Seizures and Epilepsy in Autism Spectrum Disorder

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Disclaimer

Every attempt has been made to make this presentation as accurate as possible. The information is provided without any expressed or implied warranty. This presentation should not be substituted for medical advice. All treatments in this lecture are considered off-label and are not FDA-approved.

Disclosure

Dr Frye is conducting a clinical trial using folinic acid (leucovorin calcium) for children with ASD. Dr Frye receives funding from the BLARE foundation, the Jane Bostford Johnson Foundation, and the Arkansas Biomedical Institute. Dr Frye also is the site investigator for the Forest Laboratory clinical trial on memantine HCl in children with ASD.
Seizures and Epilepsy in Autism Spectrum Disorder

Prevalence of Epilepsy

Typically Developing Population: 1-2%
Autism Spectrum Disorder: up to 35%

Prevalence of an Abnormal EEG

Autism Spectrum Disorder: up to 80%
Age and Gender Characteristics

Two Age Peaks:
- Before age 5 years of age
- Adolescents

Gender:
- Just as likely in Girls as Boys
Clinical Characteristics

More likely to have:
- Another medical diagnosis
- Lower Intelligence
- More speech problems

Less likely to:
- be Aloof
- have Poor Eye Contact
Seizures and Epilepsy in Autism Spectrum Disorder

**Long-term Studies**

Adults diagnosed with Autism as Children

- 25%-38% had clinical seizures

Adults with Autism diagnosed with seizures as a child

- Lower Intelligence
- More maladaptive behaviors
- Higher rate of psychotropic medications
Seizure and Mortality

◆ In California during 2007 and 2009, crude death rates were 8.3 times higher for ASD individuals with epilepsy as compared to those with ASD without epilepsy.

◆ The highest standardized mortality ratios for individuals with ASD, both with or without mental impairment, were seizures. Interestingly, these high rates almost exclusively occurred after 20 years of age.
Seizures and Epilepsy in Autism Spectrum Disorder

Seizure Types

Seizures

Partial

Generalized

Complex Partial

Secondary Generalization
Generalized (tonic-clonic) type Seizure

(from American Epilepsy Society)
Partial Seizure (Right temporal lobe)

Symptoms
- Focal motor seizures
- Staring Episodes
- Automatisms
- Auditory Agnosia
- Speech Arrest

(from American Epilepsy Society)
Causes of Seizure
in Autism
Brain Malformations

Onset at Birth

Microcephaly

Development Delay

Very few cases in idiopathic autism
Important Causes: Metabolic Disorders

Mitochondrial Disorders

1. Hypotonia, epilepsy, autism, and developmental delay (HEADD syndrome) 12 cases (Filano 2002).
   - 42% large mtDNA deletions or multiple deletions
   - 75% Complex III Deficiency
2. 15q11-13+ Complex III deficiency (Filipek, 2003)
3. Complex I+III deficiency (Poling, Frye et al., 2006)
4. ASD & Mito – 39% with seizures (Shoffner, 2009)
5. ASD & Mito – 20% with seizures (Weissman, 2009)

Relation to Complex III Deficiency?
Important Causes: Metabolic Disorders

Cerebral folate deficiency
  Antibody blocks folate from entering the brain
  Early regression, decrease in head growth

Testing
  Antibody tests from several laboratories
  Confirmation with Lumbar Puncture

Treatment
  Treat with Folinic Acid 1-2mg/kg/day
  Milk Free Diet
Treatments of Seizure in Autism
Antiepileptic Medications:

Controlled Trials in Autism

but not for Seizures
Levetiracetam in Autistic Children: An Open-Label Study

THOMAS A. RUGINO, M.D.
Department of Pediatrics, Marshall University Joan C. Edwards School of Medicine, Huntington, West Virginia; Children's Specialized Hospital, Mountainside and Toms River, New Jersey

TERESA C. SAMSOCK, M.S.
Helping Hands Development Center, University Pediatrics, Huntington, West Virginia

### Table 6. Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Description</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash: Diaper area</td>
<td>Transient–local treatment</td>
<td>RNE</td>
</tr>
<tr>
<td>Rash: Trunk and extremities macular</td>
<td>Transient–reduced dose</td>
<td>CM</td>
</tr>
<tr>
<td>Rash: Diffuse macular</td>
<td>Diffuse–med discontinued</td>
<td>LS</td>
</tr>
<tr>
<td>Headache, vomiting, and stomachache</td>
<td>Transient–dose reduction</td>
<td>RB</td>
</tr>
<tr>
<td>Encopresis and diarrhea</td>
<td>Occasional, inconsistent–symptomatic treatment</td>
<td>CM</td>
</tr>
<tr>
<td>Daytime somnolence</td>
<td>Occasional–managed with late afternoon nap as needed</td>
<td>CM, KF</td>
</tr>
</tbody>
</table>

