Inside the Unknown World of Autism

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Nurses 798-000-09-018-L01-N

Target Audience: Nurses, Pharmacists & Technicians

CE Credits: 1.0 Continuing Education Credit or 0.1 CEU for pharmacists/technicians
Expiration Date: 2/25/2012

Program Overview: Currently, one in 150 live births leads to a child with a condition that is a part of the autistic spectrum disorders (ASD). While non-pharmacologic therapy is important for these patients, there are a number of pharmacotherapy options for the treatment of symptoms of ASD. This presentation will focus on the facts, the common myths, and the pharmacologic options for ASD.

Objectives:
• Describe the etiology, pathogenesis and common clinical findings of autism.
• Compare and contrast the conditions that comprise the autism spectrum disorders.
• Evaluate common myths associated with autism and patients with autism.
• Describe the non-pharmacological treatment of autism.
• List the medication options for patients with autism.
• Given adequate patient information, design a complete (non-pharmacological and pharmacological) treatment plan for a patient with autism.

Speaker: Dr. Scott Stolte joined the faculty of the Bernard J. Dunn School of Pharmacy at Shenandoah University in 1998. Scott served as a faculty member and as Chair of the Department of Pharmacy Practice prior to assuming his position as Associate Dean for Academic Affairs. Dr. Stolte earned his Doctor of Pharmacy degree from Purdue University in West Lafayette, Ind in 1997. After graduation, Dr. Stolte was the initial community pharmacy resident at Family PharmaCare Center, Inc. and Purdue University.

Speaker Disclosure: Dr. Stolte has no actual or potential conflicts of interest in relation to this program.

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What is it?

- Neurobiologic/Neurodevelopmental disorder
- Lasts a person’s lifetime
- No direct decrease of life expectancy
- All racial, ethnic, social groups
- Four times more likely in boys
- Symptoms range from very mild to very severe

Proposed Etiology

- Genetic
  - Multiple genes implicated
  - ID twins – 60-90% concordance
  - Sibling with autism – 4-10% risk
- Next step – Environmental stressor or toxicant
  - Documented – prenatal or early postnatal viral infections, valproic acid, thalidomide

Other Consistent Findings

- Infant Head Size
  - Start with same size or slightly smaller brain
  - Brain size increases more from 12 – 48 months of age
- Mirror Neuron Dysfunction – fMRI observed abnormalities of brain activity when observing or imitating emotions
- Dysregulation of serotonin
- Seizure disorder (30%)
- Mental retardation (60-70% with full syndrome autism)
Three Major Deficits:

- Impairment in Communication Skills
- Impairment in Social Abilities – Social Reciprocity
- Breadth of Interest - Rigid Routines, Restricted Interests, and/or Repetitive Behaviors

Associated Behavioral Problems

- Hyperactivity
- Impulsivity
- Anxiety
- Irritability
- Aggression

These are targets of drug treatment.
**Autism Spectrum Disorders**
- Autism
- Asperger Syndrome
- Rett Syndrome
- Childhood Disintegrative Disorder
- PDD-NOS

**Diagnosis**
- Reliable at age 2, most commonly made at 3
- As young as 6 months
- Failure to reach appropriate developmental milestones
- Early intervention is critical
  - If at least two years during the preschool years – significant improvement
  - Interventions focused on communication, social skills, cognitive skills
Facts about Autism
- 1 in 150
- 1 in 94 boys is on the autism spectrum
- 67 children are diagnosed per day
- A new case is diagnosed almost every 20 minutes
- More children will be diagnosed with autism this year than with AIDS, diabetes & cancer combined

More Facts About Autism
- Autism is the fastest-growing serious developmental disability in the U.S.
- Autism costs the nation over $90 billion per year, a figure expected to double in the next decade
- Autism receives less than 5% of the research funding of many less prevalent childhood diseases
- Boys are four times more likely than girls to have autism
- There is no medical detection or cure for autism

