



# Pharmacology of Pervasive Developmental Disorders

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Dr. Lohr is an outpatient child psychiatrist at the Bingham Child Center and is assistant professor of Child Psychiatry in the Department of Psychiatry and Behavioral Sciences at the University of Louisville School of Medicine. Dr. Lohr provides diagnostic evaluation, medication management, and psychotherapy and currently serves as the Clinical Co-Director of the University of Louisville Autism Center where he evaluates and treats children with autism spectrum disorders. He received his undergraduate degree in Chemistry from Transylvania University. Dr. Lohr obtained his medical degree from Johns Hopkins University. He completed his general psychiatry residency at Washington University and child fellowship at Western Psychiatric Institute and Clinic, University Health Center of Pittsburgh. He is board certified in psychiatry and child and adolescent psychiatry. Currently, he is president-elect of the Kentucky Chapter of the American Academy of Child and Adolescent Psychiatry. Dr. Lohr precepts and supervises medical students and child psychiatry fellows and lectures on child psychiatry, pharmacologic treatment of autism, and the evaluation and treatment of aggression. Since joining the University, he has been invited to present regionally on subjects such as bipolar disorder and aggression. Areas of interest include the identification and treatment of psychiatric comorbidity of autistic spectrum disorders.

# The Evaluation Process

- Make a clear diagnosis for yourself
- Detailed psychiatric assessment
  - Historical information
    - Pregnancy, Neonatal, Developmental History
    - Medical History
    - Family and Psychosocial Factors
    - Treatment History



# The Evaluation Process

- Mental Status Examination
  - Social Interaction
  - Communication Skills
  - Play
  - Restricted Interests and Unusual Behaviors
  - Specific Target Symptoms

# The Evaluation Process

- Medical Assessment
  - Rule out medical conditions associated with autism
  - Audiological and Visual Examinations
  - Neurologic Exam
  - Lab Studies
  - Consultations with other professionals



# The Evaluation Process

- Psychological Assessments
  - IQ
  - Adaptive Skills
  - Language and Vocabulary
  - Oral-Motor Skills
  - Social Function
- OT and PT Assessments

# Treatment Plan

- Educational and Vocational Interventions
  - Foster social, communicative and cognitive skills
- Behavioral Interventions
  - ABA
  - Social Skills Training
- Family Intervention
  - Education and Support
  - Parent Management Training



# Evidence-Based Practices for Children and Youth with ASD

- Antecedent-Based Interventions, (ABI)
- Computer-Aided Instruction
- Differential Reinforcement
- Discrete Trial Training
- Extinction
- Functional Behavioral Assessment
- Functional Communication Training
- Naturalistic Intervention
- Parent-Implemented Intervention
- Peer-Mediated Instruction and Intervention
- Picture Exchange Communication System (PES)
- Pivotal Response Training
- Prompting

# Evidence-Based Practices for Children and Youth with ASD

- Reinforcement
- Response Interruption/Redirection
- Self-Management
- Social Narratives
- Social Skills Groups
- Speech Generating Devices
- Structured Work Systems
- Task Analysis
- Time Delay
- Video Modeling
- Visual Supports
- National Professional Development Center on Autism Spectrum Disorders



# Pharmacotherapy

- Core Symptoms vs. Target Symptoms
- Target symptoms must be indentified
  - Establish a hierarchy of target symptoms which may be consolidated
- Target symptoms include aggression, SIB, hyperactivity, and repetitive behaviors
- Role in the overall treatment plan
  - Best results if medications are combined with intense behavioral plans
    - Frazier TW et al, J Child Adol Psychopharm, 2010

# Pharmacotherapy

- Risk/Benefit Ratio
  - Monitor for side effects
- Assess Change
  - Efficacy based on report from parents, teachers, staff
  - Rating scales
- 34 – 55 % of children with autism are treated with medications



# Common causes of aggression in autistic children

- Impaired understanding of actions and consequences
- Impaired communication
- Impaired coping skills
- Peer conflict
- Psychosocial dysfunction
- Undiagnosed medical conditions – pain, constipation, seizures
- Psychiatric comorbidity
  - Nazeer, A, Ped Clin N Am 58 (2011)