### Outcome Measures Before Medication Administration

- **Encopresis and diarrhea**
  - Occasional, inconsistent—symptomatic treatment
  - CM

- **Rash: Diffuse macular**
  - Diffuse–med discontinued
  - LS

- **Rash: Diaper area**
  - Transient–local treatment
  - RNE

Differences are calculated as

- **Conners CGI Emotional Lability**
  - Mean SD Mean SD
  - 65.5 19.6 64.1 8.7 .86

- **Conners DSM-IV Total**
  - Mean SD Mean SD
  - 73.6 9.5 58.8 6.7 <.003

- **Conners ADHD Index**
  - Mean SD Mean SD
  - 72.0 8.9 61.1 7.3 .01

- **Achenbach Aggressive Behaviors**
  - Mean SD Mean SD
  - 65.8 6.8 64.7 7.4 .51

- **Conners CGI Global Index**
  - Mean SD Mean SD
  - 76.0 12.8 81.4 6.2 .36

- **Conners DSM-IV Hyperactive/Impulsive**
  - Mean SD Mean SD
  - 73.5 11.2 74.1 8.2 .87

- **Conners DSM-IV Inattentive**
  - Mean SD Mean SD
  - 66.4 11.5 68.4 9.7 .74

- **Conners ADHD Index**
  - Mean SD Mean SD
  - 72.0 9.3 75.2 6.8 .52

- **Achenbach Attention Problems**
  - Mean SD Mean SD
  - 76.0 7.2 64.3 7.6 <.005

- **Achenbach Aggressive Behaviors**
  - Mean SD Mean SD
  - +4.3 NS

- **Conners DSM-IV Hyperactive/Impulsive**
  - Mean SD Mean SD
  - +3.0 NS

- **Conners DSM-IV Inattentive**
  - Mean SD Mean SD
  - +5.7 NS

- **Conners CGI Emotional Lability**
  - Mean SD Mean SD
  - +7.4 NS

- **Conners CGI Global Index**
  - Mean SD Mean SD
  - +2.5 NS

- **Achenbach Aggressive Behaviors**
  - Mean SD Mean SD
  - +4.3 NS

- **Conners ADHD Index**
  - Mean SD Mean SD
  - +0.0 NS

- **Conners DSM-IV Total**
  - Mean SD Mean SD
  - +3.0 NS

- **Conners DSM-IV Hyperactive/Impulsive**
  - Mean SD Mean SD
  - +3.0 NS

- **Conners DSM-IV Inattentive**
  - Mean SD Mean SD
  - +5.7 NS

- **Conners CGI Emotional Lability**
  - Mean SD Mean SD
  - −7.4 NS

- **Conners CGI Global Index**
  - Mean SD Mean SD
  - +2.5 NS

- **Achenbach Aggressive Behaviors**
  - Mean SD Mean SD
  - +4.3 NS

- **Conners ADHD Index**
  - Mean SD Mean SD
  - +0.0 NS

- **Conners DSM-IV Total**
  - Mean SD Mean SD
  - +3.0 NS

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  - −7.4 NS

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  - Mean SD Mean SD
  - +2.5 NS

- **Achenbach Aggressive Behaviors**
  - Mean SD Mean SD
  - +4.3 NS
Levetiracetam versus placebo in childhood and adolescent autism: a double-blind placebo-controlled study
Stacey Wasserman, Rupa Iyengar, William F. Chaplin, Dryden Watner, Shulamit E. Waldoks, Evdokia Anagnostou, Latha Soorya and Eric Hollander

10 weeks of placebo (n=10) or Levetiracetam (n=10)
No significant improvement in the CGI for autism, impulsivity/aggression or affective instability, parent or teacher ratings of irritability, lethargy, stereotypy, hyperactivity or inappropriate speech on the ABC; repetitive behaviors as measured by the CY-BOCS; parent or teacher ratings of hyperactivity, ADHD, restless-impulsivity, CGI-total symptoms, DSM-IV Hyperactivity-Impulsivity or DSM-IV total symptoms as rated by the Conner's' scales
No significant difference in adverse effects
An Open Trial of Divalproex Sodium in Autism Spectrum Disorders

◆ 14 children with ASD but not epilepsy or abnormal EEG
◆ 10 (71%) completed the trial
◆ Those completing the trial rated sustained improvement in core and associated autism symptoms such as affect instability, impulsivity and/or aggression.
◆ Average dose: 768mg/day (125-2500mg/day).
◆ Average treatment length: 10.7 months (0.5-43)
◆ Average blood level: 75.8 (50-92)
Lamotrigine Therapy for Autistic Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial

