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# Pharmacogenomics of ketamine: A systematic review

Shakila Meshkat [a], Nelson B. Rodrigues [a], Joshua D. Di Vincenzo [a,c], Felicia Ceban [a,d], Saja Jaberi [a], Roger S. McIntyre [a,b,c,d], Leanna M.W. Lui [a], Joshua D. Rosenblat [a,b,*]

[a] Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON, Canada
[b] Department of Psychiatry, University of Toronto, Toronto, ON, Canada
[c] Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada
[d] Brain and Cognition Discovery Foundation, Toronto, ON, Canada

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ABSTRACT

Ketamine is a dissociative anesthetic used worldwide for anesthesia, pain management, treatment resistant depression (TRD) and suicidality. Predictors of antidepressant response and adverse effects to ketamine remain poorly understood due to contradictory results. The objective of the systematic review herein is to identify and evaluate the extant literature assessing pharmacogenomic predictors of ketamine clinical benefits and adverse effects. Electronic databases were searched from inception to July 2021 to identify relevant articles. Twelve articles involving 1,219 participants with TRD, 75 who underwent elective surgeries and received ketamine as an anesthetic, 49 with pain, and 68 healthy participants met the inclusion criteria and enrolled to this review. While identified articles reported mixed results, three predictors emerged: 1) Val66Met (rs6265) brain derived neurotrophic factor (BDNF; Met allele) was associated with reduced antidepressant and anti-suicidal effects, 2) CYP2B6*6 (e.g., CYB2B6 metabolizer) was associated with more severe dissociative effects and 3) NET allelic (rs28386840) variant were associated with greater cardiovascular complications (e.g., moderate to severe treatment emergent hypertension). Several important limitations were identified, most notably the small sample sizes and heterogeneity of study design and results. Taken together, preliminary evidence suggests the potential for pharmacogenomic testing to inform clinical practices; however, further research is needed to better determine genetic variants of greatest importance and the clinical validity of pharmacogenomics to help guide ketamine treatment planning.

## 1. Introduction

Ketamine is a stereoselective N-methyl-D-aspartate (NMDA) receptor antagonist, widely employed as a dissociative anesthetic worldwide (Domino et al., 1965). Over the past two decades, ketamine has been evaluated for additional clinical indications, such as pain management and treatment resistant depression (TRD). The utility of ketamine in the treatment of mood disorders is of particular interest with replicated randomized clinical trials (RCTs) and meta-analyses reporting replicated rapid and robust antidepressant effects and reduction in suicidal thoughts (Bahji et al., 2021; Xiong et al., 2021; McIntyre et al., 2020, 2021).

Whilst clinical trials have provided clear evidence for ketamine's efficacy, a notable challenge has been identifying predictors of response and treatment emergent adverse effects. Given the resource intensive nature of ketamine infusions, it would be instructive to personalize treatment and predict probability of response a priori. However, no predictors of clinical utility have been consistently demonstrated with contradictory results to date (Rong et al., 2018). Additionally, the identification of pharmacogenomic predictors may be beneficial insofar as increasing the accessibility and reducing the patient burden of ketamine through the prospective mitigation of treatment-emergent adverse events. Taken together, clinical or biomarker predictors of antidepressant response to ketamine would be beneficial to allow for a personalized medicine approach using this novel intervention and from the view of cost effectiveness.

The emerging field of pharmacogenomics holds promise to facilitate a more personalized approach to drug selection and dosage optimization, theoretically reducing human suffering as a consequence of suboptimal antidepressant selection. Notably, however, more research is necessary to further validate pharmacogenomic testing given the paucity of high certainty evidence supporting the overall improved

* Corresponding author. Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON, Canada.
*E-mail address:* joshua.rosenblat@uhn.ca (J.D. Rosenblat).

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outcomes for patients (Rosenblat et al., 2017, 2018; Bousman et al., 2019). Nevertheless, the theoretical benefits of pharmacogenomics for specific drugs of interest is still an active and promising area of research. Indeed, it is possible that pharmacogenomics may be beneficial to guide treatment with certain medications, even if not broadly applicable to all medications. Clinical practice guidelines such as clinical pharmacogenetic implementation consortium (CPIC), Dutch pharmacogenetics working group (DPWG), and FDA exist for psychiatric pharmacogenomics (Van Schaik et al., 2020).

Ketamine is hepatically metabolized by the highly polymorphic cytochrome P450 (CYP450) system. It should be noted that the pharmacokinetics of ketamine remains unclear as there is evidence to suggest that intravenous and intranasal ketamine skips first pass metabolism (Kamp et al., 2020). Pharmacogenomic testing may theoretically help predict ketamine's effectiveness and adverse effects, which may in turn help with patient selection, personalized informed consent, and target dose planning (Domino et al., 1965; Hijazi et al., 2001). The objective of the current systematic review is to identify and synthesize the extant literature evaluating the pharmacogenomics of ketamine response. Identifying key allelic variants which may impact the pharmacokinetics and pharmacodynamics of ketamine might allow us to predict who is more likely to respond and possibly guide dosage selection to minimize undesirable treatment-emergent adverse events while maximizing therapeutic benefits.

