Effects of Memantine in Autism

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Key Features in Autism

- Impairment in reciprocal social interactions
  - Poor eye contact, failure to develop peer relationships, lack of sharing, lack of social reciprocity
- Impairment in Communication
  - Delay in spoken language, inability to sustain conversation, lack of imaginative play
- Repetitive, stereotyped behavior
  - Rituals, hand flapping, preoccupation with objects

for Autism

- Applied behavioral analysis
- Structured teaching
- Developmental approaches
- Alternative communications strategies
- Picture Exchange communication system
- Speech and Language therapy
- Social Skills Training
- Occupational Therapy

Interventions Cont.

- Up until recently, there were no medications that treated the core symptoms of autism
- Medications were mainly centered on treating comorbidities:
  - Hyperactivity -> stimulants
  - Aggression -> anti-psychotics
  - Seizures -> antiepileptics
  - Mood dx -> SSRI

- Current therapies and interventions target young children (preschool age and younger)
- Limited interventions for older children and adolescents
- Main therapies include IEPs with transition plans – preparing adolescent for transition to adulthood
  - Vocational training
  - Further education

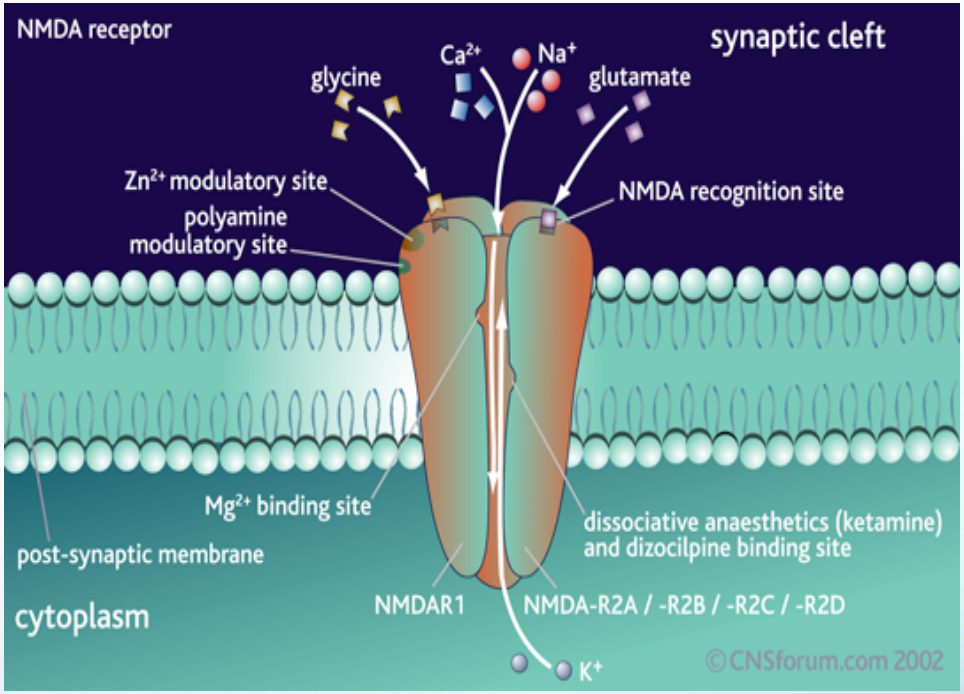
What about treating the core symptoms of Autism?

Neuroinflammation theory

- Neuroglial inflammation that impairs neuromigrational development and cortical organization and remodeling, formation of synapses
- Excess glutaminergic activity due to activation of NMDA receptor pathways
- Supporting evidence from brain tissue samples and spinal fluid studies

N-methyl-D-aspartate (NMDA) receptor

- Ligand gated cation channel
- Made up of NR1 and NR2 heteromers
- Activated by glycine (NR1) and glutamate (NR2)
- Function: synaptic transmission and plasticity, memory formation
- High activity: epilepsy, dementia, stroke
- Low activity: schizophrenia, psychosis



NMDA receptor antagonists

- Amantadine: non-competitive antagonist
  - Showed improvement in hyperactivity and inappropriate speech
  - No significant global improvement
- D-cycloserine: partial agonist of glycine site on NMDA receptor
  - Mild antagonist activity
  - Showed mild improvement in 10 patients
- Phencyclidine: high affinity antagonist
  - Psychotomimetic effects
- Memantine: moderate antagonist

