Pharmacodynamic interactions between ketamine and psychiatric medications used in the treatment of depression: a systematic review

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Abstract

Background – The use of ketamine for depression has increased rapidly in the past decades. Ketamine is often prescribed as add-on to other drugs used in psychiatric patients, but clear information on drug-drug interactions is lacking. With this review we aim to provide an overview of the pharmacodynamic interactions between ketamine and mood stabilizers, benzodiazepines, monoamine oxidase-inhibitors (MAOIs), antipsychotics and psychostimulants.

Methods – MEDLINE and Web of Science were searched.

Results – Twenty-four studies were included. For lithium, no significant interactions with ketamine were reported. Two out of five studies on lamotrigine indicated that the effects of ketamine were attenuated. Benzodiazepines were repeatedly shown to reduce the duration of ketamine's antidepressant effect. For the MAO-inhibitor tranylcypromine, case reports showed no relevant changes in vital signs during concurrent S-ketamine use. One paper indicated an interaction between ketamine and haloperidol, two other studies did not. Four papers investigated risperidone, including three neuroimaging studies showing an attenuating effect of risperidone on ketamine-induced brain perfusion changes. Clozapine significantly blunted ketamine-induced positive symptoms in patients with schizophrenia, but not in healthy subjects. One paper reported no effect of olanzapine on ketamine's acute psychotomimetic effects.

Conclusion – Current literature shows that benzodiazepines and probably lamotrigine reduce ketamine's treatment outcome, which should be taken into account when considering ketamine treatment. There is evidence for an interaction between ketamine and clozapine, haloperidol and risperidone. Due to small sample sizes, different subject groups and various outcome parameters, the evidence is of low quality. More studies are needed to provide insight into pharmacodynamic interactions with ketamine.

Keywords: ketamine, depression, pharmacodynamic interactions

Introduction

Since 2000 the rapid and robust antidepressant effects of ketamine have been reported repeatedly (Han et al., 2016; Kishimoto et al., 2016). Ketamine is increasingly being used off label for the treatment of depression in the USA (Wilkinson and Sanacora, 2017) and at a slightly slower pace in Europe (López-Díaz et al., 2019), often as add on to other psychiatric medication. Furthermore, the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) recently approved intranasal S-ketamine for treatment resistant depression (TRD) in conjunction with an oral antidepressant and for depression with imminent risk of suicide (FDA, 2019; EMA, 2019). However, to date, there are no clinical practice guidelines recommending the use of S-ketamine in depression (López-Díaz et al., 2019; Malhi et al., 2021). The use of ketamine in clinical practice entails different challenges, one of them being the acute and bothersome psychotomimetic side effects such as anxiety, perceptual changes and dissociation (Krystal et al., 1994). In case of severe agitation or anxiety, clinicians may resort to benzodiazepines or antipsychotics as rescue medication (Kasper et al., 2020). Furthermore, strategies to maintain the antidepressant effects of ketamine are considered a major unmet need (Papakostas, 2020). Ketamine is often combined with other psychiatric drugs and continuation of this psychiatric pharmacotherapy has been proposed to prevent relapse, a strategy that is already proven effective after successful electroconvulsive therapy (ECT) (Sackeim et al., 2001). Since most patients for whom ketamine treatment is considered, are already being prescribed psychiatric drugs, knowledge on pharmacodynamic interactions is crucial.

Ketamine is a noncompetitive N-methyl-d-aspartate (NMDA) glutamate receptor antagonist. In addition, it shows affinity for multiple other receptors (Mathew and Zarate, 2016). Action at the μ, k, and σ receptors may contribute to its analgesic effects. Furthermore, there is inhibition at muscarinic and nicotinic receptors and activity as a cholinesterase inhibitor. Modulation of monoaminergic systems occurs via inhibition of reuptake transporters (dopamine, serotonine and noradrenaline) and via direct activity at the monoamine receptors (dopamine and serotonine). Inhibition of the NMDA receptor also leads to downstream enhancement of monoaminergic activity (Mathew and Zarate, 2016). The main mechanism of the antidepressive action is believed to stem from antagonism of the NMDA receptor on γ-aminobutyric acid (GABA) releasing interneurons. After a reduction in GABA inhibition, the pyramidal cells in the prefrontal cortex (PFC) release glutamate. This results in enhanced stimulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors,

activating a signalling cascade that raises neurotrophic factors and induces synaptic plasticity (Krystal et al, 1994; Mathew and Zarate, 2016). Modulation of brain areas induced by ketamine are most notably found in the subgenual anterior cingulate cortex, posterior cingulate cortex, PFC and hippocampus (Ionescu et al., 2018).

Many trials have studied the efficacy and safety of ketamine treatment as add on to regular antidepressant agents such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), bupropion, mirtazapine, etc. (Kishimoto et al, 2016; Kryst et al., 2020; Memon et al., 2020). However, other psychiatric drugs are also often used in combination with ketamine. The pharmacodynamic actions of ketamine may provide leads on how to optimize treatment. For instance, hypotheses on synergistic effects of ketamine and lithium through inhibition of glycogen synthase kinase 3 (GSK3) have been proposed (Ghasemi et al., 2010). On the other hand, it can be hypothesized that lamotrigine might influence the effects of ketamine by reducing glutamate transmission as a result of sodium channel blockage. Anecdotal evidence and personal experience suggest that in some patients, lamotrigine might counteract the antidepressant effects of ketamine. A case report by Ford et al. (2015) suggests that higher doses of benzodiazepines attenuate the antidepressant effect of ketamine. While previous data show that ketamine addition to regular antidepressants is safe and accelerates the antidepressant response (Arabzadeh et al., 2018; Hu et al., 2016), there are studies presenting enhanced monoamine levels in the rat brain effectuated by ketamine (Nishimura and Sato, 1999; Tso et al., 2004). Consequently, monoamine oxidase inhibitors (MAOIs) in combination with ketamine might increase heart rate and blood pressure or cause a serotonergic syndrome. Given the affinity of ketamine for monoamine receptors, interactions may also be expected for ketamine and antipsychotics or psychostimulants. The pharmacological interactions between ketamine and other psychiatric medications commonly used in patients with TRD have not been systematically reviewed.

The aim of this review is to systematically summarize current knowledge from human studies on combined use of ketamine with psychiatric drugs commonly prescribed to patients with depression.

Method

The electronic databases MEDLINE and Web of Science were searched on July 9, 2020 for studies that examined a pharmacodynamic interaction between ketamine and a psychiatric drug consisting of antidepressants, mood stabilizers, antipsychotics, benzodiazepine(-agonist)s or psychostimulants. Filters for English, Dutch and human studies were applied. The search strategy was built as follows: ('generic name' OR 'brand name') AND ('ketamine') including multiple generic and brand names for each drug. The search strategies can be found in the supplementary material (appendix 1).