*d* Journal of Autism and Developmental Disorders, *Vol. 31, No. 2, 2001*

Karin M. Belsito,¹ Paul A. Law,² Karen S. Kirk,¹ Rebecca J. Landa,¹,² and Andrew W. Zimmerman¹,²

◆ 18 week trial.
◆ Tapered up to 5mg/kg/day over 8 weeks
◆ Maintained for 4 weeks
◆ Tapered off over 2 weeks
◆ Drug Free Period for 4 weeks

**Measurements – No significant difference**

- Aberrant Behavior Checklist
- Autism Diagnostic Observation Schedule
- Autism Behavior Checklist
- Vineland Adaptive Behavior Checklist
- Childhood Autism Rating Scale
Traditional and non-traditional treatments for autism spectrum disorder with seizures: an on-line survey

Richard E Frye¹, Swapna Sreenivasula² and James B Adams³

• On-line web-based survey
• Average Completion Time 25 Minutes 26 Seconds
  • Total 737 Questions
  • Skip logic used to minimize questions.
• Each Treatment rated for effect on
  • Seizures
  • Sleep
  • Expressive Language
  • Receptive Language
  • Verbal Communication
  • Non-verbal Communication
  • Stereotypic and repetitive behavior
  • Rigidity, flexibility and adaptability:
  • Hyperactivity
  • Attention
  • Mood
• Side Effects and Frequency of Side Effects

### Seven Point Scale

- **Substantial negative effect:** 7.61%
- **Moderate negative effect:** 6.09%
- **Mild negative effect:** 3.05%
- **No effect:** 17.26%
- **Mild positive effect:** 11.68%
- **Moderate positive effect:** 25.38%
- **Substantial positive effect:** 28.93%
Seizures and Epilepsy in Autism Spectrum Disorder

Grand mal / Generalized seizures (During a generalized seizure, a person loses consciousness and both arms and legs move synchronously either in a repetitive jerking fashion or become stiff.):

Partial seizures (During these types of seizures abnormal rhythmic movements are limited to one side or one portion of the body, for example the arm or the face. These seizures may or may not be associated with a change in consciousness):

Absence seizures (These seizures are typically associated with staring episodes in which you cannot get a person's attention by calling their name or touching them):

Landau-Kleffner syndrome, or continuous spike and wave during slow-wave sleep (These are special types of seizures that occur during sleep and are associated with language regression):

Landau-Kleffner variant or atypical Landau-Kleffner syndrome:

Subclinical epileptiform discharges (These are discharges seen on an EEG study that may or may not be associated with clinical seizures episodes):

Lennox-Gastaut:

Infantile Spasms:
Seizures and Epilepsy in Autism Spectrum Disorder

About one-third with Regression, Similar to the general autism population

Factors Associated with Regression

- Seizure(s): 41.28%
- High fever: 28.44%
- Viral illness: 19.27%
- Head Trauma: 2.75%
- Vaccination (please provide details in the text box below regarding which vaccines and the timing between the regression and the vaccination): 71.56%
Seizures and Epilepsy in Autism Spectrum Disorder

Routine EEG Most Prevalent Clinical Test
18% Diagnosed without a Clinical Test!

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine electroencephalogram (EEG)</td>
<td>74.94%</td>
</tr>
<tr>
<td>Overnight electroencephalogram (EEG) in the hospital or doctors office</td>
<td>40.32%</td>
</tr>
<tr>
<td>Ambulatory electroencephalogram (EEG)</td>
<td>20.27%</td>
</tr>
<tr>
<td>Magnetoencephalography (MEG)</td>
<td>3.42%</td>
</tr>
<tr>
<td>Positron emission tomography (PET)</td>
<td>5.47%</td>
</tr>
<tr>
<td>Single photon emission computed tomography (SPECT)</td>
<td>6.38%</td>
</tr>
<tr>
<td>Diagnosed clinically without an EEG or other clinical test</td>
<td>18%</td>
</tr>
</tbody>
</table>

One-half have emergency medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastat</td>
<td>31.66%</td>
</tr>
<tr>
<td>Valium</td>
<td>9.57%</td>
</tr>
<tr>
<td>Ativan</td>
<td>10.93%</td>
</tr>
<tr>
<td>No Emergency medication</td>
<td>48.06%</td>
</tr>
</tbody>
</table>
Seizures and Epilepsy in Autism Spectrum Disorder

