, Adeganmbi V, Adelson JD, Adetokunboh OO, Adham D, Afshari M, Afshin A, Agardh EE, Agarwal G, Agesa KM, Aghaali M, Aghamir SMK, Agrawal A, Ahmad T, Ahmadi A, Ahmadi M, Ahmadi H, Ahmadpour E, Akalu TY, Akinyemi RO, Akinyemiju T, Akombi B, Al-Aly Z, Alam K, Alam N, Alam S, Alam T, Alanzi TM, Albertson SB, Alcalde-Rabanal JE, Alema NM, Ali M, Ali S, Alicandro G, Alijanzadeh M, Alinia C, Alipour V, Aljunid SM, Alla F, Allebeck P, Almasi-Hashiani A, Alonso J, Al-Raddadi RM, Altirkawi KA, Alvis-Guzman N, Alvis-Zakzuk NJ, Amini S, Amini-Rarani M, Aminorroaya A, Amiri F, Amit AML, Amugsi DA, Amul GGH, Anderlini D, Andrei CL, Andrei T, Anjomshoa M, Ansari F, Ansari I, Ansari-Moghaddam A, Antonio CAT, Antony CM, Antriyandarti E, Anvari D, Anwer R, Arabloo J, Arab-Zozani M, Aravkin AY, Ariani F, Ärnlöv J, Aryal KK, Arzani A, Asadi-Aliabadi M, Asadi-Pooya AA, Asghari B, Ashbaugh C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396**: 1204-1222 [DOI: 10.1016/S0140-6736(20)30925-9]
 - 8 Bachmann S. Epidemiology of Suicide and the Psychiatric Perspective. *Int J Environ Res Public Health* 2018; **15** [PMID: 29986446 DOI: 10.3390/ijerph15071425]
 - 9 Mendelson T, Eaton WW. Recent advances in the prevention of mental disorders. *Soc Psychiatry Psychiatr Epidemiol* 2018; **53**: 325-339 [PMID: 29546492 DOI: 10.1007/s00127-018-1501-6]
 - 10 World Health Organization. Comprehensive Mental Health Action Plan 2013-2030 [cited 10 January 2022].
 - 11 Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006; **163**: 1905-1917 [PMID: 17074942 DOI: 10.1176/ajp.2006.163.11.1905]
 - 12 Culpepper L. Why do you need to move beyond first-line therapy for major depression? *J Clin Psychiatry* 2010; **71** Suppl 1: 4-9 [PMID: 20977873 DOI: 10.4088/JCP.9104su1c.01]
 - 13 Berlim MT, Fleck MP, Turecki G. Current trends in the assessment and somatic treatment of resistant/refractory major depression: an overview. *Ann Med* 2008; **40**: 149-159 [PMID: 18293145 DOI: 10.1080/07853890701769728]
 - 14 Berlim MT, Turecki G. Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. *Can J Psychiatry* 2007; **52**: 46-54 [PMID: 17444078 DOI: 10.1177/070674370705200108]
 - 15 Gibson TB, Jing Y, Smith Carls G, Kim E, Bagalman JE, Burton WN, Tran QV, Pikalov A, Goetzl RZ. Cost burden of treatment resistance in patients with depression. *Am J Manag Care* 2010; **16**: 370-377 [PMID: 20469957]
 - 16 Kovacs D, Gonda X, Petschner P, Edes A, Eszlari N, Bagdy G, Juhasz G. Antidepressant treatment response is modulated by genetic and environmental factors and their interactions. *Ann Gen Psychiatry* 2014; **13**: 17 [PMID: 25053968 DOI: 10.1186/1744-859X-13-17]
 - 17 Laje G, McMahon FJ. The pharmacogenetics of major depression: past, present, and future. *Biol Psychiatry* 2007; **62**: 1205-1207 [PMID: 17949692 DOI: 10.1016/j.biopsych.2007.09.016]
 - 18 Fabbri C, Di Girolamo G, Serretti A. Pharmacogenetics of antidepressant drugs: an update after almost 20 years of research. *Am J Med Genet B Neuropsychiatr Genet* 2013; **162B**: 487-520 [PMID: 23852853 DOI: 10.1002/ajmg.b.32184]
 - 19 Fabbri C, Drago A, Serretti A. Early antidepressant efficacy modulation by glutamatergic gene variants in the STAR*D. *Eur Neuropsychopharmacol* 2013; **23**: 612-621 [PMID: 22884879 DOI: 10.1016/j.euroneuro.2012.07.006]
 - 20 Myung W, Song J, Lim SW, Won HH, Kim S, Lee Y, Kang HS, Lee H, Kim JW, Carroll BJ, Kim DK. Genetic association study of individual symptoms in depression. *Psychiatry Res* 2012; **198**: 400-406 [PMID: 22429480 DOI: 10.1016/j.psychres.2011.12.037]
