Behavior management and psychopharmacology in children with autistic spectrum disorders

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Disclosures
- Dr. Coplan is author of Making Sense of Autistic Spectrum Disorders: Create the brightest future for your child with the best treatment options (Bantam-Dell, 2010), and receives royalties on its sale
- This presentation will include a discussion of off-label drug use

“Behavior”
- “The manner of conducting one’s self”
- “Anything than an organism does involving action and response to stimulation”
- “The actions or reactions of a person or animal in response to internal or external stimuli”

Behaviorism made simple
- STIMULUS (the Antecedent)
- RESPONSE (the Behavior)
- The Consequence

Antecedents
- External:
  - Imposition of a task
  - Change in routine
  - Denial of access to object or activity
  - Other....
  - Or: No apparent external antecedent

Stimulus (The “Antecedent”)
- Internal
  - Hunger
  - Thirst
  - Pain
  - Etc.
- External
  - Physical
  - Social
  - Etc.

Response (“The Behavior”)
Behaviorism made simple

STIMULUS (the Antecedent)

RESPONSE (the Behavior)

The Consequence

Behaviorism made simple

Behavior

• What is the child’s developmental level?
• Is the behavior normal for the child’s developmental level?
  – Tantrums / Noncompliance
  – “Impulsivity” / “Inattention”

Behavior

• Acute change or chronic?
• General health?
  – Vital signs, I&O, Level of consciousness
  – Pain?
• Anything new in child’s life?
  – Recent change of meds

Behavior

• What is the child’s ability to communicate?
  – Does “disruptive” behavior serve a communicative function?
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**Law of Effect**

*Animal Intelligence*, Edward Thorndike, 1911

"Of several [possible] responses...to the same situation, those which are...closely followed by satisfaction to the animal will...be more likely to recur. Those which are...followed by discomfort to the animal will...be less likely to occur. The greater the satisfaction or discomfort, the great the strengthening or weakening of the bond"

*Manipulating the Consequence for a given behavior feeds back on the probability that that behavior will recur.*

**Consequences 1: Reinforcers**

- Reinforcers lead to an increase in frequency of the antecedent behavior
  - Positive Reinforcement (adds something)
  - Negative Reinforcement (removes something)

**Positive Reinforcement**

- Attention (in neurotypical children)
- Access to desired object or activity
Negative Reinforcement

- Escape (from a task, e.g.)
- Removal of an undesirable object (non-preferred food, e.g.)
  - Negative reinforcement does not = “punishment”

Food Selectivity

Negative and Positive Reinforcement of unwanted behavior

- Parent removes non-preferred food ([+] reinforcement)
- Parent provides child with his/her preferred food ([++] reinforcement)
- Alternatives
  - First …… Then
  - Put refusal on extinction
  - The kitchen is closed between meals
  - Desensitization (non-preferred food is on table, on plate, touch, lick, mouth, eat)

Consequences 2: Aversives

- Aversives lead to a decrease in the likelihood of recurrence of the antecedent behavior
- Logical Consequences
  - If child refuses to use toilet, child must carry backpack with spare clothes, when family is in public
- Over-correction
  - Must wash out soiled diaper
  - If the child spills milk on purpose: child must mop the entire kitchen floor

Disruptive Behavior: Function & Best Response

- Attention
  - 1-2-3 ⚫ “Time Out” (T.O.)
- Access
  - Never grant access to desired object in response to disruptive behavior
- Escape
  - Never permit the child to escape from a task via disruptive behavior.
  - Walk child through task first, then ⚫ T.O.
  - OR: Send child to T.O., and as soon as T.O. is complete, resume the task where you left off.
Token Economy: The next step beyond Time Out

- Concretely specified behaviors
- Earn and Lose Points
- Points to Access to preferred items
  - Preferred toys, Computer time, etc.
  - NO access to preferred item at other times
  - “Extra” treats not as effective
- Works with children who understand rule-based play (CandyLand, Uno, etc.)
But.....

