


CLINICAL INFORMATION  
PHYSICIANS CAN OFFER TODAY  
Theoretical Future Treatments



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by

- MICHAEL G. CHEZ MD
- DIRECTOR PEDIATRIC NEUROLOGY
- SUTTER NEUROSCIENCE INSTITUTE
- SACRAMENTO, CA
- ASSOCIATE PROFESSOR NEUROLOGY
- VOLUNTEER FACULTY UNIVERSITY OF CALIFORNIA DAVIS MEDICAL SCHOOL



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Disclosures

- Consultant  
Forest Laboratories
- Consultant Accordia
- Speaker  
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## Autism: Overview

- Number one developmental disorder today
- Some Aspects Have Almost Gotten Political or Cult-like Aspects Among the Public: Myths vs. Facts
- I will try my objective best to discuss the topic today: FOCUS MEDICAL TREATMENTS

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## Autism: Definition

- First described by Kanner in 1940's
- Asperger described independently in Austria about the same time
- Clinical Definitions based on observations
- 3 Core Problems:
- Communication; Socialization; Stereotypic Behaviors



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## Autism

- State of California shows increasing diagnosis and service utilization as of 2007
- Now > 1:140 births; > 1:100 boys born
- 3/1000 autism, 7 /1000 autistic spectrum
- Cost \$3.5 million per child over lifetime

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**MEDICAL DEFINITION**

- TYPE OF AUTISM CLINICALLY
- LOW or HIGH FUNCTIONING
- PRIMARY or SECONDARY TYPE  
i.e. is there an underlying or prior medical reason
- REGRESSION or NON-REGRESSION
- CO-MORBID ISSUES: Sleep GI Immune

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**MEDICAL FACTS**

- No Current Single Cause
- Multifactorial Theories
- Heterogenous Condition
- >20 genes, also multiple genes that tie into turning on/off and also immune genes

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**Medical Facts**

- EEG factors: Abnormal/ Normal
- Epilepsy
- Immune Markers? Toxins?
- Neuroanatomical Studies Limited
- Brain Imaging Findings: functional and static imaging
- Co-Morbid Factors

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## AUTISM SPECTRUM

- Autism is clearly a clinical spectrum disease much like cancer or dementia not all being exactly from one cause
- In other words not all cases look or act the same
- Therefore no single treatment or behavior strategy will apply to all children with the label

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## Autism Spectrum

- Caution with “Cookie Cutter” Approach for everyone
- Big clinical differences from low and high functioning, with or without mental retardation, with or without seizures, etc.

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## Prenatal Factors

- Genetic
- Immune
- Environmental
- In Vitro? In Utero
- Infection and When
- Complication of Pregnancy
- Gestational Age

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## Genetics

- Genetics study features and link these to chromosome data
- Phenotype: Clinical patterns that describe genetic condition
- Genotype: Actual chromosomal data that correlates to patient genes. May or may not always match phenotype, variants occur, more than one genotype for a phenotype can occur in autism

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## Genetics

- Have studied twins
- Have studied other diseases with autistic similarities: Angelmann's, Williams, DiGeorge, Smith-Lemli Opitz, tuberous sclerosis, and others
- Also Fragile X and Retts
- These diseases are unique and different than idiopathic autism

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## Genetics

- So far > 22 genes have been linked in studies to autism
- There are other genes on the X, 17, 22, 1,7,15, 16, MECP2 and other chromosome gene sites
- Family histories of immune or psychiatric conditions
- These genetic findings support a multifactorial problem

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## Genetics

- Microarrays show numerous changes to genes and are new technology offered
- These chips find 10% may have new spontaneous mutation
- There are some that may double the risk of autism related to the immune system on chromosome 6; MET gene
- Recent work 104 families of middle east decent (Parents first degree relative) had 8% abnormalities: genes affecting synapse formation; 5 with sodium channels, 1 child had deletion

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## Genetics

- Conclusion: Complex
- Not one-gene-one disease
- May not yield single therapy except in cases like perhaps Fragile X (Fenobam)
- More studies on autism and genetics in past decade than any other area of hard science, > 10,000 articles

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## Environment

- May have environmental factors
- In utero: Infection, immune issues, medications
- Extra-utero: In vitro, toxins, pesticides, heavy metal?, other factors
- Deprivation: Orphanages

