

NIMH Autism Research Program

**Discovering the Causes & Cures of Autism and
Conducting Meaningful “Until Then” Research**

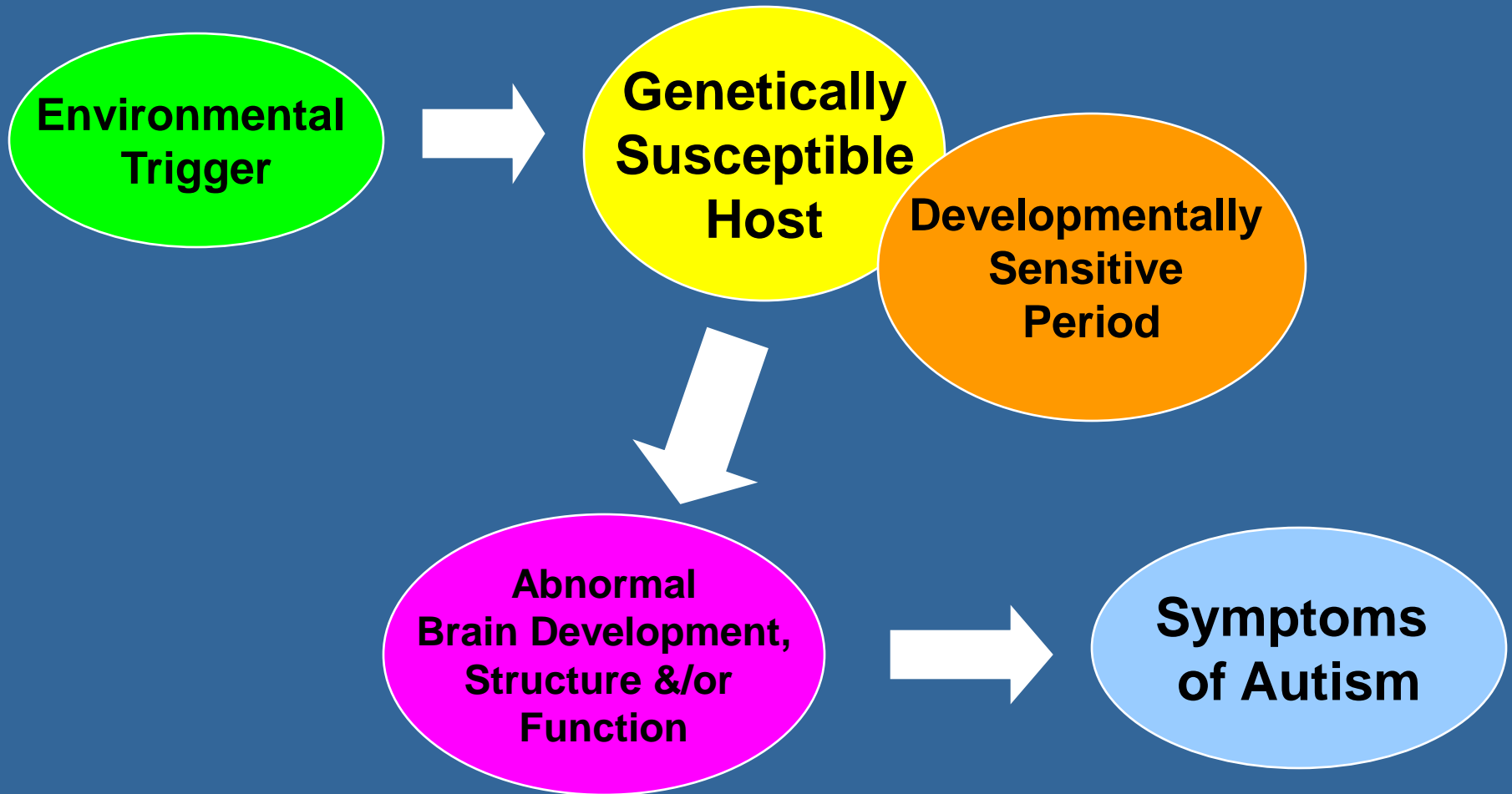
Susan E. Swedo, M.D.