# CGI

- Clinician rating of global severity
- Subscale scored from 1 (very much improved) to 7 (very much worse), 4 (no change).
- Positive response defined by an end score of 1 or 2 (much improved) at end of study



# ABC

- Measures inappropriate behavior on a 4-point severity scale, caregiver rated
- 0 indicates no problem at all, 3 indicates a severe problem
- 5 subscales (irritability, social withdrawal, stereotypy, hyperactivity, and inappropriate speech)

# Risperidone in Autism

## RUPP 2002

- DBPC study in 101 children aged 5 – 17 years, mean age 8.8 years
- Risperidone mean dose of 1.8 mg/day for 8 weeks
- Greater reductions in Irritability subscale of ABC, 57% vs. 14%, compared to placebo, effect size 1.2
- Significant improvement in stereotypy and hyperactivity subscales of ABC and repetitive behavior on CY-BOCS



# Risperidone in Autism

## RUPP 2002

- No improvement in social withdrawal or inappropriate speech
- 69% vs. 12% had a positive response – reduced irritability
- No EPS
- Significant increase in weight, mild to moderate increases in appetite in 73%, fatigue 59%, drowsiness 49%, drooling 27%, dizziness 16%
- Parents reported most benefit in reducing SIB and aggression

# Risperidone in Autism

- Shea 2004 DBPC parallel-group, 8 weeks
- 80 children aged 5 -12 years with PDD, mean dose of risperidone 1.17 mg/day
- Measures of irritability and conduct problems significantly decreased in risperidone
- No difference in EPS
- Significant more weight gain, 2.7 kg, in active treatment



# Risperidone for core symptoms of autism

- RUPP 2005. Significant improvements in restricted, repetitive, and stereotyped behaviors
- No improvement in social interactions and communication

# Risperidone

## RUPP 2005 Extension Study

- 4 month open-label phase then 8-week DBPC parallel group discontinuation trial, only responders to risperidone were included in extension study
- 32 subject completed this trial
- Relapse in 67% of placebo vs. 25% in risperidone
- Early termination by NIMH
- Mean dose 1.81 mg/day
- Support effectiveness in reducing tantrums, aggression, and SIB
- RUPP Autism Network. *Am J Psychiatry*, 2005; 162:1361-1369.



# Risperidone in Autism

- Solid support of improved aggression, irritability, SIB, temper tantrums, mood lability in DBPC trials
- Doses of 1.25 mg to 1.75 mg/day may have better response
- Well tolerated and effective for up to 6 months
- Monitor for involuntary movements, weight gain, metabolic syndrome

# Cognitive effects of Risperidone

- Aman et al 2008 study of RUPP 38 patients
- Measures of verbal learning, visuo-spatial memory, attention, hand-eye coordination
- No cognitive decline
- Improved results on measure of attention and verbal learning



# Aripiprazole

- Partial agonist DA d2 and 5-HT1a
- Antagonist 5-HT2a
- Moderate affinity for alpha1-adrenergic, histamine H1 receptors, 5-HT reuptake
- FDA approved
  - Schizophrenia age 13-17
  - Manic episode bipolar 1, mixed episode bipolar 1 age 10-17
  - Irritability in autism age 6-17.

# Aripiprazole

- Marcus et al 2009 – DBPC fixed dose study in 218 patients aged 6-17 years with autism, mean age 9.7 years
- Doses were placebo, 5, 10, and 15 mg
- All doses significant improved irritability on ABC-I and CGI-S versus placebo
- 15 mg dose showed improvement on CY-BOCS compulsion scale
  - Marcus et al., *J Am Acad Child Adolesc Psychiatry*, 2009; 48(11)1110-1119.



# Aripiprazole

- 8-week DBPC study of n=98 youth with autism, mean age 9.3 years
- Dose range 2 - 15 mg/d
- Significantly better than placebo on ABC-I and CGI-I
  - Decrease in ABC-I score by about 50% with aripiprazole vs about 17% in placebo
- Adverse effects – sedation, weight gain
  - Owen et al, *Pediatrics* 2009; 124(6):1533-1540

# Aripiprazole

- Significant Side effects
  - Sedation
  - Tremor
  - Drooling
  - EPS
  - Weight gain
  - Elevated fasting triglycerides



# Olanzapine

- 8 week DBPC study of 11 children with PDD, mean age 9 years
- Mean dose 10 mg/day
- 3 of 6 patients had a positive response with olanzapine vs 1 of 5 patients with placebo
- Weight gain 3.4 kg vs 0.7 kg
- Hollander et al, J Child Adolesc Psychopharmacol. 2006; 16(5): 541-548.

