Promises and Pitfalls of NMDA Receptor Antagonists in Treating Violent Aggression

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INTRODUCTION

Recurring violent aggression is a major societal concern with few effective treatment options. Currently, the standard of treatment for aggression is antipsychotics, benzodiazepines, or a combination of the two. Unfortunately, these drugs induce numerous side effects, including loss of appetite, fatigue, sleep disturbances, nausea, vomiting, diarrhea, weight gain, increased risk of
respiratory depression, and oxygen desaturation (Delbello et al., 2006; Haas et al., 2009; Redden et al., 2009; Geller et al., 2012; Pandina et al., 2012; Pringsheim et al., 2015; Amerio et al., 2018; Pisano et al., 2019; Solmi et al., 2020). In addition, many patients will need to take these drugs for life, increasing their dosage with time as tolerance develops. As a result, current research is devoted to finding a more effective, quick-acting, long-lasting, and well-tolerated alternative.

N-methyl-D-aspartate receptor (NMDAR) antagonists are a promising pharmacological alternative for treating aggressive behavior and aggression-related disorders. NMDARs are members of the ionotropic glutamate binding receptor family (Willard and Koochekpour, 2013). They are composed of five non-identical subunits (GluN1, GluN2A-D, and GluN3A-B) that form a central pore through which cations are conducted upon the binding of glutamate. NMDARs are unique among the ionotropic glutamate binding receptors because of their voltage-gated properties, coincidence detection, and role in synaptic plasticity (Squire and Kandel, 2009; Willard and Koochekpour, 2013). Antagonists for these receptors have been shown to interfere with these properties.

We propose in this review that NMDAR antagonists are favorable in treating aggression over traditional methods due to their quicker onset of action, fewer observed side effects, and potential as a long-lasting treatment option due to their effects on synaptic plasticity (Roberts and Geeting, 2001; Cummings et al., 2008; Wilcock et al., 2008; Hopper et al., 2015; Cole et al., 2016; Riddell et al., 2017; Tran and Mierzwinski-Urban, 2019; Barbic et al., 2021; Nordman et al., 2022). Though there are multiple clinically available NMDAR antagonists, such as the non-competitive antagonists dextromethorphan and amantadine (Hewitt, 2000) and the non-selective, NMDAR-binding opioids methadone, dextropropoxyphene, and ketobemidone (Sang, 2000), we will focus on the non-competitive antagonists ketamine and memantine, as they are the most widely used and successful NMDAR antagonists on the market.

**KETAMINE AND MEMANTINE IN TREATING HUMAN AGGRESSION**

Ketamine is a non-competitive NMDAR antagonist that has been successfully used to treat aggression in humans. Ketamine was first developed in the United States in the 1960s as an alternative anesthetic to phencyclidine (PCP; Domino et al., 1965). It was found to have a quicker onset of action (less than 5 min) and induce fewer negative emergent symptoms than PCP (Dillon et al., 2003; Tran and Mierzwinski-Urban, 2019), though both produce psychotic-like symptoms in schizophrenia patients (Lahti et al., 2001; Beck et al., 2020). Ketamine gained popularity as a party drug in the 1980s, with sub-anesthetic doses sending users into the colloquially named “K-hole”—a dissociative state commonly accompanied by out-of-body experiences, a sensation of weightlessness, and distortions of time (Dillon et al., 2003). The FDA has approved ketamine for the induction and maintenance of general anesthesia, but there are also many off-label uses of ketamine, including as a local anesthetic, in procedural sedation, pain management, asthma, and depression (Papolos et al., 2013; Burger et al., 2016; Dwyer et al., 2017; Cullen et al., 2018; Tran and Mierzwinski-Urban, 2019; Zarrinnegar et al., 2019; Barbic et al., 2021; Kim et al., 2021; Solano et al., 2021).

