Pharmacological Treatment of Autism

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Disclosure of Potential Conflicts of Interest

• Janssen
  – Donated risperidone for U.S. NIMH-funded research trial
• Eli Lilly & Company
  – Funded investigator-initiated trial (IIT) of atomoxetine
  – Donating drug for ongoing U.S. NIMH-funded research project
• Bristol-Myers Squibb
  – Funded IIT of aripiprazole
• Forest Pharmaceuticals
  – Consultant on research study development

Outline

1. Defining appropriate targets
2. Treating aggression and irritability
3. Treating “ADHD” symptoms
4. Treating interfering repetitive behavior
5. Developing treatments for core social and communication impairment

Top 25 Behavior Problems Rated as Moderate or Severe in PDD (n=487)

<table>
<thead>
<tr>
<th>Parent Rating</th>
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Using 66-item Nisonger Child Behavior Rating Form

ADHD Symptoms are Problematic in Majority of Patients with Autism

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Using 66-item Nisonger Child Behavior Rating Form
Problematic Repetitive Behaviors and Rituals are Very Common in PDD

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</thead>
<tbody>
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<td>41%</td>
</tr>
<tr>
<td>Repeatedly flaps</td>
<td>31%</td>
</tr>
<tr>
<td>Odd repetitive behavior</td>
<td>28%</td>
</tr>
<tr>
<td>Rituals</td>
<td>28%</td>
</tr>
<tr>
<td>Repetitive movements</td>
<td>28%</td>
</tr>
</tbody>
</table>


Problematic Irritability and Aggression is Less Common (but Often Serious)

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<th>Teacher Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easily frustrated</td>
<td>62%</td>
</tr>
<tr>
<td>Changes in mood</td>
<td>28%</td>
</tr>
<tr>
<td>Tantrums</td>
<td>28%</td>
</tr>
<tr>
<td>Argues</td>
<td>25%</td>
</tr>
<tr>
<td>Explosive</td>
<td>23%</td>
</tr>
<tr>
<td>Attacks people</td>
<td>10%</td>
</tr>
</tbody>
</table>


Core Social Impairment

<table>
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<th>Parent Rating</th>
<th>Teacher Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolates self</td>
<td>36%</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>26%</td>
</tr>
</tbody>
</table>


Aggression/Irritability in PDD

- Different manifestations:
  - Physical and verbal aggression
  - Self injurious behavior
  - Property destruction
  - Severe tantrums, explosiveness, agitation
- Above symptoms included in Aberrant Behavior Checklist (ABC) “Irritability” subscale
  - Derived from factor analysis
- Frequent reason for hospitalization and residential treatment

Risperidone in Adults with Autism

- Risperidone more efficacious than placebo in 31 adults with PDDs
- Mean risperidone dose = 2.9 mg/d
- Positive effects on:
  - Aggression and irritability
  - Anxiety and depression
  - Repetitive behavior
- Adverse effects: mild sedation

McDougall et al (1998): Arch Gen Psychiatry

Risperidone is FDA-approved for Treatment of Irritability in Children and Adolescents with Autism

- 101 subjects (82 boys, 19 girls)
- Diagnosis = autistic disorder
- Significant Irritability (ABC Irritability ≥ 18)
- 8 weeks, double-blind, placebo-controlled, parallel groups
- Mean age = 8.8 ± 2.7 y; range = 5-17 y
- Risperidone 1.8 mg/d; range = 0.5-3.5 mg/d

RUPP Autism Network (2002) NEJM
Acute Risperidone Trial

Response criteria: ≥25% improvement in the Aberrant Behavior Checklist Irritability score, and a rating of “much improved” or “very much improved” on the CGI-I


Reduction in Repetitive Behavior with Risperidone in Autism


Relapse Following Discontinuation


Weight Gain with Risperidone

- Weight gain was the most significant acute side-effect of risperidone in placebo-controlled trials

  - 2.7 kg weight gain over 8 weeks (0.3 kg/week) in both controlled trials (vs. 0.8 to 1.0 kg for placebo)

  - Deceleration of weight gain (2.7 kg in first 8 weeks; additional 2.9 kg in next 16 weeks)