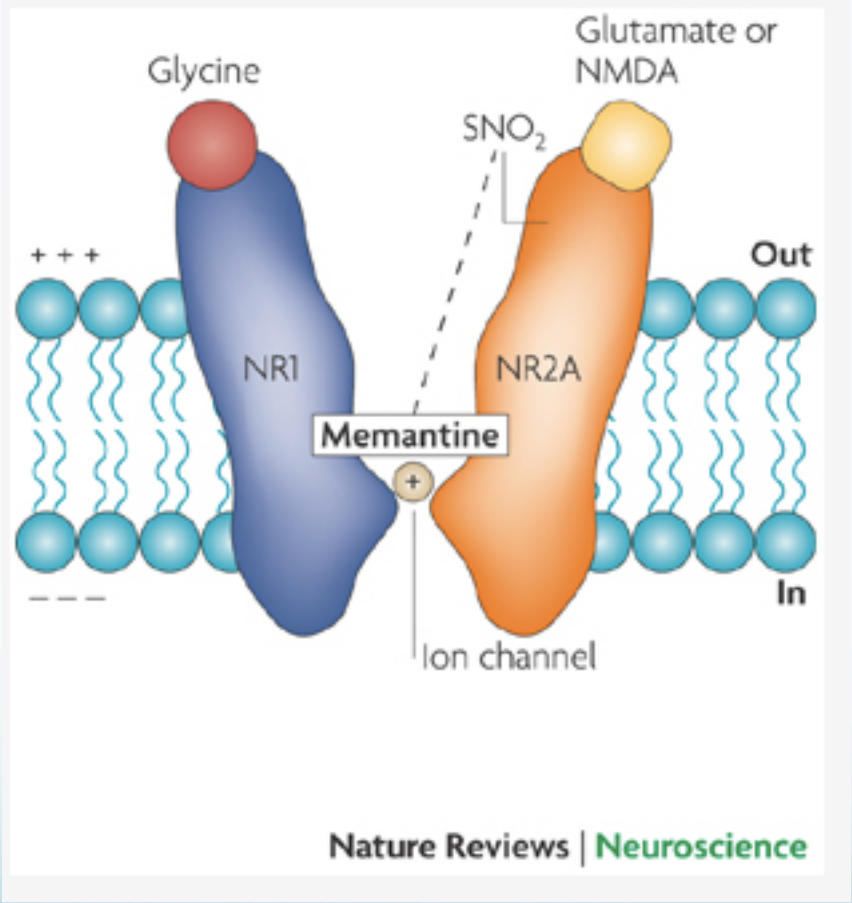
Memantine

- Also known as Namenda (trade name)
- Moderate affinity NMDA antagonist
- Currently used in Alzheimer's disease
  - Enhances cell survival
  - Enhances memory and learning by reducing nerve signal transmission noise

Ebixa®

memantine

Memantine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Memantine as Adjunctive Therapy in Children Diagnosed With Autistic Spectrum Disorders: An Observation of Initial Clinical Response and Maintenance Tolerability

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Autism and Pervasive Developmental Disorder Not Otherwise Specified are common developmental problems often seen by child neurologists. There are currently no cures for these lifelong and socially impairing conditions that affect core domains of human behavior such as language, social interaction, and social awareness. The etiology may be multifactorial and may include autoimmune, genetic, neuroanatomic, and possibly excessive glutaminergic mechanisms. Because memantine is a moderate affinity antagonist of the *N*-methyl-D-aspartic acid (NMDA) glutamate receptor, this drug was hypothesized to potentially modulate learning, block excessive glutamate effects that can include neuroinflammatory activity, and influence neuroglial activity in autism and Pervasive Developmental Disorder Not Otherwise Specified. Open-label add-on therapy was offered to 151 patients with prior diagnoses of autism or Pervasive Developmental Disorder Not Otherwise Specified over a 21-month period. To generate a clinician-derived Clinical Global Impression Improvement score for language, behavior, and self-stimulatory behaviors, the primary author observed the subjects and questioned their caretakers within 4 to 8 weeks of the initiation of therapy. Chronic maintenance therapy with the drug was continued if there were no negative side effects. Results showed significant improvements in open-label use for language function, social behavior, and self-stimulatory behaviors, although self-stimulatory behaviors comparatively improved to a lesser degree. Chronic use so far appears to have no serious side effects.