Clinical Seizure Treatments

<table>
<thead>
<tr>
<th>Antiepileptic Drugs (Cluster 1)</th>
<th>Non-Antiepileptic Drugs (Cluster 2)</th>
</tr>
</thead>
</table>

(A)

- Much Better (6)
- Better (5)
- No Change (4)
- Worse (3)
- Much Worse (2)

Legend:

- AED Cluster
- Non-AED Cluster

Significance levels:

- $\epsilon p < 0.01$
- $\dagger p < 0.001$
- $\dagger\dagger p < 0.0001$
# Seizures and Epilepsy in Autism Spectrum Disorder

## Antiepileptic Drugs (Cluster 1)

<table>
<thead>
<tr>
<th></th>
<th>AED Subcluster 1</th>
<th>AED Subcluster 2</th>
<th>AED Subcluster 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Much Better</strong></td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Better</strong></td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No Change</strong></td>
<td></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Worse</strong></td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Much Worse</strong></td>
<td></td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

### Three Anti-Epileptic Drug Treatment Subclusters

- **Seizures**
- **Sleep**
- **Communicate**
- **Behavior**
- **Attention**
- **Mood**

- €p<0.01
- †p<0.001
- ††p<0.0001
## Seizures and Epilepsy in Autism Spectrum Disorder

<table>
<thead>
<tr>
<th>AED Subcluster 1</th>
<th>AED Subcluster 2</th>
<th>AED Subcluster 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic Acid</td>
<td>Phenytoin</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Clonazepam</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Carbamazepine</td>
<td></td>
</tr>
<tr>
<td>Ethosuxidime</td>
<td>Oxcarbazepine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Topiramate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gabapentin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zonisamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Felbamate</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>
Survey of Treatments for Seizures in Autism

Seizures and Epilepsy in Autism Spectrum Disorder

Subcluster 1 Anti-Epileptic Drug Treatments

- Much Better (6)
- Better (5)
- No Change (4)
- Worse (3)
- Much Worse (2)

Parameters:
- Valproic Acid (n=246)
- Lamotrigine (n=165)
- Levetiracetam (n=148)
- Ethosuximide (n=23)

Significance levels:
- p<0.01
- *p<0.001
- **p<0.0001
Seizures and Epilepsy in Autism Spectrum Disorder

Non-Antiepileptic Drugs (Cluster 2)

<table>
<thead>
<tr>
<th>Non-AED Subcluster 1</th>
<th>Non-AED Subcluster 2</th>
<th>Non-AED Subcluster 3</th>
</tr>
</thead>
</table>

(D) Three Non-Anti-Epileptic Drug Treatment Subclusters

- Much Better (6)
- Better (5)
- No Change (4)
- Worse (3)
- Much Worse (2)

Seizures | Sleep | Communicate | Behavior | Attention | Mood

Significance levels:
- $p<0.01$
- $p<0.001$
- $p<0.0001$
<table>
<thead>
<tr>
<th>Non-AED Subcluster 1</th>
<th>Non-AED Subcluster 2</th>
<th>Non-AED Subcluster 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketogenic Diet</td>
<td>Vitamin B6, IVIG</td>
<td>Steroids VNS</td>
</tr>
<tr>
<td>Atkins Diet</td>
<td>L-Carnitine &amp; Acetyl-L-Carnitine</td>
<td></td>
</tr>
<tr>
<td>GFCF</td>
<td>CoQ10, Vitamin B12</td>
<td></td>
</tr>
<tr>
<td>HBOT</td>
<td>Dimethylglycine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Taurine, GABA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Magnesium, 5HTP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L-Carnosine, Chelation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glutathione, SCD</td>
<td></td>
</tr>
</tbody>
</table>
Survey of Treatments for Seizures in Autism

Subcluster 1 Non-Anti-Epileptic Drug Treatments

- Ketogenic diet (n=40)
- GFCF Diet (n=140)
- Atkin's Diet (n=15)
- HBOT (n=36)

Statistical significance:
- $p<0.01$
- $p<0.001$
- $p<0.0001$

Respondents' improvements:
- Much Better (6)
- Better (5)
- No Change (4)
- Worse (3)
- Much Worse (2)
Subclinical Electrical Discharges

Significance and Treatments
Landau-Kleffner syndrome (model for autism)

- Frequent Spikes in the Temporal Region

- Language regression after 3 years of age
- Only Language skills affected
- Most have clinical seizures
- Controlling discharges on EEG sometimes results in return of language

(From Ballaban-Gill and Tuchman, 2000)
Electrical Status Epilepticus during Slow Wave Sleep
• Generalized Discharges in 80% of slow wave sleep

(From Ballaban-Gill and Tuchman, 2000)
Subclinical Discharges

Specific Syndromes, such as Landau-Kleffner syndrome, are relatively rare.

