Autism spectrum disorder:
A NEUROdevelopmental disorder

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Disclosures

- I will discuss non-FDA approved medications used in Autism Spectrum Disorder.
- Member of APA DSM 5 Neurodevelopmental workgroup.
- Current and past grant support from Cure Autism Now, Autism Speaks, MIND Institute, Simons Foundation Autism Research Initiative, Nancy Lurie Marks, NIH
- One-time paid consultant for Seaside Therapeutics at a scientific advisory meeting related to studies on a new drug being used to treat ASD.
Objectives/Overview

- **Objectives**
  - Discuss the changes to the new diagnostic criteria for Autism Spectrum Disorder in DMS 5
  - Understand the medical co-morbidities in individuals with ASD
  - Explain various treatment options for individuals with ASD

- **Overview**
  - Epidemiology
  - Diagnosis
  - Heterogeneity
  - Etiological theories
  - Medical co-morbidities
  - Treatments
Epidemiology: 2014 MMWR report

- 14.7/1,000 (range 5.7-21.9)
  - 1 in 68 children, 1 in 42 boys, 1/189 girls
  - largest increases were in hispanic, non-hispanic african-american, normal IQ
  - no change in sex difference, age of dx (~4)
  - troubling racial and ethnic disparities
  - Methods of ascertainment are records based (medical and/or educational)

- Change from previous
  - 0.4/1,000 when I was in medical school!
  - 6.8/1,000 in 2000
  - 8/1,000 in 2004
  - 11.3/1,000 in 2008

- Why?
  - We don’t know
    - Increased ascertainment
    - Earlier identification
    - ? true prevalence increase
How do you diagnose autism spectrum disorder?

- Diagnosis comprised of constellation of behavioral symptoms as defined by a group of experts appointed by the APA (DSM 5)
- No biomarkers, no scans, no genetic tests
- Requires comprehensive developmental history AND direct assessment/observation
  - Needs to include assessment of cognitive function and adaptive skills
Common myths

- He doesn’t have autism because he:
  - Talks
  - Looks at me
  - Interacts with me in the office
  - Is interested in other kids
  - Doesn’t flap or rock

- He has autism because he:
  - Doesn’t talk
  - Doesn’t make eye contact
  - Flaps or rocks
ASD through the lifespan

- Autism is a DEVELOPMENTAL disorder
  - Autism affects development
  - Development affects autism
- Changes over time
What tools do you need to make the diagnosis?

- You and the child

  - Have to read the criteria and text.
  - Have to exercise good clinical judgment.
  - Have to have time
    - To take a thorough developmental history
    - To do a behavioral observation
    - Get corroborating information from other sources
Clinical Observation

- Look for behaviors that should be there and are missing
  - Communicative intent
  - Eye contact
  - Reciprocal social interaction (shared enjoyment, turn taking, response to and initiation of overtures)
  - Insight into social relationships

- Look for behaviors that are present and should not be
  - Repetitive behaviors
  - Restricted interests
  - Unusual sensory behaviors
Are there tools that can help?

- Yes
  - Diagnostic criteria can be subjective
  - Screening tests can bring kids to attention
    - M-CHAT R/F (revised with follow-up)
    - Social Communication Questionnaire (SCQ)
  - Standardized instruments have been extremely helpful in research to make sure that we are all studying the same thing
    - ADOS
    - ADI
  - Standardized instruments can help with clinical dx too
    … but they are not (usually) necessary!
Major changes:

- Name change
- 3 domains become 2
- Autistic Disorder, Asperger and PDD NOS combined into Autism Spectrum Disorder
- Rett and CDD subsumed under ASD (if appropriate)
- Adding specifiers and severity ratings
DSM-5 Criteria for ASD

In the new criteria:

Examples allow a better description of the whole range of behaviors seen across the spectrum

Examples include descriptions of higher order social communication skills

Allows mapping of many symptoms onto a given criterion rather than having to see a specific behavior

Allows more clinician judgment

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DSM-5 Criteria for ASD

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).

2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).

3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

4. Hyper-or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

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DSM-5 Criteria for ASD

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

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An important note was added

This means that no one needs to have a “re-diagnosis”

1. From a scientific viewpoint: There was never an idea to “undiagnose” anyone

2. From a practical standpoint: It would have been a disaster and would overwhelm an already overburdened system
A single spectrum does not mean lack of specificity

- Specifiers were added to better describe each individual

Specify if:
- With or without accompanying intellectual impairment
- With or without accompanying language impairment
- Associated with a known medical or genetic condition or environmental factor
  
  (Coding note: Use additional code to identify the associated medical or genetic condition.)