## 2. Methods

### 2.1. Literature search

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, a systematic search was conducted on PubMed, Scopus, and Web of Science databases from inception until July 2021 (Page et al., 2021). Additional articles were identified on Google Scholar and through a manual search of reference lists of relevant references. No language or publication date restrictions were imposed.

### 2.2. Literature search strategy

The following MeSH (Medical Subject Headings) search terms were used: ketamine"[Mesh] OR "ketamine"[tiab] AND "pharmacogenomics"[Mesh] OR "pharmacogenomic testing"[Mesh].We also used the following terms: pharmacogenetics AND ketamine, ketamine AND Gene, ketamine AND genetic, ketamine AND pharmacogenomics AND CYP450, ketamine AND pharmacogenomics AND GABA, ketamine AND pharmacogenomics AND Opioid, ketamine AND pharmacogenomics AND glutamate, ketamine AND pharmacogenomics AND BDNF.

### 2.3. Study eligibility criteria

Studies were selected for data extraction if the following inclusion criteria were met: (1) included patients treated with ketamine or esketamine; (2) genotyping was conducted and the results were reported; (3) the primary outcomes were the treatment emergent adverse events and/or therapeutic effects of ketamine or esketamine. Case studies were also included. Articles were excluded based on the following criteria: (1) non-refereed abstracts, conference abstracts, unpublished data sets, systematic reviews; (2) *in vitro* studies; (3) animal studies.

### 2.4. Data extraction

Two reviewers (SM, NBR) independently reviewed full-texts of eligible studies and extracted the following data from each article: 1) year of publication, 2) number of patients, 3) patients age, 4) dose of ketamine used, 5) ketamine method of administration, 6) genes/variants studied, 7) gene polymorphism investigated, 8) gene extraction method, 9) study outcome, 10) ethnicity, 11) main findings 12) parameters to define treatment response and study outcome, 13) underlying medical condition. Possible discrepancies were resolved through discussion. Attempts were made to complete missing data fields as necessary by contacting authors directly.

### 2.5. Risk of bias assessment

We assessed the risk of bias (RoB) using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials (Table 1). The following five domains were used to assess bias: bias arising from the randomization method, bias emerging from deviations from intended interventions, bias arising from missing outcome data, bias in outcome assessment, and bias in the selection of the reported result (Higgins et al., 2011).

## 3. Results

### 3.1. Search results

The literature search yielded a total of 2991 records. We removed duplicate articles and screened the title/abstract of the remaining records. We also found 7 articles during the manual screening of references. 2974 articles were excluded based on title/abstract. We reviewed the full text of the remaining papers (n = 24) in detail based on our inclusion criteria. Out of 24 records, 12 records were excluded; 1 article's full text was not available, 3 were *in vitro* studies, 2 were review articles, and 6 articles did not report the association of pharmacogenomics and ketamine effects. Twelve articles involving 1219 patients with TRD, 75 patients with elective surgeries who received ketamine as an anesthetic, 49 patients with pain, and 68 healthy participants met the inclusion criteria and were included in this systematic review. The study selection details are indicated in Fig. 1.

### 3.2. Characteristics of included studies

The included studies were performed in a variety of different populations, settings, and techniques (Tables 2 and 3). Out of 12 included papers, 8 were RCTs, 2 were open label studies, 1 was non randomized clinical trial and 1 was a pilot study. Nine studies included TRD patients with white ethnicity. The antidepressant effect of ketamine was assessed using Montgomery–Åsberg Depression Rating Scale (MADRS) and 17-item Hamilton Depression Rating Scale (HDRS) in five and three studies, respectively. Six studies used 0.5 mg/kg intravenous ketamine and four studies used 0.2 mg/kg or 0.5 mg/kg.

### 3.3. Genes examined in the literature

Table 4 summarizes the genes and polymorphisms reported by the included studies. *Brain derived neurotrophic factor (BDNF)* and *CYP2B* were the most frequently examined genotypes. *BDNF* was studied in six articles and *CYP2B* was studied in three articles.

#### 3.3.1. Brain derived neurotrophic factor (BDNF)

*BDNF* genetic variants designated as Val66Met (rs6265) have been examined in patients with TRD for association with ketamine antidepressant response. Ping Su et al. evaluated dose-related antidepressant effects of ketamine using HAMD score in TRD patients from a Chinese population predominantly exhibiting low activity *BDNF* rs6265 genotypes (Val/Met, Met/Met) (Su et al., 2017). Ping su et al. conducted a double-blind, randomized, parallel-group, placebo controlled trial in 71 participants using 0.2–0.5 mg/kg single dose IV ketamine. Val/Val, Val/Met and Met/Met genotypes were found in 17%, 56.3% and 26.8% of patients, respectively. The results of the foregoing study reported no significant association between the antidepressant effect of ketamine

**Table 1**
Risk of bias assessment and study quality in randomized trials.

| | Bias arising from the randomization process | Bias due to deviations from intended interventions | Bias due to missing outcome data | Bias in the measurement of the outcome | Bias in selection of the reported result |
|---|---|---|---|---|---|
| Saad et al. (2020) | Low | Low | Low | Low | Low |
| Guo et al. (2018) | Low | Low | Low | Low | Some concerns |
| Ping Su et al., 2017 | Low | Low | Low | Low | Low |
| Chen et al. (2019) | Low | Low | Low | Low | Low |
| Liebe et al. 2017 | Low | Low | Some concerns | Low | Low |
| Grunebaum et al. 2020 | Low | Low | Low | Low | Low |
| Chen et al. (2021) | Low | Low | Low | Low | Low |
| Chen et al. (2021) | Low | Low | Low | Low | Low |