Pediatrics & Developmental Neuroscience Branch

National Institute of Mental Health

NIH Intramural Research Program

Finding the Causes & Cures for Autism



NIMH Autism Research Program

- **Multi-disciplinary Clinical Research Team**
 - M.D.'s – Pediatrics, child psychiatry, neurology
 - Ph.D.'s – Developmental & clinical psychologists
 - Other professionals – Social work, biostatistics
- **Support staff and Trainees**
 - Administrative and support staff
 - Clinical and research fellows – Physicians, psychologists, speech and language pathologist
 - Post-baccalaureate IRTAs who plan to attend medical school or graduate school in 1 – 2 years

You are
here →

Our Office

To Cedar Lane



Collaborative Relationships

- **Within NIMH**
 - **CBDB: Emotional processing**
 - **CHP: DTI and Structural MRI scans**
 - **LBC: Social cognition; executive functions; fMRI (resting state)**
 - **LBN: Animal models**
 - **LNT: Proteomics/metabolomics**
 - **MAP: Co-morbid disorders; treatment trials; biostatistics**
 - **MIB: Magnetic resonance spectroscopy**
- **Within NIH**
 - **NCI: Neuroinflammatory markers**
 - **NHGRI: Specific genetic syndromes (e.g. SMS)**
 - **NIAID: Lymphocyte phenotyping and viral titers**
 - **NICHD: Clinical genetics (WAGR, SLO); CTDB; stem cell models (from skin fibroblasts)**
 - **NIDCR: Dysmorphology**
 - **NINDS: Electroencephalography & polysomnography**
 - **CIT: Database development**
 - **Clinical Center: Sedation safety; pharmaceutical development**

- **With Extramural Investigators**
 - FL State Univ: OCD in autism; speech/language abnormalities; early identification screening tool
 - Johns Hopkins: CSF/blood immune markers; cytokines response to minocycline; cholesterol study (also NICHD & OSU)
 - Mass General: MRI Clinical Findings; polysomnography studies
 - M.I.N.D: Phenome project; behavioral phenotyping
 - N.Y.U. Child Study Center: Sleep disorders in autism
 - UCLA: Genetics (expression profiling; SNPs)
 - UC Davis: Immunology; environmental factors
 - Univ Michigan: Diagnosis in toddlers
 - Vanderbilt: MET gene (Levitt); sleep and EEG abnormalities
- **Others**
 - Autism Treatment Network (Autism Speaks)
 - Clinical Trials Network (Autism Speaks)
 - Children's National Hospital: CSF collection
 - DSM-V Neurodevelopmental Disorders workgroup
 - Emory & Baylor: Genetic microarrays and MECP-2 testing
 - Medical Neurogenetics: Neurotransmitter metabolites
 - NIMH Autism Genetics Repository
 - IVIG Treatment Trial (Industry/Yale/Okla.)

Screening Study is Entry Point

- Comprehensive Diagnostic and Behavioral Evaluation
 - ADOS & ADI-R
 - IQ and Adaptive Functioning
 - Additional testing as needed



Cedar Lane clinic opened in Fall 2006

Since then, the Behavioral Evaluation Team have conducted more than 400 in-person screenings with more than 200 subjects eligible for PDN studies

Types of Investigations

- **Phenomenologic (Phenotyping) Investigations**
 - “Subtypes” study of 1 – 4 yr old children
 - Individuals with Remitted Autism
 - Specific neurodevelopmental disorders (e.g. SMS)
- **Therapeutic Trials**
 - Hypothesis-driven/generating studies
 - Minocycline for anti-inflammatory effects
 - Symptom-specific therapies
 - Riluzole for repetitive behaviors
 - Donepezil for REM sleep deficits
- **Hypothesis-testing Experiments**
 - fMRI study of oxytocin vs. vasopressin vs. placebo
 - MRS evaluation of treatment effects and response