Effects of Short- and Long-Term Risperidone Treatment on Prolactin Levels in Children with Autism


Extrapyramidal Symptoms

- Rates of EPS (except drooling) appear to be low and comparable to placebo in two placebo-controlled trials of risperidone in PDD as measured by standardized rating scales, adverse event reporting, and anticholinergic use over the short-term

  - However, tardive dyskinesia has been reported in children with PDD and is occasionally seen with long-term use

**Other Atypical Antipsychotics studied in PDD**

- Clozapine
- Olanzapine
- Quetiapine
- Ziprasidone
- Aripiprazole
- Paliperidone

**Aripiprazole in Aspergers/PDDNOS**

- 14-week open-label trial (6 weeks of flexible dose titration; 8 weeks maintenance)
- 25 youth (5-17 y; mean 8.6 y)
- Drug-free
- ABC Irritability ≥ 18
- IQ 48-122 (mean 84)
- Final dose 2.5-15 mg/day (mean 7.8 mg/d)
- Mean weight gain of +2.3 kg (range -3.3 to +7.7 lbs)
- BMI: Increase from 20.3 to 21.1

Stigler et al (in press) J Child Adolesc Psychopharmacol

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**New Research: Aripiprazole (Study CN138-179)**

- 8-weeks of fixed-dose aripiprazole (5, 10, 15 mg) better than placebo in children and adolescents (mean age 10 y) with autism and irritability (n=218)
- Side-effects occurring in ≥ 10% and at twice rate of placebo
  - Sedation, extrapyramidal symptoms,
  - Appetite
  - Weight gain of 1.5 kg (vs. 0.4 for placebo)
  - 40% less than comparable trial of risperidone


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**New Research: Aripiprazole (Study CN138-178)**

- 8-weeks of aripiprazole (flexible dosing 2-15 mg; mean dose 8.5 mg) better than placebo in children and adolescents (mean age 9 y) with autism and irritability (n=98)
- Side-effects occurring in ≥ 5% and at twice rate of placebo
  - Sedation, fatigue, extrapyramidal symptoms,
  - Weight gain of 1.9 kg (vs. 0.5 for placebo)
  - 20% less than comparable trial of risperidone


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**Anticonvulsants**

- 8 weeks of valproate (77.8 mcg/mL) no better than placebo in 30 youth (ages 6-20) with aggression and PDD

- 10 weeks of levetiracetam (863 ± 279 mg/d) no better than placebo in 20 moderately ill youth (ages 5-17) with PDD

- 12 weeks of lamotrigine (5mg/kg/d) no better than placebo in 28 children (ages 3-11) with autism
“ADHD” Symptoms in PDD
- DSM-IV: ADHD not diagnosed if symptoms occur exclusively during course of PDD
- Potential to miss other explanations for “ADHD” symptoms
  - Communication difficulties
  - Agitation
  - Anxiety
  - Disruptive behavior serving another function

Early Stimulant Trials in PDD
- Amphetamines ineffective and poorly tolerated in early studies
  - Increased stereotypies
  - Aggression
- Limited interpretability
  - Diagnostic Uncertainties
  - Very Young Children (ages 3-6)
  - Unclear targets

RUPP Autism Network Study of Methylphenidate in Children with PDD + Hyperactivity
- Children 5-14 with autism, Asperger’s, or PDDNOS and significant “ADHD” symptoms
- Study Design:
  - 7-day Test Dose period (n=72)
  - 4-week double-blind crossover trial of 3 dose levels of MPH (TID) and placebo in random order (n=66)
    - Low ~ 0.125 mg/kg/dose
    - Medium ~ 0.25 mg/kg/dose
    - High ~ 0.5 mg/kg/dose
- Primary outcome = hyperactivity

Crossover: Parent ABC Hyperactivity

ABC Hyperactivity during Continuation in Responders (n=35)

MPH Adverse Events
- 13/72 (18%) exposed to MPH dropped out due to adverse events
- Irritability (n = 6) was the most common reason for discontinuation
- Decreased appetite, delayed falling asleep, and emotional outbursts more frequent with MPH than placebo