Many studies support the use of ketamine to treat violent aggression, agitation, psychosis, self-harm, and suicidal ideation (Burger et al., 2016; Dwyer et al., 2017; Cullen et al., 2018; Zarrinnegar et al., 2019). In the majority of these cases, clinicians take advantage of ketamine’s sedative properties to control aggressive outbursts in hospital and pre-hospital settings (Roberts and Geeting, 2001; Melamed et al., 2007; Le Cong et al., 2012; Scheppke et al., 2014; Riddell et al., 2017; Barbic et al., 2021; Kent et al., 2022). Sedative doses of ketamine fall in the 1–2 mg/kg range if given intravenously, and 3–5 mg/kg if given intramuscularly. These doses are necessary to sedate acutely aggressive individuals for the safety of the patient and staff but are also associated with higher rates of intubation, emergence delirium, and other adverse effects (Woods and Almvik, 2002; Cole et al., 2016; Chang et al., 2019). Because of these risks, a low-dose treatment protocol should be followed when possible.

Sub-sedative doses of ketamine (0.2–0.5 mg/kg IV, 30–120 mg intranasal) have been successful in treating aggression in psychiatric patients (Papolos et al., 2013; Burger et al., 2016; Dwyer et al., 2017; Zarrinnegar et al., 2019). For instance, intranasal ketamine significantly reduced aggression in children and adolescents with pediatric bipolar disorder (Papolos et al., 2013). Additionally, military patients presenting to the hospital with depression and suicidal ideations experienced a rapid improvement of symptoms within 40 min of administration of ketamine (Burger et al., 2016). Numerous studies support ketamine’s rapid-acting antidepressant properties when given at low doses (Papolos et al., 2013; Burger et al., 2016; Dwyer et al., 2017; Zarrinnegar et al., 2019). Interestingly, chronic ketamine use has been found to be more addictive at these sub-sedative doses (Morgan et al., 2004; Bonnet, 2015; Schak et al., 2016). Therefore, ketamine treatment for aggression symptoms related to psychiatric disease must be carried out in a regulated, controlled fashion. These studies are discussed in the *Synaptic Plasticity* section below. A summary of our review findings on ketamine in aggression is outlined in Table 1.

Memantine is a non-competitive NMDAR antagonist, with low to moderate affinity, which is approved for treating moderate to severe Alzheimer’s disease and dementia (Huey et al., 2005; Robinson and Keating, 2006; Thomas and Grossberg, 2009). It has been reported that 5%–10% of Alzheimer’s patients and 96% of dementia patients exhibit aggressive behavior over the course of their illness (Keene et al., 1999; Jacson and Mallory, 2009). Atypical antipsychotics are among the most common treatments for agitation and aggression in Alzheimer’s and dementia patients (Ballard and Waite, 2006; Ballard et al., 2008; Cerejeira et al., 2012), but there is a significant risk of mortality, stroke, hallucination, and relapse after continued use, especially during the first 30 days of treatment (Kales et al., 2012; Calsolaro et al., 2019).

A key benefit of memantine is that, due to its long biological half-life, it is not used recreationally, is not habit-forming, and is well tolerated. Notably, memantine at a dose of 10–20 mg/day
### Table 1: Human studies on the effects of ketamine and memantine.