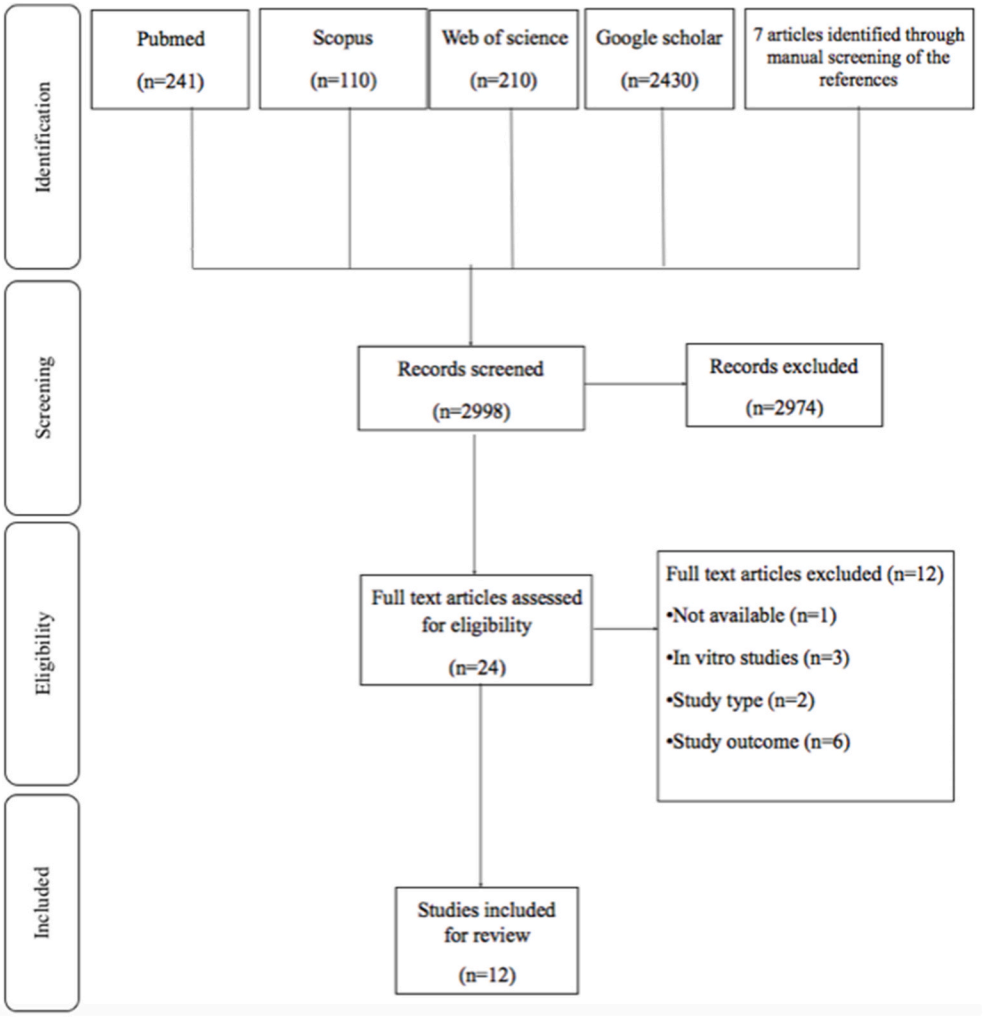


**Fig. 1.** Flow diagram for the systematic review as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

and *BDNF* rs6265 genotypes (p = 0.55) (Su et al., 2017). Chen et al. reanalyzed data from Ping su et al.'s study to evaluate the association of *BDNF* rs6265 genotypes (Val/Met, Met/Met) and the antisuicidal effect of ketamine (Chen et al., 2019). The primary outcome was changes in suicide item subscales within the HAMD and MADRS scores. The investigators reported the IV ketamine was associated with an antisuicidal effect in individuals with any Val allele of *BDNF* rs6265 (p = 0.012) but not in those with Met/Met of *BDNF* rs6265 (p = 0.215). Both 0.5 mg/kg and 0.2 mg/kg ketamine infusions were effective in reducing suicidal thoughts in individuals with Val/Val or Val/Met of *BDNF* rs6265(p = 0.007), while only 0.5 mg/kg was effective in those with Met/Met of *BDNF* rs6265 (p = 0.009) (Chen et al., 2019). The dataset was reanalyzed to assess the association of *BDNF* rs6265 Val66Met polymorphism and antidepressant response to low-dose ketamine infusion, with the primary outcome assessing changes in HDRS score (Chen et al., 2021). Investigators also reported that patients with Met/Met are less likely to respond to low-dose ketamine infusion compared to Val/Val and Val/Met (p = 0.007) (Chen et al., 2021). Laje et al. separately reported rapid antidepressant effects of 0.5 mg/kg IV ketamine in 62 patients with TRD from the USA (Laje et al., 2012). The *BDNF* rs6265 Val/Val polymorphism was identified in 41 patients, of which 21 carried either a single (n = 19) or double (n = 2) Met substitution. The foregoing