Recent studies have shown that subclinical discharges are prevalent in children with Autism.

Other reports have suggested that the location of focal discharges correlate with specific symptoms.
series included no patients with classic 3/s spike-and-wave activity as seen in absences, and TCI was found no more often during generalised than with focal discharges. As suggested by Delgado-Escueta, "in absence epilepsy interictal discharges probably do not occur".

Detection of TCI

The demonstration of TCI depends on the test used. Simple measurements of reaction time and repetitive motor tasks are insensitive. To achieve the greatest sensitivity for TCI, the task should extend the tested person to the limits of his or her capability and must be neither too easy nor too demanding, so that floor and ceiling effects are avoided. An interactive task that adapts the degree of difficulty to individual performance is ideal. Tasks using working memory and language are among the most sensitive.

Early reports suggested that the type of discharge was an important determinant of TCI, which is most readily detected during generalised 3/s spike-and-wave discharges of at least 3 s duration. Arguably, these observations merely confirm that such discharges consistently produce absence seizures.

Most early studies of TCI concerned only generalised discharges. Prechtl and colleagues found no effect of focal events but also did not demonstrate TCI during generalised discharges. Aldenkamp and co-workers confirmed that generalised discharges of 3–10 s duration were commonly accompanied by overt seizures and failed to demonstrate TCI during focal or multifocal discharges; however, they presented no evidence to support this crucial finding. Kooi and Hovey suggested that focal discharges were less disruptive of performance than generalised discharges.

Our study of TCI associated with focal events, in a series excluding patients with 3/s generalised spike-and-wave activity, found an equal prevalence of TCI of about 50% with both generalised and focal discharges.

Nature and specificity of transitory cognitive deficits

Tizard and Margerison attributed the different sensitivities of tasks to differing information load. Hutt and co-workers showed that the linear relation between choice reaction time and information content of the stimulus was maintained...
Magnetoencephalography (MEG)

“Recording neuromagnetic signals is like listening for the footsteps of an ant in the middle of a rock concert”

- Dewar filled with helium
- Magnetically-shielded room

VectorView system Neuromag
Landau-Kleffner syndrome

(From Lewine et al., Pediatrics, 1999)
Seizures and Epilepsy in Autism Spectrum Disorder

(From Lewine et al., Pediatrics, 1999)
Causes of subclinical discharges

- Metabolic and Mitochondrial Disorders

- Inflammatory
  - Some children respond to steroids or IVIG
  - Specific antibodies (Endothelia) are sometimes found

- Brain malformations
  - Too small to see on clinical MRI but focal nature might suggest small cortical dysplasias exists
Three children with ASD and epileptiform discharges but no seizures

◆ #1 EEG: short runs of spike discharges from the right frontal-temporal area during sleep. Within one month of starting valproic acid, language & social skills improved significantly.

◆ #2 EEG revealed bifrontal independent sharp waves during sleep. Three months after starting valproic acid stopped spinning/hand flapping, started to say understandable words, use toys appropriately, engage in imaginative activities, and markedly improved her eye contact and social interactions.

◆ #3 EEG revealed independent bilateral frontal-central sharp waves during sleep. One month after starting valproic acid demonstrated markedly improved speech, appropriate play, emotional expression and improved following of commands.
Valproic acid treatment of epilepsy in autistic twins.


◆ Twin boys with staring episodes.
◆ One with routine EEG with paroxysmal high voltage slow activity with spikes during drowsiness, the other with normal routine EEG without sleep obtained.
◆ Both started on valproic acid. After 10 months of treatment, the mother reported the development of independent speech and affectionate behavior toward family members.
◆ The mother reported regression in language with periods of increased staring episodes which necessitated increasing the valproic acid dose which then improved language.
**Electroencephalogram Discharges in Atypical Cognitive Development**

Richard E. Frye, MD, PhD, Ian Butler, MBBS, FRACP, David Strickland, BS, Eduardo Castillo, PhD, and Andrew Papanicolaou, PhD

**Table 1. Presenting Complaints**

<table>
<thead>
<tr>
<th>Subcategory</th>
<th>% of subcategory</th>
<th>% of all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language Regression</td>
<td>7 (1/15)</td>
<td>4.5 (1/22)</td>
</tr>
<tr>
<td>Language Fluctuations</td>
<td>20 (3/15)</td>
<td>14 (3/22)</td>
</tr>
<tr>
<td>Learning Fluctuations</td>
<td>20 (1/5)</td>
<td>4.5 (1/22)</td>
</tr>
<tr>
<td>Memory Fluctuations</td>
<td>50 (2/4)</td>
<td>9 (2/22)</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>18 (4/22)</td>
<td>18 (4/22)</td>
</tr>
<tr>
<td>Seizure</td>
<td>4.5 (1/22)</td>
<td>4.5 (1/22)</td>
</tr>
</tbody>
</table>
Patterns of Clinical Symptoms: Autism symptomatology, Attention problems and History of Speech or Language Disorder

