HHS Public Access

Author manuscript

Exp Clin Psychopharmacol. Author manuscript; available in PMC 2016 February 01.

Published in final edited form as:

Exp Clin Psychopharmacol. 2015 February ; 23(1): 1–21. doi:10.1037/a0038550.

A brief history of the development of antidepressant drugs: From monoamines to glutamate

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Abstract

Major depressive disorder (MDD) is a chronic, recurring, and debilitating mental illness that is the most common mood disorder in the United States. It has been almost 50 years since the monoamine hypothesis of depression was articulated, and just over 50 years since the first pharmacological treatment for MDD was discovered. Several monoamine-based pharmacological drug classes have been developed and approved for the treatment of MDD; however, remission rates are low (often less than 60%) and there is a delayed onset before remission of depressive symptoms is achieved. As a result of a "proof-of-concept" study in 2000 with the noncompetitive NMDA antagonist ketamine, a number of studies have examined the glutamatergic systems as viable targets for the treatment of MDD. This review will provide a brief history on the development of clinically available antidepressant drugs, and then review the possible role of glutamatergic systems in the pathophysiology of MDD. Specifically, the glutamatergic review will focus on the N-methyl-D-aspartate (NMDA) receptor and the efficacy of drugs that target the NMDA receptor for the treatment of MDD. The noncompetitive NMDA receptor antagonist ketamine, which has consistently produced rapid and sustained antidepressant effects in MDD patients in a number of clinical studies, has shown the most promise as a novel glutamatergic-based treatment for MDD. However, compounds that target other glutamatergic mechanisms, such as GLYX-13 (a glycine-site partial agonist at NMDA receptors) appear promising in early clinical trials. Thus, the clinical findings to date are encouraging and support the continued search for and the development of novel compounds that target glutamatergic mechanisms.

Major Depressive Disorder

Major depressive disorder (MDD) is the most common mood disorder in the United States with a lifetime prevalence of 14.4% (Kessler, Petukhova, Sampson, Zaslavsky & Wittchen, 2012). MDD is a chronic, recurring, and debilitating mental disorder that significantly impairs occupational and/or social functioning. Most individuals suffering from MDD have

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All authors made substantial contributions and approved the final version of the manuscript.

Disclosures: There are no conflicts of interest to declare.

recurring depressive episodes (10.3%) rather than a single lifetime episode (4.1%) (Kessler et al., 2012). It is important to differentiate MDD from major depressive episode (MDE), which includes individuals with bipolar disorder. Because of the inclusion of bipolar disorder, MDE (16.6%) typically has higher prevalence rates as compared to MDD (14.4%) (Kessler et al., 2012). MDD also has been found to have comorbidity with other DSM disorders such as anxiety disorder, substance abuse and impulse control disorder (Kessler et al., 2003).

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM) 5th edition (American Psychiatric Association, 2013), an individual is required to exhibit a minimum of five depressive symptoms every day for a period of at least two weeks, which are newly presented or clearly worsened prior to the onset of the depressive episode, in order to be diagnosed with MDD. One of these five symptoms must include a depressed mood (Criterion A1), which is described as being depressed, or having a loss of interest/pleasure in hobbies/activities that were considered pleasurable (Criterion A2). In addition to one of these two symptoms, an individual must have four other depressive symptoms which may include significant changes in appetite or weight (Criterion A3); sleep (Criterion A4); psychomotor activity (Criterion A5); loss of energy or fatigue (Criterion A6); feelings of worthlessness (Criterion A7); diminished ability to think or concentrate (Criterion A8); or suicidal ideation (Criterion A9). All of these symptoms, with the exception of weight loss/gain and suicidal ideation, need to be present every day for the two week period to meet the DSM-V criterion for MDD. Furthermore, depressive episodes must significantly impair social or occupational functioning (Criterion B). Lastly, episodes must not be attributed to substance abuse (Criterion C) or better explained by other psychological disorders (Criterion D and E) such as schizophrenia, bipolar, etc.

Depressive episodes may appear at any age; however, MDD is most prevalent in adults (18-64 years) with a median age of onset in the 20s. For example, adults are twice as likely to be diagnosed with MDD as compared to both adolescents (13-17 years) and older adults (65+ years) (Kessler et al., 2003; Kessler et al., 2012). This decline of diagnosis in older adults may be attributed to a failure to report previous episodes, memory loss of past episodes, or sampling bias. Females are two-to-three times more likely to be diagnosed with MDD as compared to their male counterparts regardless of age group (Kessler et al., 2012).

Although there are several treatment options (both pharmacological and nonpharmacological) for MDD, 34-46% of MDD patients do not adequately response to treatment (Fava & Davidson, 1996). These patients are categorized as having *treatment-resistant* depression, which typically is defined as an inadequate response (i.e. fail to achieve full remission) to one or more antidepressant treatments following adequate duration and dose (Fava & Davidson, 1996; Fava, 2003). Treatment-resistant depression is well documented in the literature and is discussed as a subtype of depression; however, there is not a unified definition. For this review, the definition above (i.e. full remission) will be used because the goal for treatment should be to return the patient to the premorbid state of social and occupational functioning. An additional serious issue for the treatment of MDD is that even for the patients that do respond to currently available antidepressant drugs, there is

a delayed onset of 4-12 weeks before adequate symptom remission is achieved (Schulberg, Katon, Simon, & Rush, 1998; Uher et al., 2011).

A group of clinicians have developed a strategic plan for treatment-resistant depression called Sequenced Treatment Alternatives to Relieve Depression (STAR*D). STAR*D provides a four step treatment plan, in which a patient proceeds to the next treatment step if they do not achieve full remission under the current treatment step (Fava et al., 2003). SSRIs are the first treatment step and as patients progress through the treatment steps they will be introduced to new antidepressant drugs with different mechanism of actions (e.g. bupropion, tricyclic antidepressants, etc.). Patients that achieve full remission and tolerate treatment at a specific step are then placed on long term treatment with that drug. The results from a large-scale long-term study found a cumulative remission rate of 67% (across all four treatment steps); however, those patients who progressed through more treatment steps had higher relapse rates as compared to those patients that achieved remission in the first treatment step (Rush et al., 2006).

MDD has significant economic and social consequences worldwide, which are driven by prevalence, medical treatment, and unemployment rates. For example, in the United States 36.7% of individuals suffering from MDD are either unemployed or out of labor force and only 59.8% of the MDD population in the workforce is receiving medical treatment for MDD (Greenberg et al., 2003). In 2000, the total economic impact of MDD was $83.1 billion for the United States. The total direct medical treatment costs (which include inpatient, outpatient, and pharmaceutical costs) reached $26.1 billion, and suicide-related costs (i.e. estimated lost lifetime earnings) exceeded $5.4 billion. Interestingly, workplace-related costs (e.g. missed worked days, reduced productivity, and health care expenses) were $51.5 billion (Greenberg et al., 2003). Individuals with severe MDD cost their employers approximately double in health care expenses, are more likely to file for disability and/or be unemployed, and missed approximately 13.7 MORE hours per month as compared to healthy individuals (Birnbaum et al., 2010).

Monoamine Hypothesis and Monoamine Based Pharmacological Treatments

Monoamine Hypothesis

It has been almost 50 years since the monoamine hypothesis of depression was articulated. The monoamine hypothesis proposes that patients with depression have depleted concentrations of serotonin, norepinephrine, and dopamine (Bunney & Davis, 1965; Delgado, 2000; Hirschfeld, 2000; Schildkraut, 1965). Two primary lines of evidence led to the development of the monoamine hypothesis: 1) the effects of reserpine on serotonin and catecholamines; and 2) the pharmacological mechanisms of action of antidepressant drugs. Reserpine, an alkaloid extracted from the *Rauwolfia serpentina*, was utilized as a treatment for hypertensive vascular disease in the 1950s; however, reserpine was found to precipitate depression in some patients. The depression produced by reserpine was reversed after the treatment was terminated and following either rest or electric shock therapy (Muller, Pryor, Gibbons, & Orgain, 1955). Additionally, reserpine was found to produce depressive-like

effects in animals (Hirschfeld, 2000). Reserpine was found to inhibit vesicular monoamine transporter, and as a result, depletes brain monoamines (i.e. serotonin and catecholamines), which provided evidence for the role of serotonin, norepinephrine, and dopamine in depression (Kirshner, 1962; Shore, Pletscher, Tomich, Carlsson, Kuntzman, & Brodie, 1957; Shore, Silver, & Brodie, 1955; Weiner, Cloutier, Bjur, & Pfeffer, 1972). The second line of evidence was based on the underlying pharmacological mechanisms of action of monoamine oxidase (MAO) inhibitors and tricyclic antidepressants (TCA). For example, antidepressant drugs primarily target the monoamine neurotransmitters (i.e. serotonin, norepinephrine, and dopamine) in an attempt to increase the presence of these monoamine neurotransmitters in the synaptic space to activate postsynaptic receptors. The selective serotonin reuptake inhibitors (SSRI), which were developed later, provided additional support for the monoamine hypothesis. More recent clinical studies have provided evidence suggesting that the monoamine hypothesis for MDD needs to be revised and is not as simple as depleted concentrations of serotonin, norepinephrine, and dopamine leading to MDD. For example, monoamine depletion in healthy subjects does not produce depressive symptoms (Salomon, Miller, Krystal, Heninger, & Charney, 1997). Furthermore, monoamine or tryptophan depletion does not increase depressive symptoms in unmediated MDD patients (Berman et al., 2002; Delgado et al., 1994). Thus, the revised monoamine hypothesis suggests that monoamine depletion may play more of a modulatory role such that it influences other neurobiological systems (e.g. intracellular signaling or other neurotransmitter and neuropeptide systems) or must be present in the context of stressors (Charney, 1998; Heninger, Delgado, & Charney, 1996). A brief history of the development and description of the mechanisms of actions for each of the seven major antidepressant drug classes is presented below.

Monoamine oxidase inhibitors

Much like the discovery of the first antipsychotic drug chlorpromazine, serendipity played an important role in the discovery the first pharmacological treatment for depression. Chemists at Hoffmann-La Roche Ltd USA had developed isonicotinyl hydrazide (isoniazid) for the treatment of tuberculosis and isoniazid proved to be a successful antitubercular compound as the mortality rate of tuberculosis significantly decreased after the drug had been on the market for only one year (Lopez-Munoz, Alamo, Juckel, & Assion, 2007; Pletscher, 1991). While developing new antitubercular compounds, Fox and Gibas (1953) synthesized isopropyl-isonicotinyl hydrazide (iproniazid), a monoalkyl derivative of isoniazid, which would later serve as a catalyst for pharmacological treatment of MDD. Clinical observations reported marked “side effects” of iproniazid in patients being treated for tuberculosis, which included euphoria, psychostimulation, increased appetite, and improved sleep. The “side effects” produced by iproniazid were not originally identified as therapeutic effects because these side effects were not consistent across studies (Lopez-Munoz et al., 2007; Pletscher, 1991). Loomer, Saunders, and Kline (1958) conducted a systematic clinical study on patients with depression, in which the patients were treated with iproniazid for several weeks. Loomer and colleagues reported significant improvements in 70% of these patients (Loomer et al., 1958). While iproniazid was marketed as an antitubercular compound under the trade name Marsilid® in 1958, it was used off-label to treat patients suffering from MDD.

Thus, iproniazid became the first successful pharmacological treatment for depression and is classified as a MAO inhibitor. MAO is an enzyme that produces oxidative disamination (or break down) of biogenic amines (e.g. serotonin, dopamine, epinephrine, and norepinephrine) and sympathomimetic amines (e.g. tyramine, benzylamine, etc). There are two isoenzymes, MAO_A and MAO_B, and the distribution of these isoenzymes varies throughout the body. MAO_A is primarily responsible for the enzyme activity for the deaminate of serotonin, melatonin, noradrenaline, and adrenaline (Billett, 2004; Shulman, Herrman, & Walker, 2013). In contrast, MAO_B is responsible for enzyme activity for the breakdown of phenethylamine and benzylamine (Campbell, Marangos, Parma, Garrick, & Murphy, 1982; Shulman et al., 2013). Interestingly, both isoenzymes deaminate dopamine, tyramine, and tryptamine. MAOs responsible for the breakdown of biogenic amines are located in the presynaptic terminal. A result of inhibiting MAO is that monoamine neurotransmitter concentrations increase in the presynaptic terminal and are readily available for release when action potentials reach the nerve terminal. Iproniazid is a non-selective irreversible MAO inhibitor, which led to safety concerns (e.g. hypertensive crises), and ultimately led to the removal of iproniazid from the US market. One example of the safety concern was termed the “cheese reaction.” The combination of foods containing high amounts of tyramine, such as cheese or dairy products, and MAO inhibitors, which increase concentrations of tyramine and norepinephrine in the sympathetic nervous system, would lead to increased heart rate, hypertension and sweating. It was later determined that inhibiting MAO_A was functionally involved in the antidepressant effects of MAO inhibitors (Lopez-Munoz et al., 2007; Shulman et al., 2013).

In an attempt to improve the safety of MAO inhibitors, drug development has focused on reversible and selective MAO_A inhibitors (e.g. moclobemide [Manerix®] and brofaromine [Consonar®]). For example, a meta-analysis revealed that the reversible inhibitor of monoamine oxidase type A (RIMAs) moclobemide was as effective as SSRIs, nonselective MAO inhibitors and TCAs for depressive symptom reduction. Additionally, moclobemide was generally well tolerated with the most common side effect being nausea and insomnia, and only one reported case of hypertensive crisis. It is important to note that moclobemide is available in over 50 countries worldwide, but is not available in the United States, and brofaromine is no longer being developed as an antidepressant drug (Lotufo-Neto, Trivedi, & Thase, 1999).

Tricyclic antidepressants

As a result of the discovery and success of chlorpromazine for the treatment of schizophrenia, the search for more potent antipsychotic drugs intensified. Many of these novel compounds were molecularly modified from the classic antihistamine structure. One compound in particular, G22355 (imipramine), was derived from promethazine by substituting a sulfur bridge of the phenothiazine ring with an ethylene bridge (Domino, 1999; Fangmann, Assion, Juckel, Gonzalez, & Lopez-Munoz, 2008). The Geigy Chemical Corp supplied imipramine, which was synthesized by Hafliger and Schinder, to Dr. Roland Kuhn to test in psychiatric patients. Although imipramine did not exhibit antipsychotic properties in patients with schizophrenia, Kuhn found that imipramine produced marked improvements in patients suffering from severe depression. In an essay written by Kuhn

(1958), he states “They commence some activity of their own, again seeking contact with other people, they begin to entertain themselves, take part in the games, become more cheerful and are once again able to laugh… The patients express themselves as feeling much better, fatigue disappears, the feeling of heaviness in the limbs vanish, and the sense of oppression in the chest gives way to a feeling of relief” (p. 459). Kuhn also stated that no serious side effects were recorded in the 500 patients treated with imipramine, which was a vast improvement over MAO inhibitors.