**Table 2**
Study demographics.

| Author | Gene | Population studied | Drug investigated | Method | Study design | Comment |
|---|---|---|---|---|---|---|
| Saad et al., (2020) (20) | OPRM | N = 406 TRD | Esketamine Nasal Spray | Genotyping arrays | Clinical trial | Variation in rs1799971 (A118G) did not affect the antidepressant response<br>Antidepressant response to placebo was increased in G-allele carriers<br>No significant genotype effects on dissociative responses was detected |
| Aroke et al., 2017 (18) | CYP2B6<br>GRIN2B | N = 75 Patients having minor elective outpatient surgeries | Ketamine | Taqman Genotyping Assays | Pilot study | EP Occurrence and severity of EP were not associated with CYP2B6 or GRIN2B |
| Guo et al., (2018) (23) | SEC11A<br>KRASP1<br>OSBP2<br>MRPL 50P1<br>C18orf42<br>RASGRF2<br>ROBO2<br>C20orf196<br>FAM179A<br>FITM2<br>LINC00923 | N = 326<br>TRD | Ketamine | GWAS | Clinical trial | No SNP exceeded the genome-wide threshold for significance of 5 Å~ 10−8 |
| Ping Su et al., 2017 (9) | BDNF | N = 71<br>TRD | Ketamine | PCR | Clinical trial | No significant differences between carriers of the Met allele and Val/Val patients for predicting response to ketamine |
| Chen et al., (2019) (10) | BDNF | N = 71<br>TRD | Ketamine | PCR | Clinical trial | Among those carrying any Val allele of BDNF, both 0.5 and 0.2 mg/kg ketamine infusions were effective in reducing suicidal thoughts; however, among those with Met/Met of BDNF, only 0.5 mg/kg ketamine infusion was effective in reducing suicidal<br>thoughts |
| Liebe et al. 2017 (22) | NET | N = 68<br>Healthy participants | Ketamine | PCR | Clinical trial | (NET) genotype is a factor predicting increased cardiovascular sequelae upon ketamine administration.<br>NET rs28386840 [T] carriers reached their maximal systolic blood pressure during ketamine administration significantly earlier than [A] homozygous carriers. |
| Li et al., (2015) (16) | CYP2B6 | N = 49 chronic pain patients who received 24 h continuous subcutaneous infusions of ketamine | Ketamine | PCR | Clinical trial | The CYP2B6*6 allele is associated with a substantial decrease in steady-state ketamine plasma clearance and higher<br>incidence of ketamine adverse effects |
| Grunebaum et al. 2020 (21) | OPRM | N = 80<br>TRD | Ketamine | PCR | Clinical trial | Results did not indicate a treatment by genotype (AA vs AG + GG) interaction effect on 24 h post-treatment scores for the SSI, POMS and HDRS-17. |
| Zarate et al., (2012) (17) | CYP2A6,<br>CYP2B6,<br>CYP2C9,<br>CYP2C19,<br>CYP3A4,<br>CYP3A5 | N = 67<br>TRD | Ketamine | Taqman Genotyping Assays | Clinical trial | Genotypes were not associated with response, side effects and metabolite levels |
| Chen et al., (2021) (11) | BDNF | N = 71<br>TRD | Ketamine | PCR | Clinical trial | Patients with TRD with any Val at rs6265 of BDNF polymorphism are more likely to respond to low dose<br>ketamine infusion than those with Met/Met |
| Laje et al., (2012) (13) | BDNF | N = 62<br>TRD | Ketamine | PCR | Clinical trial | Patients with the Val/Val BDNF allele at rs6265 are more likely to exhibit increased antidepressant response to ketamine than Met carriers. |
| Chen et al., (2021) (12) | BDNF, GRIN, NTRK, CYP2 | N = 65<br>TRD | Ketamine | Illumina Human OmniExpress Exome Bead Chips | Clinical trial | BDNF–TrkB signaling (i.e., rs2049048 in *BDNF* and rs10217777 in *NTRK2*) and the glutamatergic and GABAergic systems (i.e., rs16966731 in *GRIN2A*) were associated with the rapid (within 240 min) and persistent (up to 2 weeks) antidepressant effect of low-dose ketamine infusion and with serum ketamine and norketamine levels. |

Abbreviations used: TRD; treatment resistant depression, BDNF; Brain-derived neurotrophic factor, CYP; cytochrome P450.
OPRM; Opioid Receptor Mu, NTRK; Neurotrophic tyrosine receptor kinase, NET; norepinephrine transporter, EP; emergence phenomena, SNP; Single-nucleotide polymorphism, GRIN: glutamate ionotropic receptor NMDA type subunit.

