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Austin Brown  
*Ohio Northern University*

Katherine Liu  
*Ohio Northern University*

Pul Lee  
*Ohio Northern University*

Rachel Muhlenkamp  
*Ohio Northern University*

Manoranjan D’Souza  
*Ohio Northern University*, m-dsouza@onu.edu

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Memantine: Can it be Used to Treat Children with Autism Spectrum Disorder?

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Abstract
Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairment in social, behavior and communicative skills. The current therapy for ASD only targets the associated symptoms such as aggression, self-harming acts or temper tantrums but not the core symptoms of social dysfunction. The pathology of ASD is not fully understood. Interestingly, imaging studies in ASD patients have reported abnormal high levels of glutamate in certain brain regions that play an important role in social interaction and communication. Thus, it has been hypothesized that medications attenuating glutamate transmission may be used as treatment for some of the core symptoms of ASD. Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been approved for the treatment of Alzheimer's disease, and has shown promise in alleviating some of the symptoms of ASD in children. In this review, we will discuss the pathology of ASD, findings from studies that evaluated memantine in ASD patients, the adverse effects of memantine and the potential use of memantine in the treatment of ASD. Finally, we will discuss the role of the pharmacist in managing patients with ASD.

Key Terms
Aggression; Alzheimer Disease; Brain; Child; Child Development Disorders; Pervasive; Glutamic Acid; Humans; Interpersonal Relations; Memantine; N-Methylaspartate; Pharmacists; Review Literature; Social Behavior

Introduction
Autism spectrum disorder is a heterogeneous neurodevelopmental disorder characterized by core features including developmental delays in communication and social interaction and repetitive behaviors and/or restricted interests. Deficits in communication and social interaction manifest as shortfalls in "social-emotional reciprocity," nonverbal communication and difficulty with relationships. In addition, patients with ASD show repetitive behaviors, interests, movements or atypical interests in sensory aspects of their environment. The full clinical diagnosis of ASD is defined by the diagnostic statistical manual-V (DSM-V).

According to the Centers for Disease Control and Prevention (CDC), in 2012, about one in 68 children were identified with ASD. Interestingly, boys are about five times more likely to be diagnosed with ASD than girls. Screening for ASD is usually done at well-child doctor visits. If the physician/pediatrician notices any abnormalities, such as the ones described above, a comprehensive diagnostic evaluation is performed, which includes a detailed evaluation of the child's behavior and development and an interview with the parents. Diagnoses made by age 2 or older are considered very dependable; but ASD could possibly be identified before 18 months of age.

Currently, antipsychotic medications risperidone and aripiprazole are approved by the U.S. Food and Drug Administration (FDA) for the treatment of associated symptoms of ASD including aggression, self-harming acts and temper tantrums commonly seen in autistic patients between 5 and 16 years of age. There are currently no FDA approved medications that directly target the pathological mechanisms underlying autism or treat the core symptoms of ASD described above.

Recent studies, however, suggest abnormalities in glutamate transmission in autism that could possibly be a target for treatment. Glutamate is the primary fast-acting excitatory neurotransmitter within the central nervous system (CNS). The actions of glutamate in the CNS are mediated by ionotropic receptors such as the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), kainate and N-methyl-D-aspartate (NMDA) receptors. A few clinical studies have evaluated the effects of memantine, an antagonist of the NMDA glutamate receptor, in patients diagnosed with ASD. In this review, we will first discuss glutamate abnormalities in specific brain regions that have been reported in ASD patients. In addition, we will discuss findings from studies that evaluated memantine in ASD patients, the adverse effects of memantine and the potential adverse effects of memantine in the treatment of ASD. Finally, the role of the pharmacist in managing ASD patients will be reviewed.

Pathology in Autism Spectrum Disorder
The etiology of ASD is not known, although research has shown that there is a strong hereditary influence accompanied by genetic mutations. More than 20 different mutations have been identified. Also implicated are further epigenetic changes, which include modifications in gene expression that do not change the deoxyribonucleic acid (DNA) sequence. Overall, the genetic mutations and epigenetic changes affect proteins that are responsible for neuronal function, cell metabolism, protein synthesis and gene expression.