Imipramine (Tofranil®) was approved in 1959 by the Food and Drug Administration (FDA) for the treatment of MDD, which established the class of drugs called tricyclic antidepressants (TCA). The classification of TCAs was based on the three benzene ring molecular core, in part, because the mechanism of action was unknown at the time of discovery. Thus, the classification of TCAs differs from other classes of antidepressant drugs, which are classified based on their mechanism of action. TCAs have a diverse pharmacological profile with significant pharmacological action at two reuptake transporters and three receptor proteins: inhibiting presynaptic norepinephrine reuptake transporters; inhibiting presynaptic serotonin reuptake transporters; blocking postsynaptic adrenergic α_1 and α_2 receptors; blocking postsynaptic muscarinic receptors; and blocking postsynaptic histamine H_1 receptors (Cusack, Nelson, & Richelson, 1994; Owens, Morgan, Plott, & Nemeroff, 1997; Sánchez & Hyttel, 1999: Vaischnavi et al., 2004). The inhibitions of norepinephrine and serotonin reuptake at the transport proteins are thought to be responsible for the therapeutic effects of TCAs and result in increased concentrations of norepinephrine and serotonin in the synaptic cleft, respectively. The selectivity for norepinephrine or serotonin transporters depends on the compounds; however, as most TCAs are more selective for the norepinephrine transporter over the serotonin transporter (Owens et al., 1997; Sánchez & Hyttel, 1999; Thomas, Nelson, & Johnson, 1987). For TCAs, the antagonism of adrenergic, muscarinic, and histaminergic receptors contribute primarily to the side effects of dizziness, memory impairments, and drowsiness, respectively.

Selective serotonin reuptake inhibitors

In the late 1960s evidence began to emerge suggesting a significant role of serotonin in MDD. For example, a postmortem study revealed decreased concentrations of serotonin in depressive suicides (Shaw, Eccleston, & Camps, 1967). As a result, the pharmaceutical company Eli Lilly began developing ligands that would selectively inhibit the reuptake of serotonin at serotonin transporters, and as a result would increase serotonin concentrations within the synaptic cleft to further stimulate postsynaptic serotonin receptors. In 1974, the first report on the selective serotonin reuptake inhibitor (SSRI) LY110140 (fluoxetine) was published and in that publication the authors suggested that fluoxetine would be an antidepressant drug (Wong, Horng, Bymaster, Hauser, & Molloy, 1974). The following year Wong and colleagues demonstrated that fluoxetine, an analogue of the phenoxyphenylpropylamine nisoxetine (LY94939), was a potent and selective serotonin reuptake inhibitor with relatively weak affinity for the norepinephrine transporter (Wong, Bymaster, Horng, & Molloy, 1975), which separated fluoxetine pharmacologically from other antidepressant drugs. Fluoxetine was approved by the FDA in December of 1987 and was launched to the market in January 1988 under the trade name Prozac® (for an

excellence review on the development of fluoxetine see Wong, Bymaster, & Engleman, 1995; Wong, Perry, & Bymaster, 2005). Since the introduction of fluoxetine to the market, several other SSRIs have been approved by the FDA (e.g. sertraline [Zoloft®], citalopram [Celexa®], paroxetine [Paxil®], and escitalopram [Lexapro®]).

Although fluoxetine was the first SSRI approved and marketed in the United States, the clinical trials (Phase I-Phase III) lasted more than seven years and during that time Astra AB introduced the first SSRI zimeldine (Zelmid®) to the European market in March 1982. Zimeldine, which was derived from pheniramine, was removed from the European market in September 1983 due to severe side effects such as hypersensitivity reactions and Guillain-Barre syndrome, which is acute peripheral neuropathy. The hypersensitivity reactions resembled a flu- like syndrome which included fever, joint/muscle pain, headaches and hepatic effects. The estimated occurrence of the hypersensitivity reaction was 3:1000. Interestingly, zimeldine produced the hypersensitivity reactions in 1.5% of patients during clinical trials, but was still approved in the European market (Montgomery, Gabriel, James, Hawley, & Burkitt, 1989; Nilsson, 1983). During the 16 months that zimelidine was on the market there were 10 confirmed cases of Guillain-Barre syndrome and all of these patients were under zimeldine treatment (Fagius, Osterman, Siden, & Wiholm, 1985).

SSRIs are 20-1500 fold more selective for inhibiting serotonin over norepinephrine at their respective transporter proteins and have minimal binding affinity for other postsynaptic receptors such as adrenergic α_1, α_2, and β, histamine H_1, muscarinic, and dopamine D_2 receptors (Owens et al., 1997; Thomas et al., 1987). SSRIs (e.g. fluoxetine and citalopram) also do not stimulate the release of serotonin or norepinephrine presynaptically (Rothman et al., 2001) and have weak or no direct pharmacological action at postsynaptic serotonin receptors (e.g. 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2c}) (Owens et al., 1997; Sánchez & Hyttel, 1999; Thomas et al., 1987). Therefore, the increase in activity at the postsynaptic serotonin receptors produced by SSRIs is a result of increased concentrations of serotonin in the synaptic cleft via reuptake inhibition rather than direct binding at the postsynaptic receptor. The most common side effects associated with SSRIs are nausea, insomnia, and sexual dysfunction (Papakostas, 2008).

Atypical antidepressant drug bupropion

Several new antidepressant drugs have been developed in the past couple of decades; however, the mechanisms of action for these drugs are similar to established antidepressant drugs in that these drugs target the monoamine neurotransmitter systems. Shortly after the introduction of fluoxetine, the immediate release (IR) form of bupropion (Wellbutrin®) was approved by the FDA in 1989 for the treatment of MDD with the aim to improve efficacy and safety. Bupropion IR requires three daily doses; thus, to reduce daily dosing regimens, the sustained-release (SR) and extended-release (XL) were developed and approved by the FDA in 1996 and 2003, respectively (Fava et al., 2005; Stahl et al., 2004). Bupropion is an “atypical” antidepressant drugs belonging to a unique chemical class (aminoketone) and its binding profile is very different from other antidepressant drugs (i.e. TCAs, SSRI, SNRI). For example, bupropion is primarily a dopamine-norepinephrine reuptake inhibitor. Bupropion displays its highest binding affinity for dopamine transporters and is at least two-

fold more selective for dopamine transporters as compared to norepinephrine transporters (Bymaster et al., 2002; Letchworth et al., 2000; Pristupa, Wilson, Hoffman, Kish, & Niznik, 1994). Additionally, bupropion displays minimal or no binding affinity for serotonin transporters or other pre- and postsynaptic receptors (Bymaster et al., 2002; Cusack et al., 1994; Sánchez & Hyttel, 1999). Clinical research has shown that bupropion is as efficacious as other antidepressant drugs for the treatment of MDD and is well tolerated with the three most frequent side effects of bupropion being dry mouth, nausea, and insomnia (Feighner, Hendrickson, Miller, & Stern, 1986; Feighner, Meredith, Stern, Hendrickson, & Miller, 1984; Moreira, 2011). Furthermore, bupropion has the lowest risk of sexual dysfunction (nearly half) as compared to TCAs, MAOIs, SSRIs, and SNRIs (Clayton et al., 2002; Stahl et al., 2004). There are no other selective dopamine-norepinephrine reuptake inhibitors on the market for the treatment of depression.

Serotonin-norepinphrine reuptake inhibitors

The next “atypical” antidepressant drug, venlafaxine, was introduced to the United States market in 1993, and this drug selectively targets the serotonin and norepinephrine transporters. The immediate release form of venlafaxine (Effexor®), a serotonin-norepinephrine reuptake inhibitors (SNRI), was approved by the FDA for the treatment of MDD in 1993 and in 1997 the extended release form of venlafaxine was also approved for MDD (Papakostas, 2009). Since the approval of venlafaxine, several other SNRIs (e.g. duloxetine [Cymbalta®] and milnacipran [Savella®]) have been approved for the treatment of MDD. SNRIs are similar to TCAs in that SNRIs inhibit the reuptake of serotonin and norepinephrine at the serotonin and norepinephrine transporters, respectively. Unlike TCAs, SNRIs have minimal or no pharmacological action at adrenergic (α_1, α_2, and β), histamine (H_1), muscarinic, dopamine, or postsynaptic serotonin receptors (Bymaster et al., 2001; Millan et al., 2001; Owens et al., 1997; Sánchez & Hyttel, 1999; Vaischnavi et al., 2004). There is some evidence that suggests SNRIs may be more effective for the treatment of MDD as compared to SSRIs; however, these differences are relatively modest (Papakostas, Thase, Fava, Nelson, & Shelton, 2007; Stahl, Grady, Moret, & Briley, 2005). The clinical tolerability and the prevalence of sexual dysfunction of SNRIs are comparable with other antidepressant drug treatments (Clayton et al., 2002; Stahl, Grady, Moret, & Briley, 2005).

Atypical antidepressant drug vortioxetine

In September 2013, vortioxetine (Brintellix®) became the most recent antidepressant drug approved by the FDA for the treatment of MDD. Lu AA21004, which was named vortioxetine, was synthesized by H. Lundbeck A/S, but was co-developed by H. Lundbeck A/S and Takeda Pharmaceutical Company Ltd (Gibb & Deeks, 2014). Vortioxetine belongs to the piperazines chemical class and has been marketed as a “multi-modal” drug because vortioxetine displays high binding affinity and complementary mechanisms of action for several serotonin receptors (i.e. 5-HT_{1A}, 5-HT_{1B}, 5-HT_{3A}, 5-HT_7, and serotonin transporters). Specifically, vortioxetine is a serotonin 5-HT_{1A} receptor agonist, 5-HT_{1B} receptor partial agonist, 5-HT_{3A} and 5-HT_7 receptor antagonist, and a potent serotonin reuptake inhibitor (Bang-Andersen et al., 2011; Mork et al., 2012). Vortioxetine has considerable receptor affinity for dopamine and norepinephrine transporters; however, vortioxetine is approximately 3 to 12 times more selective for serotonin transporters as

compared to dopamine and norepinephrine transporters, respectively (Bang-Andersen et al., 2011). The clinical efficacy and tolerability of vortioxetine is comparable to other antidepressants with the most common side effects being nausea and headaches. Vortioxetine appears to have a low risk for sexual dysfunction and weight gain (Alam, Jacobsen, Chen, Serenko, & Mahableshwarkar, 2014; Boulenger, Loft, & Florea, 2012; Boulenger, Loft, & Olsen, 2014; Gibbs & Deeks, 2014; Pearce & Murphy, 2014). It is important to note that clinical (McIntyre, Lophaven, & Olsen, 2014) and preclinical (du Jardin, Jensen, Sanchez, & Pehrson, 2014; Jensen et al., 2014; Mork et al., 2013) studies have shown that vortioxetine may help improve cognitive functioning.

Although there are seven antidepressant drug classes, all of which work to produce an immediate increase in monoamine neurotransmitter concentrations, there is still a population of patients that do not respond to these medications. This lends further support for the revised monoamine hypothesis which suggests that depleted monoamine concentrations may play more of a modulatory role to other neurobiological systems, rather than a major direct role in MDD (Charney, 1998; Heninger, Delgado, & Charney, 1996). Thus, more recent research has focused on finding novel, non-monoaminergic based, receptor targets for treatment-resistant depression (e.g. Lee, Jeong, Kwak, & Park, 2010; Palucha & Pilc 2005). In particular, the glutamatergic system has become a focal point for drug development research.

Glutamatergic Systems and Major Depressive Disorder

Glutamatergic systems

In the central nervous system, glutamate is the major excitatory neurotransmitter and makes functional contributions to more than half of all synapses in the brain. The glutamate system has an integrated tripartite synapse that consists of 1) a presynaptic neuron, 2) a postsynaptic neuron, and 3) an astrocyte. The presynaptic neuron releases glutamate in response to action potentials. The released glutamate then binds to various pre- and postsynaptic receptors, as well as to receptors on the surrounding astrocytes. Synaptic glutamate reuptake is performed primarily by astrocytes, specifically, the excitatory amino acid transporter 2 (EAAT2). Within the astrocyte, glutamate is converted to glutamine (glutamate/glutamine cycle) by glutamine synthetase and then resupplied to the presynaptic neuron where it is used for synthesis of glutamate (Kew & Kemp, 2005; Machado-Vieira, Manji, & Zarate, 2009; Mathews, Henter, & Zarate, 2012). Figure 1 shows the tripartite glutamatergic synapse.

The glutamatergic system consists of two receptor types, ionotropic and metabotropic. Ionotropic glutamatergic receptors include N-methyl-D-aspartate (NMDA) receptors, α-amino-3- hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors. These ionotropic receptors are ion channels that are permeable to cations (i.e. sodium [Na^+] and calcium [Ca^{2+}]), which in turn depolarize the neuron and/or promote intracellular signaling cascades (Kew & Kemp, 2005). There are eight G-protein-coupled metabotropic glutamate receptors subtypes (mGluR1-8) that are divided into three distinct groups that are based on their homology and function: Group I (mGluR1 and mGluR5), Group II (mGluR2 and mGluR3), and Group III (mGluR4, mGluR6, mGluR7, and mGluR8). Group I mGluRs are localized on the postsynaptic neuron and are coupled to G_q/G_{11} subunits; whereas Group

II and Group III are localized on the presynaptic neuron and are couple to G_i/G_o subunits. mGluRs can mediate intracellular signaling cascades by activating second messenger pathways and/or through βγ subunits. Group I and Group II mGluRs have been investigated in the pathophysiology and treatment of MDD. Specifically, mGluR5 (e.g. AZD2066 and RO4917523) and mGluR2/3 (RO4995819) negative modulators have been tested in Phase II clinical trials for treatment-resistant patients, and some compounds (e.g. RO4917523and RO4995819) have shown promise (for full review see Holly, LaCrosse, & Hillhouse, 2014). Assessing all glutamate receptors and their respective implications in MDD are beyond the scope of this review. Therefore, the present review will primarily focus on NMDA receptors.

N-methyl-D-aspartate (NMDA) receptors

NMDA receptors are a heteromeric complex that has seven subunits, NR1, NR2A-D, and NR3A-B and functional NMDA receptors must be comprised of a NR1 subunit and at least one NR2 subunit. Unlike other ligand-gated ion channels, NMDA receptors require two distinct mechanisms in order to be activated. First, NMDA receptor channels require co-agonist binding at the glycine binding site on the NR1 subunit and at the glutamate binding site on the NR2 subunit (Kew & Kemp, 2005; Marsden, 2011). Thus, if one of these co-agonists (glycine or glutamate) is not bound to their respective binding site, the ion channel will not open. Second, the NMDA receptor channels are blocked by magnesium (Mg^{2+}) ions during the resting state. Depolarization of the neuron is required to dispel the Mg^{2+} ion from NMDA receptor channels, which is usually achieved by activation of AMPA receptors. The NMDA receptor ion channel is non-selective and will allow both Na^+ and Ca^{2+} to enter. The influx of Ca^{2+} is associated with the induction of various signaling cascades (Kew & Kemp, 2005; Marsden, 2011).

Glutamatergic dysfunction in MDD

Clinical research has used both indirect and direct measures to evaluate the glutamatergic system in patients suffering from MDD, and have found evidence of glutamatergic dysfunction in MDD. For example, clinical studies that have used indirect measures for analysis, such as plasma, cerebrospinal fluid, and serum concentrations, have found differences in glutamate and glutamine in patients diagnosed with MDD as compared to healthy controls (Table 1). Specifically, several studies have found increased concentrations of glutamate in plasma (Altamura et al., 1993; Küçükibrahimoğlu et al., 2009; Mauri et al., 1998) and increased concentration of glutamine in cerebrospinal fluid (Levine et al., 2000). Furthermore, antidepressant drug treatment has been found to reduce the serum and plasma glutamate concentrations (Küçükibrahimoğlu et al., 2009; Maes, Verkerk, Vandoolaeghe, Lin, & Scharpé, 1998), as well as cerebrospinal fluid glutamine concentrations (Garakani, Martinez, Yehuda, & Gorman, 2013). These findings suggest that these monoamine-based antidepressant drugs are modulating the glutamatergic system. However, there are limitations when using indirect measures, such as the inability to determine central and peripheral substrates and metabolic effects, which make it difficult to interpret these findings. Additionally, peripheral measurements of CNS chemicals/metabolites may be seriously compromised by their inability to easily cross the blood brain barrier.