MRI Suite

Outpatient Clinic

EEG Suite

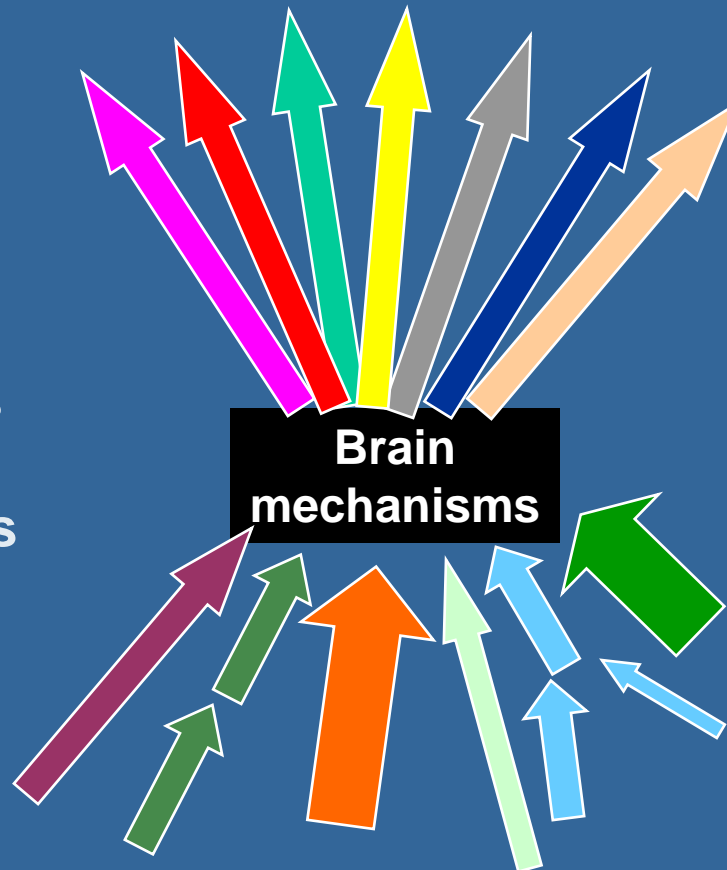
Pediatrics Unit

**To Cedar Lane
Clinic**

The Autism Phenotyping Study

CLINICAL OR PHENOTYPIC VARIABILITY

There are many ways to trigger disruption of development AND there are many different outcomes of that disruption, but all are products of the brain ... the proverbial “black box”



Common pathways leading to autistic outcomes – number and type is unknown

ETIOLOGIC VARIABILITY

The Autism Phenotyping Study

- Also called the Subtypes Study
- Comprehensive baseline evaluation with extensive behavioral and medical work-up
- Longitudinal follow-up for 3+ years
- Young children (ages 12-60 months)
 - 50 with AUTISM (no regression)
 - 50 with REGRESSIVE AUTISM
 - 50 Typically Developing CONTROLS
 - 25 with non-ASD DEVELOPMENTAL DELAY

The Regression Subtype

	No regression	Regression
No early signs	Typical child	Regressive Autism
Early signs	Autism	Autism with Regression

The Regression Subtype

- However, it's not actually that simple
- Continuum, not dichotomy
- Does pattern of onset provide clues to etiology and pathophysiology?

	No regression	<i>Some Regression</i>	Significant Regression
No early signs	Typical child		Regressive Autism
<i>Some early Signs</i>		Seen frequently	Seen occasionally
Many early signs	Autism	Seen frequently	Autism with regression

Subtypes Study: Preliminary Findings Electroencephalography (EEG)

- **EEGs in first 50 autistic pts without epilepsy**
 - **Routine EEGs abnormal in 10 studies (20%)**
 - **Nonepileptiform 3**
 - **Epileptiform 9**
 - **Overnight EEGs abnormal in 30 studies (60%)**
 - **Nonepileptiform 5**
 - **Epileptiform 25**
 - 15 frequent and 9 infrequent
 - 11 diffuse, 4 multifocal, and 11 focal (mostly left temporal)
- **Epileptiform discharges may provide new therapeutic target**