Irregularities in glutamate concentrations within the brain have been reported in ASD patients. Concentrations of glutamate in the brain can be measured using proton magnetic resonance spectroscopy (1H MRS). In a study that utilized 1H MRS, Brown et al. reported elevations in glutamate + glutamine signal (Glx) in certain brain regions of ASD patients. For example, the Glx in the auditory cortex was found to be significantly elevated in the ASD patients when compared to the control groups. It should be noted that the ASD patients (n=13) were ages 25 to 48 years, and they were compared with healthy adults (n=15) and parents of ASD children not included in the study (n=15). In addition, Page and colleagues found that adults with ASD (n=20) had a significant increase in Glx in the amygdala-hippocampal complex.

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In contrast to the above described studies, some studies report a decrease in Glx signal. For instance, Bernardi et al. found that the right anterior cingulate cortex had a decreased Glx signal in ASD adults (n=14, P<0.006) than in healthy controls (n=14). One possible reason for the contrasting findings with respect to anterior cingulate cortex Glx signal and glutamate levels between the studies of Bernardi et al. and Bejjani et al. could be due to differences in age of subjects evaluated in the two studies. For example, subjects included in the study of Bernardi et al. were adults (age range 21 to 50 years), while the subjects studied in Bejjani et al. were children (age range 6.1 to 17.5 years). In addition, Horder et al. found that ASD patients had decreased Glx in the basal ganglia (P<0.0001). Overall, the imaging studies suggest that the direction of alteration in glutamate levels in ASD patients may be dependent on the age group of patients and the particular brain region studied.

In addition to irregularities in glutamate levels described above, alterations in glutamate receptor mRNA expression or density have been reported in ASD patients. A postmortem study conducted by Purcell et al. examined brain samples from the cerebellar cortex of autistic patients (n=10) and control patients (n=23), which were matched based upon age and gender. They reported a significant increase (P<0.05) in levels of AMPA 1, 2, 3 mRNA in the cerebellar samples of autistic subjects (n=10) compared to control subjects (n=10). Furthermore, increased levels of AMPA 1 (P<0.001) and NMDA receptor 1 (P<0.05) subunit proteins were reported in brain samples of autistic subjects (n=9) compared to controls (n=11). However, despite elevations in the mRNA and protein levels of specific AMPA and NMDA receptor subunits, Purcell et al. reported decreased density of AMPA receptors in the granule (P<0.05) and molecular cell layer (P<0.01) of the cerebellum in samples of autistic subjects compared to control subjects using autoradiography. Interestingly, there was no difference in density of the NMDA receptors in the different layers of the cerebellum. In summary, the above evidence from molecular studies suggests elevation of glutamate receptor expression (mRNA and protein) in specific brain regions in ASD patients.

Binding of glutamate to the NMDA receptor allows the entry of calcium and sodium ions into the neuron. This entry of calcium and sodium ions via opening of the NMDA receptors results in depolarization and activation of the neurons. However, excessive release of glutamate and activation of the NMDA receptors can result in excitotoxicity and loss of neurons. Hence, it is hypothesized that attenuating glutamate transmission will have a neuroprotective effect and prevent loss of existing neurons. Consequently, memantine, a non-competitive NMDA receptor antagonist, may provide the desired neuroprotective effects and promotion of neurogenesis. Currently, memantine is approved by the FDA for moderate to severe dementia caused by Alzheimer's disease. Several studies have evaluated memantine in children with ASD. Because the DSM-V criteria for ASD were released only recently (May 2013), most of the studies described in this article have used the DSM-IV-TR criteria, which was the standard criteria at the time the studies were conducted.