Clinical studies that have used more direct measures (Table 2), such as proton magnetic resonance spectroscopy (^{1}H-MRS), to evaluate the glutamatergic dysfunction in MDD have found reduced metabolic, typically unresolved, glutamate/glutamine exchange (Glx) in subcortical and cortical brain regions of MDD patients. For example, a reduction of Glx were found the hippocampus (Block et al., 2009) and anterior cingulate cortex (Auer et al., 2000; Mirza et al., 2004; Pfleiderer et al., 2003), which are purported to play an important role in MDD. Further ^{1}H-MRS studies found that cortical regions also had a reduction in Glx which include the dorsomedial and ventromedial prefrontal cortex (Hasler et al., 2007), and left dorsolateral prefrontal cortex (Michael et al., 2003). Following ECT treatment, the anterior cingulate cortex and left dorsolateral prefrontal cortex Glx concentrations were significantly increased and recovered back to healthy control Glx concentrations (Michael et al., 2003; Pfleiderer et al., 2003). Furthermore, these studies found that ECT responders had a great increase of Glx as compared to the non-responders. On the other hand, Sanacora and colleagues (2004) found elevated concentrations of Glx in the occipital cortex, and while this finding is not consistent with the other ^{1}H-MRS, it is consistent with the elevated concentrations of glutamate found in plasma (Altamura et al., 1993; Küçükibrahimoğlu et al., 2009; Mauri et al., 1998) and by recent studies that found decreased concentrations of EAAT2, the main source the glutamate reuptake, in postmortem brain tissue, which would result in the accumulation of extracellular glutamate (Bernard et al., 2001; Choudary et al., 2005). It is important to note that there are limitations when using the magnetic resonance imaging protocol. For example, these studies were measuring glutamate/glutamine cycle rather than glutamate exclusively.

Several postmortem studies have found changes in the expression of NMDA receptor subunits in MDD patients (Table 3), which are likely compensatory effects to the changes in glutamatergic substrate concentrations, and appear to be brain region specific. For example, the NR2B and NR2C subunits have been shown to have increased expression in the locus coeruleus in postmortem tissue of MDD patients (Chandley et al., 2014; Karolewicz, Stockmeier, & Ordway, 2005). Additionally, the expression of NR2A subunits has been found to be elevated in the lateral amygdala (Karolewicz et al., 2009). Furthermore, MDD patients have shown an increase in glutamate binding in the hippocampus (Beneyto, Kristiansen, Oni-Orisan, McCullumsmith, & Meador-Woodruff, 2007) and a greater sensitivity to glutamate as measured by intracellular calcium influx (Berk, Plein, & Ferreira, 2001). On the other hand, the NR2A and NR2B subunits transcription have been shown to be reduced in the perirhinal and prefrontal cortices in postmortem tissue from MDD patients (Beneyto et al., 2007; Beneyto and Meador-Woodruff, 2008; Feyissa, Chandran, Stockmeier, & Karolewicz, 2009). Moreover, postmortem studies have found decreased levels of the NR1subunit in the superior temporal cortex (Nudmamud-Thanoi and Reynolds, 2004) and prefrontal cortex (Beneyto and Meador-Woodruff, 2008). NR1 and NR2 subunits are required for functional NMDA receptor heteromeric complexes, and thus, increases/ decreases in the levels of these NR1/NR2 subunits can be interpreted as changes in total number of functional NMDA receptors. Based on these results, it would be hypothesized that depression may be associated with hyperfunction of NMDA receptors in subcortical regions (i.e. hippocampus, locus coeruleus, and amygdala); whereas, depression may be associated with a hypofunction of NMDA receptors in cortical regions (i.e. prefrontal,

perirhinal and temporal cortices). Moreover, the results from the ^{1}H-MRS studies would support the notion of a hypofunction of the glutamatergic system in cortical regions. However, pervious drug treatment is a common limitation when interpreting plasma, ^{1}H-MRS, or postmortem human data. The majority of these studies used patients that were drug free for at least three to four weeks, but there is a possibility that previous pharmacological treatments produced neurobiological changes in the brain that were still evident postmortem.

Collectively, the clinical data suggest the involvement of the glutamatergic system in the pathophysiology of MDD, which includes disruptions in glutamatergic substrate concentrations and NMDA receptor alterations. Although the role of glutamatergic systems have yet to be fully elucidated, a “proof of concept” clinical study reported that the noncompetitive NMDA antagonist ketamine produced rapid and prolonged antidepressant effects in patients suffering from MDD (Berman et al., 2000). This has generated tremendous interest in developing new drugs that target glutamatergic mechanisms for the treatment of MDD. Figure 1 shows potential drug targets on the NMDA receptor and EAAT2.

Ketamine: Noncompetitive NMDA Receptor Antagonist, Drug of Abuse and Antidepressant

Drug of abuse

Ketamine, a dissociative anesthetic with hallucinogenic properties, is a derivative of phencyclidine and was developed in the 1960s by Dr. Calvin Lee Stevens of Wayne State University for the pharmaceutical company Parke-Davis. In 1964, ketamine was experimentally administered to human subjects to test the safety and general anesthetic properties of ketamine, and the subjects reported few side effects and described feelings of floating or having no feeling in their limbs. Ketamine was approved by the FDA in 1970 for use as a short-acting anesthetic in humans and animals and was given to injured American soldiers during the Vietnam War (Domino, 2010). Ketamine, which is distributed under the trade names Ketalar®, Ketaset®, and Vetamine®, is still widely used in human and veterinary medicine with approximately 16,000 dispensed ketamine prescriptions in 2012 (Domino, 2010; Drug Enforcement Administration, 2013).

Ketamine, also known as “Special K,” became popular as a recreational drug in the mid-1990s. As a result of its increased recreational use, ketamine became a Schedule III non-narcotic substance under the Controlled Substances Act in 1999 (Drug Enforcement Administration, 2013). Although the illicit use of ketamine appears to be relatively low in the United States with less than 2% of the population using hallucinogens (Substance Abuse and Mental Health Services Administration, 2013), which also includes lysergic acid diethylamide, phencyclidine, peyote, mescaline, psilocybin mushrooms, and “ecstasy,” the popularity of ketamine continues to grow in other countries. For example, ketamine (23.2%) is the second most abused substance in Hong Kong with heroin (61.7%) being the most abused substance (Shek, 2007). The use of ketamine also has been on a rise over the past decade, specifically among “dance” or “club” drug users in Europe (McCambridge, Winstock, Hunt, & Mitcheson, 2007, 2007; Shek, 2007; Winstock, Mitcheson, Gillatt, &

Cottrell, 2012). At subanesthetic or emergence from anesthetic doses, ketamine produces hallucinations (i.e. distorts perceptions of sight and sounds), mood and body image changes, and make the user feel disconnected (or dissociated) from their body/reality. The hallucinogenic effects of ketamine have been termed the "K-hole" by users, and the duration of these effects are relatively short, 30 to 60 min, as compared to phencyclidine (Drug Enforcement Administration, 2013).

Mechanism of action

Ketamine is a noncompetitive NMDA receptor antagonist (aka channel blocker) that binds to the phencyclidine site inside the ion channel of the NMDA receptor, blocking the channel in a way that is similar to how Mg^{2+} blocks NMDA receptors, and is non-selective for the NR2A-D subunits of the NMDA receptor channel (Lord et al., 2013; Yamakura, Mori, Masaki, Shimoji, & Mishina, 1993; Yamakura & Shimoji, 1999). While many have categorized ketamine as a high affinity NMDA receptor antagonist, *in vivo* autoradiography studies suggest that ketamine has relatively low affinity for the NMDA receptor (K_i = 659-1190 nM) (Bresink, Danysz, Parsons, & Mutschler, 1995; Roth et al., 2013). Additionally, selectivity of ketamine for the NMDA receptor appears to be weak as compared to other receptors. For example, ketamine has been shown to have higher receptor affinity for *in vitro* human cloned dopamine D_2 receptors (K_i = 55 nM) than for NMDA receptors (K_i = 659-1190 nM) (Seeman, Ko, & Tallerico, 2005); however, a follow up study found that ketamine did not exert functional activity (i.e. as a full agonist, partial agonist, or antagonists) at *in vitro* dopamine D_2 receptors (Jordan et al., 2006). Ketamine is approximately 12 and 20-fold more selective for NMDA receptors as compared to serotonin 5-HT_{2A} and mu opioid receptors, respectively (Kapur & Seeman, 2002; Smith et al., 1987). Furthermore, ketamine also has weak binding affinity for sigma (Mendelsohn, Kalra, Johnson, & Kerchner, 1985), muscarinic (Hirota, Hashimoto, & Lambert, 2002), and κ and δ opioid receptors (Smith et al., 1987), as well as dopamine, norepinephrine, and serotonin transporters (Nishimura et al., 1998).

Antidepressant clinical studies

Tables 4 provide a summary of the clinical trial results and the current status of ketamine for the treatment of MDD. In 2000, the noncompetitive NMDA receptor antagonist ketamine was first used in a "proof of concept" randomized, double- blind study to assess the effects of ketamine on MDD in seven patients who received both vehicle and ketamine treatment (counterbalanced). A single, subanesthetic dose of ketamine (0.5 mg/kg) was intravenously (i.v.) infused over 40 minutes, and the antidepressant effects of ketamine were assessed using the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventor (BDI). In comparison, an anesthetic dose for ketamine in humans ranges from 1.0 mg/kg to 4.5 mg/kg intravenous and from 6.5 mg/kg to 13.0 mg/kg intramuscular. In this study, ketamine produced rapid, within four hours, and prolonged antidepressant effects that lasted up to 72 hours as compared to placebo control (Berman et al., 2000). This rapid antidepressant effect of ketamine is far superior to the 4-12 week delay with current antidepressant drugs (Schulberg et al., 1998; Uher et al., 2011). The hallucinogenic (or psychotomimetic) effects (e.g. out of body experience, hallucinations, etc.) of ketamine subsided (within two hours) prior to the onset of the antidepressant effects as measured by the Visual Analog Scales for

intoxication “high” (VAS-high) and Brief Psychiatric Rating Scale (BPRS) (Berman et al., 2000). This was the first clinical study to demonstrate that glutamatergic drugs may be effective for the treatment of MDD.

One limitation of the Berman et al. (2000) study was the limited three day follow-up period. In that study, the ketamine-treated patients did not return baseline depression scores during the follow-up period, which makes it difficult to determine the duration of the antidepressant effects of ketamine. Thus, Zarate and colleagues conducted a clinical study to assess the antidepressant effects of ketamine in patients with treatment-resistant MDD and to determine a better understanding of the duration of the antidepressant effects. Following a single 0.5 mg/kg infusion of ketamine, treatment-resistant patients showed a significant reduction in depression scores at 110 min that lasted up to seven days as measured by HDRS (Zarate et al., 2006). Specifically, 71% of the patients achieved response criteria one day after the infusion, while 29% achieved full remission. Additionally, 35% maintained response criteria on day seven (Zarate et al., 2006). Again, the hallucinogenic (or psychotomimetic) effects diminished before the onset of the antidepressant effects of ketamine (within two hours). This study confirmed the finding in the Berman et al. (2000) study that ketamine produces rapid and prolonged antidepressant effects in the treatment of depression and extended ketamine's efficacy to treatment-resistant MDD.

Two studies have evaluated the effects of repeated ketamine infusion in patients suffering from treatment-resistant MDD to determine if repeating dosing could extend the antidepressant effects of ketamine beyond seven days. In both studies, patients received six ketamine infusions over approximately 12 days. One study found that the average relapse rate was 19 days after the sixth and final ketamine infusion, with one patient remaining in remission for more than three months (ann het Rot et al., 2010). In the second study, ketamine infusions produced an antidepressant effect in 70.8% of the patients and these antidepressant effects lasted for a median of 18 days (four participants were still in remission at the last follow up visit [83 days]) (Murrough et al., 2013). Both of these studies reported safety and tolerability similar to the single ketamine infusion studies.

In the study by Murrough et al. (2013), they compared the effects of a single low dose of ketamine (0.5 mg/kg, i.v.) to an active placebo, the anesthetic benzodiazepine midazolam (0.045 mg/kg, i.v.), in treatment-resistant patients. Following drug infusion, the ketamine group showed a 64% response rate at 24 hours and 46% response rate on day seven; whereas, the midazolam group showed a response rate of 28% at 24 hours and 18% on day seven (Murrough et al., 2013). These results suggested that the antidepressant effects of ketamine are not a result of its anesthetic properties. Another study compared the effects of ketamine and electroconvulsive therapy (ECT) in patients suffering from MDD. This study found that both ketamine and ECT produced antidepressant effects; however, ketamine produced superior antidepressant effects in terms of response onset. For example, ketamine produced rapid antidepressant effects starting at 24 hours; whereas, the antidepressant effects of ECT were not expressed until day two. The antidepressant effects of both ketamine and ECT lasted until the completion of the study, which was seven days (Ghasemi et al., 2014). These results suggest that ketamine is as efficacious, if not more efficacious, as ECT for treating MDD.

In addition to the previously mentioned studies, several other clinical studies have found that i.v. infusions of low-dose ketamine produce rapid and sustained antidepressant effects in patients with MDD (Machado-Vieira et al., 2009; Mathew et al., 2010; Rasmussen et al., 2013) and a rapid reduction in suicidal ideation/cognition in patients with treatment-resistant MDD (DiazGranados et al., 2010; Price, Nock, Charney, & Mathew, 2009; Price et al., 2014; Zigman & Blier, 2013). An anti-anhedonic effect of ketamine treatment in treatment-resistant bipolar depression was recently demonstrated by Lally et al. (2014). In a randomized, placebo- controlled, double-blind crossover design, 36 treatment-resistant bipolar depression patients were treated with a single, low intravenous dose of 0.5 mg/kg ketamine. They found that ketamine rapidly reduced anhedonia in these patients within 40 minutes and that these effects preceded reductions in other depressive symptoms. Also, the decrease in anhedonic symptoms persisted up to 14 days. The authors concluded that these findings demonstrate the importance of glutamatergic mechanisms for the treatment of treatment-refractory bipolar depression and especially for the treatment of anhedonia symptoms.

Researchers have started to evaluate alternative routes of administration for ketamine to improve safety and possibly reduce the psychotomimetic side effects of ketamine. Furthermore, the hospital visits and the duration associated with the i.v. administration of ketamine may become an issue for patient compliance. Two case studies have demonstrated that orally administered low doses of ketamine were effective in relieving depressive symptoms in several MDD patients (Irwin & Iglewicz, 2010; McNulty & Hahn, 2012). This finding was extended in a 28-day, open-label, proof-of-concept trial of daily, low dose (0.5 mg/kg) oral with 8 patients with symptoms of depression or depression mixed with anxiety (Irwin et al., 2013) and in a study using sublingual administration of low dose ketamine in 26 out-patients with refractory unipolar or bipolar depression (Lara, Bisol, & Munari, 2013). Both of these studies reported minimal to no psychotomimetic effects of ketamine with oral administration. Another small, open-label study found that intramuscular administration of ketamine (0.5 and 0.25 mg/kg) produced rapid (two hours) and sustained (four days) antidepressant effects to a similar magnitude to that of i.v. administration of ketamine (0.5 mg/kg). Psychotomimetic or dissociative effects were not evaluated in this study (Chilukuri et al., 2014). Finally, a double-blind, crossover clinical study has shown that intranasal administration of ketamine (50 mg) produced rapid (40 min) and sustained (two days) antidepressant effects with minimal psychotomimetic and dissociative side effects (Lapidus et al., 2014). These studies demonstrate that there may be effective alternative routes of administration of low-dose ketamine treatment for MDD that have a reduced risk of adverse side effects, which are likely a result of reduced levels of bioavailable ketamine as compared to i.v. administration of ketamine.