 - 21 Howard DM, Adams MJ, Shirali M, Clarke TK, Marioni RE, Davies G, Coleman JRI, Alloza C, Shen X, Barbu MC, Wigmore EM, Gibson J; 23andMe Research Team, Hagenaars SP, Lewis CM, Ward J, Smith DJ, Sullivan PF, Haley CS, Breen G, Deary IJ, McIntosh AM. Genome-wide association study of depression phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. *Nat Commun* 2018; **9**: 1470 [PMID: 29662059 DOI: 10.1038/s41467-018-03819-3]
 - 22 Kendall KM, Van Assche E, Andlauer TFM, Choi KW, Luyck JJ, Schulte EC, Lu Y. The genetic basis of major depression. *Psychol Med* 2021; **51**: 2217-2230 [PMID: 33682643 DOI: 10.1017/S0033291721000441]
 - 23 Nguyen TD, Harder A, Xiong Y, Kowalec K, Hägg S, Cai N, Kuja-Halkola R, Dalman C, Sullivan PF, Lu Y. Genetic heterogeneity and subtypes of major depression. *Mol Psychiatry* 2022; **27**: 1667-1675 [PMID: 34997191 DOI: 10.1038/s41380-021-01413-6]
 - 24 Kiewa J, Meltzer-Brody S, Milgrom J, Guintivano J, Hickie IB, Whiteman DC, Olsen CM, Colodro-Conde L, Medland SE, Martin NG, Wray NR, Byrne EM. Perinatal depression is associated with a higher polygenic risk for major depressive disorder than non-perinatal depression. *Depress Anxiety* 2022; **39**: 182-191 [PMID: 34985809 DOI: 10.1002/da.23232]
 - 25 Flint J, Kendler KS. The genetics of major depression. *Neuron* 2014; **81**: 484-503 [PMID: 24507187 DOI: 10.1016/j.neuron.2014.01.027]
 - 26 Chiesa A, Lia L, Lia C, Lee SJ, Han C, Patkar AA, Pae CU, Serretti A. Investigation of possible epistatic interactions between GRIA2 and GRIA4 variants on clinical outcomes in patients with major depressive disorder. *J Int Med Res* 2013; **41**: 809-815 [PMID: 23613500 DOI: 10.1177/0300060513477295]
 - 27 Phillips JL, Batten LA, Tremblay P, Aldosary F, Du L, Blier P. Impact of monoamine-related gene polymorphisms on hippocampal volume in treatment-resistant depression. *Acta Neuropsychiatr* 2015; **27**: 353-361 [PMID: 25990886 DOI: 10.1017/neu.2015.25]
 - 28 He M, He H, Yang L, Zhang J, Chen K, Duan Z. Functional tag SNPs inside the DRD2 gene as a genetic risk factor for major depressive disorder in the Chinese Han population. *Int J Clin Exp Pathol* 2019; **12**: 628-639 [PMID: 31933869]
 - 29 Border R, Johnson EC, Evans LM, Smolen A, Berley N, Sullivan PF, Keller MC. No Support for Historical Candidate

- Gene or Candidate Gene-by-Interaction Hypotheses for Major Depression Across Multiple Large Samples. *Am J Psychiatry* 2019; **176**: 376-387 [PMID: 30845820 DOI: 10.1176/appi.ajp.2018.18070881]
- 30 **Wang HQ**, Wang ZZ, Chen NH. The receptor hypothesis and the pathogenesis of depression: Genetic bases and biological correlates. *Pharmacol Res* 2021; **167**: 105542 [PMID: 33711432 DOI: 10.1016/j.phrs.2021.105542]
- 31 **Wray NR**, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, Adams MJ, Agerbo E, Air TM, Andlauer TMF, Bacanu SA, Bækvad-Hansen M, Beekman AFT, Bigdeli TB, Binder EB, Blackwood DRH, Bryois J, Buttenschön HN, Bybjerg-Grauholm J, Cai N, Castelao E, Christensen JH, Clarke TK, Coleman JIR, Colodro-Conde L, Couvy-Duchesne B, Craddock N, Crawford GE, Crowley CA, Dashti HS, Davies G, Deary IJ, Degenhardt F, Derks EM, Direk N, Dolan CV, Dunn EC, Eley TC, Eriksson N, Escott-Price V, Kiadeh FHF, Finucane HK, Forstner AJ, Frank J, Gaspar HA, Gill M, Giusti-Rodríguez P, Goes