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Use of Memantine in Autism Spectrum Disorder: a Case Report

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Abstract

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder of varying severity and phenotypic expression that is characterized by persistent deficits in social relatedness, communication skills, and interfering repetitive behaviors. Associated behavioral pathology can include inattention, aggression, irritability, hyperactivity, anxiety, and self-injury. Currently, FDA-approved treatments exist to treat secondary symptoms but not core symptomatology. The etiology of autism and other ASD is thought to be multifactorial but is not well understood. Some studies suggest that glutamate excitotoxicity may play a role in the pathogenesis of ASD. Memantine, an NMDA-receptor antagonist, could potentially address core symptoms in ASD by targeting disease-specific pathophysiology. Our patient, an 11-year-old Caucasian male, began treatment with memantine following parental request after learning of a phase II clinical trial utilizing the drug for treatment in autism. Following one month of receiving memantine 5mg daily the patient reportedly began showing increased verbal communication at home. Despite the patient not exhibiting verbal communication on patient interview at the clinic, the guardians reported that the patient had begun using 30 plus newly learned words, and had learned to communicate via sign language. Continued improvement in communication was noted over the course of one year of treatment with memantine. Memantine is not yet approved for treatment of ASD. However, in this case it appeared effective for treating core deficits in verbal and non-verbal communication in a child with autism.

Case Report

An 11 year-old Caucasian male with Autism Spectrum Disorder presented to the outpatient psychiatric clinic in October 2012 to establish care as the family wished to obtain a second opinion regarding the treatment of their child. He was accompanied by his biological mother who described a long history of severe deficits in social interaction, social reciprocity, and delayed verbal and non-verbal communication skills. He held few relationships outside of immediate family, never engaged in shared play, and showed no interest in developing age-appropriate friendships. His mother also reported that his previous baseline symptomatology included episodes of agitation and physical aggression, sleep disturbance, and hyperkinetic motor-behavior. Pharmacotherapy included dextroamphetamine extended release 10mg PO for attention deficit and hyperactivity symptoms, clonidine HCL 0.1mg for adjunctive treatment of ADHD, melatonin 6mg for sleep, mirtazapine 7.5mg also for sleep and olanzapaine 5mg as needed for agitation and irritability. He had trials of aripiprazole, then ziprasidone, and then guanfacine from November 2012 to May 2013 prior to starting memantine to target his aggressive behaviors but they were reported to increase these behaviors and therefore discontinued. Clonidine was started after he failed to have a positive response to guanfacine. The patient also received in-home behavioral therapy once per week, speech therapy for thirty minutes per week as well as twice-weekly occupational therapy. Medication changes during the course of this case report included discontinuation of dextroamphetamine in August of 2013 and as needed olanzapine in February of 2014 due to resolution of symptoms for which the medications were prescribed. Melatonin was also increased to 9mg for sleep as of April 2014.

The patient returned for a regular follow-up visit in June 2013. At that time his parents reported that the child of a family friend was involved in a clinical trial assessing use of memantine to increase social expression for patients with ASD and were interested in a trial of memantine for this purpose. After discussion of risks and benefits of the medication as well as explanation of off-label use the parents expressed their understanding and desire to go forward with treatment. Memantine was started at 2.5mg once daily dosing for seven days then

increased to 5mg daily where he was maintained. 5mg was chosen as this dose was the closest commercially available equivalent to the 3mg or 6mg dosages being used in the clinical trial. Follow-up visits were conducted with the patient and his parents roughly every 1-3 months following memantine initiation and have been ongoing for roughly two years.

Prior to initiation of memantine therapy the patient had shown a moderate decrease in agitation and aggressive symptoms but had not shown improvement in expressive or receptive linguistic capacity. Following the first month of therapy the patient's parents reported increased vocal expression at home as well as the use of new words. Over the course of subsequent follow-up visits the patient's verbal expression was reported to fluctuate. However, as verbal methods of expression would wane, new nonverbal methods had reportedly manifested through the use of sign. Four months following initiation of memantine therapy the patient learned to use rudimentary sign language to communicate basic wants and needs. By thirteen months of treatment the patient's gains in expressive language had been maintained and he was reported to regularly communicate by using both single words and signs. His parents estimated that he had learned 30 new words in total.

In addition to improved communication skills the patient's parents reported improved sleep, mood, and decreased aggression. Over roughly a year and a half he demonstrated increased receptivity to verbal redirection, improved fine motor coordination with notable gains in handwriting, and made gains in mathematics by learning to count on both hands. Observations were made in both the home and the classroom and reported by both parents and teachers respectively. Of note, no new medications were added following initiation of memantine. Dextroamphetamine was stopped in August of 2013 and he no longer required as needed olanzapine.