**Clinical evaluation of Memantine in ASD**

In a retrospective observational study, Erickson et al. evaluated the effects of memantine on symptoms associated with autism, such as social withdrawal, communication impairment, irritability and inattention/hyperactivity. The study included 18 patients (mean age of 11.4 years) who had more than one symptom and were treated at an outpatient treatment center for autism. All patients were evaluated by psychiatrists and met the DSM-IV-TR criteria for autism. Patients began with either 2.5mg or 5mg memantine daily depending on their weight, which was titrated up by either 2.5mg or 5mg every two weeks to a maximum of 20mg daily or until a response or side effects were observed. Thirteen patients were taking concurrent medications, mainly anticonvulsants, antidepressants or second-generation antipsychotics, which were maintained during the trial. Of those taking second-generation antipsychotics, three patients were either on risperidone or aripiprazole, which are FDA approved medications for autism patients. A clinical global impressions-severity subscale (CGI-S) and CGI-Improvement subscale (CGI-I) was completed at baseline and during clinical visits to document changes in symptoms. The CGI-S was rated from 1 to 7 (1-normal, 7-extremely ill) while the CGI-I was also rated from 1 to 7 (1-very much improved, 7-very much worse). Patients with a CGI-I rating of 1 or 2 after the trial were considered treatment responders. Only six patients had completed scores at baseline and post-trial conducted on the aberrant behavior checklist-community (ABC-C) irritability subscale, a 58-item subscale used to assess disruptive behavior and developmental disabilities. The range of the study period was 1.5 to 56 weeks (mean of 19.3 weeks) with a mean dose of 10.1mg/day. The CGI-S scores showed a significant decrease from baseline (p<0.01) although the CGI-I improvement was not substantial. Patients with CGI-I ratings of much improved (n=6) or very much improved (n=3) were considered as treatment responders. For patients who did have ABC data, the only significant improvement was the hyperactivity subscale (p<0.05). Adverse effects occurred in seven of the patients and included irritability (n=4), rash (n=1), emesis (n=1), increased seizure frequency (n=1) and excessive sedation (n=1). Two patients stopped treatment due to unresponsiveness, while four stopped treatment because of adverse effects. Overall, the results reflected the beneficial use of memantine, especially in improving social interaction and attention. There were, however, several limitations to this study. The sample size of the study was small, thus making it difficult to form true associations within this observational study. The length of the treatment for each patient was not addressed by the authors, which varied and may not have allowed enough time to determine the efficacy and side effects of memantine. Importantly, only five patients were on monotherapy with memantine during the study, indicating that the other 13 patients were taking other concurrent medications, which could...
have influenced the data with their varying therapies. Lastly, ratings on the CGI scales were not made by the same physician for each patient, indicating that scores may have been affected by the subjective impressions of the different physicians.

An open-label study by Chez et al. evaluated the efficacy of memantine in the treatment of language and social behavioral symptoms in patients diagnosed with autism. The study included 151 patients who were found eligible through clinical observation and the DSM-IV criteria for autism (n=105) and pervasive developmental disorder not otherwise specified (PDD-NOS; n=46). Pervasive developmental disorder is characterized by severe impairment in developing reciprocal social interaction due to impaired communication skills or behavior. Patients were predominantly male (mean age of 9.31 years). Those taking concurrent medications, which were primarily selective serotonin reuptake inhibitors, atypical antipsychotics, stimulants, alpha-adrenergic antagonists and cholinesterase inhibitors, were required to take them consistently for at least eight weeks before treatment and during the study. Of these, 31 were taking risperidone, while five were taking aripiprazole. Patients with fragile X or Rett syndrome genetic disorders, metabolic disorders or brain malformations were excluded from the study. The starting dose of memantine was 5mg/day, which was titrated up or down every four to six weeks in 2.5 or 5mg increments up to 30mg/day. Patient follow-up was carried out via phone calls or email every four weeks and clinical assessments were conducted every eight to 12 weeks. The duration of the study had a range of one to 20 months (mean=9.27 months). Assessments of the treatment were conducted by a primary clinician and caretaker through interviews, diaries, clinical examinations and observations.