| References                  | Observation                                                                 | Comments                                                                                           |
|-----------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| Roberts and Geeting (2001)  | A single dose of 5 mg/kg IM ketamine suppressed violent behavior within 2–3 min through sedation | Lorazepam was administered immediately afterward                                                   |
| Cote et al. (2016)          | A single dose of 5 mg/kg IM ketamine sedated individuals with severe acute undifferentiated agitation significantly faster than 10 mg IM haloperidol bolus. The mean time to adequate sedation was 5 min vs. 17 min, respectively. | Ketamine resulted in a higher rate of intubation and other complications                           |
| Barbic et al. (2021)        | A single dose of 5 mg/kg IM ketamine outperformed 5 mg IM midazolam and 5 mg IM haloperidol boluses in suppressing severe psychomotor agitation in hospital patients through sedation |                                                                                                     |
| Riddell et al. (2017)       | Mean single dose of 2.97 mg/kg IM and 0.87 mg/kg IV ketamine outperformed 5.71 mg/kg IM haloperidol, 2.25 mg/kg IM and 3.08 mg/kg IV midazolam, and 2.40 mg/kg IM and 1.90 mg/kg IV lorazepam in treating severely agitated emergency department patients through sedation | Dosing was not uniform throughout the study, average doses are listed.                             |
| Burger et al. (2016)        | A single dose of 0.2 mg/kg IV ketamine decreased depression and suicidal ideation seen in military members that met the criteria for inpatient psychiatric admission |                                                                                                     |
| Dwyer et al. (2017)         | 0.5 mg/kg IV ketamine infused 7x over an 8-week hospitalization decreased depressive symptoms and suicidal ideation in an adolescent with severe treatment-resistant depression. Outpatient treatments every 5–6 weeks after discharge with continued improvement in symptoms. |                                                                                                     |
| Papalos et al. (2013)       | 30–120 mg intranasal ketamine every 3–7 days elicited a substantial reduction in measures of mania, fear of harm, and aggression in youth with pediatric bipolar disorder—fear of harm phenotype |                                                                                                     |
| Solano et al. (2021)        | A single dose of 400 mg IM ketamine bolus used to treat excited delirium with concurrent cocaine intoxication had a statistically significant increased rate of intubation in ED | Symptoms of excited delirium include aggressive behavior, combativeness, and agitation            |
| Zarrinnegar et al. (2019)   | 0.5 mg/kg IV ketamine treatment 6x over a 3-week inpatient hospitalization ameliorated symptoms of psychosis, self-harm, and suicidality in an adolescent with severe treatment-resistant depression. Suppression of aggressive symptoms persisted for several months following discharge. | Prior treatment with many antidepressants, benzodiazepines, and antipsychotics failed to improve symptomology |
| Schepke et al. (2014)       | A single dose of 4 mg/kg ketamine IM suppressed aggression through sedation in 96% of patients | Average time of 2 min to achieve suitable sedation                                                  |
| Le Cong et al. (2012)       | Acute treatment of 0.5–1.5 mg/kg IV ketamine suppressed aggressive outbursts through sedation | Ketamine treatment was initiated when benzodiazepines and/or antipsychotics failed                |
| Melamed et al. (2007)       | Acute treatment of IV ketamine (dosage/concentration not listed) through sedation decreased agitation in soldiers suffering a traumatic injury | Was effective alone or in combination with other sedative agents                                    |
| Donoghue et al. (2015)      | Acute treatment with 10 mg procedural IV ketamine-induced an 8 and 13-day remission of aggressive behaviors in a child with PTSD after a tonsillectomy and sedated MRI. |                                                                                                     |
| Markowitz et al. (2018)     | A mean, single dose of 315 mg IM ketamine effectively treated undifferentiated agitation through sedation |                                                                                                     |
| Heydari et al. (2018)       | A single dose of 4 mg/kg IM ketamine outperformed 5 mg IM haloperidol bolus to sedate severely agitated patients in the emergency department |                                                                                                     |
| O’Connor et al. (2019)      | A single dose of 4 mg/kg IM ketamine had a higher intubation rate than haloperidol (5 mg IM bolus) plus benzodiazepines (2–4 mg IM bolus) in severely agitated patients |                                                                                                     |
| Olives et al. (2016)        | A single dose of 5 mg/kg IM ketamine delivered pre-hospital was found to be associated with a high rate of intubation (63%) in profoundly agitated patients |                                                                                                     |
| Kent et al. (2022)          | A single dose of 5 mg/kg IM ketamine outperformed the combination of haloperidol (5 mg IM bolus) and midazolam (5 mg IM bolus) to sedate severely agitated ED patients through sedation. The mean time to adequate sedation was 5.8 min vs. 14.7 min, respectively | The ketamine arm experienced a higher rate of serious adverse events                                |