We included human studies with a randomized controlled design. In case limited information from controlled trials was available (only 1 or no randomized controlled trials (RCTs)), we included studies with lower levels of evidence (post hoc analyses from controlled trials and open label studies). Furthermore, case reports were only included if they provided supporting evidence regarding an interaction between ketamine and psychiatric medication. Grey literature (e.g. conference abstracts) was included in the review. Studies that investigated the antidepressant effect of ketamine added to a regular antidepressant (except MAOIs) were excluded because the safety and additive antidepressant effect of ketamine has already been demonstrated irrefutably. Furthermore, studies investigating anesthetic doses of ketamine for induction or sedation were excluded. The references were imported in the reference manager Endnote. After removal of duplicates (Bramer et al., 2016), two reviewers (IB and BV) independently screened the titles and abstracts and full texts. Discrepancies were solved by discussion, if necessary, a third or fourth reviewer (JV or DT) assisted to come to an agreement. Systematic reviews were screened for studies that possibly met our criteria and were not found with the literature search. We selected information on the study design, sample size, population characteristics, details on the intervention, clinical outcomes and hypothesis on the mechanisms of action. The process is shown in figure 1. Joanna Briggs Institute's (JBI's) critical appraisal tools for RCTs, quasi-experimental studies and case reports were used for quality assessment of the included studies (JBI, 2020). This systematic review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

Results

Studies retrieved

In total 4887 studies were identified through database searching. Screening of the reference lists of systematic reviews did not result in any additional articles. Five additional papers were proposed during the review process of this manuscript. Deduplication resulted in 3845 articles. By screening titles and abstracts, 3723 studies were excluded and 1228 articles remained for full text assessment. Subsequently, 98 studies were excluded for the following reasons: anesthetic dosages (n = 20), other outcome measures (n = 22), other drugs than ketamine examined (n = 5), animal models (n = 12), a study design that does not allow conclusions on an interaction (n = 25), or for a combination of these reasons (n = 14). Finally, 24 studies met our eligibility criteria and were included in this systematic review (figure 1). The results of the quality assessment can be found in the supplementary material (appendix 2).

We included 2 RCTs on lithium and 7 studies on lamotrigine. Furthermore, we retrieved 1 case report, 3 post hoc analyses and a placebo controlled study on the interaction between ketamine and benzodiazepines. We found 2 case reports on concomitant use of ketamine and tranylcypromine. Three double blind, placebo controlled studies investigated an interaction with haloperidol. An interaction between risperidone and ketamine was studied in 4 articles (3 were already included for lamotrigine and these report on different outcome results from the same study). One RCT reported on an interaction between olanzapine and ketamine, and 3 on clozapine and ketamine. No studies were found investigating the concomitant use of ketamine with psychostimulants.

Lithium

Based on the mechanism of action of lithium and ketamine, one would expect synergistic effects in patients with depression. The study by Costi et al. (2019) included 42 patients with MDD who showed an antidepressant response to ketamine. Patients received 600-1200 mg of lithium or placebo in combination with 0.5 mg/kg intravenous (IV) ketamine. No significant difference was found on the Montgomery Åsberg Depression Rating Scale (MADRS) scores between the two groups. The study by Xu et al. (2015) investigated 0.5 mg/kg IV ketamine in 36 patients with bipolar TRD that were maintained on a therapeutic dose of lithium (plasma target level of 0.6-1.2 mEq/L) or valproate. Depressive symptoms improved significantly

after ketamine in both the lithium and valproate group and there were no significant differences between the two mood stabilizers. Taken together, lithium did not seem to potentiate ketamine's antidepressant effect in patients with depression.
[Table 1]

Lamotrigine

Since lamotrigine reduces glutamatergic activity, an impeding interaction with ketamine can be hypothesized. Seven studies reported on the effects of 300 mg lamotrigine prior to IV ketamine administration in dosages ranging from 0.12 – 0.5 mg/kg. Except from the study of Mathew et al. (2010) which included patients with MDD, these studies investigated the effects in healthy subjects (Doyle, 1990; Anand et al., 2000; Deakin et al., 2008; Joules et al., 2015; Shcherbinin et al., 2015; Abdallah et al., 2017). Lamotrigine did not block the ketamine-induced psychotomimetic effects measured by the Brief Psychiatric Rating Scale (BPRS) and Clinician-Administered Dissociative States Scale (CADSS) in the study by Abdallah et al. (2017). Anand et al. (2000) reported that pretreatment with lamotrigine in healthy subjects showed a significant reduction in ketamine-induced Hopkins Verbal Learning Test (HVLT) impairment and a significant decrease in ketamine-induced symptoms measured by the CADSS and BPRS scores. They found an increasing effect on mood elevation after ketamine measured by the Young Mania Rating Scale (YMRS) with lamotrigine. Mathew et al. (2010) observed no attenuated psychotomimetic effects in patients with MDD randomized to lamotrigine prior to ketamine. Deakin et al. (2008) recorded a significant reduction in ketamine-induced total CADSS and BPRS scores when pretreated with lamotrigine. Furthermore, areas showing blood oxygenation level- dependent (BOLD) responses to ketamine assessed by pharmacomagnetic resonance imaging (phMRI) revealed greater responses after placebo infusion than after lamotrigine infusion. In addition, a trial by Doyle et al. (2013) reported that lamotrigine administration resulted in a relatively consistent attenuation of the BOLD response in frontal and thalamic regions effectuated by IV ketamine. Joules et al. (2015) and Shcherbinin et al. (2015) (reporting other outcomes from the same study as Doyle et al.) found no interaction between lamotrigine and ketamine on the degree-centrality pattern and resting state brain perfusion. To summarize, the studies on lamotrigine seem to confirm an antagonistic interaction with ketamine, but the relevance for clinical outcomes is still unclear.
[Table 2]

Benzodiazepines

Ford et al. (2015) suggested that benzodiazepines could attenuate the action of ketamine in their case of a patient with bipolar disorder who experienced a severe episode of depression with no response to several antidepressants and antipsychotics. He was treated with lorazepam and responded to repeated doses of ketamine (0.5 mg/kg IV). The antidepressant response was prolonged from 2-3 days to 10-14 days after lorazepam (3.5 mg per day) was withdrawn.

In addition to this case report, we found four papers reporting on an interaction between ketamine and benzodiazepines. In a post hoc analysis of an open label study with patients with TRD, Albott et al. (2015) found no significant difference between four benzodiazepine users (mean daily dose 2.75 mg lorazepam equivalents) and 9 non-users in depression response rate (MADRS score $\leq$ 50%), remission (MADRS $<$ 10) or depression relapse (MADRS $\geq$ 50% of baseline) after ketamine infusions (0.5 mg/kg/40min). However, benzodiazepine users showed a significant longer time to antidepressant response ($p = 0.029$), longer time to depression remission ($p = 0.042$) and a shorter time to depression relapse ($p = 0.020$). In a post hoc analysis of Frye et al. (2015), benzodiazepines gave no significant difference in response rate in 10 patients with TRD. Nevertheless, they found that the mean benzodiazepine dose (0.75 mg lorazepam equivalents) was significantly lower ($P = 0.026$) in the responder group (response $\geq$ 50% reduction in MADRS scores) than in the non-responder group (3 mg). Andrashko et al. (2019) presented an analysis of two randomized controlled cross-over trials with 47 patients with MDD. This study found a significant difference in benzodiazepine dosage between responders (response $\geq$ 50% reduction in MADRS scores) and non-responders. Logistic regression analysis showed that benzodiazepine medication (10 mg and more in diazepam equivalent) after ketamine infusion of 0.54 mg/kg predicted nonresponse anytime during one-week follow-up (odds ratio = 1.5, $p = 0.0445$). In a study of Krystal et al. (1998), lorazepam 2 mg reduced emotional distress and it tended to reduce distorted sensory perceptions associated with ketamine infusion (0.26 mg/kg bolus, followed by 0.65 mg/kg/hour) in 30 healthy subjects. It also reduced the inability to produce a proverb interpretation, perhaps an indication of reduced thought blocking. However, it failed significantly to block psychotogenic, perceptual, cognitive, neuroendocrine and physiological ketamine responses. In conclusion, these studies indicate that higher doses of benzodiazepines can delay the time to response and remission and shorten the antidepressant effects of ketamine. Furthermore, higher doses of benzodiazepines predicted nonresponse.