- Associated with another neurodevelopmental, mental, or behavioral disorder
  
  (Coding note: Use additional code[s] to identify the associated neurodevelopmental, mental, or behavioral disorder[s].)

- With catatonia (refer to the criteria for catatonia associated with another mental disorder, pp. 119–120, for definition)
  
  (Coding note: Use additional code 293.89 [F06.1] catatonia associated with autism spectrum disorder to indicate the presence of the comorbid catatonia.)
Inclusion of severity ratings

- Previously Asperger used for “milder” ASD
- Recognition that severity in one domain is independent of the other domain
- Avoids “mild” “moderate” “severe”

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Key Concept: Heterogeneity

- It is a fact
  - If you have known one person with autism … you have known one person with autism!
  - Widely varying presentations
  - “High” and “Low” functioning usually refers to language level & IQ
  - Expressions of symptoms change over time

- It complicates diagnosis and care tremendously
  … there are implications for and interactions with etiology, co-morbidities, treatment, outcome
Core Symptom Domains – DSM 5

Social Communication Deficits

Restricted Interests Repetitive Behavior

AUTISM SPECTRUM DISORDER
Core Symptom Domains – DSM 5 plus SPECIFIERS

Social Communication Deficits

Restricted Interests Repetitive Behavior

ASD

Language Disorders

Intellectual Disability

Language & Cognition
Core Symptom Domains –DSM 5
plus associated psych symptoms

Social
Communication
Deficits

Restricted
Interests
Repetitive
Behavior

Aggression

ASD

OCD

Social Phobia

ADHD

Language Disorders

Intellectual Disability
Core Symptom Domains – DSM 5 plus associated medical problems

- Social Communication Deficits
- Restricted Interests Repetitive Behavior
- Aggression
- OCD
- Social Phobia
- ADHD
- Motor, sleep, GI, Epilepsy/EEG abnormalities, macrocephaly
- Intellectual Disability
- Language Disorders
- ASD
What we know about etiology

- Not one Disorder
- Not one Cause!
  - Genetic susceptibility
  - Neurobiology
    - Abnormal synapses, excitatory/inhibitory imbalance
    - Abnormal cellular signaling pathways
    - Abnormal functional connectivity
  - Immunologic mechanisms
  - Metabolic abnormalities
  - Interactions amongst all of the above
CO-MORBIDITIES
Family Studies Prove Heritability

- Genetic component is clear
  - Idiopathic autism is one of the most heritable of neuropsychiatric syndromes

- Twin studies:
  - Previous estimates
    - MZ twin pairs: 60-70% concordance for strict autism, 90% for autism spectrum
    - DZ twin pairs: same as sibling recurrence
  - New large twin study from CA
    - MZ 42-58% for strict autism, 64-77% for ASD
    - DZ 13-21% for strict autism, 20-31% for ASD

- Sibling recurrence risk:
  - Previous estimates 4-8%
  - Baby sibs studies showing ~20%

- Broader phenotype in families
  - Language delay, dyslexia, other learning disabilities, poor social skills, restricted interests, repetitive behaviors, other neuropsychiatric conditions (e.g. OCD, mood disorders)
TWO theories about genetics

- Rare variants
  - Genetic disorders that may be causally related to the ASD phenotype
    - Named syndromes
    - Microdeletions/duplications

- Common variants
  - Complex genetics involving genetic variants that are common in the population and combine in a way to create the ASD phenotype.
Associated Rare Diseases/Syndromes

- Rett syndrome
- Fragile X syndrome
- Tuberous sclerosis complex
- 15q duplication syndrome
- Prader-Willi/Angelman
- Timothy syndrome
- Sotos syndrome
- Noonan syndrome
- Joubert syndrome
- Neurofibromatosis I
- Hypomelanosis of Ito
- Down syndrome
- Williams syndrome
- Congenital myotonic dystrophy
- Duchenne muscular dystrophy
- Velocardiofacial syndrome
- Cohen Syndrome
- ARX mutation
- Smith-Lemli-Opitz syndrome
- Cerebral Folate Deficiency
- Untreated PKU
- Disorders of purine metabolism
- Leber’s congenital optic atrophy
- Smith Magenis syndrome
- Moebius Syndrome
Current testing recommendations

- AAN/CNS practice parameters are out of date
- American College of Medical Genetics practice parameters call for:
  - FIRST TIER
    - Chromosomal microarray in all (yield 10%)
    - Fragile X in boys (yield 1-5%) (girls only if family hx or phenotype suggestive)
    - Specific syndromic testing if signs and symptoms present
  - SECOND TIER
    - MECP2 girls (yield 4%)
    - MECP2 in any boy who has MECP2 duplication phenotype
    - PTEN in kids with HC >2.5 sd above the mean (yield 5%)