Several studies have evaluated potential biomarkers to determine which MDD patients may respond to ketamine treatment. For example, baseline D-serine plasma concentrations and baseline neurocognitive performance (specifically processing speed and attention) prior to initiation of ketamine infusions were significantly lower for treatment-resistant MDD patients that responded to ketamine as compared to non-responders (Moaddel et al., 2014; Murrough et al., 2014; Shiroma et al., 2014). Other potential predictors include higher body mass index (BMI), family history of alcohol abuse (i.e. first degree relatives), and no history

of suicide attempts (Niciu et al., 2014). Furthermore, the dissociative side effects produced by ketamine at 40 min (as measured by the Clinician Administered Dissociative States Scale [CADSS]) are negatively correlated to the antidepressant effects of ketamine at 230 min and day seven (i.e. higher CADSS scores were associated with lower HDRS scores) (Luckenbaugh et al., 2014). In contrast, the relationship between peripheral concentrations of brain-derived neurotropic factor (BDNF) and ketamine responders is not fully understood. Several clinical studies have reported a negative correlation between patients that respond to ketamine treatment and BDNF concentrations such that reductions in depressive symptoms are associated with increased concentrations of peripheral BDNF (Duncan et al., 2013; Haile et al., 2014; Laje et al., 2012). Conversely, the plasma concentrations of BDNF were not associated the antidepressant effects of ketamine as there was no difference in BDNF levels between ketamine responders and non- responders (Machado-Vieira et al., 2009). Moreover, a single ketamine infusion did not change the amino acid neurotransmitter (i.e. glutamate, glutamine, and GABA) concentrations in the occipital cortex as measured by ^{1}H-MRS (Valentine et al., 2011), suggesting that changes in the amino acid neurotransmitter concentrations in the occipital cortex are not associated with the antidepressant effects of ketamine. At the time of this review, there are more than 20 clinical trials evaluating the antidepressant effects of ketamine, which include studies focused on treatment-resistant MDD (e.g. NCT01920555 and NCT00088699), suicide risk (e.g. NCT02094898), and the potential biomarkers for ketamine responders (e.g. NCT02165449 and NCT01945047).

Other Glutamatergic Drugs for the Treatment of Major Depressive Disorder

Tables 5 provides a summary of the clinical trial results and the current status of the glutamatergic drugs described below for the treatment of MDD.

Noncompetitive NMDA receptor antagonists

Memantine, which was approved by the FDA for the treatment of Alzheimer's disease in 2013 and marketed by Forest Pharmaceuticals in the United States under the trade name Namenda® (Mount & Downton, 2006), is a selective low-affinity NMDA receptor antagonist that has been evaluated as a treatment for MDD. Unlike ketamine, memantine did not produce rapid or sustained antidepressant effects in clinical research. In fact, three clinical studies found that daily memantine (5-20 mg) was not superior to placebo for the treatment of MDD (Lenze et al., 2012; Smith et al., 2013; Zarate et al., 2006). A single clinical study found that daily memantine produced antidepressant effects in patients suffering from MDD comorbid with alcohol dependence, but it was not superior to the SSRI escitalopram (Muhonen, Lonngvist, Juva, & Alho, 2008). Memantine was generally well tolerated. Although ketamine and memantine possess similar binding affinity for the NMDA receptors, these NMDA antagonists do not produce similar antidepressant effects.

Low trapping NMDA receptor channel blocker

AstraZeneca originally developed the low affinity and low trapping NMDA receptor open-channel blocker AZD6765 (lanicemine) as a neuroprotective agent, but later decided to pursue lanicemine as a treatment for patients with treatment-resistant MDD with the goal of

improving safety and tolerability as well as reducing the hallucinogenic (or psychotomimetic) side effects associated with ketamine. There are published results on three different Phase II clinical trials with lanicemine. In two clinical trials (NCT00491686 and NCT00986479), a single i.v. infusion of lanicemine failed to produce any meaningful antidepressant effects in treatment-resistant MDD patients (Sanacora et al., 2013; Zarate et al., 2013). Specifically, in the first clinical trial (NCT00491686) lanicemine (100 mg) failed to produce a statistically significant reduction in depressive symptoms, which was confounded by a large placebo effect (Sanacora et al., 2013). In the second clinical trial (NCT00986479), lanicemine (150 mg) produced rapid (at 80 min) antidepressant effects following a single infusion, but these antidepressant effects dissipated by 230 mins (Zarate et al., 2013). In a third clinical trial (NCT00781742), three weeks of repeated lanicemine treatment (100 or 150 mg) was tested as an adjunctive treatment to ongoing antidepressant treatment. Lanicemine (100 and 150 mg) produced antidepressant effects after two weeks of repeated dosing, and these antidepressant effects continued until week five of the study, which was two weeks after the last lanicemine i.v. infusion (Sanacora et al., 2013). In these three clinical trials, lanicemine was well tolerated and did not produce a significant change in psychotomimetic effects (Sanacora et al., 2013; Zarate et al., 2013). However, by the end of 2013, AstraZeneca discontinued projects for lanicemine as a treatment for treatment-resistant MDD citing lack of efficacy in Phase II clinical trials.

NR2B subunit selective NMDA receptor antagonists

Pfizer developed the potent and NR2B subunit selective NMDA receptor antagonist CP-101,606 (traxoprodil) as a neuroprotectant for head injury and stroke, but later it was evaluated as an adjunctive treatment for patients with treatment-resistant MDD (Butler et al., 1998). The selectivity of traxoprodil for NR2B subunits of the NMDA receptor complex was believed to reduce the psychotomimetic effects that have been associated with the nonspecific NMDA receptor antagonist ketamine. A single eight hour infusion of traxoprodil (0.75 mg/kg per hour for 1.5 hours, then 0.05 mg/kg per hour for 6.5 hours) was evaluated as an adjunctive treatment to paroxetine (40.0 mg/day) in a double-blind between subjects design clinical study. Traxoprodil produced rapid (five days) antidepressant effects with 60% of the patients meeting response criteria. However, traxoprodil produced psychotomimetic effects in four of the nine patients that met response criteria (Preskorn et al., 2008). Although a phase II clinical trial was conducted in 2005-2006 to evaluate the effects of monotherapy traxoprodil in patients with treatment-resistant depression (NCT00163059), to date, there are no published results from these clinical trials.

Recently, the NR2B subunit selective NMDA receptor antagonist MK-0657, which was developed by Merck for the treatment of Parkinson's disease, was the first oral formulation NMDA receptor antagonist to be tested in treatment-resistant MDD patients. This was a double- blind, placebo-controlled study in which the patients received either MK-0657 (4.0-8.0 mg/d) or placebo for 12 days. MK-0657 produced inconsistent antidepressant effects from day 5 to day 12 as measured by HDRS and BDI, receptively; however, MK-0657 failed to produce a significant reduction in depression symptoms as measured by Montgomery-Asberg Depression Rating Scale (MADRS). MK-0657 did not produce psychotomimetic or adverse side effects. One possible explanation for the inconsistent

results is that the study was terminated after only five patients completed both phases of the study. Early termination of the study was due to recruitment challenges and Merck discontinued the manufacturing of the compound (Ibrahim et al., 2012). In April 2013, the neuroscience biotech company Cerecor Inc. announced that it had acquired exclusive rights from Merck to develop and commercialize MK-0657 for all human indications. Cerecor Inc. will continue to pursue MK-0657 as a rapid treatment for depression as well as other central nervous system disorders.

Partial agonist at the glycine binding site of NMDA receptors

D-cycloserine, which is a broad spectrum antibiotic used to treat tuberculosis and marketed by Eli Lilly under the trade name Seromycin®, has been evaluated in patients with treatment-resistant MDD because of the pharmacological actions produced by D-cycloserine at the NMDA receptor. D-cycloserine binds to the glycine binding site on the NMDA receptor complex and pharmacological functions as a partial agonist. Typically, partial agonists will produce agonist effects at low doses, but will produce antagonist effects at high doses. In 2006, the antidepressant effects of adjunctive D- cycloserine (250 mg/day) treatment was evaluated in a double-blind 6 week crossover study. While D-cycloserine was well tolerated and did not produce psychotomimetic effects, D- cycloserine failed to produce antidepressant effects (Heresco-Levy et al., 2006). In a recent study, a high dose (titrated up to 1000 mg/day) adjunctive treatment of D-cycloserine produced antidepressant effects after six weeks of treatment (or two week after the final 1000 mg/day was reached) (Heresco-Levy et al., 2013). To date, there are no published studies evaluating D- cycloserine as a monotherapy for the treatment of MDD. At the time of this review, participants with bipolar depression are being recruited for a Phase IV clinical trial to evaluate D-cycloserine for relapse prevention in patients that response to ketamine infusions (NCT01833897).

Naurex Inc. developed a novel compound, GLYX-13, which is a tetrapeptide (TPPT-amide), for the treatment of MDD with the goal of producing rapid antidepressant effects without producing psychotomimetic side effects. Unlike the NMDA receptor antagonists and channel blockers, GLYX-13 binds to the glycine-site of the NMDA receptor and acts as a functional partial agonist and this difference in pharmacological action is believed to reduce psychotomimetic side effects (Burgdorf et al., 2013; Moskal et al., 2005). In a Phase II clinical study comprised of 112 MDD patients across 12 United States centers, GLYX-13 produced rapid and sustained antidepressant effects following a single infusion (5.0-10.0 mg/kg; 3-15 min infusion), and, most importantly, did not produce psychotomimetic effects. Specifically, the antidepressant effects of GLYX-13 were apparent at the end of day one and persisted until day seven following the single infusion (Moskal et al., 2014). At the time of this review, a Phase II double-blind, placebo control, multi-dose clinical trial is underway (NCT01684163).

In addition to GLYX-13, Naurex Inc. has developed another novel compound NRX- 1074, which is similar to GLYX-13; however, NRX-1074 is an orally bioavailable compound and is more potent than GLYX-13. In Phase I clinical trials, NRX-1074 was well tolerated (Naurex Inc., 2014). At the time of this review, Naurex Inc. is recruiting for Phase I safety

and pharmacokinetics (NCT01856556) and Phase II multi-dose single infusion for patients with MDD (NCT02067793) clinical trials.

Excitatory amino acid transporter 2 (EAAT2) enhancer

The EAAT2 glutamate reuptake enhancer riluzole, which is approved by the FDA for the treatment of amyotrophic lateral sclerosis (ALS) and marketed by Sanofi-Aventis under the trade name (Rilutek®), has been evaluated under a number of conditions for the treatment of MDD including monotherapy, adjunctive therapy, and ketamine relapse prevention. Riluzole was evaluated as a treatment for MDD because of its duel pharmacological in the glutamatergic system. Specifically, riluzole increases the reuptake of glutamate into astrocytes via EAAT2 (Azbill, Mu, & Springer, 2000) and inhibits glutamate release (Wang, Wang, & Wang, 2004), which produces pharmacological effects similar to the effects NMDA receptor antagonists such that riluzole can reduce NMDA receptor activation by decreasing the concentrations of glutamate available to bind to postsynaptic NMDA receptors. The antidepressant effects of riluzole were first evaluated in an open-label clinical study in patients with treatment-resistant MDD. In the open-label clinical study, daily riluzole (mean dose of 169 mg/day) produced antidepressant effects on weeks three through week six as compared to baseline MADRS score. There was not a placebo control in this study (Zarate et al., 2004). In a small scale clinical study (n = 10), adjunctive riluzole (100 mg/day) treatment produced a rapid decrease in depressive symptoms from week one through week six as compared to baseline HDRS scores. There was not a placebo control in this study (Sanacora et al., 2007). Two double-blind clinical studies evaluated riluzole as relapse prevention for patients that response to a single infusion of ketamine; however, both studies found that riluzole was no more effective than placebo for ketamine relapse prevention (Ibrahim et al., 2012; Mathew et al., 2010). Moreover, riluzole did not produce antidepressant effects in patients that did not response to ketamine infusions (i.e. ketamine non-responders) (Niciu et al., 2014). In general, riluzole was well tolerated in these studies and psychotomimetic effects were not observed. At the time of this review, two Phase II double-blind, placebo control, adjunctive treatment clinical trial are underway for patients with treatment-resistant MDD (NCT01204918 and NCT01703039).

Conclusion

While a majority of MDD patients respond to monoamine based pharmacological treatments, there is a large subgroup of patients that do not response to these treatments (i.e. treatment-resistant patients). Since the first proof-of-concept study in 2000, researchers have evaluated the glutamatergic system and pursued glutamatergic-based drugs as novel mechanism for the treatment of these patients with some success. Specifically, the noncompetitive NMDA receptor antagonist ketamine produces rapid and sustained antidepressant effects in open-label, double-blind, and active-placebo clinical trials, but it also produces psychotomimetic effects (albeit, of short duration). Several potential biomarkers, such as baseline D-serine concentrations and neurocognitive baseline performance, have been identified as predictors for the patients that respond to ketamine treatment. Additionally, the glycine-site partial agonist GLYX-13 has produced rapid and sustained antidepressant effects in Phase II clinical trials with no significant

psychotomimetic effects. Other glutamatergic-based drugs (e.g. memantine and MK-0657) have failed to produce meaningful antidepressant effects in MDD patients. Tables 4 and 5 provide a summary of the clinical trial results and the current status of ketamine and other glutamatergic drugs for the treatment of MDD. Currently, preclinical research is evaluating the pharmacological and intracellular effects that are responsible for the antidepressant effects of ketamine (e.g. Li et al., 2010; Autry et al., 2011), which will aid the development of novel glutamatergic drugs (for an excellent review on the preclinical findings see Browne & Lucki, 2013). In conclusion, the clinical findings to date are encouraging and support the continued search for and the development of novel compounds, such as ketamine and GLYX-13, which target glutamatergic mechanisms for the treatment of MDD and for treatment-resistant depression.

Acknowledgments

Todd M. Hillhouse received funding support by the National Institute of Drug Abuse of the National Institutes of Health under Award Number T32DA07268 while working on this publication. Joseph H. Porter has previously received grant support from Eli Lilly and Company, H. Lundbeck A/S, Pfizer, Inc., Orexigen Therapeutics, Inc., and Roche Palo Alto LLC and currently has a research contract from Lundbeck A/S; however, Lundbeck A/S had no financial or intellectual role in the present review. We would like to thank Drs. Steve Negus, Adam Prus, and James McCullough Jr. for their guidance on portions of this review. Additionally, we thank Kevin McKee for his graphical/illustrative contribution to the glutamatergic system and glutamatergic drug targets image (Figure 1).

References

aan het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, Mathew SJ. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biological Psychiatry. 2010; 67:139–145.10.1016/j.biopsych.2009.08.038 [PubMed: 19897179]

Alam MY, Jacobsen PL, Chen Y, Serenko M, Mahableshwarkar AR. Safety, tolerability, and efficacy of vortioxetine (Lu AA21004) in major depressive disorder: Results of an open-label, flexible-dose, 52-week extension study. International Clinical Psychopharmacology. 2014; 29:36–44. [PubMed: 24169027]

Altamura AC, Mauri CM, Ferrara A, Moro RA, D'Andrea G, Zamberlan F. Plasma and platelet excitatory amino acids in psychiatric disorders. American Journal of Psychiatry. 1993; 150:1731–1733. [PubMed: 8214185]

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th. Arlington, VA: American Psychiatric Publishing; 2013.