FS, Gordon SD, Grove J, Hall LS, Hannon E, Hansen CS, Hansen TF, Herms S, Hickie IB, Hoffmann P, Homuth G, Horn C, Hottenga JJ, Hougaard DM, Hu M, Hyde CL, Ising M, Jansen R, Jin F, Jorgenson E, Knowles JA, Kohane JS, Kraft J, Kretzschmar WW, Krogh J, Kutalik Z, Lane JM, Li Y, Lind PA, Liu X, Lu L, MacIntyre DJ, MacKinnon DF, Maier RM, Maier W, Marchini J, Mbarek H, McGrath P, McGuffin P, Medland SE, Mehta D, Middeldorp CM, Mihailov E, Milaneschi Y, Milani L, Mill J, Mondimore FM, Montgomery GW, Mostafavi S, Mullins N, Nauck M, Ng B, Nivard MG, Nyholt DR, O'Reilly PF, Oskarsson H, Owen MJ, Painter JN, Pedersen CB, Pedersen MG, Peterson RE, Pettersson E, Peyrot WJ, Pistis G, Posthuma D, Purcell SM, Quiroz JA, Qvist P, Rice JP, Riley BP, Rivera M, Saeed Mirza S, Saxena R, Schoevers R, Schulte EC, Shen L, Shi J, Shyn SI, Sigurdsson E, Sinnamón GBC, Smit JH, Smith DJ, Stefansson H, Steinberg S, Stockmeier CA, Streit F, Strohmaier J, Tansey KE, Teismann H, Teumer A, Thompson W, Thomson PA, Thorgeirsson TE, Tian C, Traylor M, Treutlein J, Trubetskoy V, Uitterlinden AG, Umbrecht D, Van der Auwera S, van Hemert AM, Viktorin A, Visscher PM, Wang Y, Webb BT, Weinsheimer SM, Wellmann J, Willemsen G, Witt SH, Wu Y, Xi HS, Yang J, Zhang F; eQTLGen; 23andMe, Arolt V, Baune BT, Berger K, Boomsma DI, Cichon S, Dannlowski U, de Geus ECJ, DePaulo JR, Domenici E, Domschke K, Esko T, Grabe HJ, Hamilton SP, Hayward C, Heath AC, Hinds DA, Kendler KS, Kloiber S, Lewis G, Li QS, Lucae S, Madden PFA, Magnusson PK, Martin NG, McIntosh AM, Metspalu A, Mors O, Mortensen PB, Müller-Myhsok B, Nordentoft M, Nöthen MM, O'Donovan MC, Paciga SA, Pedersen NL, Penninx BWJH, Perlis RH, Porteous DJ, Potash JB, Preisig M, Rietschel M, Schaefer C, Schulze TG, Smoller JW, Stefansson K, Tiemeier H, Uher R, Völzke H, Weissman MM, Werge T, Winslow AR, Lewis CM, Levinson DF, Breen G, Børglum AD, Sullivan PF; Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet* 2018; **50**: 668-681 [PMID: 29700475 DOI: 10.1038/s41588-018-0090-3]
- 32 **Lipsky RK**, McDonald CC, Souders MC, Carpio CC, Teitelman AM. Adverse childhood experiences, the serotonergic system, and depressive and anxiety disorders in adulthood: A systematic literature review. *Neurosci Biobehav Rev* 2022; **134**: 104495 [PMID: 34919986 DOI: 10.1016/j.neubiorev.2021.12.018]
- 33 **Parel ST**, Peña CJ. Genome-wide Signatures of Early-Life Stress: Influence of Sex. *Biol Psychiatry* 2022; **91**: 36-42 [PMID: 33602500 DOI: 10.1016/j.biopsych.2020.12.010]
- 34 **Rodríguez-Muñoz M**, Sánchez-Blázquez P, Callado LF, Meana JJ, Garzón-Niño J. Schizophrenia and depression, two poles of endocannabinoid system deregulation. *Transl Psychiatry* 2017; **7**: 1291 [PMID: 29249810 DOI: 10.1038/s41398-017-0029-y]
- 35 **Feyissa AM**, Chandran A, Stockmeier CA, Karolewicz B. Reduced levels of NR2A and NR2B subunits of NMDA receptor and PSD-95 in the prefrontal cortex in major depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; **33**: 70-75 [PMID: 18992785 DOI: 10.1016/j.pnpbp.2008.10.005]
- 36 **Gray AL**, Hyde TM, Deep-Soboslay A, Kleinman JE, Sodhi MS. Sex differences in glutamate receptor gene expression in major depression and suicide. *Mol Psychiatry* 2015; **20**: 1057-1068 [PMID: 26169973 DOI: 10.1038/mp.2015.91]
- 37 **Meador-Woodruff JH**, Hogg AJ Jr, Smith RE. Striatal ionotropic glutamate receptor expression in schizophrenia, bipolar disorder, and major depressive disorder. *Brain Res Bull* 2001; **55**: 631-640 [PMID: 11576760 DOI: 10.1016/s0361-9230(01)00523-8]