**Table 3**
Study demographics.

| Author | Outcome measures | Dose | Placebo | Ethnicity | Average age (y) | Male (%) |
|---|---|---|---|---|---|---|
| Saad et al., (2020) (20) | MADRS<br>CADSS | – | – | White | 46.4 | 33% |
| Aroke et al., 2017 (18) | CADSS | 0.5 mg/kg IV ketamine | – | White | 50.8 | 46.7% |
| Guo et al., (2018) (23) | MADRS<br>HAMD<br>CADSS | 0.5 mg/kg IV ketamine | Scopolamine | White | 41 | 48.9% |
| Ping Su et al., 2017 (9) | HAMD | 0.2 or 0.5 mg/kg IV ketamine | Saline | Asian | 47.3 | 25.3% |
| Chen et al., (2019) (10) | MADRS | 0.2 or 0.5 mg/kg IV ketamine | Saline | Asian | 47.3 | 25.3% |
| Liebe et al. 2017 (22) | Time to the maximal systolic blood pressure (TÎ”MAXSys) | 0.5 mg/kg IV ketamine | Saline | White | 26.18 | 55.8% |
| Li et al., (2015) (16) | Steady-state plasma concentrations of ketamine (Css,k) and norketamine (Css,nk) were determined using HPLC< | 100 mg, 300 mg, 500 mg sc ketamine | – | White | 64 | 46.9% |
| Grunebaum et al. 2020 (21) | SSI<br>POMS<br>HDRS | 0.5 mg/kg IV ketamine | Midazolam | White | – | – |
| Zarate et al., (2012) (17) | BPRS<br>MADRS<br>CADSS | 0.5 mg/kg IV ketamine | – | White | 45.8 | 50.7% |
| Chen et al., (2021) (11) | HDRS | 0.2 or 0.5 mg/kg IV ketamine< | Saline | Asian | 47.3 | 25.3% |
| Laje et al., (2012) (13) | HAMD | 0.5 mg/kg IV Ketamine | – | White | 45.99 | 45% |
| Chen et al., (2021) (12) | HDRS<br>MADRS | 0.2 or 0.5 mg/kg IV ketamine | Saline | White | 46.7 | 24.6% |

Abbreviations used: MADRS; Montgomery–Åsberg Depression Rating Scale, CADSS; Clinician-Administered Dissociative-States Scale, HDRS; 17-item Hamilton Depression Rating Scale, SSI; Beck Scale for Suicidal Ideation, POMS; Profile of Mood States, BPRS; Brief Psychiatric Rating Scale, HAMD; 17-item Hamilton Depression Rating Scale, HPLC; High-performance liquid chromatography.

**Table 4**
Genes and polymorphism used in included studies.

| Gene | Polymorphism | Number of studies |
|---|---|---|
| OPRM | rs1799971 (A118G) | 2 |
| SEC11A | rs55945116 | 1 |
| KRASP1 | rs112647602 | 1 |
| OSBP2 | rs5997786 | 1 |
| MRPL 50P1 | rs1524145 | 1 |
| C18orf42 | rs75908125 | 1 |
| RASGRF2 | rs17211233 | 1 |
| ROBO2 | rs1400237<br>rs9713737<br>rs4855976 | 1 |
| C20orf196 | rs1287071 | 1 |
| FAM179A | rs11127199 | 1 |
| FITM2 | rs11907319 | 1 |
| LINC00923 | rs4558394 | 1 |
| BDNF | rs6265 (Val66Met)<br>rs2049048 | 6 |
| NET | rs28386840 (A-3081T) | 1 |
| CYP2 | rs3211371 (CYP2B6*5), rs3745274 (CYP2B6*6), rs1019385 (CYP2B6*6)<br>CYP2A6, CYP2B6 (rs117093559),<br>CYP2C9, CYP2C19, CYP3A4, CYP3A5, CYP2B6*1, CYP2B6*7 | 4 |
| NTRK2 | rs10868564, rs10217777, rs142580562, rs117155102, rs10868590, rs1421001, rs77918527 | 1 |
| GRIN | GRIN1, GRIN2A, GRIN2B, GRIN2C, GRIN2D, GRIN3A, GRIN3B, GRINA | 2 |

study revealed that TRD patients with the Val/Val *BDNF* rs6265 allele are more likely to have an increased antidepressant response to ketamine than Met carriers (p = 0.0007) (Laje et al., 2012).

### 3.3.2. CYP450 system

Multiple polymorphisms including *CYP2B6*5* (rs3211371), *CYP2B6*6* (rs3745274), *CYP2B6*6* (rs1019385), *CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP3A5* were studied in three papers. In adults, *CYP2A* enzymes account for a small percentage of overall hepatic CYP expression, with *CYP2A6* as the main isoform. *CYP2B6* accounts for 6–10% of total CYP450 content in the liver, with a substantial (>100-fold) variance in expression among individuals. The most frequent polymorphism is *CYP2B6*6. CYP2B6*, CYP2B6*6,* and *CYP2B6*7* are associated with decreased enzymatic activity compared to *CYP2B*1* (Zanger and Klein, 2013).