**Memantine**

| Cummings et al. (2008)     | 20 mg/day PO memantine treatment agitiation/agression in patients with Alzheimer’s disease and baseline levels of agitation/agression |                                                                                                     |
| Wilcock et al. (2008)      | 20 mg/day PO memantine decreased agitation and aggression in patients with Alzheimer’s disease |                                                                                                     |

(Continued)
TABLE 1 | Continued

| References            | Observation                                                                 | Comments                                                                 |
|-----------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Thomas and Grossberg  | 20 mg/day PO memantine treatment was associated with less severity or emergence of agitation/aggression compared to placebo |                                                                           |
| Da Re et al. (2015)   | 20 mg/day PO memantine used to treat dementia resulted in improvement of agitation in 19% of participants, but an increase in agitation in 5.6% of participants |                                                                           |
| Herrmann et al. (2011)| Significant decrease in agitation and aggression following 10 mg PO memantine treatment twice daily in patients with Alzheimer's disease |                                                                           |
| Gauthier et al. (2008)| 20 mg/day PO memantine reduced agitation and aggression in patients with Alzheimer's disease compared to the placebo group |                                                                           |
| Ichinose et al. (2021)| 20 mg/day PO memantine successfully treated aggressive behavior that was a byproduct of hepatic encephalopathy |                                                                           |
| Kishi et al. (2017)   | 10 and 20 mg/day PO memantine treatment significantly improved agitation/aggression when compared to the control group |                                                                           |
| Fox et al. (2012)     | 10 mg PO memantine twice daily did not significantly improve agitation in patients with moderate to severe Alzheimer’s disease |                                                                           |

Abbreviations: IM, intramuscular; IV, intravenous; PO, per os/by mouth; ED, emergency department.

has been effective in reducing aggression and agitation associated with Alzheimer’s disease and dementia patients without the accompanying risks of atypical antipsychotics (Cummings et al., 2008; Wilcock et al., 2008). However, some patients experience treatment-induced agitation with memantine use (Da Re et al., 2015), suggesting that a more careful clinical examination is key to proper treatment. A summary of our review findings on memantine in aggression is outlined in Table 1.

The future of ketamine and memantine is promising. Still, our limited knowledge of the mechanisms behind NMDARs and aggression, paired with the diverging effects observed in animal models warrants more research, which we discuss below.

NMDARs, KETAMINE, AND MEMANTINE IN ANIMAL AGGRESSION

NMDARs are highly expressed in regions associated with attack behavior, such as the amygdala, prefrontal cortex (PFC), hippocampus, nucleus accumbens, hypothalamus, striatum, and brain stem (Shaikh and Siegel, 1994; Shaikh et al., 1994; Petralia et al., 2007; Peregod et al., 2012; Takahashi et al., 2015; Bacq et al., 2018; Chen and Hong, 2018; Newman et al., 2018; Zoicas and Kornhuber, 2019; Falkner et al., 2020; Figure 1A). The NMDARs, particularly the GluN2 subunits, have a nuanced and varied role in species-typical and excessive aggression, as demonstrated by rodent studies. For example, decreased GluN2B expression in the lateral amygdala is associated with naturally occurring and social isolation-induced aggression (Bacq et al., 2018). However, increased GluN2A and GluN2B expression and GluN2B-dependent NMDAR currents in the hippocampus and frontal cortex are associated with social isolation-induced aggression and morphine-induced aggression, respectively (Meyer et al., 2004; Zhao et al., 2009; Chang et al., 2015; Chang and Gean, 2019). Interestingly, in the mPFC, increases in GluN2D, but not GluN2A or GluN2B, may mediate alcohol-induced aggression (Newman et al., 2018).