Incidence vs. Funding
- Leukemia: Affects 1 in 25,000 / Funding: $310 million
- Muscular Dystrophy: Affects 1 in 20,000 / Funding: $175 million
- Pediatric AIDS: Affects 1 in 8,000 / Funding: $394 million
- Type 1 Diabetes: Affects 1 in 500 / Funding: $130 million
- Autism: Affects 1 in 150 / Funding: $15 million

NIH Funding
- Total 2005 NIH budget: $29 billion
- Of this, only $100 million goes towards autism research. This represents 0.3% of total NIH funding.
Red Flags of Autism

- No big smiles or other warm, joyful expressions by six months or thereafter
- No back-and-forth sharing of sounds, smiles, or other facial expressions by nine months or thereafter
- No babbling by 12 months
- No back-and-forth gestures, such as pointing, showing, reaching, or waving by 12 months
- No words by 16 months
- No two-word meaningful phrases (without imitating or repeating) by 24 months
- Any loss of speech or babbling or social skills at any age

http://www.cdc.gov/ncbddd/autism/actearly/

The diagnosis is devastating.

- “Stages of grief” will be experienced by family and friends
  - Shock – initial “paralysis” at hearing the news
  - Denial
  - Anger
  - Bargaining – seeking a way out
  - Depression – realization of the inevitable
  - Testing – Seeking realistic solutions
  - Acceptance – finding the way forward

Vaccines and Autism

- Very emotional issue – don’t be an expert unless you are one
- This talk is not designed to make you an expert.
- As of right now – no definitive link
  - Lancet study – MMR vaccine implicated
    - Study authors now acknowledge shortcomings
- Large European RCCTs – no link

Treatments for Autism

- Occupational Therapy
- Speech Therapy
- Verbal Behavior Intervention
- TEACCH (Training and Education of Autistic and Related Communication Handicapped Children)
- Relationship Development Intervention (RDI)
- Floortime
**Applied Behavioral Analysis (ABA)**
- Positive reinforcement for a behavior by arranging for it to be followed by something of value to the person
- Useful for communication, play, social interaction, academic work, self care, community living skills, reduction in problem behavior
- Skills broken down into small steps
- Customized for every individual

**Sensory Integration Therapy**
- Sensory Integration - the process through which the brain organizes and interprets external stimuli such as movement, touch, smell, sight and sound.
- Autistic children often exhibit symptoms of Sensory Integration Dysfunction (SID) making it difficult for them to process information brought in through the senses.
  - Hypersensitive
  - Hyposensitive
  - "No pain" phenomenon

**Examples of SIT**
- Swinging in a hammock (movement through space)
- Dancing to music (sound)
- Playing in boxes filled with beans (touch)
- Crawling through tunnels (touch and movement through space)
- Hitting swinging balls (eye-hand coordination)
- Balancing on a beam (balance)
Autism and School

- Individuals with Disabilities Education Improvement Act – 2004
  - State must provide all eligible children with a free and appropriate public education that meets their unique individual needs.
  - Autism specifically listed as a disability
  - Parent is entitled to be treated as an equal partner in deciding on an educational plan that contains the elements that your child needs.
Medication Options for Autism

- No medications alter CNS abnormalities
- For now, medication aimed at behavioral symptoms
- Medications include:
  - Stimulants
  - $\alpha_2$-Agonists
  - Antidepressants
  - Anticonvulsants
  - Antipsychotics
  - Others/Alternative treatments

Stimulants

- Methylphenidate
  - Commonly prescribed for autism and PDDs
  - Small number of controlled studies
  - Improvement in hyperactivity, impulsivity, and attention
  - Increased stereotypy and irritability
  - Other adverse effects
    - Dysphoria, social withdrawal, crying, insomnia, anorexia, aggression, tics, agitation

$\alpha_2$-Agonists

- Main role is in treating hyperactivity
- Clonidine
  - Oral and transdermal
  - Improvement in hyperactivity and agitation
  - Sedation common, some hypotension
- Guanfacine
  - Less data
  - 24% response rate
Antidepressants