Li et al., examine the impact of the *CYP2* family on ketamine plasma clearance and treatment emergent adverse events in 49 chronic pain patients who received 24 h continuous subcutaneous infusions of ketamine (Li et al., 2015). *CYP2B6*1, CYP2B6*5 (rs3211371), CYP2B6*6* (rs3745274)*, and CYP2B6*7* alleles with allelic frequencies of 71%, 3%, 24%, and 1% were found. They determined steady-state plasma concentrations of ketamine (Css,k) and norketamine (Css,nk) using high-performance liquid chromatography (HPLC). Patients with the *CYP2B6*6* allele had lower steady-state ketamine plasma clearance, which was associated with a higher incidence of ketamine treatment emergent adverse events ($p < 0.001$) (Li et al., 2015). In another study by Zarate et al., the association of *CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP3A4,* and *CYP3A5* genotypes with the response and treatment emergent adverse events to ketamine infusion was examined in 67 patients with TRD (Zarate et al., 2012). They used the MADRS to evaluate the response to ketamine. The results of this study indicated that there was no significant impact of *CYP450* genotypes on response and side effects of ketamine) (p = 0.88) (Zarate et al., 2012). Furthermore, Aroke et al., investigated the link between *CYP2B6*6* (rs3745274 and rs2279343) and ketamine-induced emergence phenomena (EP) in 75 patients having minor elective outpatient surgeries. The foregoing pilot study indicated that the occurrence and severity of EP were not associated with *CYP2B6*6* (p = 1.00). The EP is a negative side effect of ketamine and is defined as a floating experience with distortions in body perceptions and objects that correlates with positive and negative symptoms of schizophrenia. They measured EP with the

Clinician-Administered Dissociative State Scale (CADSS), and found that 40% of patients experienced EP (Aroke et al., 2017).

#### 3.3.3. Mu-opioid receptor (OPRM)

Two studies assessed the *mu-opioid receptor (OPRM)* gene polymorphism rs1799971 (A118G) in patients with TRD.

The opioid receptor isoform (Asp40 variation) encoded by the *OPRM1* gene SNP A118G exhibits a threefold greater binding affinity for opioid ligands. Changes in receptor binding affinity for opioid ligands may result in higher positive reinforcement, which may lead to the development of opioid dependence. However, the function of the *OPRM1* mutation is controversial (Bart et al., 2005; Taqi et al., 2019).

Saad et al., conducted a randomized, double-blind, active-controlled, phase 3 clinical trial investigating the effect of *OPRM* gene polymorphism (rs1799971) on the antidepressant response to esketamine nasal spray in 406 patients with TRD (Saad et al., 2020). The antidepressant effect was assessed by the difference in the change in MADRS total score on day 2 and day 28. In the esketamine group, they did not detect any influence of genotype effects of A118G on overall total MADRS score reduction ($p = 0.52$) (Saad et al., 2020). A separate study that aimed to explore ketamine's anti-suicidal ideation and antidepressant effects, Grunebaum et al., performed a clinical trial in participants with and without a common *OPRM1* gene A118G SNP. The Beck Scale for Suicidal Ideation (SSI) was administered in 80 individuals with TRD who received 0.5 mg/kg IV ketamine at 24 h post-infusion. Depressive symptoms were assessed with the Profile of Mood States (POMS) and HDRS. The results did not indicate a treatment by genotype (AA vs. AG + GG) interaction effect on 24-h post-treatment scores for the SSI ($p = 0.554$), POMS ($p = 0.554$) depression subscale, HDRS- 17 ($p = 0.439$), or HDRS-24 ($p = 0.582$) (Grunebaum et al., 2020).

#### 3.3.4. Glutamate ionotropic receptor NMDA type subunit (GRIN)

*GRIN2B* polymorphism of *glutamate ionotropic receptor NMDA type subunit (GRIN)* gene was studied in one paper. Aroke et al., evaluated the association between *GRIN2B* and EP in 75 patients having minor elective outpatient surgeries. The result of this study showed no significant link between *GRIN2B* (rs1019385, rs1806191) and EP occurrence following ketamine administration ($p = 1.00$) (Aroke et al., 2017).

#### 3.3.5. Norepinephrine transporter (NET)

Liebe et al., conducted a double-blind, controlled, randomized, parallel-design trial on 68 healthy participants to investigate potential predictors of the cardiovascular response to single subanesthetic dose of ketamine. Blood pressure and heart rate were measured before and after 0.5 mg/kg IV ketamine injection. According to their data, the genotype of the *norepinephrine transporter (NET)*, gender, and baseline blood pressure were all variables that predicted greater treatment emergent hypertension after ketamine administration. *NET* rs28386840 [T] carriers attained maximum systolic blood pressure significantly earlier than [A] homozygous carriers following ketamine administration. Consequently, *NET* rs28386840 genotype was a factor that predicted increased cardiovascular sequelae after ketamine administration ($P = 0.030$) (Liebe et al., 2017).

#### 3.3.6. Genome-wide association studies

Chen et al., and Guo et al., conducted GWAS studies on 65 and 326 individuals with TRD, respectively (Chen et al., 2021; Guo et al., 2018).