Table 2. Developmental Cognitive Disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>% of subcategory</th>
<th>% of all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>25 (4/16)</td>
<td>18 (4/22)</td>
</tr>
<tr>
<td>Attention disorder with or without hyperactivity</td>
<td>75 (12/16)</td>
<td>55 (12/22)</td>
</tr>
<tr>
<td>Autism symptomatology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echolalia</td>
<td>8 (1/13)</td>
<td>4.5 (1/22)</td>
</tr>
<tr>
<td>Mild pervasive developmental disorder</td>
<td>46 (6/13)</td>
<td>27 (6/22)</td>
</tr>
<tr>
<td>Pervasive developmental disorder-not otherwise specified</td>
<td>23 (3/13)</td>
<td>14 (3/22)</td>
</tr>
<tr>
<td>High-functioning autism spectrum disorder</td>
<td>8 (1/13)</td>
<td>4.5 (1/22)</td>
</tr>
<tr>
<td>Speech or language disorder</td>
<td></td>
<td>91 (20/22)</td>
</tr>
<tr>
<td>No obvious paroxysmal symptoms</td>
<td></td>
<td>77 (17/22)</td>
</tr>
<tr>
<td>Subtle symptoms</td>
<td>53 (9/17)</td>
<td>41 (9/22)</td>
</tr>
<tr>
<td>Staring</td>
<td>89 (8/9)</td>
<td>36 (8/22)</td>
</tr>
</tbody>
</table>
## Seizures and Epilepsy in Autism Spectrum Disorder

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated with AED</td>
<td>91%</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>31%</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>19%</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>19%</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>8%</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>8%</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>4%</td>
</tr>
<tr>
<td>IVIG</td>
<td>4%</td>
</tr>
</tbody>
</table>
AED treatment Improves Symptoms

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement within One Clinic Visit</td>
<td>70%</td>
</tr>
<tr>
<td>Improvement with Increasing AED Dose</td>
<td>10%</td>
</tr>
<tr>
<td>Limited Improvement</td>
<td>5%</td>
</tr>
<tr>
<td>No Improvement</td>
<td>15%</td>
</tr>
</tbody>
</table>
Could this be due to Chance or Placebo Effect?

50% of patients were followed for several months to years before starting AED treatment

<table>
<thead>
<tr>
<th>Type of Improvement</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement within One Clinic Visit</td>
<td>72%</td>
</tr>
<tr>
<td>Improvement with Increasing AED Dose</td>
<td>9%</td>
</tr>
<tr>
<td>Limited Improvement</td>
<td>9%</td>
</tr>
<tr>
<td>No Improvement</td>
<td>9%</td>
</tr>
</tbody>
</table>
Does Discontinuing Medication Result in Regression?

AEDs were withdrawn in three patients.

This resulted in regression.

Reinstitution of AED Improved Cognitive Function
No Controlled Studies of Treatment of Subclinical Electrical Discharges in Autism

BUT studies have been done in epilepsy
Treatment of interictal epileptiform discharges can improve behavior in children with behavioral problems and epilepsy.
Pressler RM, Robinson RO, Wilson GA, Binnie CD
2005 J Pediatr 146:112–117

◆ Blinded placebo-controlled study of lamotrigine in 61 children with well-controlled epilepsy but with subclinical discharges and behavioral problems.

◆ Behavioral improvement in the children on active drug who had a significant reduction in either frequency or duration of their subclinical electrical discharges.
Effects of transitory cognitive impairment on psychosocial functioning of children with epilepsy: a therapeutic trial.


- Blinded placebo-controlled cross-over study of lamotrigine in 10 children with well-controlled epilepsy but with subclinical discharges and behavioral problems.

- Psychosocial function as assessed by Conners’ teachers’ and parents’ rating scales

- 80% (8/10) showed improved functioning on active drug than on placebo (p<0.05).

- All responders showed fewer subclinical discharges

- Confounding factor: most also had fewer seizures with treatment
Can sodium valproate improve learning in children with epileptiform bursts but without clinical seizures?