(Schaefer et al. 2014)
Differences in Brain Size

- Macrocephaly is common
  - Kanner’s original description of autism documented “large heads” in 5/11 patients.
  - Most studies say ~20%
  - Entire distribution shifted to the right – not just a subgroup.
  - Higher in family members too.
  - Present early in life – early brain growth may be a marker of autism (Courchesne et al., 2003)
Epilepsy in Autism and ASD

- Increased rates of epilepsy in patients with autism spectrum disorders (and vice versa!)
  - But - rates very variable (5-46%)
  - Probably dependent on sample characteristics:
    - AGE
      - bimodal age of onset (childhood & adolescence).
    - NON-IDIOPATHIC AUTISM
      - Neurogenetic syndromes or brain injury are associated with higher rates of epilepsy.
    - IQ and LANGUAGE skills
      - lower IQ increases the risk of epilepsy but even those with normal IQ have increased risk.
      - language regression and poorer language skills may also predict epilepsy although data are inconsistent.
EEG Abnormalities

- No surprise that the kids with epilepsy have them
- But studies started to show that some children with autism had ISOLATED epileptiform EEGs (without clinical seizures)
- Literature in the 90’s reported rates 10-20%
- More recent studies are reporting rates ~50-60%
- Overnight or prolonged more sensitive than routine studies
- What to do about it is controversial
Sleep disturbance

- Most data from parent report, PSG hard to do in these kids
- Extremely common (50-80%)
  - Insomnia most common
  - Delayed sleep onset
  - Night awakenings
  - Early morning awakening
  - Reduced need for sleep

Objective measures show

- Increased duration of stage 1 sleep
- Decreased non-REM sleep (stages 2-4)
- Shortened REM sleep
Motor impairment

- Repetitive behavior or stereotypies
- Motor Delays
- Hypotonia
- Incoordination
- Gait impairment
- Apraxia
- Motor planning
- Postural control
Known metabolic disorders with ASD phenotypes

- Purine disorders: adenylosuccinase deficiency, adenosine deaminase (ADA) deficiency
- Untreated PKU
- Creatine disorders: arginine-glycine amidinotransferase deficiency, guanidinoacetate methyltransferase deficiency, disorders of creatine transport
- Biotinidase Deficiency
- Cerebral Folate Deficiency
- Succinic semialdehyde dehydrogenase (SSADH) deficiency
- Smith Lemli-Opitz Syndrome
- SCAD deficiency
- Infantile ceroid lipofuscinosis
- Histidinemia
- Urea Cycle Defects: ornithine transcarbamylase deficiency, citrullinemia, argininosuccinic aciduria, carbamoyl phosphate synthetase deficiency
- Sanfilippo syndrome
Intellectual Disability

- Previously quoted as majority of patients
  - Rates variable 40%-100%) median at 70%.
    *Fombonne, JADD, 2003*

- Recent MMWR data for the first time showing <50%

- Take home message: it’s variable!
  - IQ tests hard to perform, many rely heavily on verbal abilities
  - Often a big discrepancy between VIQ and NVIQ
  - Huge variability among subtests.
Sensory

- Unusual behaviors related to auditory, visual, tactile senses.
- Very common finding but previously not part of diagnostic criteria.
- Can be manifested by
  - hyperreactivity (*sensory sensitivity*) to sensory stimulation
  - hyporeactivity (*sensory insensitivity*) to sensory stimulation
  - By seeking out sensory stimulation through self-stimulation
Treatment
TREATMENT for ASD

What is recommended?

“Educating Children with Autism” (2001)
May be found at: www.nap.edu

Recommendations for intensive therapy:
20-25 hours per week
Individualized
Trained professionals
Year round (without substantial breaks in service)
OT/PT/SLP
Social skills
Behavioral supports
Complementary and Alternative Treatments

- Pharmacologic methods
  - Herbal or vitamin supplements
    - DMG, High dose vitamins, Mineral supplements
  - Immune modulation
    - Steroids, IVIg, antifungals, probiotics
  - Chelation (oral, transdermal, IV)
  - Low Dose Naltrexone (LDN)

- Non pharmacologic
  - Dietary intervention
    - Gluten & casein free (GFCF), Specific carbohydrate, Body ecology
  - Hyperbaric Oxygen Therapy (H-BOT)
Traditional Pharmacologic Treatments

- No known pharmacological treatment for core deficits of autism.
  - We don’t know the neurochemistry!
  - Every neurotransmitter has been implicated.