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## Neuroimaging, Neuroanatomy

- Routine Clinical MRI not very informative in most cases
- Research over the years has implicated various regions
- Cerebellum; Temporal Region; Atypical or poss of asymmetries
- White matter thickening, Accelerated Head Growth, Regional Loss of Neurons or Asymmetry

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## Functional Neuroimaging

- SPECT Inconclusive overall; sleep studies with EEG abnormalities do correlate 80% of time; Possible microvascular issues
- PET: Again inconclusive to date
- MEG: Possible decrease in sylvian fissure or atypical occult spikes
- fMRI: Atypical activation
- Mirror Neurons

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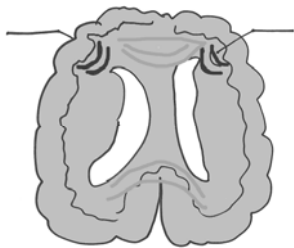
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## Brain Schematic U fibers thicker



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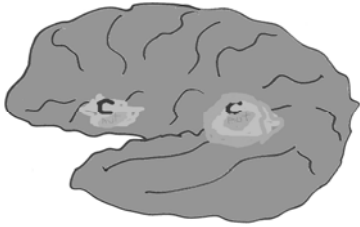
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fMRI Differences in Activation: Yellow (Control)/ Green (Autism)



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Neuroanatomy

- The expert is here at this conference  
Dr. Margaret Bauman
- However the findings so far are limited to few brain samples available, may not represent the current spectrum
- See Purkinje cell and pontine changes/ retrograde changes?
- Hypercellular and abnormal temporal regions

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Neuroanatomy

- Differences in Receptors:
- Perry in England found decreased frontal and parietal nicotinic ( alpha and beta) and frontal M1 & parietal muscarinic M2 receptor density in Autistic Brain (*Perry, et al 2001*)
- Excess Glutaminergic activity in Brain Tissue

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## Neuroimmunology

- Since that time there is now evidence of elevated cytokine inflammation and neuroglial activation in some autistic tissue and CSF samples.
- Elevated TNF-Alpha, TNF-Alpha R1 receptors, MCP-1, IL-1, IL-6
- Prior CNS anti-bodies against capillary lining tissue and Anti-BDNF

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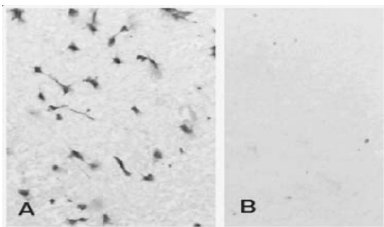
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## Anti-CNS Antibodies: A =autism B=control serum



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## Role of Innate Autoimmune Neuroglial System

- This may be primary or secondary pathological factor
- May affect neuromigration or development
- NMDA receptors may be important end-stage of glutamate damage to neurons
- Cholinergic nicotinic receptors now thought to be involved in potential repair mechanism of white matter damage due to inflammation

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## PANDAS: People with pandas



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## Neuroimmune Issues

- Findings of post-infectious neuropsychiatric conditions, still debated
- Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection (PANDAS): Not really seen in autism per se
- Mainly in children
- Usually after acute infection; 6-12 weeks later
- PITANDS: Pediatric Post-Infectious Triggered Neuropsychiatric Disorders

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## Do Vaccines Cause Autism

- Probably not directly; Not as claimed in lay public
- Can autoimmune issues that are present in mother in utero or in infant predisposed yield aberrant response in innate neuroglial reaction: Perhaps
- Mercury not likely the causes for vaccine issues
- Perhaps underlying /immune issues also

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**Electrophysiology and Autism**

- 1943 Kanner patients 3/11 had seizures
- Also Subsequent studies show 10-30% of patients develop seizures in lifetime
- If seizures present 60-80% may have EEG abnormalities
- What about patients who are under age 5 years? What about regression?