# Other atypical antipsychotics in Autism

- Open label studies in quetiapine show response rate 22% to 60%
- Open label study with ziprasidone show 75% response
  - Weight neutral
  - Malone et al. J Child Adolesc Psychopharmacol. 2007; 41:779-790.



# SSRI and Autism

- Used widely in autism, 21.4%
- Serotonin dysfunction in autism
  - Elevated levels of serotonin
  - PET imaging differences in serotonin synthesis
  - Serotonin transporter gene
- Targets repetitive behaviors
  - Compared to OCD
    - More touching, SIB, hoarding, ordering
    - Less cleaning, checking, counting

# Fluoxetine and Autism

- Hollander 2005 study of 39 children, mean age 8.2 years, 20 week, PC crossover study vs. placebo, two 8-week phases of active vs. placebo with 4-week washout
- Mean dose 9.9 mg/day, doses started at 2.5 mg/day
- Significant response in reducing repetitive behavior on CY-BOCS
- No change in speech or social function
- No significant difference in side effects, agitation lead to dose reduction of fluoxetine



# Fluoxetine and Autism

- 14 week DBPC study of 158 patients with autism, ages 5-17 years
- Fluoxetine not effective for repetitive behaviors in youth with autism
- Autism Speaks, press release 2009

# Citalopram and Autism

- Lack of efficacy in 12 week DBPC study of 149 patients aged 5-17 years, mean dose 16.5 mg/day
- No significant change in repetitive behavior, irritability, and CY-BOCS PDD, one secondary measure of irritability, ABC-I, showed advantage for citalopram
- High incidence of adverse effects 97%
  - Activation
  - Impulsiveness, decreased concentration
  - Stereotypies
- King et al. *Arch Gen Psychiatry*. 2009; 66(6)583-590.



# SSRI and Autism

- Review 7 RCT totaling 271 patients
- citalopram, fenfluramine, fluoxetine, fluvoxamine.
- Two studies in adults showed positive change in CGI and OCD symptoms
- No evidence of effect in children
- Emerging evidence of harm
- Williams et al, *Cochrane Database Syst Rev.* 2010; 8:CD004677

# SSRI and Autism

- Limited display of effectiveness.
- Some reduction in repetitive behaviors noted
- No improvement in core symptoms of autism of communication or socialization
- Common side effects included agitation, aggression, hyperactivity, insomnia
- No long-term data



# Stimulants in Autism

- Increase availability of dopamine in striatum, enhancing prefrontal cortical function
- Parents and teachers of autistic children report moderate to severe problems with concentration, attention span, distraction, fidgeting and wiggling
- ADHD symptoms may be most common symptom prompting treatment

# Stimulants in Autism

## RUPP

- RUPP Autism Network 2005 Study of methylphenidate
- DBPC, crossover design with open-label continuation
- 1 week test dose phase, 1 week each of placebo or low, medium, or high dose
  - 0.125, 0.25, and 0.5 mg/kg/dose. Tid dosing
- 8 week open-label continuation
- RUPP Autism Network. Arch Gen Psychiatry 2005; 62:1266-74.



# Stimulants in Autism

## RUPP

- 72 subjects aged 5 – 14 years, 66 tolerated test dose
- Overall 49% of 72 subjects responded to active dose. Determination of best dose was 20% placebo, 25% low, 32% medium, and 23% high dose.
- Significant effect on teacher and parent rated hyperactivity.
- Overall modest effect sizes 0.25 – 0.50

# Stimulants in Autism

## RUPP

- Significant worsening of parent-rated lethargy/social withdrawal and inappropriate speech
- Methylphenidate did not improve ABC subscale ratings for irritability, lethargy/social withdrawal, stereotypy, inappropriate speech



# Stimulants in Autism

## RUPP

- Response rate lower than 75% in typical children with ADHD
- 18% discontinued active medication due to side effects
  - Irritability most common, decreased appetite, difficulty falling asleep, and emotional outbursts were more frequent
  - Higher rate of side effects compared with 4% discontinuation in MTA study.