Chen et al., genotyped 684,616 SNPs. For the GWAS on the antidepressant impact of ketamine infusion and the ketamine blood level, twelve ketamine-related genes including *BDNF, CYP2B6, NTRK2, MTOR, GRIN1, GRIN2A, GRIN2B, GRIN2C, GRIN2D, GRIN3A, GRIN3B,* and *GRINA* were chosen. Ten SNPs mapped to *NTRK2* (rs10868564, rs10217777, rs142580562, rs117155102, rs10868590), *GRIN2A* (rs16966731, rs34413887, rs35989240, rs11640755), and *BDNF* (rs2049048) and six SNPs mapped to *NTRK2* (rs10868590, rs1421001), *GRIN2A* (rs3852749), and *GRIN3A* (rs79965951, rs147984567, rs16923933) were significantly associated with the antidepressant effect of ketamine at 40 and 240 min after infusion ($p = 2.5*10–3$), whereas the SNP rs10868590, mapped to *NTRK2*, was significantly associated with treatment response to ketamine at both timepoints ($p = 8.3*10–3$). Eight SNPs mapped to *NTRK2* (rs77918527), *GRIN2B* (rs11055619, rs4764036, rs11055619, rs10845883, rs74809794), *GRIN3A* (rs79965951), and *CYP2B6* (rs117093559) were significantly associated with treatment response to ketamine over 2–6 days after infusion ($p = 8.9*10–3$). Three SNPs mapped to *GRIN2B* (rs11055643), *GRIN2D* (rs746075), and *GRIN3A* (rs79965951) were significantly associated with treatment response to ketamine on 14 days after infusion ($p = 8.1*10–3$). Moreover, five SNPs mapped to *NTRK2* (rs77918527) and *GRIN2B* (rs11055619, rs220595, rs4764036, rs10845883) were significantly associated with or at least equal to responses to ketamine over 2–5 days after infusion ($p = 2.7*10–3$) (Chen et al., 2021). Gua et al., conducted a GWAS study on 326 patients with TRD who received 0.5 mg/kg IV ketamine (Guo et al., 2018). The primary outcome measure was MADRS score, and dissociative side effects were assessed using the CADSS. This study applied genome-wide markers to investigate the role of genetic variants in predicting acute antidepressant response to ketamine.

Gue et al., examined the association of *SEC11A, KRASP1, OSBP2, MRPL 50P1, C18orf42, RASGRF2, ROBO2, C20orf196, FAM179A, FITM2, LINC00923* genes and ketamine antidepressant effect. *RASGRF2* encodes a calcium-regulated nucleotide exchange factor which coordinates the signaling of distinct mitogen-activated protein kinase pathways. The *SEC11A* gene encodes a member of the peptidase family which is linked to cell migration and invasion.

*KRASP1* is a pseudogenes of key cancer genes and *LINC00923* is an RNA Gene, affiliated with the lncRNA class. *OSBP2, MRPL 50P1* and *FITM2* encodes for proteins containing a pleckstrin homology (PH) domain and an oxysterol-binding region, mitochondria and family of proteins involved in fat storage, respectively. *C18orf42* and *C20orf196* encodes novel protein kinasebinding proteins. *ROBO2* encodes a transmembrane receptor for the slit homolog 2 protein that functions in axon guidance and cell migration. *FAM179A* encodes for *FAM179A* antibody (Guo et al., 2018; Böhni et al., 1988; Fernández-Medarde and Santos, 2011). *ROBO2* and *SPRED2* genes were identified as promising factors in the dissociation effects to ketamine. The results of the Gua et al., indicated no association between the aforementioned gene and ketamine antidepressant effect and treatment emergent adverse events (Guo et al., 2018).

## 4. Discussion

We systematically identified, reviewed, and evaluated 12 published studies which investigated the associations between allelic variants and treatment response and adverse effects of ketamine. Collectively, these studies examined the association of 18 genes with ketamine. *BDNF, CYP450,* and *OPRM* were the most studied genes, respectively.

The principal finding of our study was that *BDNF* with Val allele is linked to increased antidepressant and anti-suicidal effects of ketamine in patients with TRD in comparison with Met allele. This finding suggests that *BDNF* Met allele expression causes baseline synaptic deficiencies, which inhibit ketamine's synaptogenic and antidepressant effects (Liu et al., 2011). *BDNF* is required for neural plasticity and the antidepressant effect of ketamine. Ketamine raises the level of *BDNF* in the hippocampus, and ketamine-induced antidepressant effects are missing in *BDNF* null mice, suggesting that *BDNF* plays a role in the ketamine mechanism of action (Autry et al., 2011). Initially, Chen et al., reported no changes in *BDNF* levels between the brains of mice with the Met allele and those of Val/Val mice, despite the fact that the hippocampus volume of mice with the Met allele was substantially lower (Chen et al., 2006). The tropomyosin-related kinase B receptor and the p75 neurotrophin receptor (p75NTR) are activated by mature *BDNF* and *proBDNF*, respectively. As a result, disruptions in p75NTR signaling,

mediated by proBDNF with a Met allele, are likely to result in a lack of synaptogenic and antidepressant effects of ketamine (Hashimoto et al., 2010). However, additional research is needed to investigate this further. We also found that TRD patients who carried any Met allele require a higher dose of ketamine to achieve an antidepressant effect. The Met *BDNF* polymorphism can affect *BDNF* messenger RNA trafficking to dendrites, as well as incorrect protein folding and decreased binding of mature *BDNF* to its receptor TrkB, resulting in neuron function deficits (Tsai et al., 2010). Our research supports Hashimoto's hypothesis that Met/Met carriers may be resistant to ketamine's rapid antidepressant effects (Hashimoto et al., 2012). Hence, the therapeutic effect of ketamine may be decreased or prevented in individuals with depression who carry the Met allele. However, further investigation is needed to determine if higher doses of ketamine infusions are beneficial in individuals with TRD who are Met carriers.