Open-Label Atomoxetine in PDD

- 8-week prospective open-label study in 16 drug-free children (ages 6-14) with PDD, nonverbal IQ of ≥ 70 and significant ADHD symptoms
- BID atomoxetine dosing: 0.5 mg/kg/d x 1 wk, then 0.8 mg/kg/d x 1 wk, then 1.2 mg/kg/d. Dose increased to 1.4 mg/kg/d at week 4 for nonresponders.
- Mean optimal dose: 1.2 ± 0.3 mg/kg/d


Open-Label Atomoxetine in PDD: Results

- 12/16 (75%) much or very much improved on CGI
- Well tolerated except for 2 who stopped drug due to irritability
- Improvement in both inattention and hyperactivity by parents and teacher ratings
- Lesser improvement seen in social withdrawal and repetitive behavior


Placebo-controlled Crossover of Atomoxetine in PDD

- 6 week treatment trials; 1 week washout
- 16 subjects, ages 5-15, with PDD
- Concomitant meds allowed
- BID dosing of atomoxetine titrated up to 1.4 mg/kg/d over 3 weeks


Placebo-controlled Crossover of Atomoxetine in PDD: Results

- Atomoxetine (ATX) better than placebo on ABC Hyperactivity
- Significant effect of ATX on DSM-IV Hyperactivity-Impulsivity, but not Inattention
- Response based on CGI
  - ATX=9/16 (56%)
  - Placebo=4/16 (25%)


Treating Hyperactivity: Other Medications

- Clonidine efficacious in two small placebo-controlled trials
- Longer-term efficacy (11 ± 12 months) of guanfacine also examined in case series of 80 youth (ages 3-18) with PDD
  - 24% response rate overall
  - Primarily helpful for tics and “ADHD” symptoms


Open-Label Guanfacine in Children with PDD

- 8 week open-label prospective study of guanfacine in 27 children (ages 5-15) with PDD
- Methylphenidate ineffective or intolerable
- TID guanfacine dosing (1-3 mg/day)
- 12/25 (48%) response rate by CGI

Antipsychotics for Hyperactivity?

- Several controlled trials of typical antipsychotics from 1965-1975 in heterogeneous samples of “disturbed” or “schizophrenic” children, a group which included children with autism
- Haloperidol efficacious for hyperactivity and other behavioral symptoms in several placebo-controlled studies of children with autism
- High rate of dyskinesias (34%) so typical antipsychotics less often used

Posey & McDougle (2000): Harvard Rev Psychiatry 8:45-63

RIS vs. MPH in ADHD/MR

- 4-week, single-blind, randomized comparison of RIS vs. MPH in ADHD + Moderate MR (n=45)
- Comparable Efficacy
- Effects favoring RIS on ADHD symptoms
  - Effect size of 1.5 vs. 1.1
- Adverse Effects
  - MPH > RIS = Insomnia, appetite decrease, weight loss
  - RIS > MPH = Somnolence, weight gain


Rationale for Comparing RUPP Studies

- Same multi-site network
- Similar baseline assessments
- Similar outcome measure rated by parent
  - Aberrant Behavior Checklist (ABC)
    - Irritability
    - Social Withdrawal
    - Stereotypy
    - Hyperactivity
    - Inappropriate Speech

Comparison of Demographic Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>MPH (n=66)</th>
<th>RIS (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>7.5 ± 2.2</td>
<td>8.8 ± 2.7</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>89</td>
<td>81</td>
</tr>
<tr>
<td>Diagnosis (% AUT)*</td>
<td>71</td>
<td>100</td>
</tr>
<tr>
<td>Vineland (V)-Social*</td>
<td>61.7</td>
<td>48.2</td>
</tr>
<tr>
<td>V-Communication*</td>
<td>62.8</td>
<td>43.5</td>
</tr>
<tr>
<td>V-Daily Living*</td>
<td>54.4</td>
<td>37.3</td>
</tr>
</tbody>
</table>

* p<.05

ABC Comparison at Baseline

- MPH Optimal Dose
  - Baseline
  - Placebo
  - Optimal
  - p < .001
  - Effect = 0.9
Risperidone comparable to MPH in Irritable Children with Autism

