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Retrospective Study Comparing the Effects of Memantine (NAMENDA) and Aripiprazole (ABILIFY) In the Treatment of Irritability in Autistic Spectrum Disorder (ASD) Patients

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ABSTRACT:

Autistic Spectrum Disorders are very common, and also very complex. At present, unfortunately, there are no medications that definitively treat the autistic spectrum disorders. Awareness about "autism" is increasing very rapidly. And, with the increase in awareness it is also becoming painstakingly clear that despite all the advancements we still do not have a clear understanding as to the etiology, pathophysiology, and most importantly treatment/management of this condition. There are medications that have been approved by the FDA for treatment of irritability symptoms and autistic disorder patients. Along with those medications, there are also anecdotal reports of numerous other "off-label medications", "remedies", "naturopathic medications", "diets", "supplements" etc., which might be of benefit in treatment of those patients who have autistic disorders. Commenting on the full spectrum of the possibilities of treatment, is beyond the scope of this article. However, the authors attempted to look into two medications (ABILIFY and NAMENDA) and compared them side-by-side to see if one of the two medications stands out as being of more benefit than the other. The choice of taking either of the two medications was based on the parent and patient preference, psychiatrist's recommendation, insurance coverage and cost. At the end, the results indicates that both medications were equally effective not only as judged by the parents/caregivers, but also by clinicians who are monitoring the symptoms on a fairly regular basis, using standardized methods (parent rated scale Aberrant Behavior Checklist (ABC), and clinician rated CGI-S & CGI-I). There are a number of limitations in this study, however, it does make us aware that ASD is complex disorder with diverse symptomatology that may change over time. It also opens our mind to the fact that there might be more than one solution to a common problem, and that as clinicians, it is our duty and responsibility to continue to search for not just the treatment, but the best treatment option available for patients. The results show the separation Therefore further research is needed to explore efficacious and safer treatment options for ASD.

INTRODUCTION:

Autism and autistic disorders have a high prevalence in the general population, some studies put it at 1 out 166 school going children in the USA have Autistic Disorders. According to 2010 estimates from CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network, about 1 in 68 or 14.7 per 1,000 children has been identified with ASD. ASD is almost 5 times (1 in 42 boys and 1 in 189 girls) more common among boys. (Jon Baio, 2014).

Although much has been written about it, Autism is still an emerging field of study. Autism spectrum disorder is a neurodevelopmental disorder of childhood onset that persists throughout the lifespan of affected individual and is characterized by deficit in socialization, difficulties in language and speech and restricted, repetitive pattern of behavior or activities. (Benjamin James Sadock, 2007) (Pine, 2013).

However a large proportion of the patients with AUTISM also have externalized irritability which negatively affect their socialization skills, and also at times effects their abilities to interact with peers, teachers, family etc. Additionally, these symptoms can also have a negative effect on the patient's abilities to learn in a classroom or outside the classroom settings. Finding a cure for Autism has alluded researchers for a long time. The most realistic treatment option that we are able to provide our patients is symptomatic relief.

There are reports that up to 20% of children with ASD have symptoms of irritability including impulsivity, aggressiveness, self-injurious behavior, and temper tan-

trums. (Lecavalier [2006] J. Autism Dev. Disord. 36:1101–1114.) (Robb, 2010). The term "irritability" is used to describe severe behavioral difficulties, e.g., verbal and physical aggression, deliberate self –injurious behavior temper tantrum and, quickly changing mood. [Gabriels et al., 2005; Johnson, 2007]

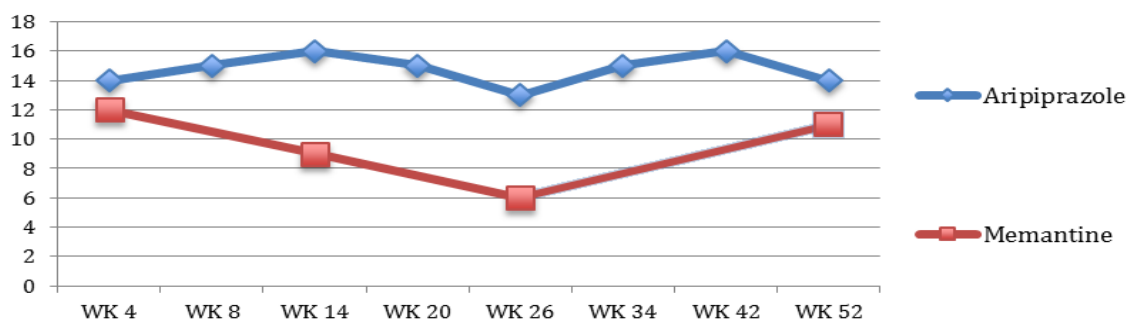
Behavioral therapy, educational and supportive programs remain the mainstay in the management of ASD. Despite the traditional treatment programs, problematic behaviors like aggression and violence tend to remain a challenge. Although irritability is not a core feature for diagnosis of ASD, it is a disruptive symptom and limits the learning, educational and behavioral intervention. It is hypothesized that treating irritability may potentially mitigate core symptoms and often improves socialization.