These were translated onto the CGI-1 seven-point scale for language by examining receptive skills and utterances, behavior through cognitive improvement in social interactions and self-stimulatory activity by observing the amount and type of patient activity. The CGI-I for behavior was observed through social interaction, ability to cooperate at home and school and attentiveness to others. A score of either 1 or 2 was considered to be significant improvement in all three categories. The CGI-I for language and behavior had a significant improvement in about 70 percent of both autism and PDD-NOS patients together, with changes occurring in the first two to four weeks. Improvement was also found to increase as length of therapy increased. When excluding the PDD-NOS patients, however, language improvement in autism alone was not found to be significant. More specifically, 65/105 and 67/105 autism patients were found to have ratings of significant improvement in language and behavior respectively. When excluding those who stopped treatment, language improvement was still significant for both the autistic and PDD-NOS patient groups, while behavioral improvement was not. Lastly, for the CGI-I for self-stimulatory stereotypic behaviors, only those observed with these behaviors at baseline were included (n=116). Only nine of the patients with autism were found to have significant improvement and there was found to be no progress in self-stimulatory behavior and duration of treatment overall for both autism and PDD-NOS patients. From the sample, 22 patients experienced worsening of symptoms and dropped out, while five patients stopped therapy because of a lack of response. Although abnormal electroencephalography findings were observed in patients, these changes were concluded to be normal for this patient population. For patients with concurrent therapy, hematological, serum chemistry and hepatic profiles were examined and found to have no changes. The results of the study seem to suggest that memantine is a safe adjunct therapy for patients with autism for improvement of language and behavioral symptoms. Importantly the study showed that memantine resulted in improvement of language and behavioral symptoms in a majority of patients, although improvements were not statistically significant when patients who withdrew from the study were excluded from the analysis. A major limitation of the study was that the researchers relied on CGI-I subscale scores, which were not scored by the same clinician or caretakers, indicating possible subjectivity in ratings, which may have affected the results. Furthermore, concurrent medications being taken by the patients were not the same for all the patients and may have influenced the results.

Chaleiha et al. examined the effects of memantine as an adjunct therapy with risperidone. Forty children between the ages of 4 and 12 years (mean age of 7.42 years), who met the diagnostic DSM IV-TR criteria for autism confirmed by a child psychologist, were included in the 10-week double-blind randomized placebo-controlled trial. Inclusion criteria also comprised a screening and baseline ABC-C irritability subscale score of ≥12. Children who had concomitant schizophrenia, psychotic disorders, a history of drug or alcohol abuse, tardive dyskinesia, active clinical seizures, significant medical problems, had taken memantine previously or had taken an antipsychotic drug treatment six months before enrollment began were excluded from the study. Patients were randomized into two equal parallel groups, and an equal number of girls and boys were included in each group. One group received memantine and risperidone, while the other group received a placebo and risperidone. The starting dose of risperidone was 0.5mg tablet/day, which was gradually titrated up to a maximum of 2mg/day for children weighing 10 to 40kg, and a maximum of 3mg/day for children weighing >40kg. Memantine doses started at 5mg caplet/day and were titrated up or down in 5mg increments each week to a maximum of 15mg/day for children weighing 10 to 40kg and 20mg/day for children weighing >40kg. All drugs, including placebo, began at the same time and any psychosocial intervention therapy was stopped. The primary outcome was the irritability subscale measured by the ABC-C. This was used to evaluate five types of behavioral abnormalities, where three were core deficits (lighargy/social withdrawal, stereotypic behavior, inappropriate speech) and two were associated disturbances (irritability, hyperactivity/noncompliance). Ratings on the ABC-C scale followed standardized instructions by a trained resident of psychiatry and the children’s parents every two weeks. Scores at baseline were compared to scores during treatment weeks 2, 4, 6, 8, and 10 (end point). The extrapyramidal symptoms rating scale was also used to measure extrapyramidal symptoms, such as tardive dyskinesia, akinesia, akathisia and parkinsonism. Independent raters and a medical
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Memantine is prescribed for the treatment of severe Alzheimer's disease. Memantine is limited to the treatment of ASD as described above, and the pharmacist has a significant role in educating parents and patients about the therapeutic efficacy and adverse effects of memantine for this patient population.23

Memantine is available in several dosage forms including tablets, capsules and extended release and solution form. The cost varies depending on the dosage forms and strengths (See Table 1). Namenda® titration packs are blister packs containing 49 tablets of 28 x 5mg and 21 x 10mg. Namenda®

Table 1. Memantine’s dosage forms and prices.*25

| Memantine | Tablets, oral | 5mg (60), 10mg (60) | $374.99 |
| Memantine Titration Pak: Tablets, oral | 5mg (28), 10mg (21) | $306.18 |
| Namenda XR: Capsules, extended release, oral | 7mg (30), 14mg (90), 21mg (30), 28mg (90) | $356.26, $1068.74, $356.26, $1068.74 |
| Namenda XR Titration Pack Oral: Capsules, extended release, oral | 7mg (7), 14mg (7), 21mg (7), 28mg (7) | $332.51 |
| Namenda: Solution, oral | 2mg/mL (360mL) | $725.32 |