- Double-blind, placebo-controlled, crossover study of valproic acid in 8 participants with subclinical epileptiform discharges without seizures
- No improvements in learning and behavior during the treatment arm
- Some worsening of attention and behavior with treatment
- Valproate blood levels were supratherapeutic, in the range in which adverse cognitive effects would be expected in several patients
- No correlation between improvements or detriments and in subclinical discharges
A review of traditional and novel treatments for seizures in autism spectrum disorder: findings from a systematic review and expert panel

Richard E. Frye¹*, Daniel Rossignol², Manuel F. Casanova³, Gregory L. Brown⁴, Victoria Martin⁴, Stephen Edelson⁵, Robert Coben⁶, Jeffrey Lewine⁷, John C. Slattery¹, Chrystal Lau¹, Paul Hardy⁸, Seyyed Hossein Fatemi⁹, Timothy D. Folsom⁹, Derrick MacFabe¹⁰ and James B. Adams¹¹

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² Rossignol Medical Center, Irvine, CA, USA
³ University of Louisville, Louisville, KY, USA
⁴ Autism Recovery and Comprehensive Health Medical Center, Franklin, WI, USA
⁵ Autism Research Institute, San Diego, CA, USA
⁶ New York University Brain Research Laboratory, New York, NY, USA
⁷ MIND Research Network, University of New Mexico, Albuquerque, NM, USA
⁸ Hardy Healthcare Associates, Hingham, MA, USA
⁹ University of Minnesota Medical School, Minneapolis, MN, USA
¹⁰ University of Western Ontario, London, ON, Canada
¹¹ Arizona State University, Tempe, AZ, USA
### Seizures and Epilepsy in Autism Spectrum Disorder

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Grade of recommendation</th>
<th>Prevalence of use</th>
<th>Important adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seizures</td>
<td>Behavioral and cognitive ASD symptoms</td>
<td>ASD with seizures</td>
</tr>
<tr>
<td>Valproate</td>
<td>B</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>C</td>
<td>D – NE</td>
<td>C</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>C</td>
<td>D – NE</td>
<td>C</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>B</td>
<td>D – NE</td>
<td>C</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>B</td>
<td>D – SC</td>
<td>C</td>
</tr>
<tr>
<td>Topiramate</td>
<td>B</td>
<td>D – PD</td>
<td>N</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>C</td>
<td>D – PD</td>
<td>N</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>B</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Phencobarbital</td>
<td>B</td>
<td>D – PD</td>
<td>N</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>B</td>
<td>D – PD</td>
<td>N</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>C</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>
Seizures and Epilepsy in Autism Spectrum Disorder

Table 3 | Seizures treatments for autism spectrum disorder.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Grade of recommendation</th>
<th>Prevalence of use</th>
<th>Important adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seizures</td>
<td>Behavioral and cognitive ASD symptoms</td>
<td>ASD with seizures</td>
</tr>
<tr>
<td>TRADITIONAL TREATMENTS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KD</td>
<td>B</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>MAD</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>VNS</td>
<td>B</td>
<td>D – NE</td>
<td>D – NE</td>
</tr>
<tr>
<td>Surgery – resection</td>
<td>C</td>
<td>D – PD</td>
<td>C</td>
</tr>
<tr>
<td>Multiple subpial transections</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Steroids</td>
<td>C</td>
<td>D – SC</td>
<td>D – SC</td>
</tr>
<tr>
<td>IVIG</td>
<td>C</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Neurofeedback</td>
<td>B</td>
<td>B</td>
<td>C</td>
</tr>
</tbody>
</table>
# Seizures and Epilepsy in Autism Spectrum Disorder

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Grade of recommendation</th>
<th>Prevalence of use</th>
<th>Important adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seizures</td>
<td>Behavioral and cognitive ASD symptoms</td>
<td>ASD with seizures</td>
</tr>
<tr>
<td><strong>SPECIFIC SYNDROME AND TREATMENTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberous sclerosis complex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>B</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Fragile X AEDs</td>
<td>C</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Mitochondrial disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-carnitine/acetyl-L-carnitine</td>
<td>N</td>
<td>B</td>
<td>N</td>
</tr>
<tr>
<td>Multivitamins</td>
<td>N</td>
<td>B</td>
<td>N</td>
</tr>
<tr>
<td>N-acetyl-L-cysteine</td>
<td>N</td>
<td>B</td>
<td>N</td>
</tr>
<tr>
<td>Cerebral folate deficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folinic acid</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Milk-free diet</td>
<td>N</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Urea cycle disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-protein diet/ammonia binders/amino acid supplementation</td>
<td>B</td>
<td>C</td>
<td>N</td>
</tr>
</tbody>
</table>
# Seizures and Epilepsy in Autism Spectrum Disorder