- 38 **Fabbri C**, Montgomery S, Lewis CM, Serretti A. Genetics and major depressive disorder: clinical implications for disease risk, prognosis and treatment. *Int Clin Psychopharmacol* 2020; **35**: 233-242 [PMID: 32084067 DOI: 10.1097/YIC.0000000000000305]
- 39 **Muthukumaraswamy SD**, Shaw AD, Jackson LE, Hall J, Moran R, Saxena N. Evidence that Subanesthetic Doses of Ketamine Cause Sustained Disruptions of NMDA and AMPA-Mediated Frontoparietal Connectivity in Humans. *J Neurosci* 2015; **35**: 11694-11706 [PMID: 26290246 DOI: 10.1523/JNEUROSCI.0903-15.2015]
- 40 **Kalmoe MC**, Janski AM, Zorumski CF, Nagele P, Palanca BJ, Conway CR. Ketamine and nitrous oxide: The evolution of NMDA receptor antagonists as antidepressant agents. *J Neurol Sci* 2020; **412**: 116778 [PMID: 32240970 DOI: 10.1016/j.jns.2020.116778]
- 41 **Moghaddam B**, Adams B, Verma A, Daly D. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci* 1997; **17**: 2921-2927 [PMID: 9092613 DOI: 10.1523/JNEUROSCI.17-08-02921.1997]
- 42 **Andrade C**. Ketamine for Depression, 6: Effects on Suicidal Ideation and Possible Use as Crisis Intervention in Patients at Suicide Risk. *J Clin Psychiatry* 2018; **79** [PMID: 29659211 DOI: 10.4088/JCP.18f12242]
- 43 **Chen MH**, Cheng CM, Gueorguieva R, Lin WC, Li CT, Hong CJ, Tu PC, Bai YM, Tsai SJ, Krystal JH, Su TP. Maintenance of antidepressant and antisuicidal effects by D-cycloserine among patients with treatment-resistant depression who responded to low-dose ketamine infusion: a double-blind randomized placebo-control study. *Neuropsychopharmacology* 2019; **44**: 2112-2118 [PMID: 31421635 DOI: 10.1038/s41386-019-0480-y]
- 44 **Lally N**, Nugent AC, Luckenbaugh DA, Niciu MJ, Roiser JP, Zarate CA Jr. Neural correlates of change in major depressive disorder anhedonia following open-label ketamine. *J Psychopharmacol* 2015; **29**: 596-607 [PMID: 25691504 DOI: 10.1177/0269881114568041]
- 45 **Zanos P**, Moaddel R, Morris PJ, Riggs LM, Highland JN, Georgiou P, Pereira EFR, Albuquerque EX, Thomas CJ, Zarate CA Jr, Gould TD. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. *Pharmacol Rev* 2018; **70**: 621-660 [PMID: 29945898 DOI: 10.1124/pr.117.015198]

- 46 **Boczek T**, Lisek M, Ferenc B, Wiktorska M, Ivchevska I, Zylinska L. Region-specific effects of repeated ketamine administration on the presynaptic GABAergic neurochemistry in rat brain. *Neurochem Int* 2015; **91**: 13-25 [PMID: 26492822 DOI: 10.1016/j.neuint.2015.10.005]
- 47 **Silberbauer LR**, Spurny B, Handschuh P, Klöbl M, Bednarik P, Reiter B, Ritter V, Trost P, Konadu ME, Windpassinger M, Stimpfl T, Bogner W, Lanzenberger R, Spies M. Effect of Ketamine on Limbic GABA and Glutamate: A Human *In Vivo* Multivoxel Magnetic Resonance Spectroscopy Study. *Front Psychiatry* 2020; **11**: 549903 [PMID: 33101078 DOI: 10.3389/fpsy.2020.549903]
- 48 **McIntyre RS**, Rosenblat JD, Nemeroff CB, Sanacora G, Murrrough JW, Berk M, Brietzke E, Dodd S, Gorwood P, Ho R, Iosifescu DV, Lopez Jaramillo C, Kasper S, Kratiuk K, Lee JG, Lee Y, Lui LMW, Mansur RB, Papakostas GI, Subramaniapillai M, Thase M, Vieta E, Young AH, Zarate CA Jr, Stahl S. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. *Am J Psychiatry* 2021; **178**: 383-399 [PMID: 33726522 DOI: 10.1176/appi.ajp.2020.20081251]