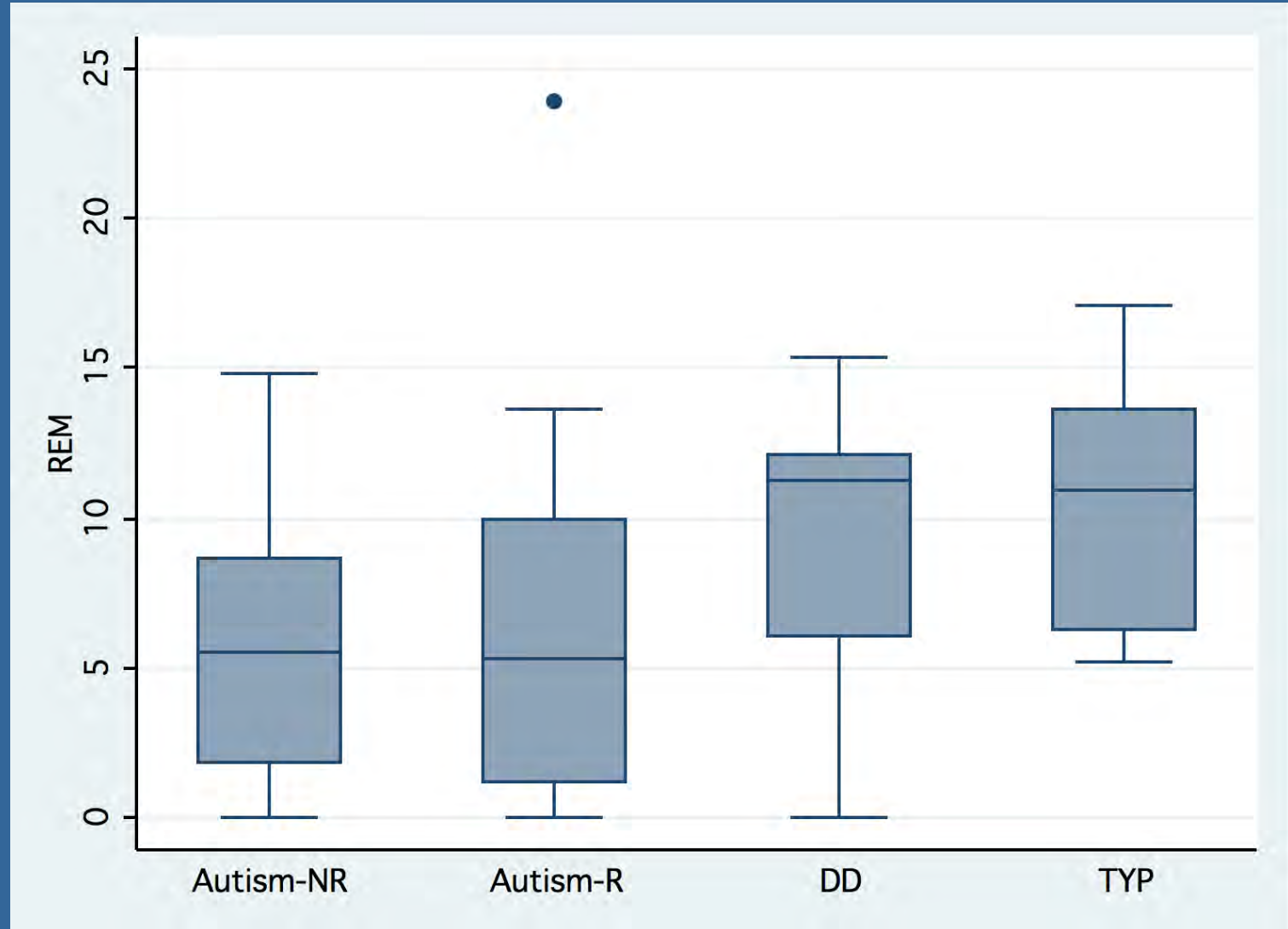
Subtypes Study: Preliminary Findings

Sleep Abnormalities

- **Modified Polysomnography (PSG) can measure sleep parameters in real-time**
- **Preliminary Findings (n = 50):**
 - **Decreased sleep efficiency**
 - **Prolonged latency to REM sleep**
 - **Decreased total time spent in REM sleep**