[Table 3]

Tranylcypromine

No reports were found that confirmed the hypothesized risk of hypertensive crisis or serotonergic syndrome caused by the combination of MAOIs and ketamine. We retrieved two case reports about patients with depression receiving tranylcypromine in dosages ranging from 10-80 mg daily in combination with S-ketamine (Bartova et al., 2015; Dunner et al., 2019). Two patients were administered intravenous (IV) S-ketamine (dosages 12.5-75 mg) while the other patient received intranasal (IN) S-ketamine (dosages 28-56 mg). No relevant cardiovascular or hemodynamic changes were observed.

[Table 4]

Haloperidol

Even though the clinical impact in humans remains unknown, ketamine has shown dopamine enhancing effects in vitro. The dopamine D_2 receptor antagonist haloperidol might therefore interact with ketamine's effects. Krystal et al. (1999) reported that in 35 healthy subjects, impairments in executive cognitive functions (assessed with the Wisconsin card sorting test (WCST) and the Gorham's Proverb's test) produced by ketamine infusion, bolus of 0.26 mg/kg followed by 0.65 mg/kg per hour, were reduced by haloperidol pretreatment (5 mg). In addition, haloperidol reduced the anxiogenic effects and increased the sedative and prolactine responses to ketamine.

The study of Oranje et al. (2009) found an improving effect of 2 mg of oral haloperidol on ketamine-induced (0.3 mg/kg IV) reduction of processing negativity ($p < 0.05$) in 18 healthy male subjects. Processing negativity is a negative deflection in the event-related potential (ERP), representing the ability to focus on one source of information, when multiple sources of information are present.

Lahti et al. (1995) found that a fixed high dose of haloperidol (0.3 mg/kg/day) did not blunt ketamine-induced psychosis in 9 patients with schizophrenia receiving ketamine (injections of 0.1, 0.3 and 0.5 mg/kg) while on and off haloperidol. In fact, the patients experienced greater increases in psychosis ratings after ketamine administration during haloperidol treatment when compared to a drug free period. Interestingly, ketamine did not produce a significant worsening in the latter group. In summary, some acute effects of ketamine

(impairments in executive cognitive functions and anxiogenic effects) were reduced by haloperidol pretreatment whereas no blunting of ketamine-induced psychosis was achieved with haloperidol in schizophrenic patients.
[Table 5]

Risperidone

The strong antiserotonergic and antidopaminergic effects of risperidone might counteract ketamine's monoaminergic enhancement. For the combined use of risperidone and ketamine, we found three phMRI studies and one study investigating oculomotor performance. Schmechtig et al. (2013) reported no effect of 2 mg of risperidone on ketamine-induced (IV targeted to a concentration of 100 ng/ml) eye movement changes. In the study of Doyle et al. (2013) in healthy subjects, analysis of different regions of interest (ROI) revealed significant positive and negative BOLD responses to ketamine infusion (targeted to a plasma level of 75 ng/ml). Risperidone 2 mg attenuated the ketamine effect across most ROIs, including the medial prefrontal and cingulate regions and the thalamus. For the negatively responding regions in the subgenual cingulate and ventromedial prefrontal cortex, risperidone strongly attenuated the negative BOLD response. In the same sample, Joules et al. (2015) found that ketamine increased the degree centrality (DC), defined as the number of links incident upon a node in phMRI. Risperidone pre-treatment significantly modulated the ketamine-induced centrality changes in 20 healthy males. Shcherbinin et al. (2015) performed an analysis of resting brain perfusion in the same subjects. Ketamine showed positive weights (post-ketamine > pre-ketamine) in prefrontal and cingulate regions, thalamus and lateral parietal cortex in comparison with pre-ketamine in phMRI, with strongest negative contributions in the occipital lobes. Pretreatment with risperidone significantly increased the ketamine-induced perfusion changes ($p < 0.02$). To summarize, an interaction between ketamine and risperidone was found based on brain perfusion changes in imaging studies but no clinical studies have yet investigated whether this would also result in an attenuation of the antidepressant effects.
[Table 6]

Clozapine

Clozapine has a wide spectrum of pharmacological actions, including blockade of the dopamine D_1- and serotonergic 5-hydroxytryptamine $(5\text{-HT})_2$ receptors. Hypotheses on possible interactions are not straightforward. Lipschitz et al. (1997) showed that clozapine 50

mg pretreatment before 0.5 mg IV ketamine did not reduce the BPRS 5 key positive or 3 key negative scores in 7 healthy subjects, but there was a trend for a reduction in perceptual alteration as measured by the CADSS ($p = 0.09$). Clozapine in a mean dose of 430 mg a day for several weeks significantly blunted the positive symptoms induced by ketamine in 10 patients with schizophrenia, but not the negative symptoms as reported by Malhotra et al. (1997). An imaging study (Vollenweider et al., 2012) with 20 healthy subjects shows that a low dose of clozapine (30 mg oral) reduced some of the S-ketamine (0.006 mg/kg/min) responses. The results of these three studies are inconsistent on interactions between ketamine and clozapine.

[Table 7]

Olanzapine

The antagonistic effects of olanzapine on serotonin and dopamine receptors might cause an interaction with ketamine. One paper studied an interaction between olanzapine and ketamine. Lahti et al. (1999) investigated ketamine administration (0.3 mg/kg) in 5 healthy subjects treated with a low dose of 5 mg olanzapine and an unknown number of schizophrenic patients treated with 10 mg. They found no difference in blocking ketamine-induced psychotic symptoms between olanzapine and placebo.

[Table 8]

Discussion

This review summarizes currently available information on interactions between ketamine and other psychiatric drugs, derived from human studies investigating clinical, neuroimaging and electrophysiological outcomes. Knowledge on potentiating and antagonistic interactions are of utmost importance for the optimization of ketamine treatment for depression.

Mood stabilizers

We found no evidence for interactions between lithium and ketamine, nor for the hypothesis that lithium would strengthen the antidepressant effect through inhibition of GSK3. Three studies (Anand et al., 2000; Deakin et al., 2008; Doyle et al., 2013) reported attenuating effects of lamotrigine pretreatment on ketamine-induced effects on the BPRS, dissociative symptoms and BOLD responses. As lamotrigine reduces glutamate transmission by sodium channel blockage, these ketamine responses are thought to result from an increase in glutamatergic activity. Four other studies (Mathew et al., 2010; Joules et al., 2015;

Shcherbinin et al., 2015; Abdallah et al., 2017) did not confirm the interaction. This might be explained by differences in dose or infusion speed of ketamine, or differences in drug metabolism and functional brain characteristics between TRD patients and healthy controls could contribute to the contrasting results. Interestingly, Anand et al. (2000) described an increasing effect on mood elevation in healthy subjects. These participants may have benefitted from the decrease of dissociative, psychiatric and learning impairment symptoms which could have resulted in increased awareness of mood elevating effects. This however could reflect a different mechanism than antidepressant effects in patients with depression.

Benzodiazepines

All papers reporting on benzodiazepines in combination with ketamine indicate an interaction. This could be the result of GABA-receptor agonism by benzodiazepines. By increasing the inhibitory tone of GABAergic interneurons, benzodiazepines might decrease excitatory glutamatergic signal transduction and attenuate the antidepressant effects of ketamine. Moreover, an animal study (Eintrei et al., 1999) has shown a ketamine-induced enhanced metabolism in the limbic system, and this action is selectively blocked by administration of diazepam. Ketamine-induced dopamine release was similarly blocked by diazepam as reported by another animal study (Irifune et al., 1998).

MAOIs

Both included case reports on S-ketamine in combination with tranylcypromine correspond to previous literature stating no relevant cardiovascular or hemodynamic changes (Doyle, 1990; Bartova et al., 2015; Dunner et al., 2019). Also, no serotonergic syndrome has been reported in the combination of MAOIs and ketamine, but clinical experience is limited. An increase in monoamines is probable not the most relevant pharmacodynamic effect of ketamine.