- 49 **Alfredsson G**, Wiesel FA, Lindberg M. Glutamate and glutamine in cerebrospinal fluid and serum from healthy volunteers-analytical aspects. *J Chromatogr* 1988; **424**: 378-384 [PMID: 3372631 DOI: 10.1016/s0378-4347(00)81116-0]
- 50 **Adinoff B**, Kramer GL, Petty F. Levels of gamma-aminobutyric acid in cerebrospinal fluid and plasma during alcohol withdrawal. *Psychiatry Res* 1995; **59**: 137-144 [PMID: 8771228 DOI: 10.1016/0165-1781(95)02739-4]
- 51 **Petty F**. Plasma concentrations of gamma-aminobutyric acid (GABA) and mood disorders: a blood test for manic depressive disease? *Clin Chem* 1994; **40**: 296-302 [PMID: 8313610]
- 52 **Altamura C**, Maes M, Dai J, Meltzer HY. Plasma concentrations of excitatory amino acids, serine, glycine, taurine and histidine in major depression. *Eur Neuropsychopharmacol* 1995; **5** Suppl: 71-75 [PMID: 8775762 DOI: 10.1016/0924-977x(95)00033-1]
- 53 **Gao SF**, Bao AM. Corticotropin-releasing hormone, glutamate, and γ -aminobutyric acid in depression. *Neuroscientist* 2011; **17**: 124-144 [PMID: 20236945 DOI: 10.1177/1073858410361780]
- 54 **Hashimoto K**, Sawa A, Iyo M. Increased levels of glutamate in brains from patients with mood disorders. *Biol Psychiatry* 2007; **62**: 1310-1316 [PMID: 17574216 DOI: 10.1016/j.biopsych.2007.03.017]
- 55 **Sanacora G**, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology* 2012; **62**: 63-77 [PMID: 21827775 DOI: 10.1016/j.neuropharm.2011.07.036]
- 56 **Romeo B**, Choucha W, Fossati P, Rotge JY. Meta-analysis of central and peripheral γ -aminobutyric acid levels in patients with unipolar and bipolar depression. *J Psychiatry Neurosci* 2018; **43**: 58-66 [PMID: 29252166 DOI: 10.1503/jpn.160228]
- 57 **Okada M**, Kawano Y, Fukuyama K, Motomura E, Shiroyama T. Candidate Strategies for Development of a Rapid-Acting Antidepressant Class That Does Not Result in Neuropsychiatric Adverse Effects: Prevention of Ketamine-Induced Neuropsychiatric Adverse Reactions. *Int J Mol Sci* 2020; **21** [PMID: 33114753 DOI: 10.3390/ijms21217951]
- 58 **Park LT**, Kadriu B, Gould TD, Zanos P, Greenstein D, Evans JW, Yuan P, Farmer CA, Oppenheimer M, George JM, Adejo LW, Snodgrass HR, Smith MA, Henter ID, Machado-Vieira R, Mannes AJ, Zarate CA. A Randomized Trial of the N-Methyl-D-Aspartate Receptor Glycine Site Antagonist Prodrug 4-Chlorokynurenine in Treatment-Resistant Depression. *Int J Neuropsychopharmacol* 2020; **23**: 417-425 [PMID: 32236521 DOI: 10.1093/ijnp/pyaa025]
- 59 **Vyklicky V**, Korinek M, Smejkalova T, Balik A, Krausova B, Kaniakova M, Lichnerova K, Cerny J, Krusek J, Dittert I, Horak M, Vyklicky L. Structure, function, and pharmacology of NMDA receptor channels. *Physiol Res* 2014; **63**: S191-S203 [PMID: 24564659 DOI: 10.33549/physiolres.932678]
- 60 **Traynelis SF**, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK, Hansen KB, Yuan H, Myers SJ, Dingledine R. Glutamate receptor ion channels: structure, regulation, and function. *Pharmacol Rev* 2010; **62**: 405-496 [PMID: 20716669 DOI: 10.1124/pr.109.002451]
- 61 **Mueller HT**, Meador-Woodruff JH. NR3A NMDA receptor subunit mRNA expression in schizophrenia, depression and bipolar disorder. *Schizophr Res* 2004; **71**: 361-370 [PMID: 15474907 DOI: 10.1016/j.schres.2004.02.016]
- 62 **Dean B**, Gibbons AS, Boer S, Uezato A, Meador-Woodruff J, Scarr E, McCullumsmith RE. Changes in cortical N-methyl-D-aspartate receptors and post-synaptic density protein 95 in schizophrenia, mood disorders and suicide. *Aust N Z J Psychiatry* 2016; **50**: 275-283 [PMID: 26013316 DOI: 10.1177/0004867415586601]