Auer DP, Pütz B, Kraft E, Lipinski B, Schill J, Holsboer F. Reduced glutamate in the anterior cingulate cortex in depression: an in vivo proton magnetic resonance spectroscopy study. Biological Psychiatry. 2000; 47:305–313.10.1016/s0006-3223(99)00159-6 [PubMed: 10686265]

Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Peng-fei C, et al. Monteggia LM. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature. 2011; 475:91–95.10.1038/nature10130 [PubMed: 21677641]

Azbill RD, Mu X, Springer JE. Riluzole increases high-affinity glutamate uptake in rat spinal cord synaptosomes. Brain Research. 2000; 871:175–180. doi: http://dx.doi.org/10.1016/S0006-8993(00)02430-6. [PubMed: 10899284]

Bang-Andersen B, Ruhland T, Jørgensen M, Smith G, Frederiksen K, Jensen KG, et al. Stensbøl TB. Discovery of 1-[2-(2,4- Dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): A novel multimodal compound for the treatment of major depressive disorder. Journal of Medicinal Chemistry. 2011; 54:3206–3221.10.1021/jm101459g [PubMed: 21486038]

Beneyto M, Kristiansen LV, Oni-Orisan A, McCullumsmith RE, Meador-Woodruff JH. Abnormal glutamate receptor expression in the medial temporal lobe in schizophrenia and mood disorders. Neuropsychopharmacology. 2007; 32:1888–1902. [PubMed: 17299517]

Beneyto M, Meador-Woodruff JH. Lamina-Specific Abnormalities of NMDA Receptor-Associated Postsynaptic Protein Transcripts in the Prefrontal Cortex in Schizophrenia and Bipolar Disorder. Neuropsychopharmacology. 2008; 33(9):2175–2186. doi: http://www.nature.com/npp/journal/v33/n9/suppinfo/1301604s1.html. [PubMed: 18033238]

Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. Biological Psychiatry. 2000; 47:351–354.10.1016/s0006-3223(99)00230-9 [PubMed: 10686270]

Berman RM, Sanacora G, Anand A, Roach LM, Fasula MK, Finkelstein CO, et al. Charney DS. Monoamine depletion in unmedicated depressed subjects. Biological Psychiatry. 2002; 51:469–473. doi: http://dx.doi.org/10.1016/S0006-3223(01)01285-9. [PubMed: 11922881]

Bernard R, Kerman IA, Thompson RC, Jones EG, Bunney WE, Barchas JD, et al. Watson SJ. Altered expression of glutamate signaling, growth factor, and glia genes in the locus coeruleus of patients with major depression. Molecular Psychiatry. 2011; 16:634–646.10.1038/mp.2010.44 [PubMed: 20386568]

Berk M, Plein H, Ferreira D. Platelet glutamate receptor supersensitivity in major depressive disorder. Clinical Neuropharmacology. 2001; 24:129–132. [PubMed: 11391122]

Billett EE. Monoamine oxidase (MAO) in human peripheral tissues. Neurotoxicology. 2004; 25(1–2):139–148. doi: http://dx.doi.org/10.1016/S0161-813X(03)00094-9. [PubMed: 14697888]

Birnbaum HG, Kessler RC, Kelley D, Ben-Hamadi R, Joish VN, Greenberg PE. Employer burden of mild, moderate, and severe major depressive disorder: mental health services utilization and costs, and work performance. Depression & Anxiety. 2010; 27:78–89.10.1002/da.20580 [PubMed: 19569060]

Block W, Träber F, von Widdern O, Metten M, Schild H, Maier W, et al. Jessen F. Proton MR spectroscopy of the hippocampus at 3 T in patients with unipolar major depressive disorder: correlates and predictors of treatment response. The International Journal of Neuropsychopharmacology. 2009; 12:415–422.10.1017/S1461145708009516 [PubMed: 18845018]

Boulenger JP, Loft H, Florea I. A randomized clinical study of Lu AA21004 in the prevention of relapse in patients with major depressive disorder. Journal of Psychopharmacology. 2012; 26:1408–1416.10.1177/0269881112441866 [PubMed: 22495621]

Boulenger JP, Loft H, Olsen CK. Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: A randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. International Clinical Psychopharmacology. 2014; 29:138–149. [PubMed: 24257717]

Bresink I, Danysz W, Parsons CG, Mutschler E. Different binding affinities of NMDA receptor channel blockers in various brain regions—Indication of NMDA receptor heterogeneity. Neuropharmacology. 1995; 34:533–540.10.1016/0028-3908(95)00017-z [PubMed: 7566488]

Browne CA, Lucki I. Antidepressant effects of ketamine: Mechanisms underlying fast-acting novel antidepressants. Frontiers in Pharmacology. 2013; 4:1–18.10.3389/fphar.2013.00161 [PubMed: 23346057]

Bunney WE Jr, Davis JM. Norepinephrine in depressive reactions: A review. Archives of General Psychiatry. 1965; 13:483–494.10.1001/archpsyc.1965.01730060001001 [PubMed: 5320621]

Burgdorf J, Zhang Xl, Nicholson KL, Balster RL, David Leander J, Stanton PK, et al. Moskal JR. GLYX-13, a NMDA receptor glycine-site functional partial agonist, induces antidepressant-like effects without ketamine-like side effects. Neuropsychopharmacology. 2013; 38:729–742. [PubMed: 23303054]

Butler TW, Blake JF, Bordner J, Butler P, Chenard BL, Collins MA, et al. Zhao D. (3R,4S)-3-[4-(4-Fluorophenyl)-4-hydroxypiperidin-1-yl]chroman-4,7-diol: A conformationally restricted analogue of the NR2B subtype-selective NMDA antagonist (1S,2S)-1-(4-Hydroxyphenyl)-2- (4-hydroxy-4-phenylpiperidino)-1-propanol. Journal of Medicinal Chemistry. 1998; 41:1172–1184.10.1021/jm9707986 [PubMed: 9544217]

Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, Shaw JL, Thompson L, Nelson DL, et al. Wong DT. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors.

Neuropsychopharmacology. 2001; 25:871–880. doi: http://dx.doi.org/10.1016/S0893-133X(01)00298-6. [PubMed: 11750180]

Bymaster FP, Katner JS, Nelson DL, Hemrick-Luecke SK, Threlkeld PG, Heiligenstein JH, et al. Perry KW. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: A potential mechanism for efficacy in attention deficit/hyperactivity disorder. Neuropsychopharmacology. 2002; 27:699–711. [PubMed: 12431845]

Campbell I, Marangos P, Parma A, Garrick N, Murphy D. Localization of monoamine oxidases A and B in primate brains relative to neuron-specific and non- neuronal enolases. Neurochemical Research. 1982; 7:657–666.10.1007/bf00965519 [PubMed: 7121716]

Chen TY, Tzeng NS. Aripiprazole: A dopamine modulator that mimics methylphenidate in producing faster antidepressant effects. Medical Hypotheses. 2013; 81:183–185. doi: http://dx.doi.org/10.1016/j.mehy.2013.05.009. [PubMed: 23751312]

Chilukuri H, Pothula Reddy N, Mohan Pathapati R, Nagesha Manu A, Jollu S, Basha Shaik A. Acute antidepressant effects of intramuscular versus intravenous ketamine. Indian Journal of Psychological Medicine. 2014; 36:71–76.10.4103/0253-7176.127258 [PubMed: 24701015]

Choudary PV, Molnar M, Evans SJ, Tomita H, Li JZ, Vawter MP, et al. Jones EG. Altered cortical glutamatergic and GABAergic signal transmission with glial involvement in depression. Proceedings of the National Academy of Sciences of the United States of America. 2005; 102:15653–15658. [PubMed: 16230605]

Chandley MJ, Szebeni A, Szebeni K, Crawford JD, Stockmeier CA, Turecki G, et al. Ordway GA. Elevated gene expression of glutamate receptors in noradrenergic neurons from the locus coeruleus in major depression. The International Journal of Neuropsychopharmacology. 2014:1–10.10.1017/S1461145714000662 [PubMed: 23953038]

Charney DS. Monoamine dysfunction and the pathophysiology and treatment of depression. Journal of Clinical Psychiatry. 1998; 59(Suppl):11–14. [PubMed: 9818625]

Clayton AH, Pradko JF, Croft HA, Montano CB, Leadbetter RA, Bolden-Watson C, et al. Metz A. Prevalence of sexual dysfunction among newer antidepressants. Journal of Clinical Psychiatry. 2002; 63:357–366. [PubMed: 12000211]

Cusack B, Nelson A, Richelson E. Binding of antidepressants to human brain receptors: focus on newer generation compounds. Psychopharmacology. 1994; 114:559–565.10.1007/bf02244985 [PubMed: 7855217]

Delgado PL. Depression: The case for a monoamine deficiency. Journal of Clinical Psychiatry. 2000; 61(Supp 6):7–11. [PubMed: 10775018]

Delgado PL, Price LH, Miller HL, et al. Serotonin and the neurobiology of depression: Effects of tryptophan depletion in drug-free depressed patients. Archives of General Psychiatry. 1994; 51:865–874.10.1001/archpsyc.1994.03950110025005 [PubMed: 7944875]

DiazGranados N, Ibrahim L, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA, et al. Zarate CA Jr. A randomized add-on trial of an n-methyl-d-aspartate antagonist in treatment-resistant bipolar depression. Archives of General Psychiatry. 2010; 67:793–802.10.1001/archgenpsychiatry.2010.90 [PubMed: 20679587]

Domino EF. History of modern psychopharmacology: A personal view with an emphasis on antidepressants. Psychosomatic Medicine. 1999; 61:591–598. [PubMed: 10511010]

Domino EF. Taming the Ketamine Tiger. Anesthesiology. 2010; 113:678–684. [PubMed: 20693870]

Drug Enforcement Administration. Ketamine. Springfield, VA: US Department of Justice, Drug Enforcement Administration; 2013.

du Jardin KG, Jensen JB, Sanchez C, Pehrson AL. Vortioxetine dose- dependently reverses 5-HT depletion-induced deficits in spatial working and object recognition memory: A potential role for 5-HT1A receptor agonism and 5-HT3 receptor antagonism. European Neuropsychopharmacology. 2014; 24:160–171. doi: http://dx.doi.org/10.1016/j.euroneuro.2013.07.001. [PubMed: 23916504]

Duncan WCJ, Sarasso S, Ferrarelli F, Selter J, Riedner BA, Hejazi NS, et al. Zarate CAJ. Concomitant BDNF and sleep slow wave changes indicate ketamine- induced plasticity in major depressive disorder. The International Journal of Neuropsychopharmacology. 2013; 16:301–311.10.1017/S1461145712000545 [PubMed: 22676966]

Faguis J, Osterman PO, Siden A, Wiholm BE. Guillain-Barre syndrome following zimeldine treatment. Journal of Neurology, Neurosurgery, and Psychiatry. 1985; 48:65–69.

Fangmann P, Assion HJ, Juckel G, Gonzalez CA, Lopez-Munoz F. Half a century of antidepressant drugs: On the clinical introduction of monoamine oxidase inhibitors, tricyclics, and tetracyclics. Part II: Tricyclics, and tetracyclics. Journal of Clinical Psychopharmacology. 2008; 28:1–4. [PubMed: 18204333]

Fava M. Diagnosis and definition of treatment-resistant depression. Biological Psychiatry. 2003; 53:649–659. [PubMed: 12706951]

Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. The Psychiatric Clinics of North America. 1996; 19:179–200. [PubMed: 8827185]

Fava M, Rush JA, Thase ME, Clayton A, Stahl SM, Pradko JF, Johnston AJ. 15 years of clinical experience with bupropion HCl: From bupropion to bupropion SR to bupropion XL. Primary Care Companion to The Journal of Clinical Psychiatry. 2005; 7:106–113.

Fava M, Rush AJ, Trivedi MH, Nierenberg AA, Thase ME, Sackeim HA, et al. Kupfer DJ. Background and rationale for the sequenced treatment alternatives to relieve depression (STAR*D) study. The Psychiatric Clinics of North America. 2003; 26:457–494. [PubMed: 12778843]

Feighner JP, Hendrickson G, Miller LL, Stern WC. Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. Journal of Clinical Psychopharmacology. 1986; 6:27–32. [PubMed: 3081600]

Feighner JP, Meredith CH, Stern WC, Hendrickson G, Miller LL. A double-blind study of bupropion and placebo in depression. American Journal of Psychiatry. 1984; 141:525–529. [PubMed: 6422779]

Feyissa AM, Chandran A, Stockmeier CA, Karolewicz B. Reduced levels of NR2A and NR2B subunits of NMDA receptor and PSD-95 in the prefrontal cortex in major depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2009; 33:70–75.10.1016/j.pnpbp.2008.10.005 [PubMed: 18992785]

Fox HH, Gibas JT. Synthetic tuberculostats. VII monoalkyl derivatives of isonicotinylhydrazine. Journal of Organic Chemistry. 1953; 18:994–1002.

Garakani A, Martinez JM, Yehuda R, Gorman JM. Cerebrospinal fluid levels of glutamate and corticotropin releasing hormone in major depression before and after treatment. Journal of Affective Disorders. 2013; 146:262–265. doi: http://dx.doi.org/10.1016/j.jad.2012.06.037. [PubMed: 22840611]

Ghasemi M, Kazemi MH, Yoosefi A, Ghasemi A, Paragomi P, Amini H, Afzali MH. Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder. Psychiatry Research. 2014; 215:355–361. doi: http://dx.doi.org/10.1016/j.psychres.2013.12.008. [PubMed: 24374115]

Gibb A, Deeks E. Vortioxetine: First global approval. Drugs. 2014; 74:135–145.10.1007/s40265-013-0161-9 [PubMed: 24311349]

Greenberg P, Kessler R, Birnbaum H, Leong S, Lowe S, Berglund P, Corey-Lisle P. The economic burden of depression in the United States: How did it change between 1990 and 2000? Journal of Clinical Psychiatry. 2003; 64:1465–1475. [PubMed: 14728109]

Haile CN, Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Foulkes A, et al. Mathew SJ. Plasma brain derived neurotrophic factor (BDNF) and response to ketamine in treatment-resistant depression. The International Journal of Neuropsychopharmacology. 2014; 17:331–336.10.1017/S1461145713001119 [PubMed: 24103211]

Hashimoto K, Sawa A, Iyo M. Increased levels of glutamate in brains from patients with mood disorders. Biological Psychiatry. 2007; 62:1310–1316.10.1016/j.biopsych.2007.03.017 [PubMed: 17574216]

Hasler G, van der Veen J, Tumonis T, Meyers N, Shen J, Drevets WC. Reduced prefrontal glutamate/glutamine and γ-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. Archives of General Psychiatry. 2007; 64:193–200.10.1001/archpsyc.64.2.193 [PubMed: 17283286]

Heninger GR, Delgado PL, Charney DS. The revised monoamine theory of depression: a modulatory role for monoamines, based on new findings from monoamine depletion experiments in humans. Pharmacopsychiatry. 1996; 29:2–11. [PubMed: 8852528]

Heresco-Levy U, Gelfin G, Bloch B, Levin R, Edelman S, Javitt DC, Kremer I. A randomized add-on trial of high-dose d-cycloserine for treatment-resistant depression. The International Journal of Neuropsychopharmacology. 2013; 16:501–506.10.1017/S1461145712000910 [PubMed: 23174090]

Heresco-Levy U, Javitt DC, Gelfin Y, Gorelik E, Bar M, Blanaru M, Kremer I. Controlled trial of d-cycloserine adjuvant therapy for treatment-resistant major depressive disorder. Journal of Affective Disorders. 2006; 93(1–3):239–243. doi: http://dx.doi.org/10.1016/j.jad.2006.03.004. [PubMed: 16677714]

Hirota K, Hashimoto Y, Lambert DG. Interaction of intravenous anesthetics with recombinant human M1-M3 muscarinic receptors expressed in Chinese hamster ovary cells. Anesthesia & Analgesia. 2002; 95:1607–1610.10.1213/01.ane.0000037146.52925.d5 [PubMed: 12456425]

Hirschfeld RMA. History and evolution of the monoamine hypothesis depression. Journal of Clinical Psychiatry. 2000; 61(Supp 6):4–6. [PubMed: 10775017]

Holly, EN.; LaCrosse, AL.; Hillhouse, TM. Review of Group I and Group II metabotropic glutamate receptors, and their role in the pathophysiology of major depressive disorder. In: Foster, OM., editor. Metabotropic Glutamate Receptors: Molecular Mechanisms, Role in Neurological Disorders, and Pharmacological Effects. Hauppauge, NY: Nova Science Publishers; 2014.