Antipsychotics

An interaction with the dopamine D_2 receptor antagonist haloperidol can be expected because ketamine shows modest activity at the dopamine transporter at subanesthetic doses. Two studies in healthy subjects reported a reduction in ketamine induced effects (impairments in executive cognitive functions, anxiogenic effects and processing negativity) with haloperidol pretreatment. This implies that these effects of ketamine are caused by its (direct or indirect) agonistic effect on dopaminergic D_2 receptor activity. The only study investigating schizophrenic patients on and off a high dose of haloperidol did not find blunting effects on

ketamine-induced psychosis. These results suggest that the mechanism by which ketamine causes psychotic symptoms, is not affected by D_2 blockade.

We found no studies investigating the effects of an interaction between risperidone and ketamine on the clinical antidepressant effect or side effects. Risperidone had no effect on ketamine-induced changes in eye movements, which are biomarkers in drug development and the evaluation of treatment effects (Sweeney et al., 1998; Levy et al., 2010). However, three imaging studies showed attenuating effects of risperidone on ketamine's brain perfusion changes in healthy subjects (Doyle et al., 2013; Joules et al., 2015; Shcherbinin et al., 2015). The opposing effects of ketamine and risperidone at the D_2 receptor, similar to the interaction with haloperidol, may play a role here. Furthermore, 5-HT_{2A} receptor antagonism by risperidone might also mitigate the effects of ketamine. Although no clear conclusions can be drawn from these case reports, a few examples of concomitant ketamine and risperidone use in patients with depression suggest that use of risperidone does not attenuate ketamine's antidepressant effects in doses of 1 - 4 mg/day (Zigman and Blier, 2013; López-Díaz et al., 2017; Zheng et al., 2018).

The results of three studies investigating clozapine and ketamine were inconsistent. No significant interaction was reported in the study investigating a low dose of clozapine (50mg) on ketamine's effects on the BPRS and CADSS in healthy subjects. On the other hand, an even lower dose of 30 mg clozapine did reduce some of the S-ketamine responses on neuroimaging outcomes. Furthermore, a higher dose of clozapine (mean 430 mg) did alter ketamine's positive symptoms in patients with schizophrenia. The differences in subject characteristics, dosages and ketamine formulation (racemic vs. S-ketamine) are reason to compare and interpret the results with caution. Dose-response studies with clozapine show that doses of at least 300-600 mg/day are required to achieve a therapeutic response in patients (VanderZwaag et al., 1996; Simpson et al., 1999). Clozapine is a relatively weak antagonist at striatal dopamine D_2-receptors, and produces a more potent blockade of central dopamine D_1-, cholinergic, serotonergic $5HT_2$-, histamine H_1-, and adrenergic α_1- and α_2-receptors (Fitton and Heel, 1990).

One paper found no blocking of ketamine induced psychotic symptoms with olanzapine, which corresponds to the results with haloperidol but is in contrast with higher doses of clozapine. Some evidence from uncontrolled trials suggests that concomitant use of

olanzapine may attenuate the antidepressant effects of ketamine or S-ketamine. One patient with TRD receiving olanzapine 10 mg (in addition to lithium, mirtazapine and zopiclone 11.25 mg) did not achieve response or remission (Hamilton Depression Rating Scale scores decreased from 19 to 11) after six infusions 0.25 mg/kg S-ketamine (Segmiller et al., 2013). The open label study of Zheng et al. (2018) reports olanzapine use (2.5 – 20 mg/day) in 22.7% of responders and 25.8% of nonresponders to six ketamine infusions of 0.5 mg/kg in patients with depression. It should be noted that other causes of reduced antidepressant effect cannot be excluded in these reports.

Limitations

The present study should be interpreted in the light of some limitations. First, our review contains multiple conference abstracts (N = 4) that have not been published in peer reviewed full text. Second, the studies have small sample sizes, ranging from 1 – 72 subjects. As the different outcomes in patients and healthy subjects of the clozapine studies show, the underlying mechanism of the interaction may be different in patients than in healthy subjects. In addition, there may be a concentration dependent effect regarding interactions. Many studies included in this review used ketamine as a model for psychosis. In these studies, the focus is not necessarily on exploring an interaction with respect to the antidepressant effect of ketamine. Furthermore, results were based on various intervention methods (racemic vs. S-ketamine and different dosages, intermittent/bolus administration vs. continuous infusion), and outcome measures which complicates comparison of the trials. Finally, the case reports gave new insights but have to be interpreted with great caution due to limited generalizability.

Conclusion

In conclusion, this systematic review provides new insights for the clinical practitioner. The pharmacodynamic interactions between ketamine and generally prescribed psychiatric drugs were analyzed based on published evidence. The literature provided no reports of an interaction between lithium and ketamine. Some but not all studies on lamotrigine provided evidence for attenuation of ketamine-induced effects. Based on available literature it is very likely that benzodiazepines shorten the duration of ketamine's antidepressant effects. This should be taken into account when considering ketamine treatment. In addition, several cases suggested that no relevant changes in vital signs occurred when ketamine was combined with the MAOI tranylcypromine. There are indications for an interaction between the

antipsychotic drugs haloperidol, risperidone and clozapine but not evidently for olanzapine in combination with ketamine. No information was found yet about ketamine's possible interactions with psychostimulants.

Clinical implications and future directions

Clinical practitioners should be aware of possible drug-to-drug interactions when prescribing ketamine. To optimize treatment effects, we would recommend minimizing benzodiazepine (and Z-drug) use in patients receiving ketamine for depression. Furthermore, a possible interaction with lamotrogine should be considered when patients show a lack of response to ketamine during concomitant lamotrigine use. We believe prescribing ketamine as add-on to lower doses of MAOI is possible but only with careful monitoring of vital signs.

For future studies, we recommend trials focusing on the antidepressant efficacy and side effects of the combination of ketamine and psychiatric drugs in patients with depression. It would for instance be worthwhile to investigate whether lower doses of benzodiazepines, or temporary benzodiazepine withdrawal before ketamine administration, could prevent an efficacy attenuating interaction. Additional research on the safety of combining ketamine and MAOIs is warranted. Furthermore, we suggest that researchers and clinicians systematically record and report the use of co-medication in ketamine trials to detect possible interactions.

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Author contributions

JKEV: provided the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, revised it critically for important intellectual content, final approval of the version to be submitted and agreement to be accountable for all aspects of the work.

SYSA: interpretation of data, critical revision for important intellectual content, final approval of the version to be submitted and agreement to be accountable for all aspects of the work

IMB: acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted and agreement to be accountable for all aspects of the work

BAEV: acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted and agreement to be accountable for all aspects of the work

JK: interpretation of data, critical revision for important intellectual content, final approval of the version to be submitted and agreement to be accountable for all aspects of the work

RAS: interpretation of data, critical revision for important intellectual content, final approval of the version to be submitted and agreement to be accountable for all aspects of the work

DJT: provided the conception and design of the study, analysis and interpretation of data, critical revision for important intellectual content, final approval of the version to be submitted and agreement to be accountable for all aspects of the work.