- 63 **Fan N**, An L, Zhang M, He H, Zhou Y, Ou Y. GRIN2B Gene Polymorphism in Chronic Ketamine Users. *Am J Addict* 2020; **29**: 105-110 [PMID: 31957106 DOI: 10.1111/ajad.12984]
- 64 **Ibrahim L**, Diazgranados N, Franco-Chaves J, Brutsche N, Henter ID, Kronstein P, Moaddel R, Wainer I, Luckenbaugh DA, Manji HK, Zarate CA Jr. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. *Neuropsychopharmacology* 2012; **37**: 1526-1533 [PMID: 22298121 DOI: 10.1038/npp.2011.338]
- 65 **Preskorn SH**, Baker B, Kolluri S, Menniti FS, Krams M, Landen JW. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. *J Clin Psychopharmacol* 2008; **28**: 631-637 [PMID: 19011431 DOI: 10.1097/JCP.0b013e31818a6cea]
- 66 **Aragam N**, Wang KS, Anderson JL, Liu X. TMRSS9 and GRIN2B are associated with neuroticism: a genome-wide association study in a European sample. *J Mol Neurosci* 2013; **50**: 250-256 [PMID: 23229837 DOI: 10.1007/s12031-012-9931-1]
- 67 **Myers SJ**, Yuan H, Kang JQ, Tan FCK, Traynelis SF, Low CM. Distinct roles of *GRIN2A* and *GRIN2B* variants in neurological conditions. *F1000Res* 2019; **8** [PMID: 31807283 DOI: 10.12688/f1000research.18949.1]
- 68 **Narita S**, Onozawa Y, Yoshihara E, Nishizawa D, Numajiri M, Ikeda K, Iwahashi K. Association between N-methyl-D-aspartate Receptor Subunit 2B Gene Polymorphisms and Personality Traits in a Young Japanese Population. *East Asian Arch Psychiatry* 2018; **28**: 45-52 [PMID: 29921740]
- 69 **Zhang C**, Li Z, Wu Z, Chen J, Wang Z, Peng D, Hong W, Yuan C, Yu S, Xu Y, Xu L, Xiao Z, Fang Y. A study of N-methyl-D-aspartate receptor gene (*GRIN2B*) variants as predictors of treatment-resistant major depression. *Psychopharmacology (Berl)* 2014; **231**: 685-693 [PMID: 24114429 DOI: 10.1007/s00213-013-3297-0]

- 70 **Arnold PD**, Macmaster FP, Richter MA, Hanna GL, Sicard T, Burroughs E, Mirza Y, Easter PC, Rose M, Kennedy JL, Rosenberg DR. Glutamate receptor gene (GRIN2B) associated with reduced anterior cingulate glutamatergic concentration in pediatric obsessive-compulsive disorder. *Psychiatry Res* 2009; **172**: 136-139 [PMID: [19324536](#) DOI: [10.1016/j.psychres.2009.02.005](#)]
- 71 **Gerhard DM**, Pothula S, Liu RJ, Wu M, Li XY, Girgenti MJ, Taylor SR, Duman CH, Delpire E, Picciotto M, Wohleb ES, Duman RS. GABA interneurons are the cellular trigger for ketamine's rapid antidepressant actions. *J Clin Invest* 2020; **130**: 1336-1349 [PMID: [31743111](#) DOI: [10.1172/JCI130808](#)]
- 72 **Sokolowski M**, Ben-Efraim YJ, Wasserman J, Wasserman D. Glutamatergic GRIN2B and polyaminergic ODC1 genes in suicide attempts: associations and gene-environment interactions with childhood/adolescent physical assault. *Mol Psychiatry* 2013; **18**: 985-992 [PMID: [22850629](#) DOI: [10.1038/mp.2012.112](#)]
- 73 **Engdahl E**, Alavian-Ghavanini A, Forsell Y, Lavebratt C, Rüegg J. Childhood adversity increases methylation in the GRIN2B gene. *J Psychiatr Res* 2021; **132**: 38-43 [PMID: [33038564](#) DOI: [10.1016/j.jpsychires.2020.09.022](#)]
- 74 **Buji RI**, Abdul Murad NA, Chan LF, Maniam T, Mohd Shahrir MS, Rozita M, Shamsul AS, Mohamad Hussain R, Abdullah N, Jamal R, Nik Jaafar NR. Suicidal ideation in systemic lupus erythematosus: NR2A gene polymorphism, clinical and psychosocial factors. *Lupus* 2018; **27**: 744-752 [PMID: [29161964](#) DOI: [10.1177/0961203317742711](#)]