Ibrahim L, DiazGranados N, Franco-Chaves J, Brutsche N, Henter ID, Kronstein P, et al. Zarate CA Jr. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: Results from a 4-week, double- blind, placebo-controlled study. Neuropsychopharmacology. 2012; 37:1526–1533. [PubMed: 22298121]

Ibrahim L, DiazGranados N, Jolkovsky L, Brutsche N, Luckenbaugh DA, Herring WJ, et al. Zarate CA Jr. A randomized, placebo-controlled, crossover pilot trial of the oral selective NR2B antagonist MK-0657 in patients with treatment-resistant major depressive disorder. Journal of Clinical Psychopharmacology. 2012; 32:551–557. [PubMed: 22722512]

Irwin SA, Iglewicz A. Oral ketamine for the rapid treatment of depression and anxiety in patients receiving hospice care. Journal of Palliative Medicine. 2010; 13:903–908.10.1089/jpm.2010.9808 [PubMed: 20636166]

Irwin SA, Iglewicz A, Nelesen RA, Lo JY, Carr CH, Romero SD, Lloyd LS. Daily oral ketamine for the treatment of depression and anxiety in patients receiving hospice care: A 28-day open-label proof-of-concept trial. Journal of Palliative Medicine. 2013; 16:958–965.10.1089/jpm.2012.0617 [PubMed: 23805864]

Jensen JB, du Jardin KG, Song D, Budac D, Smagin G, Sanchez C, Pehrson AL. Vortioxetine, but not escitalopram or duloxetine, reverses memory impairment induced by central 5-HT depletion in rats: Evidence for direct 5-HT receptor modulation. European Neuropsychopharmacology. 2014; 24:148–159. doi: http://dx.doi.org/10.1016/j.euroneuro.2013.10.011. [PubMed: 24284262]

Jordan S, Chen R, Fernalld R, Johnson J, Regardie K, Kambayashi J, et al. Kikuchi T. In vitro biochemical evidence that the psychotomimetics phencyclidine, ketamine and dizocilpine (MK-801) are inactive at cloned human and rat dopamine D2 receptors. European Journal of Pharmacology. 2006; 540(1–3):53–56.10.1016/j.ejphar.2006.04.026 [PubMed: 16730695]

Kapur S, Seeman P. NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D2 and serotonin 5-HT2 receptors implications for models of schizophrenia. Molecular Psychiatry. 2002; 7:837–844.10.1038/sj.mp.4001093 [PubMed: 12232776]

Karolewicz B, Stockmeier CA, Ordway GA. Elevated levels of the NR2C subunit of the NMDA receptor in the locus coeruleus in depression. Neuropsychopharmacology. 2005; 30:1557–1567. [PubMed: 15920498]

Karolewicz B, Szebeni K, Gilmore T, Maciag D, Stockmeier CA, Ordway GA. Elevated levels of NR2A and PSD-95 in the lateral amygdala in depression. The International Journal of Neuropsychopharmacology. 2009; 12:143–153.10.1017/S1461145708008985 [PubMed: 18570704]

Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. Wang PS. The epidemiology of major depressive disorder: Results from the national comorbidity survey

replication (NCS-R). JAMA: The Journal of the American Medical Association. 2003; 289:3095–3105.10.1001/jama.289.23.3095

Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. International Journal of Methods in Psychiatric Research. 2012; 21:169–184.10.1002/mpr.1359 [PubMed: 22865617]

Kew JC, Kemp J. Ionotropic and metabotropic glutamate receptor structure and pharmacology. Psychopharmacology (Berl). 2005; 179:4–29.10.1007/s00213-005-2200-z [PubMed: 15731895]

Kirshner N. Uptake of Catecholamines by a Particulate Fraction of the Adrenal Medulla. Journal of Biological Chemistry. 1962; 237(7):2311–2317. [PubMed: 14456353]

Küçükibrahimoğlu E, Saygın M, Çalışkan M, Kaplan O, Ünsal C, Gören MZ. The change in plasma GABA, glutamine and glutamate levels in fluoxetine- or S- citalopram-treated female patients with major depression. European Journal of Clinical Pharmacology. 2009; 65:571–577.10.1007/s00228-009-0650-7 [PubMed: 19373461]

Laje G, Lally N, Mathews D, Brutsche N, Chemerinski A, Akula N, et al. Zarate C Jr. Brain-Derived Neurotrophic Factor Val66Met Polymorphism and Antidepressant Efficacy of Ketamine in Depressed Patients. Biological Psychiatry. 2012; 72:e27–e28. doi: http://dx.doi.org/10.1016/j.biopsych.2012.05.031. [PubMed: 22771240]

Lally N, Nugent AC, Luckenbaugh DA, Ameli R, Roiser JP, Zarate CA. Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression. Translational Psychiatry. 2014; 4:e469.10.1038/tp.2014.105 [PubMed: 25313512]

Lapidus, KAB.; Levitch, CF.; Perez, AM.; Brallier, JW.; Parides, MK.; Soleimani, L.; et al. Murrough, JW. A randomized controlled trial of intranasal ketamine in major depressive disorder; Biological Psychiatry. 2014. p. 1-7.doi: http://dx.doi.org/10.1016/j.biopsych.2014.03.026

Lara DR, Bisol LW, Munari LR. Antidepressant, mood stabilizing and procognitive effects of very low dose sublingual ketamine in refractory unipolar and bipolar depression. The International Journal of Neuropsychopharmacology. 2013; 16:2111–2117.10.1017/S1461145713000485 [PubMed: 23683309]

Lee S, Jeong J, Kwak Y, Park SK. Depression research: where are we now? Molecular Brain. 2010; 3:1–10. [PubMed: 20205802]

Lenze EJ, Skidmore ER, Begley AE, Newcomer JW, Butters MA, Whyte EM. Memantine for late-life depression and apathy after a disabling medical event: a 12-week, double-blind placebo-controlled pilot study. International Journal of Geriatric Psychiatry. 2012; 27:974–980.10.1002/gps.2813 [PubMed: 22173933]

Letchworth SR, Smith HR, Porrino LJ, Bennett BA, Davies HML, Sexton T, Childers SR. Characterization of a tropane radioligand, [3H]2β-Propanoyl-3β- (4-tolyl) Tropane ([3H]PTT), for dopamine transport sites in rat brain. Journal of Pharmacology and Experimental Therapeutics. 2000; 293:686–696. [PubMed: 10773045]

Levine J, Panchalingam K, Rapoport A, Gershon S, McClure RJ, Pettegrew JW. Increased cerebrospinal fluid glutamine levels in depressed patients. Biological Psychiatry. 2000; 47:586–593.10.1016/s0006-3223(99)00284-x [PubMed: 10745050]

Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, et al. Duman RS. mTOR-Dependent Synapse Formation Underlies the Rapid Antidepressant Effects of NMDA Antagonists. Science. 2010; 329:959–964.10.1126/science.1190287 [PubMed: 20724638]

Lopez-Munoz F, Alamo C, Juckel G, Assion HJ. Half a century of antidepressant drugs: On the clinical introduction of monoamine oxidase inhibitors, tricyclics, and tetracyclics. Part I: Monoamine oxidase inhibitors. Journal of Clinical Psychopharmacology. 2007; 27:555–559. [PubMed: 18004120]

Lord B, Wintmolders C, Langlois X, Nguyen L, Lovenberg T, Bonaventure P. Comparison of the ex vivo receptor occupancy profile of ketamine to several NMDA receptor antagonists in mouse hippocampus. European Journal of Phamacology. 2013; 715(1-3):21–25. doi: http://dx.doi.org/10.1016/j.ejphar.2013.06.028.

Luckenbaugh DA, Niciu MJ, Ionescu DF, Nolan NM, Richards EM, Brutsche NE, et al. Zarate CA Jr. Do the dissociative side effects of ketamine mediate its antidepressant effects? Journal of

Affective Disorders. 2014; 159:56–61. doi: http://dx.doi.org/10.1016/j.jad.2014.02.017. [PubMed: 24679390]

Lotufo-Neto F, Trivedi M, Thase ME. Meta-Analysis of the Reversible Inhibitors of Monoamine Oxidase Type A Moclobemide and Brofaromine for the Treatment of Depression. Neuropsychopharmacology. 1999; 20:226–247. [PubMed: 10063483]

Machado-Vieira R, Manji HK, Zarate CA. The role of the tripartite glutamatergic synapse in the pathophysiology and therapeutics of mood disorders. The Neuroscientist. 2009; 15:525–539.10.1177/1073858409336093 [PubMed: 19471044]

Machado-Vieira R, Yuan P, Brutsche N, DiazGranados N, Luckenbaugh D, Manji HK, Zarate CA Jr. Brain-derived neurotrophic factor and initial antidepressant response to an N-Methyl-D-Aspartate antagonist. Journal of Clinical Psychiatry. 2009; 70:1662–1666. [PubMed: 19744406]

Maes M, Verkerk R, Vandoolaeghe E, Lin A, Scharpé S. Serum levels of excitatory amino acids, serine, glycine, histidine, threonine, taurine, alanine and arginine in treatment-resistant depression: modulation by treatment with antidepressants and prediction of clinical responsivity. Acta Psychiatrica Scandinavica. 1998; 97(Suppl):302–308.10.1111/j.1600-0447.1998.tb10004.x [PubMed: 9570492]

Marsden WN. Stressor-induced NMDAR dysfunction as a unifying hypothesis for the aetiology, pathogenesis and comorbidity of clinical depression. Medical Hypotheses. 2011; 77:508–528. doi: http://dx.doi.org/10.1016/j.mehy.2011.06.021. [PubMed: 21741771]

Mathew SJ, Murrough JW, aan het Rot M, Collins KA, Reich DL, Charney DS. Riluzole for relapse prevention following intravenous ketamine in treatment- resistant depression: a pilot randomized, placebo-controlled continuation trial. The International Journal of Neuropsychopharmacology. 2010; 13:71–82.10.1017/S1461145709000169 [PubMed: 19288975]

Mathews DC, Henter ID, Zarate CAJ. Targeting the glutamatergic system to treat major depressive disorder: Rationale and progress to date. Drugs. 2012; 72:1313–1333. 1310.2165/11633130-000000000-000000000. [PubMed: 22731961]

Mauri MC, Ferrara A, Boscati L, Bravin S, Zamberlan F, Alecci M, Invernizzi G. Plasma and platelet amino acid concentrations in patients affected by major depression and under fluvoxamine treatment. Neuropsychobiology. 1998; 37:124–129. [PubMed: 9597668]

McCambridge J, Winstock A, Hunt N, Mitcheson L. 5-Year trends in use of hallucinogens and other adjunct drugs among UK dance drug users. European Addiction Research. 2007; 13:57–64. [PubMed: 17172780]

McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo- controlled study of vortioxetine on cognitive function in depressed adults. The International Journal of Neuropsychopharmacology. 2014:1–11.10.1017/S1461145714000546 [PubMed: 23953038]

McNulty JP, Hahn K. Compounded oral ketamine. The International Journal of Pharmaceutical Compounding. 2012; 16:364–368.

Mendelsohn LG, Kalra V, Johnson BG, Kerchner GA. Sigma opioid receptor: characterization and co-identity with the phencyclidine receptor. Journal of Pharmacology and Experimental Therapeutics. 1985; 233:597–602. [PubMed: 2989489]

Michael N, Erfurth A, Ohrmann P, Arolt V, Heindel W, Pfleiderer B. Metabolic changes within the left dorsolateral prefrontal cortex occurring with electroconvulsive therapy in patients with treatment resistant unipolar depression. Psychological Medicine. 2003; 33:1277–1284.10.1017/S0033291703007931 [PubMed: 14580081]

Millan MJ, Gobert A, Lejeune F, Newman-Tancredi A, Rivet JM, Auclair A, Peglion JL. S33005, a novel ligand at both serotonin and norepinephrine transporters: I. receptor binding, electrophysiological, and neurochemical profile in comparison with venlafaxine, reboxetine, citalopram, and clomipramine. Journal of Pharmacology and Experimental Therapeutics. 2001; 298:565–580. [PubMed: 11454918]

Mirza Y, Tang J, Russell A, Banerjee SP, Bhandari R, Ivey J, et al. Rosenberg DR. Reduced anterior cingulate cortex glutamatergic concentrations in childhood major depression. Journal of the American Academy of Child & Adolescent Psychiatry. 2004; 43:341–348.10.1097/00004583-200403000-00017 [PubMed: 15076268]

Moaddel R, Luckenbaugh D, Xie Y, Villaseñor A, Brutsche N, Machado-Vieira R, et al. Wainer I. D-serine plasma concentration is a potential biomarker of (R,S)- ketamine antidepressant response in subjects with treatment-resistant depression. Psychopharmacology. 2014:1–11.10.1007/s00213-014-3669-0

Montgomery SA, Gabriel R, James D, Hawley C, Burkitt P. The specificity of the zimelidine reaction. International Clinical Psychopharmacology. 1989; 4:19–23. [PubMed: 2531772]

Moreira R. The efficacy and tolerability of bupropion in the treatment of major depressive disorder. Clinical Drug Investigation. 2011; 31:5–17.10.2165/1159616-s0-000000000-00000 [PubMed: 22015858]

Mørk A, Pehrson A, Brennum LT, Nielsen SM, Zhong H, Lassen AB, et al. Stensbøl TB. Pharmacological effects of Lu AA21004: A novel multimodal compound for the treatment of major depressive disorder. Journal of Pharmacology and Experimental Therapeutics. 2012; 340:666–675.10.1124/jpet.111.189068 [PubMed: 22171087]

Mørk A, Montezinho LP, Miller S, Trippodi-Murphy C, Plath N, Li Y, et al. Sanchez C. Vortioxetine (Lu AA21004), a novel multimodal antidepressant, enhances memory in rats. Pharmacology Biochemistry and Behavior. 2013; 105:41–50. doi: http://dx.doi.org/10.1016/j.pbb.2013.01.019.