Discussion

ASD is one of the most common pervasive developmental disorders, with a roughly 1% prevalence worldwide. The diagnosis of ASD is based on deficits from two primary symptom clusters: social-communication deficits and restricted or repetitive behaviors. Patients often present with multiple comorbidities such as sensory and motor abnormalities, epilepsy, ADHD, mood disorders and intellectual disability. Aripiprazole and risperidone are the only medications with a FDA-approved indication specifically related to ASD. However, both of these agents target "irritability related to Autistic Disorder" only. Additionally these medications are associated with a varying severity of adverse

drug events such as somnolence, weight gain, dyskinesias and prolactinemia.[1] No pharmacologic agent is currently approved to treat the core deficits of autism.

Memantine is a medication within the NMDA receptor antagonist category and is typically used to treat the cognitive deficits associated with Alzheimer's dementia. This family of medications acts on the NMDA-glutamate pathway to down-regulate glutamate induced neuronal excitation thought to contribute to the neurological pathology of dementia-related illnesses.[2] A similar mechanism of glutamate excitotoxicity is theorized to be underlay ASD and its associated core deficits.[3] At the time of this writing memantine is undergoing phase II clinical trials for the purpose of autism therapy. Memantine however is not without its adverse drug reactions as increased irritability, GI disturbance, rash, excessive sedation, vomiting and possible speech problems are all possible with the medication.[2]

A review of published reports has suggested that memantine can be used in therapy to improve core areas of deficit, such as eye contact and communication. A retrospective study conducted by Erickson et al elucidated that inattention and social interaction may in fact be the most significant areas affected by the medication, as was seen in 61% of the 18 patients studied over a course of 19.3 weeks.[4] Memantine also shows promise in areas of function peripheral to the major core deficits, possibly expanding its therapeutic range. An open-trial performed by Chez et al demonstrated that over a two month period of therapy 26 of 30 (87%) patients showed improvement in one or more categories of attention, motor planning, language function and self-stimulatory behaviors.[5] Memantine has also been reviewed as an adjunctive to currently used therapies such as risperidone. In another open-label study performed by Chez et al, it was demonstrated that of the patient population studied 82.7% showed a positive response in language improvement with receptive language showing the most improvement alongside improvements in length of sentence and speech fluency.[2]

Not all trials and case reports have shown positive effect however. One study by Owley et al found no increase in baseline of expressive or receptive language despite an 8-week trial of memantine. The authors did however describe improvement in memory-related testing and suggested that language improvement may have occurred with a longer medication trial.[6] A more recent study by Aman et al demonstrated some moderate improvement in communication, sustained over the course of a 48-week study arm, however the changes were ultimately found to be statistically non-significant.[7] An additional case report performed by Alaghband-Rad et al suggested a possible adverse drug related event of stuttering and difficulty with speech initiation that appeared to begin and resolve with memantine initiation and cessation respectively. However the case report only included two individuals, one of which did have prior history of stuttering beginning at the age of four. Additionally, the case report mentions that the episodes of speech impediment decreased over time but only returned to baseline with the withdrawal of mementine.[8]

Our case report contributes to the relatively sparse literature describing NMDA antagonist therapy for treatment of core ASD symptomatology. Similar to previous reports our patient was observed to demonstrate improvement in multiple areas of function. Observations from both parents and the patient's school consistently reported improvement in sociality, communication and aggressive behavior with the most notable gains occurring in the use of both verbal and non-verbal expressive language. Despite reported overall symptomatic improvement, it must be noted that the patient did not demonstrate increased verbal or non-verbal communication skills during clinical appointments, however it is felt that this was likely due to discomfort with interaction in a non-routine and relatively unfamiliar environment. With a single case it is impossible to definitively show causality but the timing of medication administration and subsequent symptom improvement is suggestive. Spontaneous rapid improvement in language skills outside of a developmentally sensitive period seems unlikely. We cannot entirely exclude uncontrolled environmental influences such as increased attention to language instruction by parents and teachers once the medication was started. Further, it is unclear how much associated symptom improvement was due to medication effect and how much may have been attributed to improved communication alone. For example, as the patient's ability to express his wants and needs increased perhaps his frustration, mood, openness to redirection and instruction, and overall daily functioning may have improved as a consequence.

Conclusion

The core symptoms of ASD are highly impairing and negatively

impact function across settings. There are currently no medications with FDA indications that target core illness symptomatology. Published reports describing improved social and communication skills with use of memantine are promising and deserve further study.

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