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**EEG and Autism Spectrum**

The Clinical Need for an EEG in Children with Language Developmental Delays and Pervasive Developmental Disorders or Autism:  
*What Does an Abnormal EEG Potentially Mean?*

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**EEG and Autism Spectrum**

- EEG abnormalities may represent dysfunction or inflammation causing epileptogenesis
- EEG abnormalities may represent GABA deficits or Glutamate excess
- EEG abnormalities may be part of a spectrum of clinical presentation/ worsen morbidity

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## EEG and Autism Spectrum

- 1943: 1 of the 11 children described as autistic by Leo Kanner experienced seizures
- 1957: Landau-Kleffner Syndrome (LKS) is first described
  - Regression of language skills between the ages of 3 and 5 years
  - Usually mild epilepsy

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## EEG and Autism Spectrum

- A relationship between regressive PDD and epileptiform disorder was suggested in 1997 by Tuchman and Rapin
  - Children who regress after 18 months may be more likely to have abnormal EEGs
  - But it does not appear that epilepsy is a *cause* of regression

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## EEG and Autistic Spectrum

- Tuchman and Rapin (1997) saw centrotemporal spikes in children with language regression, regardless of the presence of epilepsy.
  - no differences in the localization of EEG discharges in AR and epilepsy.
- Rapin reported that by adulthood, 1/3 of those with autism will develop epilepsy
  - Risk peaks in adolescence

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## EEG and AUTISM

- Lewine et al. studied 50 children with AR or LKS in 1999 using MEG
  - Abnormalities found in 93% with AR and epilepsy
  - Abnormalities found in 77% with AR and no epilepsy
  - Primary or secondary sites of activity in the intrasylvian and perisylvian regions
  - Multifocal abnormalities observed in 75% of AR patients.

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## EEG and Autism

- Epilepsy and abnormal EEGs are relatively common in those with developmental language disorders, according to Tuchman's 1994 review
- There is a generally accepted association between epilepsy (especially in the temporal lobe) and language-based cognitive difficulties

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## EEG and Autism

- 2007: Spence et al at NIH show high percentage of sleep abnormalities in young Children > 60%
- 2006: Chez, et al show abnormal rate at least 61% over 10 year study in 889 children with autism or PDD-NOS
- Chez 2007 presents 60% abnormality rate in PDD-NOS and autism, around 80% PDD-NOS; 45% Autism in kids under 6 years ( N=50)

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## Treatment of EEG Abnormalities

- Studies by Hollander et al in autism shows benefits in behavior, however no EEG correlation
- Treatment with Valproate
  - Pliopys in 1994 described it to be possibly effective in improving language and social skills in children with autism and abnormal EEGs.
- Chez, et al shows several studies with EEG correlation of clinical and EEG response

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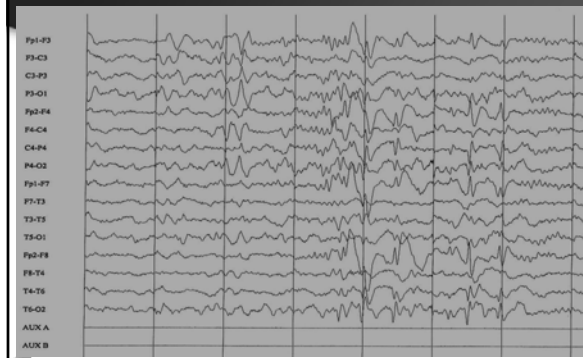
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## Spikes in Autism



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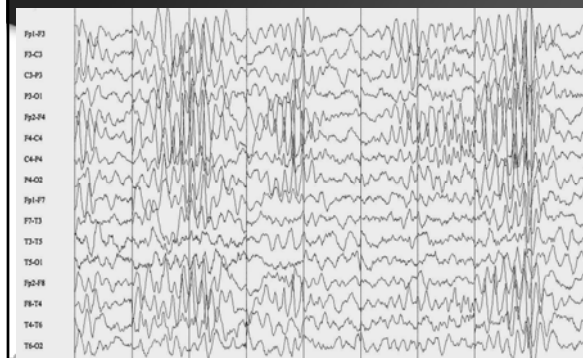
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## Spikes in Sleep