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Table 1. Lithium

Source: 1st author, year	Study design	Number of subjects (males)	Population	Drug, dosage, route of administration, time interval with ketamine administration	Ketamine dosage, route of administration and duration	Clinical outcome	Possible mechanism of interaction
Costi et al. (2019)	Randomized, double blind, placebo controlled trial	42, 34 completed the study (16)	Patients with a diagnosis of MDD of at least moderate severity (QIDS-SR score ≥14) with recurrent or chronic MDD, an average MADRS score of 32 and failed to respond to ≥2 lifetime AD trials. Only patients who showed an AD response to ketamine were included.	Lithium 600-1200 mg oral[a,b], or placebo	Ketamine 0.5 mg/kg IV for 40 min	There was no significant difference on the MADRS scores between lithium and placebo in combination with ketamine.	No synergistic AD effect of lithium in combination with ketamine described.
Xu et al. (2015)	Randomized, double blind, placebo controlled, crossover trial	36 (15)	Patients with bipolar TRD and a MADRS score ≥20. They were all maintained on therapeutic doses of lithium or valproate.	Lithium blood target level 0.6-1.2 mEq/L[a,b,c], or valproate	Ketamine 0.5 mg/kg IV in 40 min	Both lithium and valproate significantly improved depressive symptoms, but no statistically significant difference was observed between the mood stabilizers. Serum lithium and valproate levels did not correlate with ketamine's AD efficacy.	Although the study was potentially underpowered, the results suggest that ketamine may not potentiate the AD efficacy of lithium and valproate in bipolar TRD.

a time interval uncertain
b dosage adjusted to a target blood level in the range of 0.6–0.9 mEq/L
c route of administration not reported

AD = antidepressant; **IV** = intravenous; **MADRS** = Montgomery-Asberg Depression Rating Scale; **MDD** = major depressive disorder; **QIDS-SR** = Quick Inventory of Depressive Symptomatology - Self Report; **TRD** = treatment resistant depression.

Table 2. Lamotrigine

Source: 1st author, year	Study design	Number of subjects (males)	Population	Drug, dosage, route of administration, time interval with ketamine administration	Ketamine dosage, route of administration and duration	Clinical outcome	Possible mechanism of interaction
Abdallah et al. (2017)	Randomized, double blind, placebo controlled crossover trial	18 (18)	Healthy subjects	Lamotrigine 300 mg oral, or placebo, about 2 hours prior to ketamine[a]	Ketamine 0.23 mg/kg IV in 2 min followed by 0.58 mg/kg for approximately 70 min	Ketamine significantly increased BPRS and CADSS scores but pretreatment with lamotrigine had no significant effect on the ketamine-induced increases in BPRS and CADSS scores. Lamotrigine significantly reduced the ketamine-induced GBCr surge in clusters of the bilateral dorsomedial and left frontolateral prefrontal cortex. Significantly higher GBCr was found in the vPFC of TRD patients compared to healthy controls. Ketamine did not significantly reduce vPFC GBCr in TRD subjects but it did reduce vPFC GBCr in healthy subjects. Following pretreatment with lamotrigine, ketamine showed no significant effects on the GBCr in the vPFC.	The inhibition of glutamate transmission reduces GBCr in the prefrontal cortex. Ketamine induces the glutamate level and so increases the GBCr in the prefrontal cortex. The glutamate release inhibitor lamotrigine reduces the glutamate level induced by ketamine and so reduces the GBCr and attenuates the effect of ketamine.

Anand et al. (2000)	Randomized, double blind, balanced order trial	19, 16 completed the study (8)	Healthy subjects	Lamotrigine, 300 mg, oral, 2 hours prior to ketamine	0.26 mg/kg IV in 1 min followed by 0.65 mg/kg for 90 min	Lamotrigine led to an increase in ketamine-induced mood elevation (measured by YMRS). It led to a decrease in ketamine-induced impairment of learning a wordlist (measured by HVLT) and dissociative symptoms (measured by CADSS score. There was also a significant decrease in ketamine-induced positive and negative symptoms (measured by BPRS symptom score).	Lamotrigine may reduce the hyperglutamatergic consequences of NMDA receptor dysfunction implicated in the pathophysiologic processes of neuropsychiatric illnesses. It decreases the glutamate release by blocking sodium channels and so reduces the increased glutamate levels effectuated by ketamine.
Deakin et al. (2008)	Randomized, double blind, placebo controlled, crossover, counterbalanced-order trial	21 (21), 19 completed the study	Healthy right-handed subjects	Lamotrigine, 300 mg, oral, 2 hours prior to ketamine	0.26 mg/kg IV in 1 min followed by 0.25 mg/kg/hb	After ketamine infusion with lamotrigine pretreatment, the BPRS total, thought disorder, activation and hallucinations scores were significantly lower. Similarly, the CADSS total, derealization and depersonalization scores were significantly lower. Several areas showing BOLD signal responses to ketamine in the ketamine-placebo experiment also showed significantly greater respons to ketamine after placebo infusion than after lamotrigine infusion.	The effects of ketamine are mediated by enhaned glutamate release. The glutamate system is being challenged by ketamine through an upstream effect of glutamate on the neural activity and this is being isolated by the glutamate inhibitor lamotrigine.

Mathew et al. (2010)	Randomized, double blind, placebo controlled continuation trial	26 (16)	Medication free patients with a diagnosis of MDD (chronic and/or recurrent), of at least moderate severity, >32 on the IDS-C30 and insufficient response to >2 adequate AD trials in the current episode.	Lamotrigine 300 mg oral, or placebo, 2 hours prior to ketamine infusion	Ketamine 0.5 mg/kg IV for 40 min	Lamotrigine failed to attenuate the mild, transient side-effects associated with ketamine. There was no difference detected in MADRS scores and no differences on BPRS positive symptoms between lamotrgine and placebo treatment groups. Besides that, also no difference in CADSS scores was found.	No interaction reported beween ketamine and lamotrigine.

Doyle et al. (2013)	Randomized, double blind, placebo controlled, crossover trial	20 (20), 16 completed the study	Healthy subjects	Lamotrigine 300 mg oral, or placebo, 4.75 hours prior to ketamine	Ketamine 0.12 (mean) mg/kg IV in 1 min followed by approximately 0.31 mg/kg/hb,c	A significant BOLD response was revealed to ketamine infusion including positive and negative responses. For the positively responding regions (frontal and thalamic regions), pretreatment with lamotrigine resulted in a relatively consistent attenuation of the ketamine responses. For the negatively responding regions (subgenual cingulate and ventral medial prefrontal cortex) the attenuating effect of lamotrigine was weak. The pretreated (lamotrigine) scans were dissimilar to the placebo scans. Pretreatment with lamotrigine resulted in no significant effect of ketamine on the alert-drowsy scale, whereas significant differences remained for the muzzy-clear scale.	Lamotrigine produces a widespread inhibition of the relative blood volume response and produces a global attenuation of this positive ketamine response with downstream effects resulting in inhibition of glutamate release and reduce the ketamine-induced changes in BOLD signal.