**Children with ASD have atypical responses to internal and external stimuli**
- What good is Time Out if the child has no eye contact?
- Obsessive behavior not the same as "ordinary" task refusal

**Neuropsychological Abnormalities in Persons with ASD**
- Cognitive Rigidity
- Abnormal Regulation of Attention
- Abnormal Regulation of Arousal
- Abnormal Regulation of Sleep
- Abnormal Sensory Processing

**Neuropsychological Deficits in Persons with ASD**
- Abnormal Sensory Processing
- Abnormal regulation of attention
- Abnormal regulation of arousal
- Abnormal regulation of sleep
- Cognitive Rigidity

**Neuropsychological Deficits in Persons with ASD**
- Abnormal Sensory Processing
- Abnormal regulation of attention
- Abnormal regulation of arousal
- Abnormal regulation of sleep
- Cognitive Rigidity

**Agitation**

**Disruptive behavior**

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Abnormal regulation of arousal

Abnormal regulation of attention

Abnormal Sensory Processing

Abnormal regulation of sleep

Cognitive Rigidity

Routines

Stereotypies

Agitation

SIB

Routines blocked

Stereotypies blocked

Abnormal regulation of arousal

Abnormal regulation of attention

Abnormal Sensory Processing

Cognitive Rigidity

Rigid

Cognitive Rigidity

“Externalizing Behaviors”

• Insistently repetitious behavior
  – Insistently repetitious behavior
  – Compulsions
  – Perfectionism
  – Obsessions
  – (Anxiety)
  – (Depression)

“Internalizing Behaviors”

Perfectionism

Cognitive Rigidity

• Insistently repetitious behavior
• Problems with changes in routine, transitions, unmet expectations
• Perfectionism / Perseveration
• Compulsions
• (Anxiety)
• (Depression)
Cognitive Rigidity

- **Insistently** repetitious behavior
- Problems with changes in routine, transitions, unmet expectations
- Perfectionism
- (Anxiety)
- (Depression)
Depression

KO; 10 yr old female, PDD-NOS, normal IQ

A.D.: 9 y.o. girl with ASD (my MRN: 06-0227)
Throughout the session, “Alice” delivered a steady stream of self-deprecating comments, calling herself “stupid,” or perseveratively asking if she was “fat.” During the Bender, she anxiously and angrily twisted the eraser off the tip of the pencil, while declaring “Why do I keep making stupid mistakes?” As her stress level rose, she escalated to slapping herself, and then punching herself in the face.

How do you kill a blue elephant?

Shoot it with a blue elephant gun.

How do you kill a pink elephant?

Hold it by the trunk until it turns blue, then shoot it with a blue elephant gun.
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**“An ounce of prevention is worth a pound of cure”**

- Internalizing Behavior
  - Anxiety
  - Depression
  - Perfectionism
  - etc

- Externalizing Behavior
  - Task aversion
  - Tantrums
  - Aggression
  - SIB
  - etc

**Positive Behavior Support Plan:**
Proactively avert, or identify and dissipate anxiety

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**Positive Behavior Support Plan for Cognitive Rigidity**

- Staff Awareness
- Visual Schedules
  - What am I supposed to be doing now?
  - What am I supposed to do next?
- Relaxation Techniques
  - Mental Imagery
  - Isometrics
  - Deep Breathing
  - “Break” cards
- Cognitive Behavioral Therapy (CBT)
- SSRIs

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**The Story of Billy’s Box - 1**
(or, why it’s important to ID internalizing behavior)

- 8 y.o. boy with ASD and normal Nonverbal IQ
- Severe tantrums at school
- Antecedents:
  - TRANSITIONS
- Function?
  - Not attention, escape, access
  - “Biological” (i.e. just part of his ASD)?

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**The Story of Billy’s Box - 2**
(or, why it’s important to ID internalizing behavior)

Q: “Billy – You’re always getting in trouble at school. What’s going on?”

A: “I’m afraid that if I hand in my work, I’ll never get a chance to go back and make it perfect.”

---

**The Story of Billy’s Box - 3**
(or, why it’s important to ID internalizing behavior)

“Put your papers in the box, and we promise you will be able to go back later and work on them some more, if you want to.”