Interfering Repetitive Behavior


Serotonin Reuptake Inhibitors in Autism
- Clomipramine better than placebo and desipramine in children and young adults with autism
  Gordon et al (1993): *Arch Gen Psychiatry*
- Fluvoxamine better than placebo in adults with autism
  McDougle et al (1996): *Arch Gen Psychiatry*
- Fluvoxamine no better than placebo and poorly tolerated in children with PDDs
  McDougle et al (2000): *J Aut Dev Disord*

Fluoxetine in PDD
- 39 children (ages 5-16) with PDDs
- 20-week randomized crossover of fluoxetine (8 weeks) and placebo (8 weeks)
- Fluoxetine started at 2.5 mg/day; max dose 0.8 mg/kg/d
- Mean dose was 0.4 mg/kg/d or 9.9 mg/d
  Hollander et al (2005): *Neuropsychopharmacol*

Fluoxetine in PDD: Results
- Significant reduction in repetitive behaviors
- No significant effect on speech or social interaction
- Side-effects not significantly different
  Hollander et al (2005) *Neuropsychopharmacology*
**Other Selective Serotonin Reuptake Inhibitor (SSRI) studies**
- Positive case reports and open-label studies involving sertraline, paroxetine, citalopram, and escitalopram
- Many studies used low doses and reported agitation even with small incremental increases in dose

**New Research: SSRIs**
- Negative NIH-sponsored multi-site trial of citalopram in children and adolescents with PDD and interfering repetitive behavior (n=149) presented at AACAP Annual Meeting
- Negative Autism Speaks and industry-sponsored trial of fluoxetine in children and adolescents with PDD and interfering repetitive behavior (n=158) presented through press release

**Case**
- 4-year old boy with classic autism presents with social withdrawal, limited communication, but no other disruptive behaviors.
- The family is interested in whether medication could possibly augment his current educational program and facilitate his development of language or social interaction

**Medications Studied for Core Symptoms in Autism**
- Not effective
  - Fenfluramine
  - Naltrexone
  - Secretin
- Not proven effective; may deserve further study
  - Cholinergic Agents
  - Glutamatergic Agents

**Cholinergic Agents for Core Symptoms**
- Donepezil better than placebo in crossover study of 43 patients with PDD (mean age = 6.8 years) on CARS score and language tests
- Emerging research on donepezil and other anticholinesterase inhibitors

**Memantine in PDD**
- Retrospective study of 150 children (mean age 9) with PDD treated with memantine (12.7 mg/d)
  - Significant improvement in social behavior and language in 70%
  - Chez et al (2007) J Child Neurol
- Open trial of memantine (0.4 mg/kg/d) in 14 children (ages 3-12)
  - Improvement in parent ratings of behavior
  - Improved memory on one cognitive test
  - No improvement in clinician ratings
Memantine in PDD

- 18 youth with PDD (ages 6-19) consecutively treated with memantine (10.1 ± 6.3 mg/d) for 19 ± 20 weeks
- Target symptoms identified at baseline
  - Social withdrawal (n=11)
  - Inattention (n=7)
  - Communication impairment (n=10)
  - Irritability (n=5)
  - Repetitive behavior (n=1)
  - Hyperactivity (n=1)


Global Improvement with Open-Label Memantine

Limited Research on...

- Anxiety in PDD and its treatments
- Sleep disturbance in PDD and its treatments
- Efficacy of Complementary and Alternative Medicine Treatments
- Combined Pharmacotherapy (which is often necessary given diverse targets of drug therapy)

Internet Resources

- Comprehensive review of management including nonpharmacologic treatments (2007)
  - http://pediatrics.aappublications.org/cgi/content/full/120/5/1162

Autism Research Opportunities

- Aripiprazole for Autism/PDDNOS + Irritability
- Paliperidone (Invega) for Autism + Irritability
- Atomoxetine (Strattera) for ASD + Hyperactivity
- DCS Augmentation of Social Skills Training
- Memantine in Autism
- Pancreatic Enzymes in Autism
- Contact Info for Research Referrals
  - For patients: http://psychiatry.medicine.iu.edu/participateinresearch
  - kidpsych@iupui.edu
  - For providers: David J. Posey (email: dposey@iupui.edu)

Acknowledgments

- NIMH
- NARSAD
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