Unsurprisingly, ketamine and memantine also have a nuanced role in aggression that depends on dosage, context, experience, and species (Table 2). For example, in mice and zebrafish, high doses of ketamine suppress territorial aggression while low doses increase it (Newman et al., 2012; Michelotti et al., 2018). In rats, low doses, but not high doses, of ketamine suppress muricide behavior (Takahashi et al., 1984). Memantine, by contrast, has no effect on species-typical aggression (Sukhotina and Bespalov, 2000; Newman et al., 2012, 2018).

As with humans, substance use plays a significant role in the effects of ketamine and memantine on aggression. In alcohol-challenged mice, ketamine reduces territorial aggression at high doses and reduces motivated aggression at low doses (Newman et al., 2012; Covington et al., 2018). Memantine increases alcohol-heightened aggression at low doses but has no effect at high doses (Newman et al., 2012, 2018). By contrast, high doses of memantine, but not low doses, decrease morphine withdrawal-facilitated aggressive behavior in mice (Sukhotina and Bespalov, 2000).

Stress also appears to be a strong factor. For example, ketamine increases aggression in sleep-deprived rats and socially isolated mice (Takahashi et al., 1984). In adolescent mice, ketamine decreases aggression induced by neonatal maternal separation (Shin et al., 2019) but increases aggression induced by chronic social isolation followed by acute non-contingent foot shock (Nordman et al., 2022). Interestingly, memantine suppresses aggression induced by chronic social isolation stress followed by acute non-contingent foot shock, similar to what has been seen with the non-competitive NMDAR antagonist MK-801 (Chang et al., 2015; Nordman et al., 2022).

While these findings clearly demonstrate a role for NMDARs in aggression and NMDAR antagonists as a potential treatment option, dosage, context, experience, and brain region all need to be considered (Figure 1B). Furthermore, the effects of ketamine and memantine suggest they operate through distinct mechanisms, which we discuss in the "Mechanistic Differences" section below.
FIGURE 1 | Summary of NMDAR-dependent aggression in mice. (A) Brain regions associated with attack behavior are enriched in and regulated by NMDARs. Red regions indicate known areas involved in NMDAR-dependent synaptic plasticity-induced aggression. (B) Effects of low or high doses of ketamine and memantine on species-typical, stress-induced, and drug or alcohol-induced aggression. Red arrows—increased aggression; blue arrows—decreased aggression; gray arrows—no change in aggression. The PFC, prefrontal cortex; NAc, nucleus accumbens; BNST, bed nucleus of the stria terminalis; LA, lateral amygdala; VmH, ventromedial hypothalamus; MeA, medial amygdala; PAG, periaqueductal gray; DR, dorsal raphe.

SYNAPTIC PLASTICITY

NMDARs are one of the primary sources of synaptic plasticity in the brain (Squire and Kandel, 2009; Willard and Koochekpour, 2013). When bound by glycine and glutamate at certain voltage thresholds, NMDARs conduct large amounts of the second messenger cation calcium into the synapse. This sudden, large increase in calcium concentration activates a series of kinases and phosphatases that promote the insertion or removal of another type of ionotropic glutamate binding receptor, the
TABLE 2 | Animal studies on the effects of ketamine and memantine.