Till date two medications have been approved by the FDA to treat Irritability in patients who have AUTISM (RISPERDAL and ARIPIPRAZOLE). There are also anecdotal reports that other medications have been tried and used by various physicians with varying reports of benefits or otherwise.

One such medication, MEMANTINE (NAMENDA) has a mechanism of action different from both, RISPERDAL or ABILIFY.

Some investigators propose connection between Alzheimer's disease and autism. (Sokol DK, 2011). Memantine partially block NMDA receptor thus protect cell against excess glutamate. Increased Glutamate level leads to neurotoxicity and neurodegeneration and increased receptor density. Excess glutamate overstimu-

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The graph shows Comparison of mean ABC-I Subscale scores over 52 weeks, between patients using ABILIFY and NAMENDA

lates NMDA receptors to allow too much Calcium into the nerve cell leading to cell death. Aripiprazole is a modulator, rather than blocker, acting on both postsynaptic D2 receptor and presynaptic autoreceptor. Thus it addresses excessive limbic dopamine (hyperdopaminergic) activity and decreased dopamine (hypodopaminergic) activity in frontal and prefrontal areas. (Stahl, 2013)

Effects of Memantine have also been written about by numerous authors with varying results (Chez MG1, 2007) (Ritter M, 2014) (Ephraim Katz, April 8, 2014)

In our clinical setting, there were a number of parents who came to the clinic requesting that their children who had pre-existing diagnosis of "AUTISM" be treated with MEMANTINE. These parents came with the knowledge that MEMANTINE is being used off-label

It is to be noted that MEMANTINE (NAMENDA) has also been studied in two clinical trial conducted by Forest Pharmaceuticals, in a double-blind, placebo-controlled method to see if it is beneficial in control of the symptoms.

In many clinical setting physicians use ABILIFY to control Irritability/externalized symptoms in patients with Autism.

The use of Namenda was novel to our clinic, however it was noted that parents and caregivers were mostly satisfied with the results, and per their report it appeared that they were getting the results that they were expecting.

Therefore the authors decided to analyze data comparing the effects of NAMENDA with ABILIFY. It is to be noted that the comparison was not with placebo. And the purpose of the study was to see how these two medications compared to each other in a clinical setting.

METHOD:

A retrospective chart review of patients in an out-patient clinical setting was conducted. We studied patient who had a diagnosis of Autism and whose primary focus for being in treatment was to address their irritability. The

diagnosis were confirmed by DSM criteria and Autistic Diagnostic Interview-Revised (ADI-R) or Autism Diagnostic Observation Schedule (ADOS), conducted by trained professionals (Psychiatrist or Psychologist).

Our data sources were the caregivers, the patients themselves, and chart documentation by the treating psychiatrist. To minimize confound, charts of patients who had any other acute or ongoing psychiatric, neurological or any other physical conditions; or who were on other psychiatric medications were excluded from review. 20 patient charts chosen for review, it was noted that the gender ratio was nineteen males to one female patient. The age range of these patients was from 7 to 14 years.