A number of CYP450 enzymes have been identified that contribute to the metabolism of ketamine, in which *CYP2B6*6* allele was associated with treatment-emergent adverse effects of ketamine. Enzymes encoded by the *CYP2B6* gene predominantly metabolize ketamine to hydroxynorketamine (HNK). The *CYP2B6*6* allele is the most prevalent loss-of-function allelic variant of the *CYP2B6* gene and can decrease the intrinsic clearance of ketamine by up to 89% in human liver microsomes and 55% in cDNA-expressed *CYP2B6* protein, which may lead to increased adverse effect (McIntyre et al., 2020; Rong et al., 2018). Despite the *CYP2B6*6* allele, other *CYP2B6* genotypes including *CYP2B6*1, CYP2B6*5* and *CYP2B6*7* were not association with ketamine treatment-emergent adverse effects. This can be due to very low genotype frequencies which prevent a feasible analysis. Chen et al., reported the positive association of *CYP2B6* and antidepressant impact of ketamine (Chen et al., 2021). However, Zarate et al. did not find a significant association (Zarate et al., 2012). Other *CYP2* genotypes such as *CYP2A6, CYP2C9, CYP2C19, CYP3A4,* and *CYP3A5* were not associated with antidepressant effect of ketamine either. The pathophysiological influence of conditions including but not limited to obesity, inflammation, infection, diabetes, on the phenotypic expression of the *CYP2* gene might be one reason for the lack of connection. The foregoing diseases have an effect on CYP expression and activity, which can change drug metabolism and disposition (Cheng and Morgan, 2001). Furthermore, EP can be experienced by up to 55% of individuals given ketamine and can closely resemble schizophrenia and increases their risk of harm. To date, there is no evidence of the association between *CYPB6* and ketamine-induced dissociation. Nevertheless, future genetic investigations of ketamine's antidepressant effects and ketamine-induced EP metabolism should examine the influence of inflammatory indicators, diabetes management (glycosylated hemoglobin), obesity, and other systemic or metabolic factors (Aroke et al., 2017).

*OPRM* regulates dopamine pathways and is the major target of endogenous opioids and opioid analgesics. A118G is a functional variant of *OPRM* that has no significant impact on antisuicidal and antidepressant effects of ketamine, indicating that these effects of ketamine may not be opioid-related and be mediated by mu-opioid receptor activation (Taqi et al., 2019; Saad et al., 2020). However, Williams et al., suggested that ketamine's acute antidepressant or dissociative effects requires opioid system activation. Further studies are required to examine the role of opioids in ketamine's antidepressant effect (Williams et al., 2018). Furthermore, *GRIN* gene was associated with the rapid antidepressant effect of ketamine but not linked to EP occurrence. Glutamate is an endogenous agonist at the NMDA receptor. Abnormalities in the glutamine glutamate cycle in the communication between glia and neurons may be involved in the pathophysiology of depression (C. Zhang et al., 2014). Studies have demonstrated that *GRIN* appears to be associated with suicidality and treatment resistance. Gary et al. discovered that patients with suicidality have greater levels of *GRIN* gene expression than those without (A.L. Gray et al., 2015). The results of genetic research might corroborate the conclusions of clinical trials. A history of suicide attempts and severe treatment resistance, may be linked to a poor antidepressant response to ketamine infusion, implying that suicide-related genes like *GRIN2B* and disease severity–related genes like *GRIN2A, GRIN2B,* and *GRIN2C* are linked to the antidepressant response of ketamine (A.L. Gray et al., 2015; C. Zhang et al., 2014). The sympathetic nervous system is influenced by genetic polymorphisms in components of the noradrenergic system, such as *NET*, as evidenced by the link between *NET* and blood pressure.

People with a certain *NET* genotype (rs28386840) are more likely to develop essential hypertension (Li et al., 2013). *NET* polymorphism is also associated with increased cardiovascular complications following ketamine administration. However, it is unknown whether the cardiovascular adverse effects are primarily influenced by a peripheral increase of norepinephrine via *NET* inhibition or a central action of ketamine on noradrenergic or glutamatergic transmitter systems (Rong et al., 2018; Liebe et al., 2017).

To our knowledge, the present study is the most comprehensive review designed in a systematic manner to investigate the association of genetic variations and treatment response and adverse effects of ketamine. Notwithstanding, there are limitations which may affect interpretation of our results. Firstly, most of the included articles had small sample sizes and sample size of individuals with variants is often low and therefore may skew results. As this is still a relatively new research topic, the number of published articles is low. Also, most antidepressant studies last 6–12 weeks, most esketamine and ketamine studies are only 28 days. Future studies should aim to include larger and more representative samples of patients. Notwithstanding, the papers included were diverse in terms of study design, genes evaluated, and outcomes examined. Quantitative synthesis was not feasible owing to considerable heterogeneity amongst component studies in terms of study design and population.

## 5. Conclusion

The current systematic review summarizes the pharmacogenomics findings to date of ketamine. Over the next decade, as the period of personalized medicine develops, the barriers and costs of pharmacogenomic testing will continue to fall, and the incorporation of pharmacogenomics data into clinical treatment will likely become more common. Preliminary results reviewed herein suggest that pharmacogenomics might play a role in ketamine treatment in the future. However, more prospectively designed studies are needed to confirm or refute the gene-treatment connections revealed in the present literature and to find novel linkages that will allow for safer and more effective medication in individuals with chronic disorders. Additionally, evaluating the clinical utility of genetic testing for improving clinical outcomes will also be of great importance to justify clinical use with guiding ketamine treatment.

## Declaration of competing interest

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