| References            | Sex/Age/Species                      | Observation                                                                 |
|-----------------------|--------------------------------------|------------------------------------------------------------------------------|
| **Ketamine**          |                                      |                                                                              |
| Nordman et al. (2022) | 7–8-week-old male mice               | IP injections of 10 mg/kg ketamine enhance early life stress-induced aggression |
| Newman et al. (2018)  | Adult male mice                      | IP injections of 3–10 mg/kg ketamine increased aggression                     |
|                       |                                      | IP injections of 30 mg/kg ketamine decreased aggression                      |
|                       |                                      | IP injections of 30 mg/kg ketamine decreased alcohol-heightened and alcohol-non-heightened aggression |
| Newman et al. (2012)  | Adult male mice                      | IP injections of 3–10 mg/kg ketamine increased aggression                     |
|                       |                                      | IP injections of 30 mg/kg decreased aggression                               |
| Michelotti et al. (2018)| Adult zebrafish, 50:50 male:female | Low dose (2 mg/kg) ketamine increased aggression                              |
|                       |                                      | High (20–40 mg/kg) dose reduced aggression                                   |
| Takahashi et al. (1984)| Male rats                             | IP injections of low doses (3–5 mg/kg) of ketamine increased aggression in rats deprived of REM sleep and in mice after social isolation |
| Covington et al. (2018)| Adult male rats and mice             | IP injections of low dose (10 mg/kg) ketamine reduced motivated aggression    |
| Shin et al. (2019)    | Adolescent mice                      | IP injection of low doses (7.5 and 10 mg/kg) of ketamine reduced alcohol-escalated motivated aggression |
| **Memantine**         |                                      |                                                                              |
| Nordman et al. (2022)| 7–8-week-old male mice               | IP injections of MK-801 and memantine suppress early life stress-induced aggression |
| Newman et al. (2018)  | Adult male mice                      | IP injection of 1–10 mg/kg memantine increased aggression                    |
| Newman et al. (2012)  | Adult male mice                      | 20–30 ug/ul memantine infused into the mPFC increased aggression in mice that consumed alcohol |
|                       |                                      | IP injection of 1–10 mg/kg memantine increased aggression in mice that consumed ethanol |
| Sukhotina and Bespalov (2000)| Adult male mice| IP injection of 17 mg/kg memantine decreased aggression compared to vehicle controls |
|                       |                                      | IP injection of 10–30 mg/kg memantine lessened morphine withdrawal-facilitated aggression |

Abbreviations: Intraperitoneal, IP.

AMPA receptor. AMPA receptors are not voltage-gated, so the more AMPA receptors there are in the synapse, the more the membrane will be depolarized when AMPARs are bound by glutamate, thus increasing the likelihood that a neuron will fire an action potential. Conversely, the fewer AMPA receptors there are in the synapse, the less the membrane will be depolarized when AMPARs are bound by glutamate, thus decreasing the likelihood that a neuron will fire an action potential when activated. Insertion and removal of AMPA receptors by NMDARs is the principal mechanism for synaptic plasticity at excitatory synapses in the brain.

Excessive chronic aggression brought on by early life stress and social isolation is mediated by the persistent effects of NMDAR-dependent synaptic plasticity, which can be suppressed using NMDAR antagonists (Chang et al., 2015, 2018; Nordman et al., 2020a,b). Therefore, NMDAR antagonists possess a feature more popular mood-stabilizing and aggression-suppressing drugs lack: they can inhibit certain persistent forms of maladaptive social behaviors such as excessive and recurring aggression from ever forming, likely through their effects on synaptic plasticity. This is best seen in animal models, where a single dose can inhibit depression-like, anxiety-like, or aggressive behavior when administered before a potentiating event (da Silva et al., 2010; Ma et al., 2013; Yang et al., 2016; Chang et al., 2018; Nordman et al., 2020a,b) or reverse maladaptive behaviors when administered after the potentiating event (Maeng et al., 2008; Moda-Sava et al., 2019).

In a recent study, we showed that NMDAR antagonism could alter aggression induced by early life stress after a single dose (Nordman et al., 2022). Our early life stress paradigm involves social isolation during early adolescence followed by acute physical stress in the form of non-contingent foot shock during late adolescence. Combining these stressors produces prolonged increases in excessive aggression when measured seven days later. When we systemically injected a single dose of the non-competitive NMDAR antagonists MK-801 or memantine...
in vivo synthesis within the aggression circuit. Specifically, heightened aggression by synaptically potentiating glutamatergic stimulation of aggression brain pathways, and early life stress we found that attack experience, high-frequency optogenetic increases the likelihood and severity of a future attack within priming is a phenomenon where previous attack experience dependent synaptic plasticity (Nordman et al., 2020a). Attack on synaptic plasticity.

