

Psychopharmacology of Autism

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Question 1

- A 3 year old girl presents with impaired receptive and expressive language. She has stereotyped hand movements although her parents say that up to the age of 18 months she seemed to have purposeful hand skills. Her height and weight are age appropriate but her head growth has decelerated after she passed her second birthday. The most appropriate diagnosis is:
 - A Autistic disorder
 - B Rett's disorder
 - C Asperger's disorder
 - D Childhood disintegrative disorder
 - E Pervasive developmental disorder NOS

Question 2

- The RUPP study on the treatment of aggression in Autism presents evidence on the use of which atypical antipsychotic for this presentation?
 - A Haloperidol
 - B Quetiapine
 - C Olanzapine
 - D Risperidone
 - E Aripiprazole

Question 3

- Which of the following is a semi-structured interactive assessment that can be conducted with a during an evaluation for an autism spectrum disorder in children?
 - A. Autism Diagnostic Observation Schedule (ADOS)
 - B. Autism Diagnostic Interview Revised (ADI-R)
 - C. Childhood Autism Rating Schedule (CARS)
 - D. Pervasive Developmental Disorders Screening Test (PDDST)
 - E. Checklist for Autism in Toddlers (CHAT)

Teaching Points

- PDDs are characterized by deficits in social relatedness, communication and repetitive behaviors
- Autism is much more commonly associated with mental retardation as compared to Asperger's disorder
- Rett's disorder has been associated with mutations in the MECP2 gene
- Risperidone and Aripiprazole are FDA approved for treatment of irritability in autism

Pervasive Developmental Disorders

- **Autistic Disorder**
- **Asperger's Disorder**
- **Rett's Disorder**
- **Childhood Disintegrative Disorder**
- **Pervasive Developmental Disorder Not Otherwise Specified**

Leo Kanner



Autistic Disorder

CORE SYMPTOM DOMAINS

- 1) Impairment in Social Interaction**
- 2) Impairment in Communication**
- 3) Restricted repetitive patterns of behavior, interests, and activities**

Autistic Disorder

- **Symptom criteria met before the age of 3 y**
- **Boys:Girls = 4:1**
- **75% have comorbid mental retardation**
- **Nearly 50% never develop functional verbal communication**
- **33% eventually develop seizure disorder**

Hans Asperger



Asperger's Disorder

- **Impairment in Social Interaction**
- **Restricted repetitive patterns of behavior, interests, and activities**
- **No clinically significant delay in language**
- **No clinically significant delay in cognitive development**
- **“All-encompassing” preoccupation**

Andreas Rett



Rett's Disorder

- **Females**
- **Deceleration of head growth**
- **Stereotyped hand movements**
- **Loss of purposeful hand skills**
- **Loss of social engagement**
- **Severe language disorder**
- **Severe to profound mental retardation**

Childhood Disintegrative Disorder

- **Normal Development for ≥ 2 years**
- **Significant loss of previously acquired skills (before age 10 years)**
- **Abnormalities in 2 of 3 areas:**
 - **Social**
 - **Communication**
 - **Repetitive behavior**

PDD NOS

- **Presentations that do not meet the criteria for Autistic Disorder because of late age of onset, atypical symptomatology, or subthreshold symptomatology, or all of these.**

PDDs: Assessment I

- Medical work-up
 - Audiological
 - Neurological (seizures in $\sim 1/3$)
 - Genetic screening
 - Fragile X in $\sim 1\%$: CGG repeats in Xq27.3
 - Rett: X-linked, rare boys, mutations in the MECP2 (Methyl-CpG-binding protein) gene
 - Amino/organic acid metabolism
 - Other genetic diseases associated with autism include: Angelman syndrome, duplication of 15q11-q13, Down syndrome, San Filippo syndrome, phenylketonuria, Smith–Magenis syndrome, 22q13 deletion, adenylosuccinate lyase deficiency, Cohen syndrome, and Smith–Lemli–Opitz syndrome) see Cohen, D et al, Journal of Autism and Developmental Disorders, Vol. 35, No. 1, February 2005
 - Physical examination with close attention to skin and dysmorphology

Assessment II

- Family history
- Developmental milestones
- Syndromal vs non syndromal autism
- Genetic testing for rare syndromes should be based on clinical findings
- For isolated autism with moderate mental retardation consider:
 - karyotyping,
 - Check for Fragile X mutation,
 - FISH for 15q11-q13 duplication (Angelman's) and 22 q13 deletion (VCFS)
 - Bratton-Marschall test (adenylosuccinate lyase deficiency)
 - check for mucopolysaccharides in urine (San Fillipo disease)