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**Cognitive Rigidity**

- Interventions
  - Visual Schedules
    - What am I supposed to be doing now?
    - What am I supposed to do next?
  - CBT, Relaxation Techniques
  - SSRIs
SSRIs in ASDs

• Primary targets
  – Cognitive Rigidity
  • Anxiety
  • Obsessions (thoughts)
  • Compulsions (behavior)
  • Perfectionism
  – Depression
  – Stereotypies: Probably not

• “Downstream” benefit:
  – Disruptive Behavior
  – Quality of Life
Serotonin (5 HT)

**Limbic System**
- Nucleus accumbens
- Amygdala
- Hippocampus
- Nucleus basalis

Serotonin (5 HT) Pathways

Stahl, *Essential Psychopharmacology*, fig 5.52-3

Mechanisms of Drug Action

A: Release of transmitter by 1st neuron
B: Transmitter acts at receptor sites on 2nd neuron
C: Transmitter is taken up, and re-stored in 1st neuron
D: Autoreceptor on 1st neuron: detects release of transmitter

Serotonin promoting (serotoninergic) drugs

A. Promote release of serotonin (Mirtazapine)
B. Mimic the action of serotonin at the 2nd neuron (Buspirone)
C. Block re-uptake of serotonin (SSRIs)

Serotonin-promoting (serotoninergic) drugs

Selective Serotonin Reuptake Inhibitors block the re-uptake of Serotonin

Nestler, *Molecular Neuropharmacology*, Fig 9.3

Stahl, *Essential Psychopharmacology*, fig 5.52-3

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SSRIs in ASDs

- Primary targets
  - Cognitive Rigidity
    - Anxiety
  - Obsessions (thoughts)
  - Compulsions (behavior)
  - Perfectionism
  - Depression
  - Stereotypies: Probably not
- "Downstream" benefit:
  - Disruptive Behavior
  - Quality of Life

SSRIs in ASDs

- Side Effects
  - Activation
    - Hyperactivity
  - Irritability
  - Insomnia
  - Agitation
  - Uncommon or irrelevant
    - GI dysfunction
    - Sexual dysfunction
    - "Black Box" warning (suicidal mentation)

Selective Serotonin Reuptake Inhibitors (SSRIs)

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<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Fluoxetine</td>
<td>Prozac</td>
<td>The first selective SRI</td>
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<tr>
<td>Fluvoxamine</td>
<td>Luvox</td>
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</tr>
<tr>
<td>Sertraline</td>
<td>Zoloft</td>
<td>May be less activating</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Celexa</td>
<td>Prolonged QT interval</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Lexapro</td>
<td>Prolonged QT interval</td>
</tr>
<tr>
<td>And others...</td>
<td></td>
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</tr>
</tbody>
</table>

Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorder (ASD).

- Studies reviewed: 7 randomized controlled trials / 271 participants
  - Fluoxetine (2), fluvoxamine (2), fenfluramine (2), citalopram (1)
  - Subjects: Children (5); Adults (2)
  - Varying inclusion criteria for Dx of ASD and IQ
  - 17 different outcome measures
- "Data were unsuitable for meta-analysis"

Authors’ conclusion:

"There is no evidence that SSRIs are effective as a treatment for children with autism. In fact, there is emerging evidence that they are not effective and can cause harm. As such SSRIs cannot be recommended as a treatment for children with autism at this time."

Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorder (ASD).

- Treatment-emergent symptoms
  - Citalopram: 1 child with new onset seizures (continued to have seizures after citalopram was stopped)
  - Fenfluramine: Stereotypies; withdrawal, sadness; appetite
  - "With monitoring, dose adjustment and time, all but one of these adverse effects were resolved"
  - Fluoxetine (Hollander 2005): 6 of 37 children had their dosage reduced due to agitation
  - 2 children in the placebo group also had their “dosage” reduced. Difference between groups: Not significant
  - Reviewers disregard the fact that by the end of the trial, “anxiety and nervousness” was lower in the fluoxetine group compared to placebo: 15.9% vs. 33%.
  - Fluvoxamine: No significant difference in side effects between SSRI and placebo
Pharmacotherapy for anxiety disorders in children and adolescents


- Studies reviewed: 22 RCTs/ 2,519 participants
  - Short-term (average 11 wks)
  - Mean age 12 yrs
  - Drugs studied (versus placebo)
    - SSRIs: 15 (fluoxetine 6, fluvoxamine 2, paroxetine 3, sertraline 4)
    - SNRIs: 5 (clomipramine 3, venlafaxine 2)
    - Benzodiazepines: 2 (alprazolam 1, clonazepam 1)
    - Tricylic antidepressants: 1 (desipramine)