## Specific Syndrome and Treatments

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Grade of recommendation</th>
<th>Prevalence of use</th>
<th>Important adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinic semialdehyde dehydrogenase deficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>D – NE</td>
<td></td>
<td>Retinal degeneration and central visual loss (infrequent)</td>
</tr>
<tr>
<td>Creatine deficiency syndromes</td>
<td>C</td>
<td></td>
<td>None reported</td>
</tr>
<tr>
<td>Creatine monohydrate</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biotin deficiency</td>
<td>D – NE</td>
<td></td>
<td>None reported</td>
</tr>
<tr>
<td>Smith–Lemli–Opitz syndrome</td>
<td>N</td>
<td></td>
<td>None reported</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Branched-chain ketoacid dehydrogenase kinase deficiency</td>
<td>D – PD</td>
<td></td>
<td>None reported</td>
</tr>
<tr>
<td>BCAA supplement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyridoxine-dependent and responsive seizures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>C</td>
<td>D – NE</td>
<td>27%</td>
</tr>
<tr>
<td>Cobalamin metabolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cobalamin</td>
<td>C</td>
<td>N</td>
<td>32%</td>
</tr>
<tr>
<td>Organic aciduria – d-glyceric aciduria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fructose restriction</td>
<td>N</td>
<td>D – SC</td>
<td>D – SC</td>
</tr>
</tbody>
</table>
## Seizures and Epilepsy in Autism Spectrum Disorder

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Grade of recommendation</th>
<th>Prevalence of use</th>
<th>Important adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seizures</td>
<td>Behavioral and cognitive ASD symptoms</td>
<td>ASD with seizures</td>
</tr>
<tr>
<td>Magnesium (Mg)</td>
<td>A</td>
<td>D – NE</td>
<td>N</td>
</tr>
<tr>
<td>Pyridoxine and Mg</td>
<td>N</td>
<td>B</td>
<td>N</td>
</tr>
<tr>
<td>Zinc</td>
<td>D – BR</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Dimethylglycine</td>
<td>D – NE</td>
<td>D – NE</td>
<td>N</td>
</tr>
<tr>
<td>Taurine</td>
<td>D – PD</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>L-Carnosine</td>
<td>D – BR</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>C</td>
<td>B</td>
<td>N</td>
</tr>
<tr>
<td>Homeopathy</td>
<td>N</td>
<td>D – PD</td>
<td>N</td>
</tr>
<tr>
<td>Gluten-free casein-free diet</td>
<td>N</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Feingold/elimination diet</td>
<td>D – SC</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Slow repetitive transcranial magnetic stimulation</td>
<td>B</td>
<td>B</td>
<td>N</td>
</tr>
</tbody>
</table>
A CONSENSUS STATEMENT FROM THE ELIAS TEMBENIS
SEIZURES THINK TANKS

By Richard E. Frye, M.D., Ph.D., Arkansas Children’s Hospital Research Institute, Little Rock, AR; Manuel Casanova, M.D., University of Louisville, Louisville, KY; Gregory L Brown, M.D. and Victoria Martin, R.N., Autism Recovery and Comprehensive Health Medical Center, Franklin, WI; Stephen Edelson, Ph.D., Autism Research Institute, San Diego, CA; Robert Cohen, Ph.D., New York University Brain Research Lab, New York, NY; Jeffrey Lewine, Ph.D., MIND Research Network, Albuquerque, NM; Daniel Rossignol, M.D., Rossignol Medical Center, Irvine, CA; Derrick MacFabe, M.D., University of Western Ontario, London, Ontario, Canada; John Slattery, B.S., Arkansas Children’s Hospital Research Institute, Little Rock, AR; and James B. Adams, Ph.D., Arizona State University, Tempe, AZ.
1. Seizures are a significant concern and are relatively common in autism.

2. Subclinical Electrical Discharges on electroencephalogram, not necessarily associated with clinical seizures are very prevalent in individuals with ASD and deserve careful study.

3. Pathophysiological processes that cause seizures and epilepsy are not well defined and require careful study.

4. Subtle symptoms of seizures are very difficult to differentiate from abnormal behaviors commonly associated with autism, so an extended overnight electroencephalogram should be strongly considered for all individuals with autism.
5. Children with ASD and comorbid seizures or subclinical electrical discharges should have a systematic workup.

6. Research on treatments for seizures is children with autism is needed.

7. It is reasonable to consider treating subclinical electrical discharges in a carefully controlled fashion with close follow-up.

8. Some alternative treatments commonly prescribed to children with autism could have a positively influence on seizures

9. There are several areas that are ripe for future research efforts on seizures in individuals with autism.
Questions?