- 75 **Chandley MJ**, Szebeni A, Szebeni K, Crawford JD, Stockmeier CA, Turecki G, Kostrzewa RM, Ordway GA. Elevated gene expression of glutamate receptors in noradrenergic neurons from the locus coeruleus in major depression. *Int J Neuropsychopharmacol* 2014; **17**: 1569-1578 [PMID: [24925192](#) DOI: [10.1017/S1461145714000662](#)]
- 76 **Pacheco A**, Aguayo FI, Aliaga E, Muñoz M, García-Rojo G, Olave FA, Parra-Fiedler NA, García-Pérez A, Tejos-Bravo M, Rojas PS, Parra CS, Fiedler JL. Chronic Stress Triggers Expression of Immediate Early Genes and Differentially Affects the Expression of AMPA and NMDA Subunits in Dorsal and Ventral Hippocampus of Rats. *Front Mol Neurosci* 2017; **10**: 244 [PMID: [28848384](#) DOI: [10.3389/fnmol.2017.00244](#)]
- 77 **Sathyanesan M**, Haiar JM, Watt MJ, Newton SS. Restraint stress differentially regulates inflammation and glutamate receptor gene expression in the hippocampus of C57BL/6 and BALB/c mice. *Stress* 2017; **20**: 197-204 [PMID: [28274152](#) DOI: [10.1080/10253890.2017.1298587](#)]
- 78 **Jernigan CS**, Goswami DB, Austin MC, Iyo AH, Chandran A, Stockmeier CA, Karolewicz B. The mTOR signaling pathway in the prefrontal cortex is compromised in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2011; **35**: 1774-1779 [PMID: [21635931](#) DOI: [10.1016/j.pnpbp.2011.05.010](#)]
- 79 **Chen MH**, Kao CF, Tsai SJ, Li CT, Lin WC, Hong CJ, Bai YM, Tu PC, Su TP. Treatment response to low-dose ketamine infusion for treatment-resistant depression: A gene-based genome-wide association study. *Genomics* 2021; **113**: 507-514 [PMID: [33370585](#) DOI: [10.1016/j.ygeno.2020.12.030](#)]
- 80 **Weder N**, Zhang H, Jensen K, Yang BZ, Simen A, Jackowski A, Lipschitz D, Douglas-Palumberi H, Ge M, Perepletchikova F, O'Loughlin K, Hudziak JJ, Gelernter J, Kaufman J. Child abuse, depression, and methylation in genes involved with stress, neural plasticity, and brain circuitry. *J Am Acad Child Adolesc Psychiatry* 2014; **53**: 417-24.e5 [PMID: [24655651](#) DOI: [10.1016/j.jaac.2013.12.025](#)]
- 81 **Kaut O**, Schmitt I, Hofmann A, Hoffmann P, Schlaepfer TE, Wüllner U, Hurlmann R. Aberrant NMDA receptor DNA methylation detected by epigenome-wide analysis of hippocampus and prefrontal cortex in major depression. *Eur Arch Psychiatry Clin Neurosci* 2015; **265**: 331-341 [PMID: [25571874](#) DOI: [10.1007/s00406-014-0572-y](#)]
- 82 **Duric V**, Banasr M, Stockmeier CA, Simen AA, Newton SS, Overholser JC, Jurjus GJ, Dieter L, Duman RS. Altered expression of synapse and glutamate related genes in post-mortem hippocampus of depressed subjects. *Int J Neuropsychopharmacol* 2013; **16**: 69-82 [PMID: [22339950](#) DOI: [10.1017/S1461145712000016](#)]
- 83 **Adell A**. Brain NMDA Receptors in Schizophrenia and Depression. *Biomolecules* 2020; **10** [PMID: [32585886](#) DOI: [10.3390/biom10060947](#)]
- 84 **McKendrick G**, Graziane NM. Drug-Induced Conditioned Place Preference and Its Practical Use in Substance Use Disorder Research. *Front Behav Neurosci* 2020; **14**: 582147 [PMID: [33132862](#) DOI: [10.3389/fnbeh.2020.582147](#)]
- 85 **O'Neill MJ**, Bleakman D, Zimmerman DM, Nisenbaum ES. AMPA receptor potentiators for the treatment of CNS disorders. *Curr Drug Targets CNS Neurol Disord* 2004; **3**: 181-194 [PMID: [15180479](#) DOI: [10.2174/1568007043337508](#)]