Moskal JR, Burch R, Burgdorf JS, Kroes RA, Stanton PK, Disterhoft JF, Leander JD. GLYX-13, an NMDA receptor glycine site functional partial agonist enhances cognition and produces antidepressant effects without the psychotomimetic side effects of NMDA receptor antagonists. Expert Opinion on Investigational Drugs. 2014; 23:243–254.10.1517/13543784.2014.852536 [PubMed: 24251380]

Moskal JR, Kuo AG, Weiss C, Wood PL, O'Connor Hanson A, Kelso S, et al. Disterhoft JF. GLYX-13: A monoclonal antibody-derived peptide that acts as an N-methyl-d-aspartate receptor modulator. Neuropharmacology. 2005; 49:1077–1087. doi: http://dx.doi.org/10.1016/j.neuropharm.2005.06.006. [PubMed: 16051282]

Mount C, Downton C. Alzheimer disease: progress or profit? Nature Medicine. 2006; 12:780–784.10.1038/nm0706-780

Muhonen LH, Lonngvist J, Juva K, Alho H. Double-blind, randomized comparison of memantine and escitalopram for the treatment of major depressive disorder comorbid with alcohol dependence. Journal of Clinical Psychiatry. 2008; 69:392–399. [PubMed: 18348597]

Muller JC, Pryor WW, Gibbons JE, Orgain ES. Depression and anxiety occurring during rauwolfia therapy. Journal of the American Medical Association. 1955; 159:836–839.10.1001/jama.1955.02960260006002 [PubMed: 13263127]

Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, et al. Mathew SJ. Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site randomized controlled trial. American Journal of Psychiatry. 2013; 170:1134–1142.10.1176/appi.ajp.2013.13030392 [PubMed: 23982301]

Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, et al. Iosifescu DV. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biological Psychiatry. 2013; 74:250–256. doi: http://dx.doi.org/10.1016/j.biopsych.2012.06.022. [PubMed: 22840761]

Murrough J, Wan LB, Iacoviello B, Collins K, Solon C, Glicksberg B, et al. Burdick K. Neurocognitive effects of ketamine in treatment-resistant major depression: association with antidepressant response. Psychopharmacology. 2014; 231:481–488.10.1007/s00213-013-3255-x

National Institute of Mental Health's Psychoactive Drug Screening Program. 2014. Contract # HHSN-271-2013-00017-C (NIMH PDSP). Available from http://pdsp.med.unc.edu/

Naurex Inc. Naurex reports positive top-line phase 2b results for novel antidepressant GLYX-13 and advances NRX-1074 into phase 2 depression study. 2014. Retrieved from http://naurex.com/wp-content/uploads/2014/05/Naurex_Clinical_Advances-2014.05.06.pdf

Niciu MJ, Luckenbaugh D, Ionescu DF, Guevara S, Machado-Vieira R, Richards EM, et al. Zarate CA Jr. Clinical predictors of ketamine response in treatment- resistant major depression. Journal of Clinical Psychiatry. 2014; 75:417–423.

Niciu, MJ.; Luckenbaugh, DA.; Ionescu, DF.; Richards, Erica M.; Vande Voort, JL.; Ballard, ED.; et al. Zarate, CA, Jr. Riluzole likely lacks antidepressant efficacy in ketamine non-responders;

Journal of Psychiatric Research. 2014. p. 1-3.doi: http://dx.doi.org/10.1016/j.jpsychires.2014.07.022

Nilsson BS. Adverse reactions in connection with zimeldine treatment--a review. Acta Psychiatrica Scandinavica. 1983; 308(Suppl):115–119. [PubMed: 6230884]

Nishimura M, Sato K, Okada T, Yoshiya I, Schloss P, Shimada S, Tohyama M. Ketamine inhibits monoamine transporters expressed in human embryonic kidney 293 cells. Anesthesiology. 1998; 88:768–774. [PubMed: 9523822]

Nudmamud-Thanoi S, Reynolds GP. The NR1 subunit of the glutamate/NMDA receptor in the superior temporal cortex in schizophrenia and affective disorders. Neuroscience Letters. 2004; 372(1–2):173–177. doi: http://dx.doi.org/10.1016/j.neulet.2004.09.035. [PubMed: 15531111]

Owens MJ, Morgan WN, Plott SJ, Nemeroff CB. Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. Journal of Pharmacology and Experimental Therapeutics. 1997; 283:1305–1322. [PubMed: 9400006]

Papakostas GI. Tolerability of modern antidepressants. Journal of Clinical Psychiatry. 2008; 69(suppl E1):8–13. [PubMed: 18494538]

Palucha A, Pilc A. The involvement of glutamate in the pathology of depression. Drug News Perspective. 2005; 18:262–268. doi:101358/dmp.2005.18.4.908661.

Papakostas GI. Serotonin norepinephrine reuptake inhibitors: Spectrum of efficacy in major depressive disorder. Primary Psychiatry. 2009; 16(Suppl 4):16–24.

Papakostas GI, Thase ME, Fava M, Nelson JC, Shelton RC. Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. Biological Psychiatry. 2007; 62:1217–1227. doi: http://dx.doi.org/10.1016/j.biopsych.2007.03.027. [PubMed: 17588546]

Pearce EF, Murphy JA. Vortioxetine for the treatment of depression. Annals of Pharmacotherapy. 2014; 48:758–765.10.1177/1060028014528305 [PubMed: 24676550]

Pfleiderer B, Michael N, Erfurth A, Ohrmann P, Hohmann U, Wolgast M, et al. Heindel W. Effective electroconvulsive therapy reverses glutamate/glutamine deficit in the left anterior cingulum of unipolar depressed patients. Psychiatry Research: Neuroimaging. 2003; 122:185–192. doi: http://dx.doi.org/10.1016/S0925-4927(03)00003-9.

Pin JP, Duvoisin R. The metabotropic glutamate receptors: Structure and functions. Neuropharmacology. 1995; 34:1–26. doi: http://dx.doi.org/10.1016/0028-3908(94)00129-G. [PubMed: 7623957]

Pletscher A. The discovery of antidepressants: A winding path. Experientia. 1991; 47:4–8.10.1007/bf02041242 [PubMed: 1999242]

Preskorn SH, Baker B, Kolluri S, Menniti FS, Krams M, Landen JW. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-Methyl-D-Aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. Journal of Clinical Psychopharmacology. 2008; 28:631–637. [PubMed: 19011431]

Price RB, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Iqbal SZ, et al. Mathew SJ. Effects of ketamine on explicit and implicit suicidal cognition: A randomized controlled trial in treatment-resistant depression. Depression and Anxiety. 2014; 31:335–343.10.1002/da.22253 [PubMed: 24668760]

Price RB, Nock MK, Charney DS, Mathew SJ. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biological Psychiatry. 2009; 66:522–526. doi: http://dx.doi.org/10.1016/j.biopsych.2009.04.029. [PubMed: 19545857]

Pristupa ZB, Wilson JM, Hoffman BJ, Kish SJ, Niznik HB. Pharmacological heterogeneity of the cloned and native human dopamine transporter: disassociation of [3H]WIN 35,428 and [3H]GBR 12,935 binding. Molecular Pharmacology. 1994; 45:125–135. [PubMed: 8302271]

Rasmussen KG, Lineberry TW, Galardy CW, Kung S, Lapid MI, Palmer BA, et al. Frye MA. Serial infusions of low-dose ketamine for major depression. Journal of Psychopharmacology. 2013; 27:444–450.10.1177/0269881113478283 [PubMed: 23428794]

Rothman RB, Baumann MH, Dersch CM, Romero DV, Rice KC, Carroll FI, Partilla JS. Amphetamine-type central nervous system stimulants release norepinephrine more potently than

they release dopamine and serotonin. Synapse. 2001; 39:32–41.10.1002/1098-2396(20010101)39:1<32: :aid-syn5>3.0.co;2-3 [PubMed: 11071707]

Roth BL, Gibbons S, Arunotayanun W, Huang XP, Setola V, Treble R, Iversen L. The ketamine analogue methoxetamine and 3- and 4-Methoxy analogues of phencyclidine are high affinity and selective ligands for the glutamate NMDA receptor. PLoS ONE. 2013; 8:e59334.10.1371/journal.pone.0059334 [PubMed: 23527166]

Rush A, Trivedi M, Wisniewski S, Nierenberg A, Stewart J, Warden D, et al. Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. American Journal of Psychiatry. 2006; 163:1905–1917. [PubMed: 17074942]

Salomon RM, Miller HL, Krystal JH, Heninger GR, Charney DS. Lack of behavioral effects of monoamine depletion in healthy subjects. Biological Psychiatry. 1997; 41:58–64. doi: http://dx.doi.org/10.1016/0006-3223(95)00670-2. [PubMed: 8988796]

Sanacora G, Gueorguieva R, Epperson C, Wu YT, Appel M, Rothman DL, et al. Mason GF. Subtype-specific alterations of γ-aminobutyric acid and glutamatein patients with major depression. Archives of General Psychiatry. 2004; 61:705–713.10.1001/archpsyc.61.7.705 [PubMed: 15237082]

Sanacora G, Kendell SF, Levin Y, Simen AA, Fenton LR, Coric V, Krystal JH. Preliminary evidence of riluzole efficacy in antidepressant-treated patients with residual depressive symptoms. Biological Psychiatry. 2007; 61:822–825. doi: http://dx.doi.org/10.1016/j.biopsych.2006.08.037. [PubMed: 17141740]

Sanacora G, Smith MA, Pathak S, Su HL, Boeijinga PH, McCarthy DJ, Quirk MC. Lanicemine: A low-trapping NMDA channel blocker produces sustained antidepressant efficacy with minimal psychotomimetic adverse effects. Molecular Psychiatry. 2013:1–8.10.1038/mp.2013.130 [PubMed: 23250327]

Sánchez C, Hyttel J. Comparison of the effects of antidepressants and their metabolites on reuptake of biogenic amines and on receptor binding. Cellular and Molecular Neurobiology. 1999; 19:467–489.10.1023/a:1006986824213 [PubMed: 10379421]

Schildkraut JJ. The catecholamine hypothesis of affective disorders: A review of supporting evidence. American Journal of Psychiatry. 1965; 122:509–522. [PubMed: 5319766]

Schulberg HC, Katon W, Simon GE, Rush A. Treating major depression in primary care practice: An update of the agency for health care policy and research practice guidelines. Archives of General Psychiatry. 1998; 55:1121–1127.10.1001/archpsyc.55.12.1121 [PubMed: 9862556]

Seeman P, Ko F, Tallerico T. Dopamine receptor contribution to the action of PCP, LSD and ketamine psychotomimetics. Molecular Psychiatry. 2005; 10:877–883. [PubMed: 15852061]

Shaw DM, Eccleston EG, Camps FE. 5-Hydroxytryptamine in the hind-brain of depressive suicides. The British Journal of Psychiatry. 1967; 113:1407–1411.10.1192/bjp.113.505.1407 [PubMed: 6078496]

Shek DTL. Tackling adolescent substance abuse in Hong Kong: Where we should and should not go. The Scientific World Journal. 2007; 7:2021–2030.10.1100/tsw.2007.315

Shiroma PR, Albott CS, Johns B, Thuras P, Wels J, Lim KO. Neurocognitive performance and serial intravenous subanesthetic ketamine in treatment- resistant depression. The International Journal of Neuropsychopharmacology. 2014:1–9.10.1017/S1461145714001011 [PubMed: 23953038]

Shore PA, Silver SL, Brodie BB. Interaction of reserpine, serotonin, and lysergic acid diethylamide in brain. Science. 1955; 122:284–285.10.2307/1751305 [PubMed: 13246633]

Shore PA, Pletscher A, Tomich EG, Carlsson A, Kuntzman R, Brodie BB. Role of brain serotonin in reserpine action. Annals of the New York Academy of Sciences. 1957; 66:609–617.10.1111/j.1749-6632.1957.tb40751.x [PubMed: 13425244]

Shulman K, Herrmann N, Walker S. Current place of monoamine oxidase inhibitors in the treatment of depression. CNS Drugs. 2013; 27:789–797.10.1007/s40263-013-0097-3 [PubMed: 23934742]

Smith DJ, Bouchal RL, DeSanctis CA, Monroe PJ, Amedro JB, Perrotti JM, Crisp T. Properties of the interaction between ketamine and opiate binding sites in vivo and in vitro. Neuropharmacology. 1987; 26:1253–1260. [PubMed: 2823161]

Smith ER, Deligiannidis KM, Ulbricht CM, Landolin CS, Patel JK, Rothschild AJ. Antidepressant augmentation using the N-Methyl-D-Aspartate antagonist memantine: A randomized, double-

blind, placebo-controlled trial. Journal of Clinical Psychiatry. 2013; 4:966–973. [PubMed: 24229746]

Stahl SM, Grady MM, Moret C, Briley M. SNRIs: Their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. CNS Spectrums. 2005; 10:732–747. [PubMed: 16142213]

Stahl SM, Pradko JF, Haight BR, Modell JG, Rockett CB, Learned-Coughlin S. A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor. Primary Care Companion to The Journal of Clinical Psychiatry. 2004; 6:159–166.

Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-46, HHS Publication No (SMA) 13-4795. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.

Thomas DR, Nelson DR, Johnson AM. Biochemical effects of the antidepressant paroxetine, a specific 5-hydroxytryptamine uptake inhibitor. Psychopharmacology. 1987; 93:193–200.10.1007/bf00179933 [PubMed: 2962217]

Uher R, Mors O, Rietschel M, Rajewska-Rager A, Petrovic A, Zobel A, et al. McGuffin P. Early and delayed onset of response to antidepressants in individual trajectories of change during treatment of major depression: a secondary analysis of data from the genome-based therapeutic drugs for depression (GENDEP) study. Journal of Clinical Psychiatry. 2011; 72:1478–1484. [PubMed: 22127194]

Vaishnavi SN, Nemeroff CB, Plott SJ, Rao SG, Kranzler J, Owens MJ. Milnacipran: a comparative analysis of human monoamine uptake and transporter binding affinity. Biological Psychiatry. 2004; 55:320–322. [PubMed: 14744476]

Valentine GW, Mason GF, Gomez R, Fasula M, Watzl J, Pittman B, et al. Sanacora G. The antidepressant effect of ketamine is not associated with changes in occipital amino acid neurotransmitter content as measured by [1H]-MRS. Psychiatry Research: Neuroimaging. 2011; 191:122–127. doi: http://dx.doi.org/10.1016/j.pscychresns.2010.10.009.

Wang SJ, Wang KY, Wang WC. Mechanisms underlying the riluzole inhibition of glutamate release from rat cerebral cortex nerve terminals (synaptosomes). Neuroscience. 2004; 125:191–201. doi: http://dx.doi.org/10.1016/j.neuroscience.2004.01.019. [PubMed: 15051158]

Weiner N, Cloutier G, Bjur R, Pfeffer RI. Modification of Norepinephrine Synthesis in Intact Tissue by Drugs and during Shor-term Adrenergic Nerve Stimulation. Pharmacological Reviews. 1972; 24:203–221. [PubMed: 4405385]

Winstock AR, Mitcheson L, Gillatt DA, Cottrell AM. The prevalence and natural history of urinary symptoms among recreational ketamine users. BJU International. 2012; 110:1762–1766.10.1111/j.1464-410X.2012.11028.x [PubMed: 22416998]

Wong DT, Bymaster FP, Horng JS, Molloy BB. A new selective inhibitor for uptake of serotonin into synaptosomes of rat brain: 3-(p-trifluoromethylphenoxy). N- methyl-3-phenylpropylamine. Journal of Pharmacology and Experimental Therapeutics. 1975; 193:804–811. [PubMed: 1151730]

Wong DT, Bymaster FP, Engleman EA. Prozac (fluoxetine, lilly 110140), the first selective serotonin uptake inhibitor and an antidepressant drug: Twenty years since its first publication. Life Sciences. 1995; 57:411–441. doi: http://dx.doi.org/10.1016/0024-3205(95)00209-O. [PubMed: 7623609]

Wong DT, Horng JS, Bymaster FP, Hauser KL, Molloy BB. A selective inhibitor of serotonin uptake: Lilly 110140, 3-(p-Trifluoromethylphenoxy)-n-methyl-3- phenylpropylamine. Life Sciences. 1974; 15:471–479. doi: http://dx.doi.org/10.1016/0024-3205(74)90345-2. [PubMed: 4549929]

Wong DT, Perry KW, Bymaster FP. The discovery of fluoxetine hydrochloride (Prozac). Nature Reviews Drug Discovery. 2005; 4:764–774.