Keywords: autism treatment; pervasive developmental disorders; memantine

Patient Profile

- Total of 151 patients
  - 105 (69.7%) who met diagnostic criteria for autism
  - 46 (30.3%) with PDD-NOS
  - 129 male, 22 female
  - Age: 2.58 – 26.33 years (mean 9.31)
- 124/151 patients continued on memantine as chronic tx
- Of the 27 that stopped tx, 22 had worsened behavior, the other 5 stopped due to lack of effect
- Exclusion criteria
  - Pts with history of Fragile X, Rett syndrome, brain malformations, metabolic disorders were excluded
  - Abnormal EEGs were allowed. Sixty percent of children with autism have EEGs with epileptiform abnormalities without clinical seizures

Concurrent Medications

- SSRIs
- Atypical antipsychotics
- Stimulants, alpha adrenergic antagonist, SNRI
- Lithium
- Cholinesterase inhibitors
- Antiepileptics

- Not allowed: Lamotrigine as it may inhibit glutamate

Methods

- Started Memantine at 5mg/day, once or twice daily
- Titrated up or down in 2.5-5mg increments every 4-6 wks based on clinical response
- Overall dosing ranged up to a maximum of 30mg/day
- Performed assessments initially every 4 wks, then 8-12 wks, then 12-16 wks
- Based assessment on Clinical Global Impression Improvement scale

Clinical Global Impression Improvement Scale

- 1 = very much improved
- 2 = much improved
- 3 = mildly improved
- 4 = no change
- 5 = mildly worse
- 6 = much worse
- 7 = very much worse

- 3 Core Areas of autism dysfunction were assessed on the scale
  - Language – based on both receptive skills and expressive utterances
  - Behavior – based on cognitive improvement, increased social interest or efforts
  - Self-stimulatory activity – based on the quantity and type of activity observed
    - Only assessed in patients who had baseline self-stimulatory activity before trial (76.8%)

Results

- Language Domain
  - 31/150 scored 1 (very much improved)
  - 71/150 scored 2 (much improved)
  - Total percentage of 70% with significant improvement
  - Only 3/150 (2%) had a score of 5 (mildly worse)
  - No 6 or 7s given
  - Changes in language were noted in the first 2-4 wks of therapy
  - Most improvements in receptive language, however expressive language also improved in patients who had higher verbal skills at baseline

Results

- Behavior domain
  - Showing interest in others, making efforts in social interaction, showing ability to be more cooperative at home and school, and following schedules and directions
  - 12/150 scored 1 (very much improved)
  - 94/150 scored 2 (much improved)
  - Total of 70.7% with significant improvement
  - Slightly worse in 18/150: 11.8% - manifested with irritability, hyperactivity and manic behavior
  - Significant improvement of behavior over time, the greater the duration, the better the outcome

Results

- Self-Stimulatory stereotypic behavior
  - 2/116: scored 1
  - 12/116: scored 2
  - 96/116 (82.8%): no changes reported
  - Overall 12.1% showing significant improvement
  - Only 2/116 reported worsening

	Overall		
	% Improvement (CGII = 1-2)	Significant Improvement (*P*)	Improvement Trajectory[a] (*P*)
Language	70	<.001*	.004*
Behavior	71	<.001*	.403
Self-stimulatory	12	<.001*	.121
	Autism		
	% Improvement (CGII = 1-2)	Significant Improvement (*P*)	Improvement Trajectory[a] (*P*)
Language	65	<.001*	.069
Behavior	67	<.001*	.406
Self-stimulatory	9	.004*	.009*
	PDD-NOS		
	% Improvement (CGII = 1-2)	Significant Improvement (*P*)	Improvement Trajectory[a] (*P*)
Language	80	<.001*	.015*
Behavior	78	<.001*	.201
Self-stimulatory	27	.011*	.810

Case Example

- AB is a 14yo boy with autism
  - Started on memantine initially at 5mg daily, then titrated up to 10mg after 1 wk and up to 15mg after 5 weeks
  - At 1 month f/u visit: parents reported improved social interaction at home and school
    - Started talking on the phone and introducing himself to others
    - At clinic appt, he made eye contact with examiner and discussed his interests
    - At school, reports from teachers said that he began to initiate conversation at school
    - However, he still was easily distracted and had preoccupations with strange things
    - No adverse effects after 7 months of treatment

Shortcomings of the Study

- No placebo, not blinded study
- Largest study on memantine to date, however still overall small sample size
- Lack of commentary on early intervention with memantine vs late intervention
  - Variations in response based on age
- Short Observation Time (1-20 months)
- No standardized outcome measures

Next Steps

- Perform a controlled blinded study with placebo
- Extended observation for assessment of long-term tolerability and safety
- Standardized outcome measures to fully measure behavior and language outcomes
- Perform studies in patients with Rett Syndrome

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