# Stimulants in Autism

- Lower response rates and higher side effects than in non-autistic population
- Modest benefits in hyperactivity, inattention, and irritability
- No effect on core symptoms
- Should we expect more for longer acting stimulants?



# Clonidine and autism

- Individuals with autism studied to show hyper arousal in response to stimuli
- Clonidine lowers production of catecholamines as alpha-2 adrenergic agonists

# Clonidine and autism

- Jaselskis 1992 study of 8 males age 5-13.4 years, 6 weeks, DBPC cross-over design, mean dose 0.15-0.20 mg/day
- Significantly, 33%, lower irritability subscale of ABC as rated by teacher, no change in clinician ratings
  - Also improvement in hyperactivity and stereotypies
  - 4/6 relapsed in a follow up study



# Clonidine and Autism

- Frankhauser 1992 placebo vs. clonidine in 7 males ages 5-33 years.
- Significant improvements in clinician and parent global scales
- No improvement in parent Conners ratings

# Guanfacine and autism

- Posey 2004 retrospective review of 80 children age 3-18 years, mean dose of 2.6 mg
- Open label support in 8 week study, 48% response
  - Scahill et al , J Child Adolesc Psychopharmacol. 2006; 16:589-598.
- Considered effective in 24% to reduce hyperactivity, inattention, impulsivity



# Atomoxetine and autism

- DBPC crossover trial of 16 children age 5-15 years, 6 week study, 1 week washout, mean dose 44.2 mg/day
- Significant improvement on hyperactivity scale of ABC, ratings of DSM-IV hyperactive/impulsive symptoms, CGI
- Significant improvement in lethargy/social withdrawal
- All 16 subject showed upper GI symptoms, significant side effects also included fatigue, racing heart
  - 1/16 terminated early due to aggression and psychosis
- Arnold et al. *J Am Acad Child Adolesc Psychiatry*, 2006; 45(10): 1196-1205.

# Atomoxetine and autism

- Overall response rate of 57% rated by parents and 43% rated by teachers
  - Lower than in typical population
  - Similar to stimulants in RUPP
- Lower rate of side effect than stimulant studies.
  - Allowed concomitant medication
- Arnold et al. *J Am Acad Child Adolesc Psychiatry*, 2006; 45(10): 1196-1205.



# Amantadine

- 39 patients with autism, age 5–19 years old;
- 1 week placebo, then single daily dose of amantadine (2.5 mg/kg per day) or placebo for the next week, and then bid dosing (5.0 mg/kg per day) for the subsequent 3 weeks.
- parent-rated ABC-CV ratings of irritability and hyperactivity, the mean placebo response rate was 37% versus amantadine at 47% (not significant).
- However, in the amantadine-treated group there were statistically significant improvements in absolute changes in clinician-rated ABC-CVs for hyperactivity) and inappropriate speech
- CGI scale ratings were higher in the amantadine group

○ King et al, J.Am.Acad.Child Adolesc.Psychiatry, 2001, 40(6):658–665.

# Mood stabilizers in autism

- 1/3 patients with autism have seizures
- Antiaggressive effects of mood stabilizers
- Kindling theory



# Valproate in autism

- Hellings 2005 DBPC parallel-group design, 8 weeks, age 6-20 years, 30 subjects PDD-NOS with significant aggression, dose 20 mg/kg/day, mean level 77.7
- No significant differences on irritability subscale of ABC or Overt Aggression Scale
- Significant side effect of increased appetite

# Valproate in autism

- Hollander 2006 8-week DBPC study of 13 patients, mean age 9 years with ASD, mean dose 833.9 mg/day
- Improved repetitive behaviors measured by CY-BOCS
- Hollander 2010 12 week DBPC significantly better than placebo in 27 youth
  - Higher serum levels in responders 89.8 mcg/mL



# Lamotrigine and autism

- DBPC parallel group design in 35 youths age 3-11 years, 18 weeks, 8 week titration to 5 mg/kg/day then maintained for 4 weeks. 2 week taper then 4 week drug free phase
- No significant difference in the irritability subscale of ABC
- No preselection for aggression
- No significant difference in side effects
  - Belsito et al, J Autism Dev Disord. 2001; 31:175-181.