- **Tricyclic antidepressants**
  - Limited data
  - Not often used because not well tolerated

- **Clomipramine**
  - Serotonin reuptake blocker
  - Varying success and adverse effects
  - Reduces repetitive behaviors and thoughts
  - Reduces aggression and anger
  - Improved eye contact and verbal responsiveness
  - May increase seizure risk
  - Less effective in younger children than adults and adolescents

SSRIs

- Various agents used
- **Fluoxetine** – most studied in children and adults
  - Benefits – reduced rituals, stereotypies, repetitive behaviors, and overadherence to routines
  - Adverse effects – agitation, hyperactivity, hypomania, disinhibition
- Similar benefits and adverse effects with fluvoxamine
- Others: sertraline, paroxetine, citalopram, escitalopram

Venlafaxine

- 10 patient case series
- Mean dose 24 mg/day
- 60% response rate
- Improvement in repetitive behaviors, restricted interest, social deficits, communication and language, inattention, and hyperactivity
- Adverse effects – agitation, hyperactivity

Anticonvulsants

- **Divalproex sodium**
  - Used to treat mood instability
  - In PDD, improved affective instability, impulsivity, and aggression
  - 71% response rate
  - All pts. with seizures and abnormal EEG responded
- Lamotrigine and levetiracetam also used, questionable efficacy
Antipsychotics

- Typical antipsychotics have been used
- Haloperidol has demonstrated efficacy
- Others used
- Concern over EPS and tardive dyskinesia
- Atypical agents used more commonly

Clozapine

- Primarily used for treatment resistant patients
- Improves aggression and hyperactivity
- Limited use:
  - Required hematologic monitoring
  - Lowered seizure threshold

Risperidone

- Most researched medication, FDA indication
- Efficacy compared to placebo confirmed by 3 double-blind, placebo-controlled trials
- 60-70% response rate
- Average doses used – 1.2 – 2.9 mg/day
- Primary efficacy is to reduce aggression and irritability
- Also effective for repetitive behavior, depression, anxiety, and nervousness
- Adverse effects – transient sedation, weight gain, increased appetite

Other Atypical Antipsychotics

- Olanzapine
  - No strong, controlled trials
  - Low EPS risk
- Quetiapine
  - Two open label trials
  - Minimal efficacy
- Ziprasidone
  - Retrospective case series, some benefit
- Aripiprazole
  - No placebo-controlled trials, possible benefit
### Other agents

- **Buspirone**
  - Several small, prospective trials
  - Benefits: anxiety, irritability, tantrums, hyperactivity
  - Dosed 10-45 mg/day
- **Propranolol**
  - Case series
  - Benefits: aggression, anxiety, hyperarousal

- **D-Cycloserine**
  - Placebo-controlled case series
  - Improved social responsiveness
- **Cholinesterase inhibitors (donepezil, galantamine, rivastigmine)**
  - No placebo-controlled trials
  - Benefit: dysfunctional behaviors, hyperactivity, expressive speech
- **Naltrexone**
  - Extensively studied, minimal benefit, little use

### Other/Alternative treatments

- **GF-CF diet**
  - Studies not convincing
- **Omega-3 fatty acids for hyperactivity**
  - Mixed results
- **Secretin**
  - Multiple trials have not demonstrated efficacy
- **Vitamins/Nutritional supplements**
  - Vitamin B6 and dimethylglycine (DMG) not superior to placebo
- **Chelation therapy**
  - Two trials underway
Autism Thoughts and Quotes

- AUTISM IS A SEPARATE WORLD: LOVE CAN BUILD A BRIDGE
- AUTISM: WORDS A PART, WORLDS APART
- A MIND IS A TERRIBLE THING DISPLACED
- AUTISTIC FORECAST FOR TODAY: SCATTERED BRAINSTORMS
- RAIN MAN FOR PRESIDENT: HEY, THE PRESS CONFERENCES WILL BE INTERESTING

Thanks for your time and attention!

Questions?

References