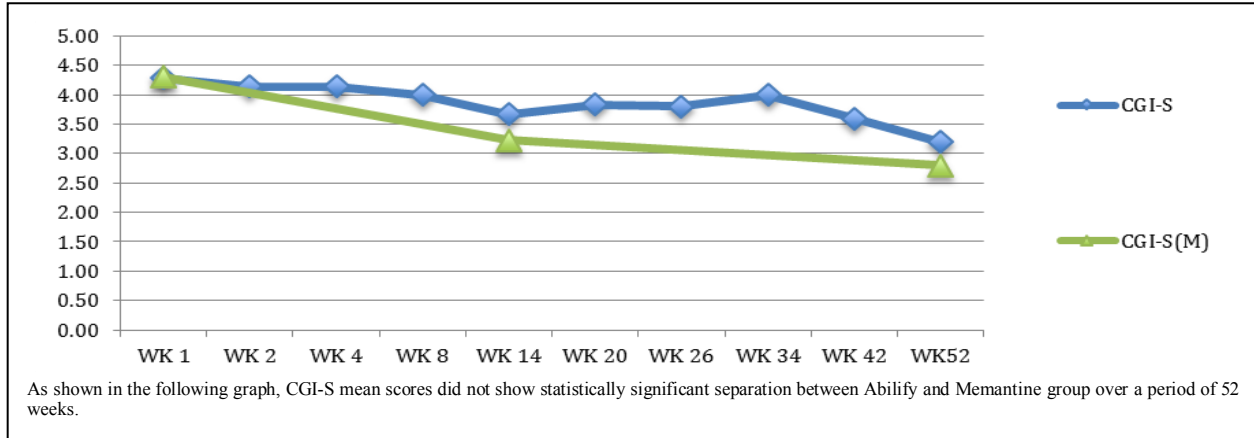
Of the 20 patients, 13 were on Memantine and 7 were on Aripiprazole. The authors observed that the gender and treating medication ratios are skewed; there were more male patients and more patients on Memantine, however this was not by design.

It was accepted that Autism is more prevalent in males, and may have more externalized behaviors such as irritability. It was also hypothesized that that there were more patients on MEMANTINE as compared to ABILIFY, because of reports in the media at that time, about the possibility of Memantine being beneficial in the treatment of ASD irritability. Parents/guardians all were aware of the various medication options, and were well versed with treatment options, having their preferences for medications. The choice of using either Aripiprazole or Memantine was made collaboratively in a treatment team approach by prescriber and parents/guardians, with appropriate informed consent.

The severity, improvement and progress of the ASD patients regarding their irritability had been followed by the standardized measures such as parent/caregiver reported Aberrant Behavior Checklist- irritability subscale (ABC) and Clinician Rated Clinical Global Impression (Severity and Improvement) scales. It was noted that the same parent/caregiver and clinicians completed the forms, such as the ABC and CGI throughout the observation and review period.

The Aberrant Behavior Checklist (ABC), is a parent/

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caregiver completed form. ABC consists of 58 items, organized within five subscales. Each item is scored on a scale from zero (no problems) to three (severe problems). A low score correlates with less symptoms, and a high score correlates with more symptoms in that category. ABC Irritability Subscale has 15 items, maximum 45 points. Symptoms assessed on this 15-item subscale include self-injurious behaviors, physical aggression towards others, screaming, yelling, temper tantrums, demanding behaviors, mood changes, and crying in response to minor annoyances (Aman MG 1994)

The Clinical Global Impression Scale is a global rating scale that measures illness severity (CGI-S) and global improvement (CGI-I).

CGI-S AND CGI-I are scales which are rated one through seven. For CGI-S, one would be considered being normal, four being moderately ill, and seven being most severely ill. And for CGI-I, a score of one would be considered very much improved, four meaning no change and seven being very much worse. Thus, a decrease in scores for both CGI-S and CGI-I, indicates an improvement in disease state.