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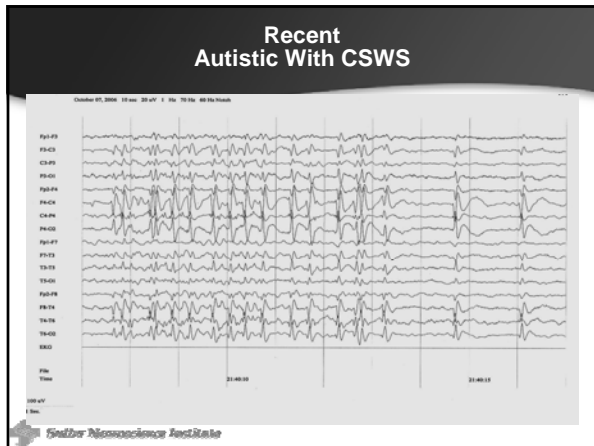
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- ### Treatment Results
- Chez, et al 2006
  - 176 patients treated with valproic acid formulations after first abnormal EEG.
    - Normalization in 82 (46.6%)
    - Improvement without normalization in 30 (17.0%)
    - No change in 64 (36.3%).
    - None worsened by follow-up overnight EEG.
      - Performed on average 10.1 months after first study
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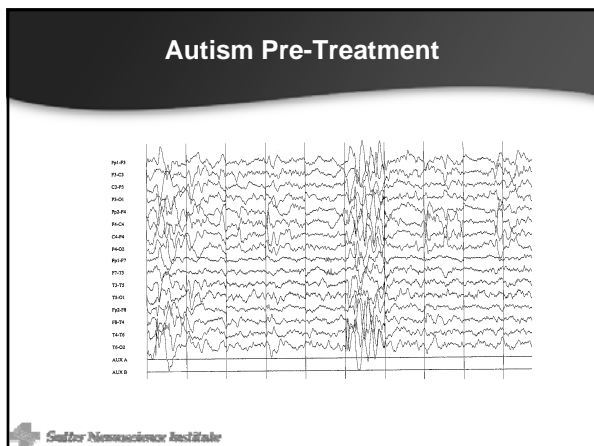
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### Autism Post-Treatment With Valproic Acid



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### Treatment

- Valproic acid was chosen empirically based on the open-label and controlled benefits previously reported in ASDs.
  - Treatment of the sub-clinical epileptic spikes may be preventative and provide neuroprotective measures
- Patients treated when younger now not having clinical seizures as adolescents

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### Discussion of Results

- The 2006 Chez et al study showed both regression and non-regression groups having similar percentages of EEG abnormalities
- The large population showing abnormalities indicates this may be a factor in pathology or comorbidity
- There is generally a seizure resolution rate of 16% over lifespan without treatment, but this study shows much higher EEG normalization with treatment.
- This shows hope for prophylactically preventing future clinical seizure development

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## EEG and Autism

- The data should encourage early screening of patients with ASDs using prolonged sleep EEGs
- It should dispel the myth that children with ASDs cannot participate in prolonged EEG studies

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## Medical Management

- No Cure, Quality of Life and maximize function
- Need to assess Individually
- Core Symptoms:
  - Language/Communication
  - Behavioral Issues
  - Socialization

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## Medical Management of Autism

- Clinically assess subtype of autism
- Regression or not
- Behavioral Problems to be addressed
- Family History: Psychiatric, Autoimmune
- Comorbid Issues: Immune, GI, Sleep
- Seizures or epileptiform EEG
- Genetics
- Prior Treatments tried

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### Medical Treatments

- Clinical Model: Assessment First
- History and Physical
- Genetic Screening where appropriate:  
Fragile X, Karyotype, microarray, mitochondrial genetics
- Overnight sleep EEG
- Medical Laboratory data as needed:  
General labs and metabolic(rare)

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### Medical Assessment

- Neuroimaging: MRI most common usually normal
- May in future do more lumbar punctures:
- Study CSF for Neurotransmitters, folinic acid deficiency, amino acids, inflammatory markers in future may be standard procedure

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### Medical Management

- If EEG abnormal, do MRI
- If EEG abnormal consider medical treatment options: such as Valproic acid etc. Studies in autism to support trials of valproic acid, more in progress
- Once try this establish clinical and EEG improvements
- Need to keep levels high therapeutic with valproic acid for example(90-110mg/ml)

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## Medical Management

- Language: May improve with treatment of abnormal EEG
- Receptive language first response with valproic acid
- May improve with L-carnosine
- May improve with certain medications that treat Alzheimers currently: Acetyl Choline esterase inhibitors or NMDA Antagonists