Joules et al. (2015)	Randomized, double blind, placebo controlled, crossover trial	20 (20), 16 completed the study Same sample as Doyle et al. (2013) and Shcherbinin et al. (2015)	Healthy subjects	Lamotrigine 300 mg oral, or placebo, 4.75 hours prior to ketamine	Ketamine 0.12 (mean) mg/kg IV in 1 min followed by approximately 0.31 mg/kg/hb.c	It was not possible to discriminate lamotrigine from placebo suggesting similar patterns of degree-centrality. There was no supportive evidence of a significant modulation effect of the ketamine-induced degree-centrality pattern by lamotrigine.	No interaction reported between ketamine and lamotrigine. Pre-treatment with lamotrigine does not alter the ketamine-induced functional connectivity pattern. This suggests that the observed changes in connectivity are more likely a result of NMDA receptor blockade and possible serotonergic modulation rather than purely modulation of glutamate release.
Shcherbinin et al. (2015)	Randomized, double blind, placebo controlled, crossover trial	20 (20), 16 completed the study Same sample as Doyle et al. (2013) and Joules et al. (2015)	Healthy subjects	Lamotrigine 300 mg oral, or placebo, about 2,5 hour prior to ketaminea	Ketamine 0.12 (mean) mg/kg IV in 1 min followed by approximately 0.31 mg/kg/hb,c	The lamotrigine condition was not distinguished from placebo for post-infusion scans. Lamotrigine had no significant effect on resting brain perfusion.	No clear interaction of lamotrigine in combination with ketamine on brain perfusion described.

a time interval uncertain
b total duration of infusion not reported
c dosage adjusted to a target plasma level of 75 ng/ml in accordance with the subject's height and weight
d route of administration not reported

AD = antidepressant; **BOLD =** blood oxygenation level- dependent; **BPRS =** Brief Psychiatric Rating Scale; **CADSS =** Clinician-Administered Dissociative States Scale; **GBCr =** global brain connectivity with global signal regression; **HVLT** = Hopkins Verbal Learning Test; **IDS-C_{30}** = Inventory of Depressive Symptomatology - Clinician Rated; **IV** = intravenous; **MADRS** = Montgomery-Asberg Depression Rating Scale; **MDD** = major depressive disorder; **NMDA** = N-methyl-D-aspartate; **TRD** = therapy resistant depression; **vPFC** = ventral prefrontal cortex; **YMRS =** Young Mania Rating Scale.

Table 3. Benzodiazepines

Source (1st author, year)	Study design	Number of subjects (males)	Population	Drug, dosage and route of administration	Ketamine dosage, route of administration (and duration)	Clinical outcome	Possible mechanism	Remarks
Ford et al. (2015)	Case report	1	Patient with BD, experiencing a severe prolonged episode of depression, with no response to several antidepressants and antipsychotics	Lorazepam, 3.5mg per day (lorazepam was not taken every morning). Fixed dose of lithium, fluoxetine and quetiapine.	Ketamine IV, 10 infusions of 0.5mg/kg	The response to the first two infusions extended over 2–3days. Subsequent infusions produced responses of no more than 24hours. After lorazepam was withdrawn the duration of the response to ketamine extended from several days to 10–14days.	In animals administration of ketamine causes increased metabolism in the limbic system and this action is selectively blocked by administration of diazepam. Ketamine-induced dopamine release is similarly blocked by benzodiazepines.	
Krystal et al. (1998)	Randomized, double blind placebo controlled trial	30 (23 completed the study)	Healthy subjects	Lorazepam, 2 mg oral or matched placebo 2 hours prior to infusion	Ketamine IV, bolus of 0.26 mg/kg followed by an infusion of 0.65 mg/kg per hour or saline infusion	Lorazepam did not significantly alter ketamine-induced BPRS positive symptoms. Lorazepam failed to block psychotogenic, perceptual, cognitive, neuroendocrine and physiologic ketamine responses as measured with the BPRS, VAS, CADSS and the WCST. It reduced emotional distress (BPRS) and it tended to reduce distorted sensory perceptions associated with ketamine infusion (CADSS). It also reduced the inability to produce a Gorham's Proverb interpretation. Ketamine sedative effects and amnestic actions were intensified by lorazepam.	NMDA antagonists reduce GABAergic inhibition in the cortex and the septum. In addition, benzodiazepine pretreatment reduces NMDA antagonist stimulation of frontal cortical dopamine turnover and cortical metabolism. They also weakly inhibit NMDA antagonist neurotoxicity. However, other data question the significance of subanesthetic ketamine effects on GABA function. For example, subanesthetic doses of NMDA antagonists have modest effects on GABA synthesis and metabolism may reduce GABA reuptake and they maintain extracellular GABA levels in the frontal cortex.	
Albott et al. (2017)	Post hoc analysis of an open label study	13 (4 with benzodiazepines)	Patients with TRD (defined as failure to achieve remission from 2 adequately dosed antidepressants of different	Benzodiazepines (mean daily dose = 2.75 mg lorazepam equivalents) vs no use of benzodiazepines	Ketamine IV, six infusions of 0.5 mg/kg over 40 min thrice weekly during 12 days	There was no statistically significant difference between benzodiazepine users and benzodiazepine nonusers in depression response rate or remission rate or in depression relapse rate during the 28-day	One hypothesis suggests that ketamine modulates NMDARs on inhibitory GABAergic interneurons that exert tonic suppression of excitatory glutamatergic networks. By blocking NMDARs on these	

			pharmacologic classes per the ATH)			follow-up period. However, benzodiazepine users showed a significantly longer time to antidepressant response (P = .029), a significantly longer time to depression remission (P = .042), and a significantly shorter time to depression relapse (P = .020).	interneurons, ketamine decreases inhibition, resulting in a burst of glutamate, signaling through AMPA-receptor, and up-regulation of neuroplasticity-related transcription factors. Consistent with this model, agonism of the GABA-A receptor (as occurs with benzodiazepines) would increase inhibitory tone of these interneurons, thereby decreasing excitatory glutamatergic signal transduction and blocking the therapeutic effects of ketamine.	
Andrashko et al. (2019)	Analysis of two consecutive randomized, placebo controlled, cross-over trials	47 (13 benzodiazepine users)	Patients with MDD, MADRS ≥ 20, ≥1 prior non-response to antidepressant treatment in current episode, on a stable dose of antidepressants minimum four weeks prior to admission	Benzodiazepines in doses higher than 10 mg diazepam equivalent pro die vs. no use of benzodiazepines	Ketamine IV, infusion 0.54 mg/kg	The benzodiazepine dosage between responders and nonresponders (≥10 mg diazepam equivalent in 12 patients from the responders group vs. 1 patient in the responders group, was significantly different. Logistic regression revealed that concomitant benzodiazepine medication predicted nonresponse anytime during one-week follow-up after ketamine infusion (Odds ratio = 1.5; p = 0.0445).	No hypothesis described.	Conference abstract.
Frye et al. (2015)	Post-hoc analysis of an open label study	10	Patients with TRD (defined as a major depressive episode as part of either major depressive disorder (recurrent or single episode) or BD II and refractory to at least two antidepressant medication trials in the current episode of depression)	Glutamatergic drugs (carbamazepine, lamotrigine or divalproex sodium) vs. GABAergic drugs (benzodiazepines, gabapentin)	Ketamine IV, four infusions 0.5 mg/kg over 100 min. Infusions were administered twice weekly	There was no significant difference in percentage of patients on glutamatergic drugs or GABAergic drugs in the response versus nonresponse groups. However, the mean (SD) daily dose of benzodiazepine use in the responder group (n = 4; mean [SD] dose, 0.75 [0.29] mg) was significantly lower than in the nonresponder group (3.0 [1.4] mg) (n = 2, P = 0.026). There was no significant difference in the percentage of patients on glutamatergic drugs, GABAergic	Inhibition of ketamine response through GABAergic mechanisms, or perhaps enhancement of ketamine response through antiglutamatergic mechanisms may limit drug response.	

						drugs, or mean (SD) daily dose of benzodiazepines in the remission versus nonremission groups.		

Abbreviations:
AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; **ATH =** Antidepressant Treatment History; **BD II=** bipolar disorder type 2; **BPRS =** Brief Psychiatric Rating Scale; **CADSS =** Clinician-Administered Dissociative States Scale; **GABA(ergic) =** γ-aminobutyric acid–ergic; **IV =** Intravenous; **MADRS** = Montgomery-Asberg Depression Rating Scale; **MDD** = major depressive disorder; **NMDA(R)** = N-methyl-D-aspartate (receptor); **SD =** standard deviation; **TRD =** Treatment resistant depression; **VAS** = Visual Analog mood Scale; **WCST** = The Wisconsin Card Sorting Test.