# Levetiracetam and autism

- Wasserman 2006 DBPC parallel-group study of 20 children with ASD, mean age 8.7 years, mean dose of 862.5 mg/day
- No significant differences in parent ratings of irritability, ABC-I
- Teacher ratings showed increased irritability in levetiracetam
- No statistical analysis of side effects



# Propranolol may improve language and social function in autism

- 14 adolescents and adults with autism and 14 matched controls were given 40 mg of propranolol and asked to solve word puzzles
- 60 minutes after medication improved performance in “category fluency” were noted
  - Beversdorf DQ, et al

# Naltrexone and autism

- Endogenous opioid system involved in aggression
- Elevated levels of beta-endorphin in some youths with autism
  - SIB maintained by need to attenuate pain
- Long acting opiate antagonist
- No significant effects noted in DBPC studies on aggression
- Some evidence of improvements in irritability



# D-cycloserine

- Partial agonist of NMDA receptor for glutamate, cognitive enhancing properties in Parkinson's disease.
- D-cycloserine reduced ABC social withdrawal in small placebo-controlled study
- no difference in larger, 8-week DBPC of 80 children with autism
  - Posey et al 2004 and 2008

# D-cycloserine and enhanced social skills training

- 52 children aged 5 to 11 years with PDD vs 26 normal controls
- Parent rated SRS T-score  $> 60$ , SRS will also be primary outcome measure.
- Combines D-cycloserine and Social Skills Training based on ABA principles.
- Study underway at Indiana Univ School of Medicine



# Arbaclofen

- Selective GABA-B agonist
- 8 week open-label flexible dose trial of 32 children with ABC  
Irritability score > 16, age 6-17 years
- Adverse effects of agitation, irritability, fatigue, and hyperactivity
- ABC-I improved from mean of 24.7 to 17.3
- Social Withdrawal from mean score 18.1 to 12.6
- CGI very much improved or much improved in 63%
- Manufacturer sponsored study,
  - Erickson CA et al, AACAP Research Poster 2011

# Sapropterin

- Used to control phenylalanine levels in PKU.
- 46 children aged 3-6 years old with ASD, 16-week DBPC study
- No difference in CGI-I scales
- Significant improvement in social interactions based on the ABC-social withdrawal scale



# N-Acetylcysteine

- Antioxidant, modulates glutamine - excitatory/inhibitory system (tylenol OD)
- 12 week DBPC in 24 children with autism
- 900 mg/day for 4 weeks, 900 mg bid for 4 weeks, 900 mg tid for 4 weeks
- Significant improvement in ABC total and irritability and stereotypy subscale
- Fung et al, AACAP poster presentation, 2010.

# Oxytocin

- Peptide with 9 amino acids made in the supraoptic nucleus of the hypothalamus
- Involved in affiliative and sexual behaviors
- Autistic children have lower plasma oxytocin levels
- IV synthetic oxytocin given to 15 adults with autism had reduced repetitive-compulsive behaviors and enhanced social memories
  - Hollander E, 2003 and 2007
- Increased measures of eye gazing in youth aged 12 to 19 years
  - Guastella AJ 2010



# Future studies in pharmacology of autism

target	agent
Hyperactivity, impulsivity	Atomoxetine, guanfacine-extended release
Repetitive behaviors	riluzole
Irritability	paliperidone
Social deficits	D-cycloserine, metamine, oxytocin

# Complimentary/Alternative Medicine

- Methylcobalamine (methyl B12) open label
- Memantine - case report
- Hyperbaric Oxygen open label treatment - inflammatory response?
- High dose Vitamin D3 “improved core measures”
- Secretin failed to show significant differences from placebo in 5 DBPC trials
- Omega 3 - preliminary support in pilot study on hyperactivity



# Conclusions

- Careful diagnosis and evaluation
- Pharmacotherapy is only part of an overall approach
  - Target symptoms not core symptoms
- Go slow, go low
  - Side effects
- Study the data, anticipate future studies

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