In support of this, in another recent study, we showed that NMDARs regulate aggression priming through NMDAR-dependent synaptic plasticity (Nordman et al., 2020a). Attack priming is a phenomenon where previous attack experience increases the likelihood and severity of a future attack within a narrow time window (~30–60 min). Notably, in that study, we found that attack experience, high-frequency optogenetic stimulation of aggression brain pathways, and early life stress heightened aggression by synaptically potentiating glutamatergic synapses within the aggression circuit. Specifically, in vivo electrophysiological recordings of optically evoked excitatory postsynaptic potentials indicate that both attack experience and acute footshock after social isolation potentiate glutamatergic synapses between the posterior ventral segment of the medial amygdala (MeApv) and its downstream synaptic partners the ventrolateral aspect of the ventromedial hypothalamus (MeApv-VmHvl) and the medial aspect of the bed nucleus of the stria terminalis (MeApv-BNSTm; Nordman et al., 2020a,b). A single systemic injection of the non-competitive NMDAR antagonist MK-801 30 min before aggression testing suppressed both aggression priming and synaptic potentiation at these synapses, indicating that both are NMDAR-dependent.

Since (1) aggression priming and early life stress-induced aggression both involve synaptic plasticity within the same glutamatergic MeApv pathways; and (2) aggression priming is NMDAR-dependent, it stands to reason that early life stress-induced aggression is NMDAR-dependent as well. However, the distinct effects of MK-801, memantine, and ketamine on aggression suggest these drugs have opposing effects on synaptic plasticity within MeApv pathways. Future studies should explore this possibility.

Nevertheless, NMDAR antagonists are an exciting treatment option for excessive aggression and aggression associated with early life stress because it bypasses one of the great challenges of traditional pharmacological methods: daily and lifelong administration of a dangerous drug that only diminishes in its efficacy over time. In support of this, it has been found that in some psychiatric patients, ketamine can suppress aggressive behavior long past the time it takes for the body to metabolize the drug (plasma half-life is 79 +/- 8 min; Hirot a and Lambert, 1996; Donoghue et al., 2015; Dwyer et al., 2017; Zarrinnegar et al., 2019). For example, a single sedating dose (10 mg) of ketamine successfully suppressed aggressive behavior for 13 days in a 7-year-old child diagnosed with PTSD displaying reactive attachment disorder and disruptive behavior disorder (Donoghue et al., 2015). Three months later, the same sedating dose of ketamine reduced aggression and increased the patient’s receptivity to psychiatric care for another 8 days, showing that ketamine can be effectively readministered while retaining its persistent effects on aggression. Similarly, patients receiving ketamine treatment for depression showed significant improvements in aggression symptoms (e.g., psychosis, self-harm, and suicidality) that lasted for weeks to months afterward (Dwyer et al., 2017; Zarrinnegar et al., 2019). Synaptic plasticity could explain the vast difference between the time it takes to metabolize ketamine and the sustained decrease in aggressive symptoms seen in these patients.

Therefore, in this review, we argue that NMDAR antagonists like ketamine and memantine could reduce the frequency of taking, or even alleviate the patient’s need to remain on, increasingly tolerant and dangerous drugs like antipsychotics, benzodiazepines, lithium, or anticonvulsants for the treatment of aggression. In addition, we argue that NMDAR antagonists could be used to suppress aggression induced by a potentiating event like stress. Of course, it is difficult to predict when a potentiating event might occur. However, NMDAR antagonists could suppress the susceptibility of individuals with psychiatric diseases to develop aggressive behavior during periods of heightened stress or substance abuse, a significant advantage over current options. We note though that the distinct effects of ketamine and memantine on aggression associated with early life stress in our animal model suggest the need for great care when prescribing NMDAR drugs to treat excessive aggression.

MECHANISTIC DIFFERENCES

We highlight ketamine and memantine in this review as they are the most common and successful NMDAR-drugs for treating excessive aggression in humans and are potent synaptic plasticity blockers. While both drugs are similar in their effects on channel function (Johnson et al., 2015), important differences remain. Perhaps the most important differences are the receptor types each drug targets.