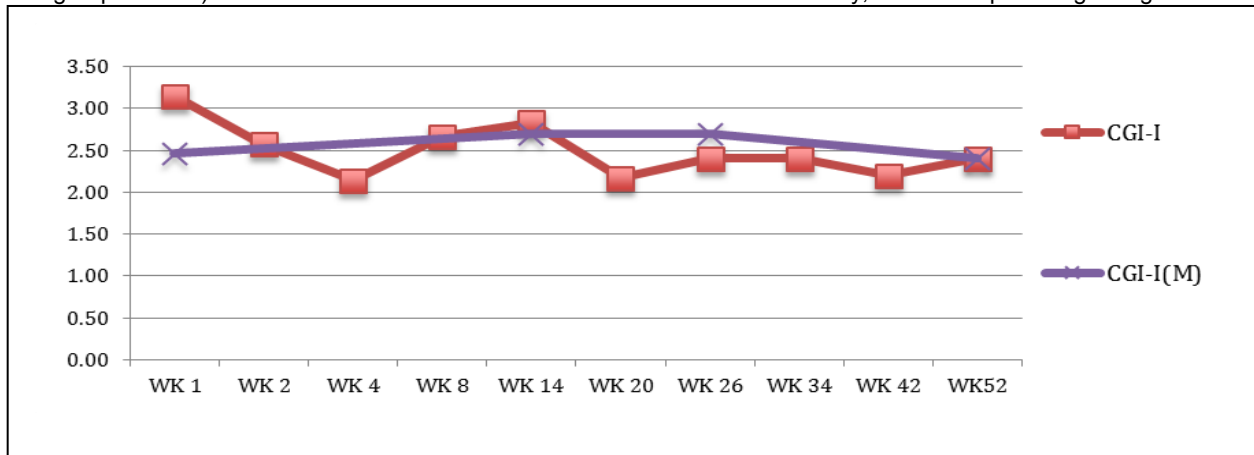
RESULTS:

At the onset it was noted that both group of patients, i.e. those who chose to be on ABILFIY and those who chose to be on Namenda had very similar ABC-I subscale scores at the starting point (mean score for ABILFIY subgroup was 14 and mean score for NAMENDA subgroup was 12) as well as at the end of the observa-

tion period week 52 (mean score for ABILIFY subgroup was 14 and mean score for NAMENDA subgroup was 11). The mean scores for CGI-S scores for both subgroups was also very similar (at the start of the observation period the score was 4.31 for both groups; and at week 52 the mean score was 3.2 for the ABILIFY subgroup and the NAMENDA subgroup had a mean score of 2.8), by the end of the observation period of 52 weeks it was observed that the mean CGI-I scores for both subgroups were exactly the same (2.40). The results of the data show that both ABILIFY and NAMENDA decreased the severity of the targeted symptoms as noted by CGI-S, and CGI-I, indicating an improvement in the clinical picture. However the ABC-I subgroup scores showed no statistically significant change from the start of the study. Aripiprazole is effective medication in reducing irritability. Chart review indicated that both medications were well tolerated by the patients with no adverse events warranting the discontinuation of the treatment regime.

DISCUSSION:

The results that we got by analyzing the data were very interesting. It is to be noted that at the beginning of the chart review the authors were of considering that the results might indicate Abilify being much more effective than Namenda. It was expected that Abilify would do very well based on its past performance in double-blind, placebo-controlled pivotal studies based on which the FDA gave its approval to Abilify for use in Autistic patients with Irritability, and the reports regarding Meman-



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tine have been that it has been reported to both either improve or worsen irritability in its double-blind placebo controlled trials.

The authors tried to decrease bias and confound by having strict criteria for inclusion or exclusion of charts in that were selected for review. Hence the small number of patients whose charts were reviewed. Even though this is one of the limitations of our study, i.e. a small sample size. However, it also appears to be one of the strengths of our review that confound was minimized. At the end of our analysis, it is interesting to note that both ABILIFY and NAMENDA did equally well and there was no statistical difference. Once again we have to point out that the limit of our study was the small sample size and it is possible that if the sample size was larger, we could have seen a significant statistical difference between the two subgroups of patients. However, this can be considered a typical setting in a clinic where the number of patients with autistic spectrum disorder are not in the thousands, especially when we take into account all the compounds. It also emphasizes the already known fact that medications alone are not the answer and along with medications. We do need treatment regimens, which include, psychoeducation, supportive therapy, behavioral interventions, as well as family support groups. More research is needed not only in order to find better treatment options, but also to compare different medications that are either approved by the FDA for certain conditions, or are commonly being used in the community as part of the standard of care doctrine.

The result that we got may be interpreted as implying that there might be subgroups of children with ASD that respond optimally to Memantine or to Abilify. Clearly larger, well-designed, and blinded studies are needed to further evaluate the efficacy of medications in children with ASD as well as a need to define the subgroups that might optimally respond to this or other medication. (Daniel A. Rossignol, 2014)

With the information available to us from this study, and other such studies we in the scientific community need to come up with a treatment algorithm for patients with various subtypes of the autistic spectrum disorder. In a way this would mean that we are treating patients symptoms rather than their diagnoses, which is already the standard of care.

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