Table 4. Tranylcypromine

Source: 1st author, year	Study design	Number of subjects (males)	Population	Drug, dosage, route of administration, time interval with ketamine administration	Ketamine dosage, route of administration and duration	Clinical outcome	Possible mechanism of interaction
Bartova et al. (2015)	Case report	2 (0)	Two cases of inpatients with TRD and recurrent severe suicidal crises.	(1st case): Tranylcypromine 10 mg daily oral, increased to 80 mg during ketamine treatment[a] (2nd case): Tranylcypromine 20 mg daily oral, concomitant with ketamine[a]	(1st case): S-ketamine 12.5 mg IV increased up to 75 mg[b] administered repeatedly (2nd case): S-ketamine 25 mg IV and increased up to 50 mg administered twice a week[b]	In both cases, no relevant changes in blood pressure and heart rate were observed.	Ketamine is thought to inhibit monoamine-reuptake. The combination with tranylcypromine is hypothesized to increase blood pressure and heart rate. These cases put in doubt whether mono-aminereuptake inhibition leads to a relevant pharmacodynamic interaction with the effect of ketamine in humans.
Dunner et al. (2019)	Case report	1 (0)	Patient with persistent chronic MDD with moderately severe anxious distress and melancholic features. Nonresponsive to at least 8 adequate treatment trials.	Tranylcypromine, 60 mg[a,c]	S-ketamine 28 mg nasal spray for the first 2 visits, for the third visit 56 mg and the final 4 doses were 42 mg	At the end of the 4 week acute treatment phase all of the mood and anxiety ratings were in the normal range. Blood pressure increases during treatment were within the normal range and there was no evidence of hypertension. S-ketamine nasal spray was well tolerated and there was no evidence of a serotonin syndrome.	No evidence for monoamine enhancement by ketamine.

a time interval uncertain
b total duration of infusion not reported
c route of administration not reported

IV = intravenous; **MDD** = major depressive disorder; **TRD** = treatment resistant depression.

Table 5. Haloperidol

Source (1st author, year)	Study design	Number of subjects (males)	Population	Drug, dosage and route of administration	Ketamine dosage, route of administration (and duration)	Clinical outcome	Possible mechanism	Remarks
Krystal et al. (1999)	Randomized, double blind placebo controlled trial	34 (10) (20 completed the study)	Healthy subjects	Haloperidol, 5 mg oral, or placebo 2 hours before saline or ketamine infusion	Ketamine IV, bolus of 0.26 mg/kg followed by 0.65 mg/kg per hour or placebo (saline) infusion	Haloperidol pretreatment reduced ketamine-induced impairments in executive cognitive functions as assessed with the WCST and the Gorham's Proverb's test and the anxiogenic effects of ketamine measured with a VAS. The production of the BPRS positive and negative symptoms as induced by ketamine, perceptual changes similar to dissociative states, amnestic effects, euphoric effects and attention impairments were not reduced by haloperidol. Haloperidol increased the sedative and (in men) prolactin responses to ketamine.	The capacity of haloperidol to reduce ketamine effects on the WCST and to improve the capacity to interpret proverbs abstractly suggests that these medications interact to modulate cognitive functions associated with networks involving the frontal cortex. Haloperidol pretreatment may have prevented ketamine-induced impairments in cognitive functions associated with the frontal cortex by blocking the consequences of excessive D2 receptor stimulation while permitting the possible beneficial effects of enhanced D1 and D5 receptor stimulation to continue unimpeded.	
Lahti et al. (1995)	Double blind, placebo controlled trial	9 (5)	Schizophrenic patients. All subjects were actively psychotic, but stable	Haloperidol, fixed dose of 0.3 mg/kg/day for 4 weeks. Compared to ketamine administration after a drug free period of 4-8 weeks	Ketamine IV, 3 doses (0.1, 0.3, and 0.5 mg/kg) over 60 seconds vs. 1 placebo infusion	Ketamine increased the total BPRS score significantly in patients on haloperidol for the 0.3- ($p = .005$) and 0.5- ($p = .01$) mg/kg dose. The increase in BPRS total and psychosis score was not statistically different between conditions. Haloperidol did not prevent a ketamine-induced worsening of mental status.	These data suggest that antagonism of NMDA-sensitive glutamatergic transmission in brain exacerbates symptoms of schizophrenia.	

Oranje et al. (2009)	Randomized double blind, placebo controlled trial	18 (18)	Healthy subjects	Haloperidol, 2mg oral or placebo	Ketamine IV, 0.3 mg/kg during the loading phase (first 40 min), 0.0495 mg/kg during the next 10 min, and 0.213 mg/kg for the sustaining phase (last 85 min)	Placebo/ketamine reduced both processing negativity and P300 amplitude. In contrast to the P300 amplitude, the disruptive effect of ketamine on processing negativity could be prevented by pretreatment with haloperidol ($p<0.05$).	The current results suggest that ketamine reduced P300 amplitude by its antagonistic effect on glutamatergic activity, while it reduced processing negativity by its agonistic effect on D2 activity.	Processing negativity is a negative deflection in the ERP appearing above the (pre)frontal areas of the brain, whenever healthy subjects are asked to selectively attend to stimuli defined by certain features, while ignoring others. P300 amplitude is elicited by infrequent stimuli appearing in a sequence of frequent stimuli. Maximum P300 amplitude is commonly found when the subject is requested to respond to these deviant stimuli, e.g. by pressing a button.

Abbreviations: BPRS = Brief Psychiatric Rating Scale; **D1/2/5 =** dopamine receptor 1/2/5;-aspartate receptor; **ERP=** event-related potential; **IV =** Intravenous; **NMDAR** = N-methyl-D
VAS = Visual Analog mood Scale; **WCST** = The Wisconsin Card Sorting Test.

Table 6. Risperidone

Source (1st author, year)	Study design	Number of subjects (males)	Population	Drug, dosage and route of administration	Ketamine dosage, route of administration (and duration)	Clinical outcome	Possible mechanism	Remarks
Doyle et al. (2013)	Randomized, double blind, placebo controlled, crossover trial	20 (20) (16 completed the study)	Healthy subjects	Risperidone, 2 mg or placebo	Ketamine IV, (mean ± S.D.) 0.12 ± 0.003 mg/kg during the first minute followed by a pseudo-continuous infusion of approximately 0.31 mg/kg/h or placebo (saline) infusion	The ROI analysis revealed a significant BOLD response to ketamine infusion relative to saline in phMRI ($P < 0.001$). Risperidone attenuated the ketamine effect across most ROIs, including the medial prefrontal and cingulate regions and the thalamus. No effects were observed in the striatum. For the negatively responding regions in the subgenual cingulate and ventromedial prefrontal cortex, risperidone strongly attenuated the negative BOLD response ($P < 0.001$).	Risperidone has high affinity for D2 receptors, which may conceivably have an impact on its interaction with ketamine. Given the high density of D2 receptors in the striatum and the lack of effects of risperidone on ketamine-induced BOLD changes in the striatum, this supports the proposal that antagonism at 5-HT2AR is the prevailing mechanism underlying the risperidone induced attenuation of the ketamine BOLD response via attenuated glutamate release.	ROI's responsive to ketamine were prespecified based on previous studies, including the anterior cingulate cortex, supragenual paracingulate cortex, thalamus, posterior cingulate cortex, supplementary motor area, left anterior insula, right anterior insula, left operculum, right operculum, precuneus, and medial occipital lobes.
Joules et al. (2015)	Randomized, double blind, placebo controlled, crossover trial	20 (20) (16 completed the study) Same sample as Doyle et al. (2013) and Shcherbinin et al. (2015)	Right handed healthy subjects	Risperidone, 2 mg oral or placebo	Ketamine IV, (mean ± S.D.) 0.12 ± 0.003 mg/kg during the first minute followed by a pseudo-continuous infusion of approximately 0.31 mg/kg/h or placebo (saline) infusion	When compared to placebo, ketamine increased DC in phMRI. ($p<0.003$) Risperidone pre-treatment significantly modulated the ketamine-induced centrality changes. ($P< 0.001$), resulting in increased DC in the frontal and temporal cortices and decreased DC in the basal ganglia, occipital and parietal regions. Furthermore, the ORGP	The authors theorize that it is the twofold mechanism of risperidone acting upon ketamine that is responsible for the observed DC effects. It is likely that the potentiation of the NMDAR is the primary mechanism. The results are suggestive that risperidone may interact with, and in opposition to ketamine resulting in a pattern of DC dissimilar to that of ketamine; the	DC is defined as the number of links incident upon a node (i.e., the number of ties that a node has).