For example, ketamine is non-selective for the NMDAR, binding to muscarinic, monoaminergic, and opioid receptors, among others (Hirota and Lambert, 1996). It has been hypothesized that these interactions mediate the psychotomimetic effects many patients experience and may account for the more persistent effects of ketamine on pain and as an antidepressant (Sleigh et al., 2014; Zorumski et al., 2016). This would suggest that the effects of ketamine on aggression-related disorders are not exclusively mediated through NMDARs.

Ketamine and memantine also differ in their NMDAR dissociation rates, with ketamine binding to the NMDAR for longer periods of time than memantine (Johnson et al., 2015; Glasgow et al., 2017). This has been used to explain ketamine’s high and memantine’s low sedative and psychotomimetic effects (Lanthorn et al., 2000; Bolshakov et al., 2003; Kotermanski and Johnson, 2009; Kitanaka et al., 2018).

The location of NMDARs may also explain the differences between these drugs. There is evidence that memantine binds more readily to extrasynaptic NMDARs than ketamine
chirality, and tolerance may explain why memantine and ketamine have such diverging clinical and experimental effects and provide a mechanism for the unique effects of these drugs on excessive and stress-induced aggression.

**CLINICAL ASSESSMENT**

Our studies and others have demonstrated that different NMDAR antagonists can promote or exacerbate aggressive behavior depending on a prior history of substance abuse, traumatic stress, or aggressive behavior. A proper assessment would decrease the incidence of aggression by ruling out those NMDAR antagonists as treatment options. Therefore, a complete evaluation of the patient’s history of psychiatric and physical illness and an assessment of past substance use should be performed before administering and prescribing these drugs. Fortunately, there are standard methods for assessing whether an individual has a history of traumatic stress or aggressive behavior or is currently using or abusing drugs or alcohol that would exclude them from being prescribed specific NMDAR antagonists.

Tests that evaluate a history of traumatic stress include The Primary Care PTSD Screen for DSM-5 (Prins et al., 2016), The Short Post-Traumatic Stress Disorder Rating Interview (Connor and Davidson, 2001), and the Trauma Screen Questionnaire (Brewin et al., 2002). Tests for individuals with a history of aggressive behavior or who are in an actively aggressive state include the Dynamic Appraisal of Situational Aggression (DASA; Ogloff and Daffern, 2006) and the Bivrost Violence Checklist (BVC; Woods and Almvik, 2002), which assess the likelihood that a patient will become aggressive through factors such as physical or verbal threats, negative attitudes, and impulsivity. Initially, tests like the Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) Tool (McNeely et al., 2016) and the Brief Screener for Alcohol, Tobacco, and Other Drugs (BSTD) tool (Kelly et al., 2014) are used to evaluate drug and alcohol abuse in adults and adolescents, respectively. Importantly, these assessment tools can be implemented in the hospital setting, significantly reducing the likelihood of unintended aggressive behavior by NMDAR antagonists, and paving the way for more nuanced administration.

**CONCLUSION**

This review highlights some of the promises and pitfalls of the non-competitive NMDAR antagonists, and in particular ketamine and memantine, in treating excessive and recurring violent aggression. On the one hand, NMDAR antagonists are clearly powerful clinical tools in managing violent aggression. They possess a quicker onset of action and fewer observed side effects than current alternatives. NMDARs also have great potential as a long-lasting treatment option due to their effects on synaptic plasticity (Roberts and Geeting, 2001; Cummings et al., 2008; Hopper et al., 2015; Cole et al., 2016; Riddell et al., 2017; Barbic et al., 2021), where these drugs can induce persistent changes in synaptic function, neural firing, and animal behavior, in some cases, even after a single dose (Wilcock et al., 2008;
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DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

CB and JN wrote the manuscript. All authors contributed to the article and approved the submitted version.

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