NOTE: Most of these children did NOT have reported sleep difficulties

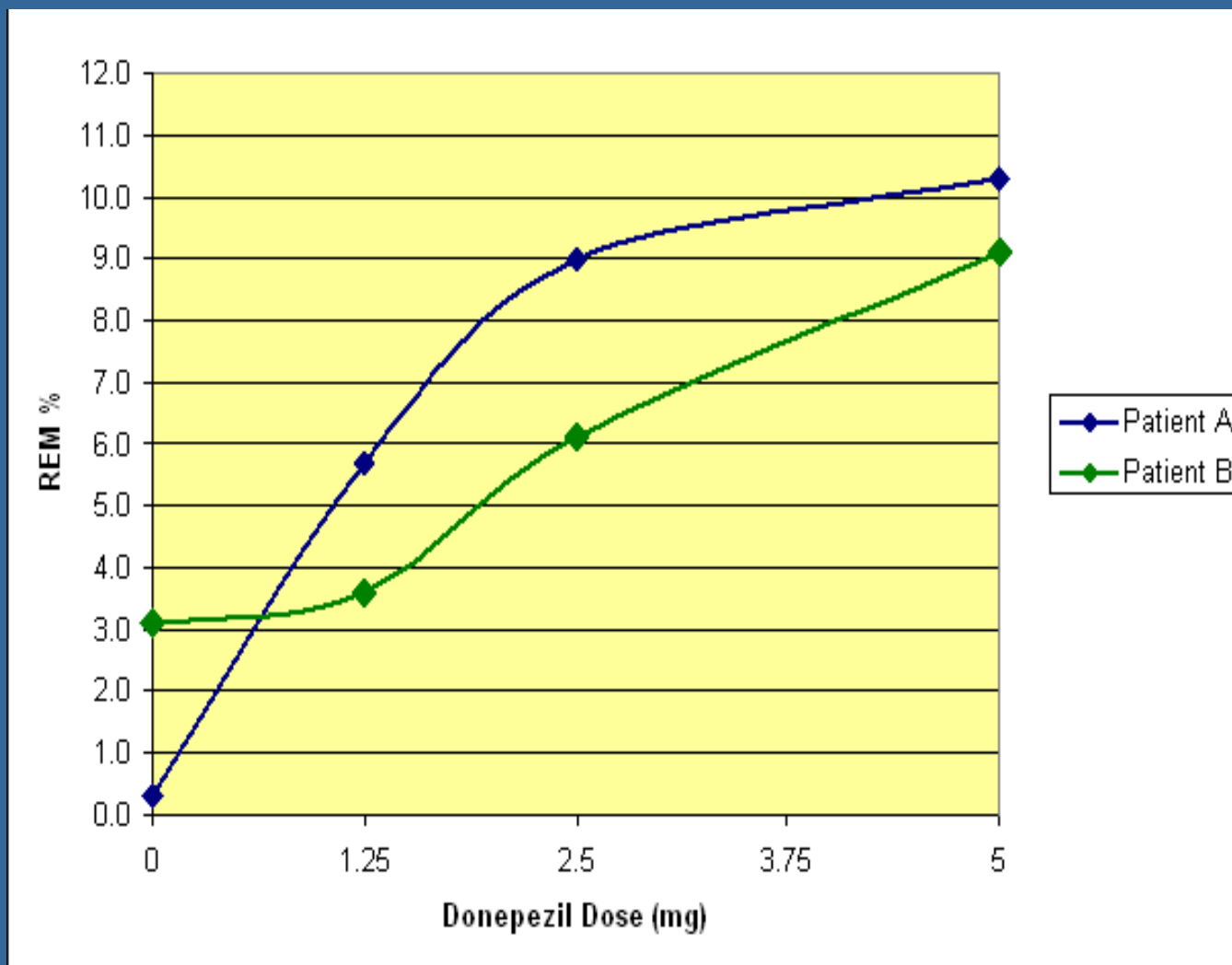
Comparison of Mean REM Percentages for Regressive and Non-Regressive Autism, Dev. Delay and Typically Developing Groups



Trial of Donepezil to Treat Sleep Abnormalities in Autism

- **Clinical trial to determine whether donepezil (Aricept) has an effect on REM sleep.**
- **Among elderly adults, donepezil increases REM.**
- **Open label trial with 3 doses of donepezil and repeated overnight sleep studies (polysomnography)**
- **Titrate dose to maximize response and ensure sustained effects**