- But until we figure it out we do symptom modification.
  - Target symptoms
    - based on similarity to other psychiatric disorders.
    - those that interfere most with child’s activities (school, therapies, home)
  - Borrow currently used medications
Data from IAN Registry 2007-08 with 5181 children with reported ASD

Usage is common and increases with age \( (Rosenberg\ et\ al\ 2010)\)
Psychopharmacology

- Goal: improve function without side effect
- Rule out other causes (medical, environment)
- Make sure other interventions are in place
  - School program & other therapies
  - Medical care
- Practicalities:
  - Document details of the symptom
  - Start low, increase slowly
  - Monitor closely and reassess over time
Unfortunate Truths

- Only 2 medications currently are FDA approved for children with autism
  - Both atypical neuroleptics – worst side effect profile!
    - risperidone & aripiprazole
    - can be associated with dyskinesias, cause significant weight gain, hyperprolactinemia
    - need to monitor for metabolic syndrome: glucose (HbA1c or fasting insulin), lipids, transaminases, CBC, prolactin

- Most medication use is “off-label”
- The more likely the medication is to be effective, the more likely it is to have substantial side effects
- Children with ASD are
  - Less likely to respond
  - More likely to have side effects
Meds matched to symptoms

- **Restricted interests/repetitive behaviors**
  - SSRIs: fluoxetine*, citalopram*, paroxetine, sertraline

- **Aggression/severe behavioral dyscontrol/irritability**
  - Atypical neuroleptics: risperidone*, aripiprazole*, ziprasidone, olanzapine, quetiapine
  - Anti-convulsants: carbamazepine, valproate*, lamotrigine,* leveteracitam*

- **Attention/hyperactivity**
  - Stimulants: methylphenidate*, dextroamphetamine
  - Alpha agonists: clonidine*, guanfacine*
  - Atomoxetine

- **Sleep**
  - Melatonin*, clonidine, trazodone, remeron, (iron if ferritin <50)
  * Those with some randomized placebo controlled data
Translational medicine and ASD therapeutics

- Novel therapies are showing some promise
  - GABA and glutamate agents (based on E/I imbalance theory)
  - Oxytocin (based on social affiliation theories)
- Discovery of the underlying pathophysiology in ASD is allowing identification of treatments to target core deficits
- Animal models of single gene disorders are showing the ability to reverse deficits … even in adult animals
- Human trials are underway
GABA and glutamate agents

- Old and new agents tested:
  - Valproate (GABA agonist)
  - Memantine, D-cycloserine, dextromethorphan (glutamate NMDA receptor antagonists)
  - Arbaclofen (known GABA B agonist, ? glutamate receptor modulator)
    - Fragile X trial (Berry-Kravis et al., 2012) found improvements on a social avoidance scale. BUT … it failed to improve study’s primary outcome (ABC-irritability)
    - Similar findings in sample of idiopathic ASD (unpublished data from Seaside Therapeutics)
  - Trials of various agents are still underway
Oxytocin

- The “pro-social” peptide
  - IV and intranasal preparations
- Published trials showed improvement in number of behaviors
  - repetitive behaviors, affective speech comprehension, theory of mind, social learning, face processing
  - some effects persisted beyond treatment period

(Hollander et al., 2003; Hollander et al., 2007; Andari et al., 2010; Guastella et al., 2010; Anagnostou et al., 2012; Anagnostou et al., 2014)
Oxytocin

- Small trial of intranasal administration in 13 adults with high functioning autism (Andari et al., 2010)
  - Simulated “game of catch” with one neutral player, one good and one bad
  - Then tested preferences for each player & face processing

Results showed:
- Enhanced ability to process socially relevant cues
- Increasing trust feelings toward the good player
- Improved time spent looking at socially relevant part of face (eyes)
So … where are we?

What we know:
- Autism is a neurological disorder
- Genetic susceptibility
- Prevalence is increasing
- Increased co-morbidities (eg epilepsy)
- Behavioral treatments proved efficacious

What we don’t know:
- What is the neurological basis
- Which genes are involved
- Why prevalence is increasing
- Which environmental factors
- What is the significance of the co-morbidities
- Which treatments are most beneficial for which individuals
For more information…

- **Autism information**
  - Boston Children’s Hospital
    - [http://www.childrenshospital.org/health-topics/conditions/a/autism-spectrum-disorders](http://www.childrenshospital.org/health-topics/conditions/a/autism-spectrum-disorders)
  - Autism Consortium
    - [http://autismconsortium.org/](http://autismconsortium.org/)
  - NIH
  - CDC
  - Foundations
    - [http://www.autismspeaks.org/](http://www.autismspeaks.org/)
    - [http://www.autism-society.org/site/PageServer](http://www.autism-society.org/site/PageServer)
    - [http://sfari.org/](http://sfari.org/)

- **Clinical trials**
  - [http://clinicaltrials.gov](http://clinicaltrials.gov)