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## Medical Management

- Use of these medications are currently being considered off-label.
- Memantine being studied in double blind fashion
- Prior Double blind placebo controlled studies in literature for donezepil, and L-Carnosine
- Open label studies for memantine, rivastigmine, donezepil, amantidine, and others

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## Medical Management

- Improvements reported with medications on language and socialization: Donezepil: Most experience
- Most literature to date
- Limited to open label and a single cross-over double blinded study
- Measurements used: 43 patients, average age 6.8 yr dosage 2.5-5mg
- CARS, Gardners POWVT, CGI
- Changes in receptive language and behavior at 12 weeks, trend at 6 weeks

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## Donepezil

- Harden and Handen found 8 patients average age 11 yr with open treatment and used ABC and CGI. Dose 2.5-5mg
- Better irritability and attention but no language change
- ( limited perhaps by scales chosen and small study)

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## Rivastigmine

- Single open label study
- Works on Ach and BuCh
- 32 children age 6.9yr dose .2-.4mg BID
- POWVT, GARS, CARS, Connors
- Improved after 6 and 12 weeks
- Sig for POWVT-E, Trend for POWVT-R
- Better CARS Score Improved

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## NMDA Receptors

- Possible Glutamate excess in autism
- NMDA mechanisms in epilepsy
- Many children in spectrum have epileptic spikes on EEG or clinical epilepsy
- Perhaps NMDA could play a role modulating behaviors; Neuroprotective?

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## NMDA

- King et al showed Amantidine may have an affect
- Lamictal study did not show help suggesting more than glutamate effect alone
- Posey et al, 2004 D-Cycloserine an antibiotic with NMDA effect may help

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## Memantine Findings in large open label study

- Chez et al J Child Neurology June 2007
- 151 patients with PDD-NOS (46) or Autism (105)  
Clinical and DSM-IVTR criteria  
Age 2.56-26.33 (mean 9.31)  
129 M, 22F
- Improved language and speech
- Improved motor planning
- Less toe walking, better handwriting or drawing, better coordination
- Better length of speech utterances
- More complex social awareness

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## NMDA RECEPTOR

- NMDA may play a role in neuroglial activation
- May modulate some cytokine activity and in turn be modulated by some cytokine
- Important in neuronal migration and Synaptic Formation
- End point of glutamate regulation in inflammation

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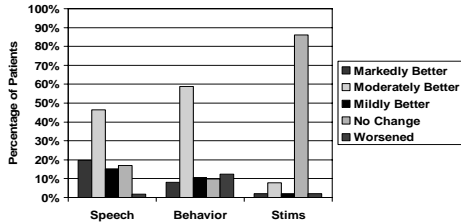
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### Clinical Experience: M. Chez, MD Efficacy: CGI- Autistic Patients



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### Memantine and NMDA

- Studies to develop for FDA approval in progress. Still many physicians are using off label for now
- Other new data for anxiety, OCD: Riluzole another NMDA antagonist is being studied.

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### Treatment of Autism

- Behaviors of aggression and aggitation:
- Also tics and anxiety and OCD or "manic" symptoms
- Use of atypical antipsychotics; previously used older antipsychotics
- Risperidone approved by FDA, soon aripiprazole also to get approval
- Other atypicals also useful, these all blocok dopamine receptors and some increase serotonin effect

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## Anxiety, Depression

- Mainly use SSRIs
- Some benefit mainly at low dose, higher doses tend to activate or induce manic type or agitated behaviors
- OCD usually better managed with atypical antipsychotics, perhaps NMDA drugs, as SSRIs have only had limited success overall in autism population, may work better in Asperger or high functioning group

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## ATTENTION

- Troublesome
- Sometimes language deficit, auditory processing issue
- Sometimes opposite effects with stimulants or atomoxetine
- Stimulants perhaps 30-40% affective, again better in higher functioning older group and Aspergers overall in my and others experiences

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## GI Issues

- Most patients with autism have not got sensitivity to milk or hwaet or gluten, very rare actual issues.
- However some do have rare food allergies, spastic colon, encoporesis, GE reflux, and also lactose intolerance
- Prudent pediatric care or referral for GI specialty care is important if symptoms are present

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### GI Issues

- Rigidity about textures, sensory issues, poor diet for meats etc can yield iron deficiency which can cause problems.
- Gluten Casein Diets need to be carefully monitored for nutrition as well as problems with various high dose vitamin supplementation
- Appetite suppression can occur with certain megavitamin therapy, Mg toxicity etc.
- Dietician monitoring these diets is essential
- Variation on low or complex carbohydrate diets may be mechanism