PDDs: Assessment III-Diagnostic Assessment

Screening instruments:

- ▣ Checklist for Autism in toddlers (CHAT)
- ▣ Childhood Autism Rating Scale (CARS)
observational assessment-15 items-score of 30-36=mild-mod Autism
- ▣ Pervasive Developmental Disorders Screening Test (PDDST)
- ▣ Autism Behavior Checklist (57 item checklist)

PDDs: Assessment III- Diagnostic Assessment

Structured Evaluation- 'gold standard'

- ADI-R (Autism Diagnostic Interview - Revised) a comprehensive parent interview
- ADOS (Autism Diagnostic Observation Schedule) a semi structured interactive assessment conducted with the child

PDDs: Assessment III

- Neuropsychological & Language
 - Developmentally Appropriate Instruments: WISC-IV, Leiter International Test of Intelligence-revised, Mullen Scale of Early Development, Bayley
- Rating Scales
 - Aberrant Behavior Checklist (Aman et al 1985)
58 items: Subscales:
 - Irritability/Lethargy/Stereotypy/Hyperactivity/Speech
 - Normative data, reliable, valid, sensitive to change (Scahill 2005)
 - Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS, version for PDD (McDougle in press)
 - Repetitive behaviors

Potential Targets of Pharmacotherapy

1. Motor hyperactivity, inattention
2. Repetitive behavior
3. Aggression, self-injury, property destruction
4. Impaired social relatedness

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Stimulants in Autism

- Historical data and beliefs negative
- Small studies support use of MPH in autism^{1,2}
- Anecdotal reports of a high frequency of adverse drug effects including stereotypies and social withdrawal

MPH = methylphenidate.

¹Quintana H et al. *J Autism Dev Disord.* 1995;25:283-294.

²Handen BL et al. *J Autism Dev Disord.* 2000;30:245-255.

RUPP Autism Network Study of MPH in Children With PDD + Hyperactivity

- 72 Children (age, 5–14 y) with autism, Asperger's Disorder, or PDD NOS and significant "ADHD" symptoms
- Study design
 - 7-day test-dose period
 - 4-week double-blind trial of 3 dose levels (0.125, 0.25, 0.50 mg/kg/dose) of MPH TID and placebo in random order

PDDNOS = pervasive developmental disorder not otherwise specified.

ADHD = attention deficit/hyperactivity disorder.

RUPP Autism Network. *Arch Gen Psychiatry* 2005; 62:1266-1274.

Test-Dose Phase

- 6 out of 72 subjects were unable to tolerate ≥ 2 dose levels of MPH and were dropped from the study
- 16 out of the remaining 66 subjects had intolerable adverse effects at the highest dose of MPH; entered modified crossover phase
- Irritability was the most common reason for intolerability

Crossover Phase

- 58/66 subjects completed the crossover phase
- 7 subjects dropped out due to intolerable adverse effects
- There was a statistically significant main effect of dose of MPH on the ABC Hyperactivity subscale score as rated by both teacher (Primary Outcome Measure; $P = .009$) and parent ($P < .001$)

Crossover Phase: Other ABC Subscales

- Statistically significant worsening of parent-rated Social Withdrawal at high-dose MPH
($P < 0.0001$)
- No statistically significant changes in other subscales (Irritability, Stereotypy, Inappropriate Speech)

Categorical Response

- 44 subjects were rated as responders to at least 1 week of treatment (MPH or placebo) – MPH (n = 35) – Placebo (n=9)
- Subject age, IQ, *diagnosis (trend, $P = .07$), and weight did not moderate treatment response
- *Subjects diagnosed with Asperger's disorder and PDD NOS were more likely to be classified as responders to both placebo and MPH than those with autism

Categorical Response

	Placebo	Low	Medium	High
Asperger's disorder/ PDD NOS (n=19)	6 (32%)	7 (37%)	7 (37%)	6 (32%)
Autism (n=47)	6 (13%)	13 (28%)	15 (32%)	12 (26%)

Response to each dose of MPH was superior to placebo for autism subgroup ($P < .001$), but not for the Asperger's disorder/PDD NOS subgroup ($P > .05$)

MPH Summary

- 35/72 subjects (49%) responded to MPH
- 13/72 (18%) exposed to MPH dropped out due to adverse events