- 86 **Li X**, Tizzano JP, Griffey K, Clay M, Lindstrom T, Skolnick P. Antidepressant-like actions of an AMPA receptor potentiator (LY392098). *Neuropharmacology* 2001; **40**: 1028-1033 [PMID: [11406194](#) DOI: [10.1016/s0028-3908\(00\)00194-5](#)]
- 87 **Alshammari TK**. The Ketamine Antidepressant Story: New Insights. *Molecules* 2020; **25** [PMID: [33297563](#) DOI: [10.3390/molecules25235777](#)]
- 88 **Widman AJ**, McMahon LL. Disinhibition of CA1 pyramidal cells by low-dose ketamine and other antagonists with rapid antidepressant efficacy. *Proc Natl Acad Sci U S A* 2018; **115**: E3007-E3016 [PMID: [29531088](#) DOI: [10.1073/pnas.1718883115](#)]
- 89 **Koike H**, Chaki S. Requirement of AMPA receptor stimulation for the sustained antidepressant activity of ketamine and LY341495 during the forced swim test in rats. *Behav Brain Res* 2014; **271**: 111-115 [PMID: [24909673](#) DOI: [10.1016/j.bbr.2014.05.065](#)]
- 90 **Pandis C**, Sotiriou E, Kouvaras E, Asprodingi E, Papatheodoropoulos C, Angelatou F. Differential expression of NMDA and AMPA receptor subunits in rat dorsal and ventral hippocampus. *Neuroscience* 2006; **140**: 163-175 [PMID: [16542781](#) DOI: [10.1016/j.neuroscience.2006.02.003](#)]
- 91 **Chiesa A**, Crisafulli C, Porcelli S, Han C, Patkar AA, Lee SJ, Park MH, Jun TY, Serretti A, Pae CU. Influence of GRIA1, GRIA2 and GRIA4 polymorphisms on diagnosis and response to treatment in patients with major depressive disorder. *Eur Arch Psychiatry Clin Neurosci* 2012; **262**: 305-311 [PMID: [22057216](#) DOI: [10.1007/s00406-011-0270-y](#)]
- 92 **Pochwat B**, Nowak G, Szewczyk B. An update on NMDA antagonists in depression. *Expert Rev Neurother* 2019; **19**: 1055-1067 [PMID: [31328587](#) DOI: [10.1080/14737175.2019.1643237](#)]
- 93 **Nowak G**, Li Y, Paul IA. Adaptation of cortical but not hippocampal NMDA receptors after chronic citalopram treatment. *Eur J Pharmacol* 1996; **295**: 75-85 [PMID: [8925878](#) DOI: [10.1016/0014-2999\(95\)00585-4](#)]
- 94 **Horstmann S**, Lucae S, Menke A, Hennings JM, Ising M, Roeske D, Müller-Myhsok B, Holsboer F, Binder EB.

- Polymorphisms in GRIK4, HTR2A, and FKBP5 show interactive effects in predicting remission to antidepressant treatment. *Neuropsychopharmacology* 2010; **35**: 727-740 [PMID: 19924111 DOI: 10.1038/npp.2009.180]
- 95 **Serretti A**, Chiesa A, Crisafulli C, Massat I, Linotte S, Calati R, Kasper S, Bailer U, Lecrubier Y, Fink M, Antonijevic I, Forray C, Snyder L, Bollen J, Zohar J, De Ronchi D, Souery D, Mendlewicz J. Failure to replicate influence of GRIK4 and GNB3 polymorphisms on treatment outcome in major depression. *Neuropsychobiology* 2012; **65**: 70-75 [PMID: 2222462 DOI: 10.1159/000329553]
- 96 **Ho MF**, Correia C, Ingle JN, Kaddurah-Daouk R, Wang L, Kaufmann SH, Weinshilboum RM. Ketamine and ketamine metabolites as novel estrogen receptor ligands: Induction of cytochrome P450 and AMPA glutamate receptor gene expression. *Biochem Pharmacol* 2018; **152**: 279-292 [PMID: 29621538 DOI: 10.1016/j.bcp.2018.03.032]
- 97 **Elhussiny MEA**, Carini G, Mingardi J, Tornese P, Sala N, Bono F, Fiorentini C, La Via L, Popoli M, Musazzi L, Barbon A. Modulation by chronic stress and ketamine of ionotropic AMPA/NMDA and metabotropic glutamate receptors in the rat hippocampus. *Prog Neuropsychopharmacol Biol Psychiatry* 2021; **104**: 110033 [PMID: 32640261 DOI: 10.1016/j.pnpbp.2020.110033]



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