Yamakura T, Mori H, Masaki H, Shimoji K, Mishina M. Different sensitivities of NMDA receptor channel subtypes to non-competitive antagonists. NeuroReport. 1993; 4:687–690. [PubMed: 8347808]

Yamakura T, Shimoji K. Subunit- and site-specific pharmacology of the NMDA receptor channel. Progress in Neurobiology. 1999; 59:279–298. doi: http://dx.doi.org/10.1016/S0301-0082(99)00007-6. [PubMed: 10465381]

Zarate CA Jr, Mathews D, Ibrahim L, Chaves JF, Marquardt C, Ukoh I, et al. Luckenbaugh DA. A randomized trial of a low-trapping nonselective N- Methyl-D-Aspartate channel blocker in major depression. Biological Psychiatry. 2013; 74:257–264. doi: http://dx.doi.org/10.1016/j.biopsych.2012.10.019. [PubMed: 23206319]

Zarate CA Jr, Payne JL, Quiroz J, Sporn J, Denicoff KK, Luckenbaugh D, et al. Manji HK. An open-label trial of riluzole in patients with treatment-resistant major depression. American Journal of Psychiatry. 2004; 161:171–174.10.1176/appi.ajp.161.1.171 [PubMed: 14702270]

Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. Manji HK. A randomized trial of an n-methyl-d-aspartate antagonist in treatment-resistant major depression. Archives of General Psychiatry. 2006; 63:856–864.10.1001/archpsyc.63.8.856 [PubMed: 16894061]

Zarate CA Jr, Singh JB, Quiroz JA, De Jesus G, Denicoff KK, Luckenbaugh DA, et al. Charney DS. A double-blind, placebo-controlled study of memantine in the treatment of major depression. American Journal of Psychiatry. 2006; 163:153–155.10.1176/appi.ajp.163.1.153 [PubMed: 16390905]

Zigman D, Blier P. Urgent ketamine infusion rapidly eliminated suicidal ideation for a patient with major depressive disorder: A case report. Journal of Clinical Psychopharmacology. 2013; 33:270–272. [PubMed: 23422387]

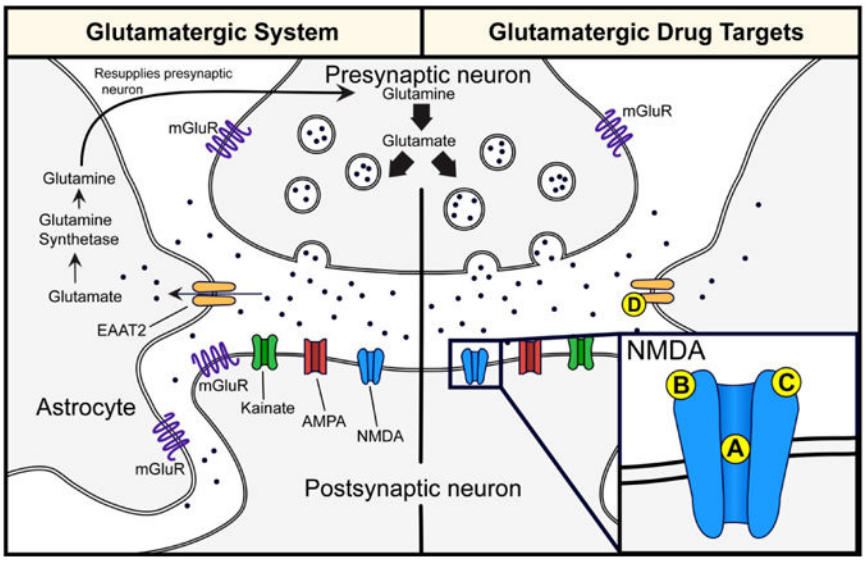

Figure 1.

Tripartite glutamatergic synapse and potential drug targets. *Left panel*: The presynaptic neuron releases glutamate in response to action potentials. Glutamate can bind to ionotropic (i.e. NMDA, AMPA, kainate) and metabotropic (i.e mGluR) receptors located on the presynaptic and postsynaptic neuron as well as on astrocytes. Synaptic glutamate reuptake is performed primarily by the EAAT2 located on astrocytes. Within the astrocyte, glutamate is converted to glutamine (glutamate/glutamine cycle) via glutamine synthetase and then resupplied to the presynaptic neuron where it is used for synthesis of glutamate. *Right panel*: Potential NMDA and EAAT2 drug targets: (A) Noncompetitive NMDA receptor antagonist (e.g. ketamine and memantine) and low-trapping NMDA receptor channel blockers (lanicemine [AZD6765]); (B) NR2B subunit selective NMDA receptor antagonists (e.g. traxoprodil [CP-101,606] and MK-0657); (C) Partial agonist at the glycine binding site of NMDA receptors (e.g. D-cycloserine, GLYX-13, and NRX- 1074); (D) EAAT2 enhancers (e.g. riluzole). Abbreviations: NMDA, N-methyl-$_D$-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; mGluR, metabotropic glutamate receptors; EAAT2, excitatory amino acid transporter 2.

Table 1

Alterations in glutamatergic substrates in major depressive disorder using indirect measures for analysis

Interest	Region of Analysis	Change	Reference
Glutamate	Serum	No Difference	Maes et al., 1998[a]
	Plasma	Increased	Altamura et al., 1993
			Mauri et al., 1998
			Küçükibrahimoğlu et al., 2009
	Platelet-rich plasma[c]	Supersensitivity to glutamate	Berk et al., 2001
Glutamine	Serum	Increased	Maes et al., 1998[a]
	Plasma	Decreased	Altamura et al., 1993
	Cerebrospinal fluid	Increased	Levine et al., 2000
		No Difference	Garakani et al., 2013[b]

[a] decrease after 5-week antidepressant; however, no difference prior to treatment

[b] decrease after 8-week antidepressant; however, no difference prior to treatment

[c] platelet intracellular calcium response to glutamate stimulation

Table 2

Alterations to glutamatergic concentrations measured by proton magnetic resonance spectroscopy (^{1}H-MRS)

Interest	Region of Analysis	Change	Reference
Glutamate	Occipital cortex	Increased	Sanacora et al., 2004
Glutamate/Glutamine (Glx)	Anterior cingulate cortex	Decreased	Auer et al., 2000
			Pfleiderer et al., 2003[a]
			Mirza et al., 2004
	Hippocampus	Decreased	Block et al., 2009[b]
	Dorsolateral prefrontal cortex	Decreased	Michael et al., 2003[a]
	Dorsomedial and ventromedial prefrontal cortex	Decreased	Hasler et al., 2007

[a] Glx major depressive disorder levels recovered to healthy control following ECT treatment

[b] no change in Glx levels following 8-weeks of citalopram treatment

Table 3

Alterations in N-methyl-$_D$-aspartate (NMDA) receptor subunit expression in postmortem tissue from major depressive disorder patients

Receptor Subunit/site	Region of Analysis	Molecular Assay	Change	Reference
NR1	Superior temporal cortex	Western blot	Decreased	Nudmamud-Thanoi et al., 2004
	Prefrontal cortex	In situ hybridization	Decreased	Beneyto et al., 2008
		Western blot	No change	Feyissa et al., 2009
NR2A	Perirhinal cortex	In situ hybridization	Decreased	Beneyto et al., 2007
	Prefrontal cortex	In situ hybridization	Decreased	Beneyto et al., 2008
		Western blot	Decreased	Feyissa et al., 2009
	Lateral amygdala	Western blot	Increased	Karolewicz et al., 2009
NR2B	Perirhinal cortex	In situ hybridization	Decreased	Beneyto et al., 2007
	Prefrontal cortex	Western blot	Decreased	Feyissa et al., 2009
	Locus coeruleus	Polymerase chain reaction (PCR)	Increased	Chandley et al., 2014
NR2C	Locus coeruleus	Western blot	Increased	Karolewicz et al., 2005
		Polymerase chain reaction (PCR)	Increased	Chandley et al., 2014
Glutamate Binding site	Hippocampus	Autoradiography [^{3}H]CGP39653	Increased binding	Beneyto et al., 2007

Table 4

Selected clinical trial results and current status of ketamine for the treatment of major depressive disorder.

Drug	Primary Mechanism of Action	Study/reference	TRD	N	Study Design	Main Findings	Current Status/Clinical Trials
Ketamine	Noncompetitive NMDA receptor antagonist	Breman et al., 2000	No	7	Randomized, double-blind, single infusion (0.5 mg/kg)	Improvement from 4 hours to 3 days	*Phase 1:* Biomarkers of rapid onset for MDD. NCT02165449
		Zarate et al., 2006	Yes	17	Randomized, double-blind, single infusion	Improvement from 110 min to 7 days; full remission in 5/17 patients	*Phase 2:* There are >20 clinical trials evaluating ketamine for MDD. NCT01945047;
		Ann het Rot et al., 2010	Yes	10	Open-label, repeated infusion (6 infusions over 12 days)	9/10 met response criteria after first ketamine infusion; mean relapse rate of 19 days after last ketamine infusion	NCT01880593; NCT01920555; NCT01868802; NCT00088699; NCT 01179009; NCT01667926; etc.
		Murrough et al., 2013	Yes	24	Open-label, repeated infusion (6 infusions over 12 days)	17/24 met response criteria following 6 ketamine infusions; 4 patients did not relapse after 83 days	
		Murrough et al., 2013	Yes	73	Two-site, randomized, active placebo control (midazolam), single infusion	30/47 patients met response criteria following ketamine; 7/25 met response criteria following midazolam; no effect of site	
		Ghasemi et al., 2014	No	18	Randomized, active control (ECT), repeated infusion and repeated ECT (3 infusion or ECT treatments)	Improvement with ketamine following first infusion and lasted 1 week; improvement with ECT after second treatment and lasted 1 week	
		Irwin et al., 2010	No	2	Open-label, case study, single oral dose	Both cases showedimprovement from 60 min to 8days	
		McNulty et al., 2012	No	1	Open-label, case study, repeated oral dosing (40 mg/5 mL flavored syrup)	Patient was in remission at 2 month follow up	
		Irwin et al., 2013	No	8	Open-label, repeated nightly oral dosing (0.5 mg/kg; 28 days)	Improvement after 14 days of ketamine dosing and continued until day 28.	
		Lara et al., 2013	Yes	26	Open-label, single sublingual dose (10 mg)	20/26 achieved remission or improvement 90 min after ketamine dose	
		Chilukuri et al., 2014	No	27	Randomized, open-label parallel group (0.25-0.5 mg/kg IM or 0.5 mg/kg IV)	Improvement after 2 hours: 8/9 following IV; 7/9 follwing 0.25 mg IM; 6/9 following 0.5 mg IM	
		Lapidus et al., 2014	No	18	Randomized, double-blind, crossover study (50 mg intranasal ketamine)	8/18 met response criteria at 24 hours	

TRD, treatment-resistant depression; N, represents the number of participants to complete the study; MDD, major depressive disorder; NMDA, N-methyl-D-aspartate; IV, intravenous; IM, intramuscular.

Exp Clin Psychopharmacol. Author manuscript; available in PMC 2016 February 01.

Table 5

Clinical trial results and current status of glutamatergic drugs for the treatment of major depressive disorder.

Drug	Primary Mechanism of Action	Study/reference	TRD	N	Study Design	Main Findings	Current Status/Clinical Trials
Memantine	Noncompetitive NMDA receptor antagonist	Zarate et al., 2006	No	26	Randomized, double-blind, placebo-controlled, repeated dosing (5-20 mg/day)	No significant effects of treatment after 8 weeks	*Phase 4:* Treatment resistant geriatric depression in primary care. NCT01392287
		Lenze et al., 2012	No	27	Randomized, double-blind, placebo-controlled, repeated dosing (10-20 mg/day)	No significant effects of treatment after 8 weeks	
		Smith et al., 2013	Yes	31	Randomized, double-blind, placebo-controlled, add-on repeated dosing (5-20 mg/day)	No significant effects of treatment after 8 weeks	
		Muhonen et al., 2008	No	58	Randomized, double-blind, active control (escitalopram), repeated dosing (5-20 mg/day); use patients with comorbid alcohol dependence	Improvement from 1 to 6 months; no difference between memantine and escitalopram	
AZD6765 (Lanicemine)	Low trapping NMDA receptor open-channel blocker	Zarate et al., 2013	Yes	21	Randomized, double-blind, crossover study, single infusion (150 mg)	Improvement from 80 to 110 min. No other improvement	AstraZeneca terminated the development of AZD6765 for MDD.
		Sanacora et al., 2013	Yes	34	Randomized, double-blind, placebo-controlled, single infusion (100 mg)	No significant effects of treatment	
		Sanacora et al., 2013	Yes	152	Randomized, double-blind, placebo-controlled, add-on repeated dosing (100-150 mg; 3 infusions per week)	Improvement from week 3 to week 5 (2 weeks post last infusion)	
CP-101,606 (traxoprodil)	NR2B subunit selective NMDA receptor antagonist	Preskorn et al., 2008	Yes	30	Randomized, double-blind, placebo-controlled, add-on single infusion (0.75 mg/kg for 1hour and 0.15 for 6.5 hours)	60% met response criteria; 33% met remission criteria on day 5	No clinical trials listed.
MK-0657	NR2B subunit selective NMDA receptor antagonist	Ibrahim et al., 2012	Yes	5	Randomized, double-blind, placebo-controlled, repeated dosing (4-8 mg/day)	Inconsistent improvement from days 5 to 12	Merck discontinued the manufacturing of MK-0657. Cerecor Inc. purchased the rights from Merck and will continue to develop MK-0657 for MDD. No clinical trials listed.
D-cycloserine	Glycine site partial agonist	Heresco-Levy et al., 2006	Yes	15	Randomized, double-blind, placebo-controlled, add-on repeated dosing (250 mg/day)	No significant effects of treatment	*Phase 4:* Bipolar depression. NCT01833897
		Heresco-Levy et al., 2006	Yes	22	Randomized, double-blind, placebo-controlled, add-on	7/13 met response criteria; 5/13 met remission criteria after 6 weeks of treatment	

Drug	Primary Mechanism of Action	Study/reference	TRD	N	Study Design	Main Findings	Current Status/Clinical Trials
					repeated dosing (titrated up to 1000 mg/day)		
					repeated dosing (titrated up to 1000 mg/day)		
GLYX-13	Glycine site partial agonist	Moskal et al., 2014	No	112	Randomized, double-blind, placebo-controlled, single infusion (1-30 mg/kg)	Improvement from day 1 to day 7	*Phase 1:* Safety, tolerability and pharmacokinetics. NCT01014650 *Phase 2:* Inadequate/partial response to antidepressant for MDD. NCT01684163; NCT02192099
NRX-1074	Glycine site partial agonist	No published clinical trials					*Phase 1:* Safety and Pharmacokinetics. NCT01856556 *Phase 2:* IV administration in MDD. NCT02067793
Riluzole	EAAT2 glutamate reuptake enhancer	Zarate et al., 2004	Yes	13	Open-label, repeated oral dosing (50-200 mg/day)	Improvement from week 2 to week 6	*Phase 2:* TRD. NCT01204918; NCT01703039; NCT00088699
		Sanacora et al., 2007	Yes	10	Open-label, add-on repeated dosing (100 mg/day)	Improvement from week 1 to week 6	
		Mathew et al., 2010	Yes	13	Randomized, double-blind, placebo-controlled, relapse prevention (100-200 mg/day)	No significant effect of treatment for relapse prevention	
		Ibrahim et al., 2012	Yes	27	Randomized, double-blind, placebo-controlled, relapse prevention (100-200 mg/day)	No significant effect of treatment for relapse prevention	
		Niciu et al., 2014	Yes	18	Randomized, double-blind, placebo-controlled, ketamine non-responder (100-200 mg/day)	No significant effect of treatment in ketamine non-responders	

TRD, treatment-resistant depression; N, represents the number of participants to complete the study; MDD, major depressive disorder; NMDA, N-methyl-D-aspartate; EAAT2, excitatory amino acid transporter 2; IV, intravenous.