* Costs without insurance coverage

In summary, studies published to date in the literature assessing memantine either as an adjunct therapy or monotherapy for the core symptoms of ASD had limitations either due to small sample size or study design. Therefore, these trials have limited external validity. Although all of these published studies suggested positive benefit using memantine, further double-blind studies with robust sample sizes and study design will be required to determine the role of memantine in the treatment of ASD patients. Based on more recent studies, the data of which is available only to the FDA currently, the FDA clinical review has recommended approval of the memantine indication for adolescents/children with autism despite lack of efficacy to treat the core symptoms of autism. Further scrutiny of the data and the FDA clinical review will only be possible when the complete studies are available for review to the larger clinical community.

Pharmacist Role and Counseling Points
Memantine is approved by the FDA to treat moderate-severe Alzheimer's disease. Memantine is prescribed off-label for treatment of ASD as described above, and the pharmacist has a significant role in educating parents and patients about the therapeutic efficacy and adverse effects of memantine for this patient population.23

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extended release titration packs are blister packages containing 28 capsules of 7 x 7mg, 7 x 14mg, 7 x 21mg and 7 x 28mg. The solution form may contain sorbitol, and capsules may contain sugar. Oral pediatric dosing adjustment is not yet established, but the clinical studies involving adolescents start with a low dose of 2.5mg daily or 5mg daily, and titrate up to maximum of 15mg, 20mg or 30mg daily depending on the weight of the patient.  

Memantine is well tolerated with low adverse events when it is used to treat dementia. In addition, no significant side effects were observed when the medication was given to adolescents for autism. Adverse reactions are similar to immediate and extended release formulations. If the patient has hypersensitivity to memantine or any component of the formulation, the drug should not be used. Bupropion, carbonic anhydrase inhibitors, sodium bicarbonate and trimethoprim are known to interact with memantine. Memantine is a substrate of organic cation transporter (OCT 2), and bupropion may increase the serum concentration of OCT 2 substrates. Carbonic anhydrase inhibitors and sodium bicarbonate may decrease the excretion of memantine with the exception of brinzolamide and dorzolamide. Trimethoprim may enhance the adverse and toxic effects, especially the risk of myoclonus and/or delirium. Therefore, these four drugs should be monitored when memantine is given to patients.

The CDC has analyzed several alternative treatment options including behavior and communication approaches, dietary approaches and complementary and alternative medicine (CAM). One behavior and communication approach, known as applied behavior analysis (ABA), is a widely accepted treatment option to help children with ASD. The objective of ABA treatment is to encourage positive behaviors and discourage negative behaviors so that patients can progress toward positive activities. Applied behavior analysis includes different types of treatment, and other therapies can be a part of a program (See Table 2). Dietary approaches are not recommended because treatments are based on the unproven idea that some food or lack of vitamins and minerals may cause symptoms of autism. Removing certain types of foods may be harmful to a child, so refer to the physician if this treatment option is being considered. In addition, CAM is not recommended. Complementary and alternative medicine includes special diets, chelation (a treatment to remove heavy metals such as lead from the body) and body-based systems such as deep pressure. The efficacy of these treatments are very controversial and may even cause dangerous consequences to a child's health. Therefore, patients should consult with their physician prior to implementing treatment.

Conclusion
Currently, there are no medications to treat the core symptoms of autism such as communication and social deficits. The FDA approved medications for autism, namely risperidone and aripiprazole, treat related symptoms of aggression, self-harming acts or temper tantrums in children between
the ages of 5 and 16 years. An FDA approved drug for treating Alzheimer's disease, memantine, has been suggested as a possible treatment option to treat the core symptoms of ASD. Imaging studies report increased glutamate levels in certain brain regions in ASD patients. Similarly, postmortem studies suggest increased mRNA levels of NMDA receptors in certain brain regions of ASD patients. Consistent with these findings, several published clinical studies reviewed here demonstrate possible benefits of using memantine, an NMDA antagonist. However, the studies published thus far are not very robust due to their small sample sizes and weak study designs. Based on studies still not available to the larger scientific community, the FDA clinical review has recently recommended approval of memantine for use in ASD patients despite lack of efficacy. Pharmacists must undertake a significant role in understanding memantine's use in ASD patients in light of unreliable efficacy, as well as in understanding other therapies widely utilized for ASD management.

References