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### Sleep Issues

- > 50% can have sleep issues
- Onset and maintenance issues occur for sleep
- EEG abnormalities can occur
- If wake up screaming in first couple hours possible night terrors, later in evening of sleep could be seizures

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### Sleep Issues

- Onset treatment: Melatonin, clonidine, tizanidine, rozerem
- Hyponotics less desired
- Maintain sleep: Make sure not restless legs, iron/ferritin deficiency
- If not seizure or sleep apnea or restless legs may be lack of deep sleep as seen in other psychiatric conditions

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## Sleep Issues

- May need medications for anxiety or depression
- May need medications that change sleep cycles: Tricyclics, Gabapentin, others
- Obviously sleep behavior modifications are included as first steps to any sleep problem
- EEG or polysomnogram may be helpful

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## Future Treatments

- Again more updates on NMDA receptors
- Immune Mechanisms: Prenatal diagnosis of at risk mothers or early screening for those at autoimmune risk
- Treatment for those with regression or autoimmune cytokine markers?
- Treatments to reverse genetic defects
- Neurotransmitter problems, folinic acid therapy

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## Medical Management Conclusions

- Autism is Spectrum Disorder
- Not one type of treatment
- Future treatments will look at core mechanisms or reversal of genetic or environmental factors
- Current therapy aimed at quality of life
- Early medical interventions aid other therapeutic and educational efforts

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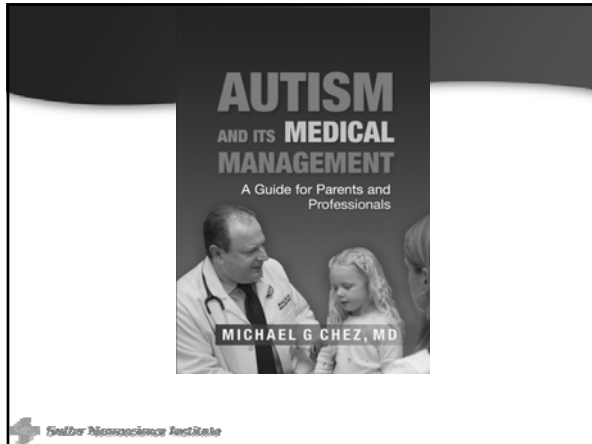
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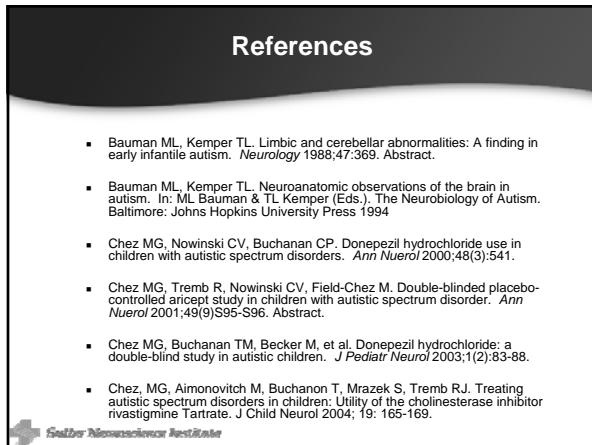
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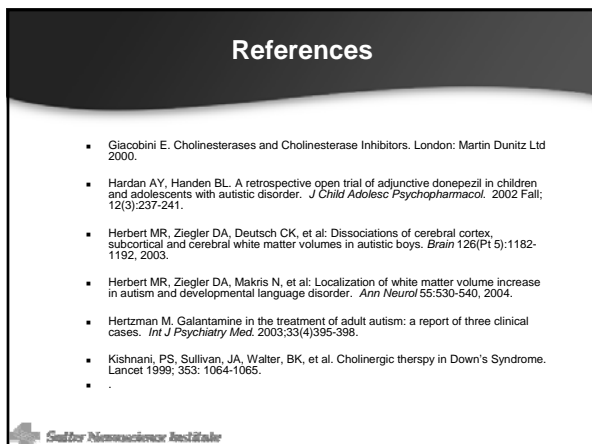
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