						results suggest risperidone does not attenuate the ketamine DC response in an ordinal manner; instead, the combined results support the conclusion that risperidone may have an opposing effect on the ketamine response.	dissimilarity from the saline state and ordinal regression results preclude a linear attenuation effect of risperidone on ketamine. These observations may be predominantly due to serotonergic effects. In addition to the NMDAR, ketamine also has affinity for other receptors including dopamine, D2 and opioid receptors, particularly at high doses, effects can also be elicited through downstream serotonergic and muscarinic receptors. Whilst they cannot preclude effects at other receptors contributing to our findings, they would favour a major contribution from glutamatergic effects. The opposing effects of ketamine and risperidone in the striatum may conceivably be related to their opposing effects at the D2 receptor, where risperidone acts as an antagonist and ketamine an agonist.	
Schmechtig et al. (2013)	Randomized double blind, placebo controlled study	72 (35)	Healthy subjects	Risperidone, 2 mg oral or placebo	Ketamine IV, infusion of 100 ng ml^{-1}	Ketamine increased saccadic frequency and decreased velocity gain of SPEM (all $P<0.01$) but had no significant effects on PS or AS. Risperidone did not reverse ketamine-induced deteriorations.	This indicates that risperidone did not attenuate ketamine oculomotor performance deficits.	
Shcherbinin et al. (2015)	Randomized, placebo controlled, crossover trial	20 (20) (16 completed the study) Same sample as Doyle et al. (2013) and Joules et al. (2015)	Healthy subjects	Risperidone, 2 mg oral, or placebo	Ketamine IV, 0.12±0.003 mg/kg in the first minute, followed by a pseudo-continuous infusion at a rate of approximately 0.31 mg/kg/h or saline infusion	Ketamine showed positive weights (post-ketamine>pre-ketamine) in prefrontal and cingulate regions, thalamus and lateral parietal cortex with strongest negative contributions in the occipital lobes during phMRI. However, these effects were only nominally significant in the univariate, voxel-level analysis,	No hypothesis described.	

						using a very liberal cluster forming threshold and only when the perfusion maps were global signal corrected. ROI-level univariate analyses did not detect significant effects. Pre-treatment with risperidone significantly increased the ketamine-induced perfusion changes.		

Abbreviations: 5-HT2AR = 5-hydroxytryptamine 2A receptor; **AS =** antisaccades; **BOLD =** blood oxygenation level- dependent; **D2 =** dopamine receptor 2; **DC** = degree centrality; **IV =** Intravenous; **NMDAR** = N-methyl-D-aspartate receptor; **ORGP** = Ordinal regression using Gaussian processes; **phMRI=** pharmacological magnetic resonance imaging; **PS =** prosaccades; **ROI** = Regions of interest; **SPEM =** smooth pursuit eye movement.

Table 7. Clozapine

Source (1st author, year)	Study design	Number of subjects (males)	Population	Drug, dosage and route of administration	Ketamine dosage, route of administration (and duration)	Clinical outcome	Possible mechanism	Remarks
Lipschitz et al. (1997)	Randomized, double blind placebo controlled crossover trial	7 (4)	Healthy subjects	Clozapine, 50 mg or placebo pretreatment	Ketamine IV, 0.5mg/kg over 60 minutes	Clozapine pretreatment did not reduce the BPRS 5 key positive or 3 key negative scores, but there was a trend for a reduction in perceptual alteration as measured by the CADSS (p=0.09).	No hypothesis described.	Conference abstract.
Malhotra et al. (1997)	Randomized, double blind, placebo controlled crossover trial	10 (6)	Patients meeting DSM-III-R criteria for schizophrenia or schizoaffective disorder (2 patients entered the study APD free)	Clozapine, [mean dose = 430 (±48.3) mg/day for 51.8 (±17.7) days] followed by ketamine/placebo infusion after drug-free period [mean drug free period = 20.5 (±9.0) days for 8 patients;]	Ketamine IV, bolus of 0.12 mg/kg followed by infusion of 0.65 mg/kg of ketamine (maximum dose of 58 mg) vs. placebo (saline) bolus followed by infusion of a total dose of 0.77 mg/kg over 1hour	Clozapine treatment significantly blunted the ketamine-induced BPRS positive symptoms (p=0.05), but not the negative symptoms, paranoia, or anxiety–depression. Clozapine specifically blunted ketamine-induced conceptual disorganization. (p=0.05)	It is tempting to speculate that these patients' resistant psychotic symptoms may be related to NMDAR dysfunction and are therefore more amenable to clozapine, rather than typical, antipsychotic therapy.	
Vollenweider et al. (2012)	Randomized, double blind placebo controlled trial	20 (20)	Healthy subjects	Clozapine, 30 mg oral or placebo	S-ketamine, 0.006mg/kg/min	S-ketamine produced positive symptoms and cognitive disturbances that were differentially associated with increased brain activity in an extended neural network including prefrontal regions, anterior cingultate,	These findings suggest that a disruption of NMDAR but not of 5HT2AR- mediated neurotransmission within fronto-temporal-striato-thalamic pathways mainly contributes to ketamine-induced psychotic symptoms.	Conference abstract.

						putamen, thalamus and the temporomedial and insular cortex (as measured with H125O-PET). Reduced activity was found in parietal and occipital cortex regions, and cerebellum ($p<0.00001$). Pretreatment with clozapine moderately reduced some of the S-ketamine-induced symptoms and partially reversed the alterations in anterior cingulate, insula, temporomedial cortex and cerebellum.		

Abbreviations: 5-HT2AR = 5-hydroxytryptamine 2A receptor; **APD free =** Antipsychotic drug free; **BPRS =** Brief Psychiatric Rating Scale; **CADSS =** Clinician-Administered Dissociative States Scale; **DSM** = Diagnostic and Statistical Manual; **H215O-PET =** H215O-positron emission tomography; **IV =** Intravenous; **NMDAR** = N-methyl-D-aspartate receptor.

Table 8. Olanzapine

Source (1st author, year)	Study design	Number of subjects (males)	Population	Drug, dosage and route of administration	Ketamine dosage, route of administration (and duration)	Clinical outcome	Possible mechanism	Remarks
Lahti et al. (1999)	Randomized, double blind placebo controlled crossover trial	5	Healthy subjects (5) and unknown number of schizophrenic patients	Olanzapine, 5mg for healthy subjects and 10 mg for schizophrenic patients vs. placebo 5 hours prior to ketamine infusion	Ketamine IV, 0.3mg/kg or saline IV	Both dosages (5mg and 10mg olanzapine) were no different than placebo in blocking ketamine-induced psychosis in respectively normal and schizophrenic volunteers.	No hypothesis described.	Conference abstract.

Abbreviations: IV = Intravenous

Results