Donepezil Dose-Response Curves

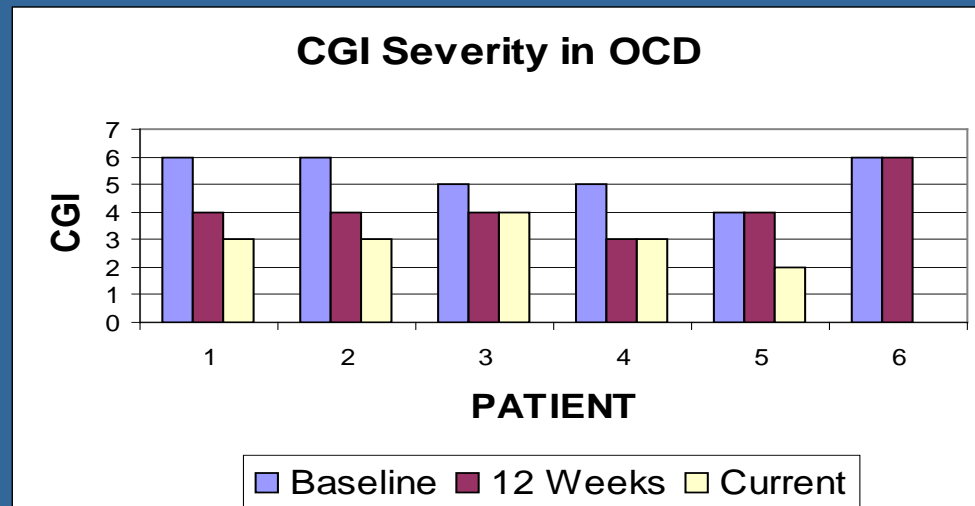
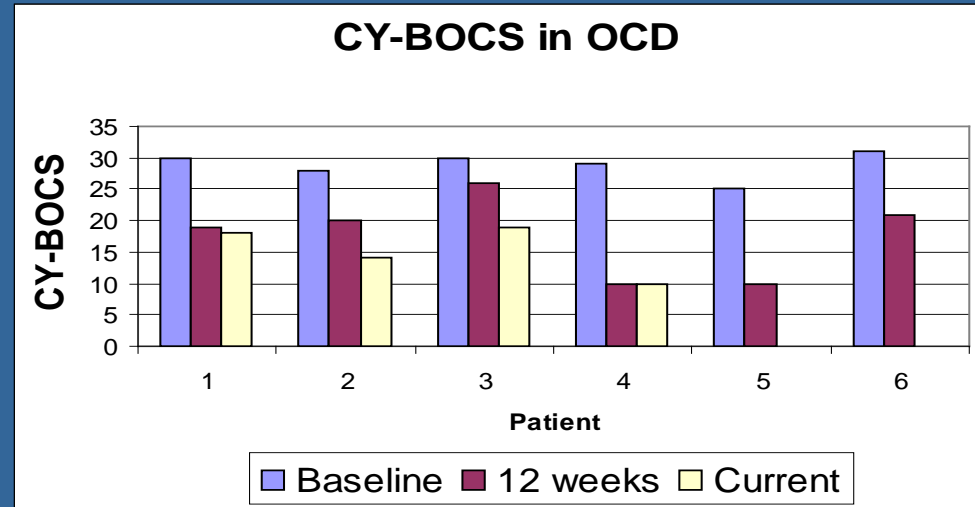


Minocycline Treatment Trial

- Has shown benefits in neurodegenerative conditions (Huntington's, ALS, MS)
- Mechanism may be its anti-inflammatory properties (blockade of NF-kappa B)
- OPEN LABEL trial in 15(10) children with regressive autism
- Measures include:
 - Changes in CSF & serum cytokine and chemokine analyses before and after therapy (Analyses by Dr. Carlos Pardo at Johns Hopkins Univ)
 - Effect on behavioral change
- Placebo-controlled trial will enroll children with “responders” pre-treatment CSF profile

Riluzole Treatment Trial

- Riluzole is a glutamate “antagonist” -- glutamate is the primary excitatory neurotransmitter in the fronto-cortical-striatal circuit (involved in OCD and tic disorders).
- Placebo-controlled trial
 - 30 subjects w/ OCD
 - 30 subjects w/ OCD + ASD
- 12 weeks double-blind
- 9 months open-label
- Recruitment is ongoing



Open Label Trial in 6 pts w/ OCD

REMITTED AUTISM STUDY

- Purpose is to identify effective treatment regimens and predictors of remission as first step in developing new, more effective therapies.
- Comprehensive evaluation of:
 - 40 children whose symptoms have remitted
 - 40 children (similar at baseline) who retain symptoms of autism.

REMITTED AUTISM STUDY

- NIH review of medical and developmental records
- Comprehensive medical and behavioral evaluation
- MRI, EEG, and Neuropsychological testing during 2 days inpatient stay



NIMH Contact Information

- Remitted Autism Study
 - Phone: 301-435-6205
 - AutismOutcomeStudy@mail.nih.gov
- Other Studies
 - Phone: 301-435-7962
 - NIMH-ASD@mail.nih.gov
 - <http://patientinfo.nimh.nih.gov>