- Meta-analysis
  - Response rate: Medication 59%; Placebo 31%
  - 7.3% of subjects treated with SSRIs withdrew because of side effects
  - “The overwhelming majority of evidence of efficacy was for the SSRIs, with the most evidence in paediatric OCD”

Anxiety

RD. 7 y.o. F, nl IQ, PDD-NOS & Anxiety. Father: GAD

RD. 9 y.o. F, nl IQ, PDD-NOS & Anxiety. Father: GAD

Anxiety after Rx with CBT & Escitalopram

Fluoxetine 10 mg/d

A.D.: 9 y.o. girl with ASU (MRN: 16-0227)
Throughout the session, “Alice” delivered a steady stream of self-deprecating comments, calling herself “stupid,” or perseveratively asking if she was “fat.” During the Bender, she anxiously and angrily twisted the eraser off the tip of the pencil, while declaring “Why do I keep making stupid mistakes?” As her stress level rose, she escalated to slapping herself, and then punching herself in the face.

Anxiety, Perfectionism, and Self-Injurious Behavior

A.W.: 9 year old boy with PDD-NOS and normal IQ (MRN: 11-07710)

“I’m in the fire.”

“The house is on fire and we are running for our life.”
After one week on Sertraline

Sent: Thursday, May 31, 2012  
To: James Coplan  
Subject: amazing shift in A.D.  
Importance: High

Dr. Coplan,  
I "know" that it takes several weeks for SSRI's to "kick in" but the child I saw in my office today is simply a different child and the improvements are being noted across settings by multiple adults. There was NO self abuse, NO negative self statements, an availability for interventions, just a complete transformation. We "fixed" mistakes, "re-did" errors, told jokes, and played together. The "core" Autistic symptoms are obviously still there - perseveration on bras, drawing, etc. - but mood-wise there is no question that A. is already benefitting from the Sertraline... Impossible perhaps but really visibly clear... Thank you very much.  
S.S. Ph.D.

Regulation of Attention

Let go & Shift  
Attend to stimulus #1  
Attend to stimulus #2

Abnormal Regulation of Attention - 1

- Perseveration  
  - Inability to "Let go and shift"  
  - Gets "stuck"  
  - "Overattention Deficit Disorder"  
- Compounds the effects of cognitive rigidity
Abnormal Regulation of Attention (Perseveration)

- Interventions
  - Verbal preparation for transitions
  - Visual Schedules
  - SSRIs (OCD: Proven; ASD: likely)

SSRIs
Abnormal Regulation of Attention - 2

- Inattention
  - Inability to focus
  - Impulsive
  - Distractible

Inattention

- Interventions
  - Limited stimuli
  - Short work periods
  - Medication
    - Stimulants (may $$\downarrow$$ anxiety / rigidity / agitation)
    - alpha-2 agonists

Noradrenergic pathways (Norepinephrine)

- Locus Ceruleus (“blue spot”): Principal noradrenergic source in brain.

Noradrenergic pathways

- Insufficient activation of frontal cortex $$\rightarrow$$ Inattention

Stahl, Essential Psychopharmacology, fig 12.1

Stahl, Essential Psychopharmacology, fig 5.25

Nestler, Molecular Neuropharmacology, Fig 8.5

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Hyperactivity

Stimulants in children with ADHD → “Paradoxical” calming

Stahl, Essential Psychopharmacology, fig 12.1

Stimulants

(Dopaminergic; Noradrenergic; Sympathomimetic)

A. Promote release of Dopamine & Norepinephrine (Stimulants)
B. Mimic the action of Dopamine & Norepinephrine (Stimulants)
C. Block re-uptake of Dopamine & Norepinephrine (Atomoxetine)

Stahl, Essential Psychopharmacology, fig 5.26

Stimulants, NRI’s

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<tr>
<th>Generic Name(s)</th>
<th>Brand Name(s)</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Amphetamine</td>
<td></td>
<td>FDA Schedule II</td>
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<tr>
<td>Dextroamphetamine</td>
<td>Dextrostat</td>
<td>FDA Schedule II</td>
</tr>
<tr>
<td>Dextroamphetamine +</td>
<td>Adderall</td>
<td>FDA Schedule II</td>
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<tr>
<td>Methylphenidate</td>
<td>Concerta, Ritalin,</td>
<td>FDA Schedule II</td>
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<tr>
<td>Dexmethylphenidate</td>
<td>Focalin</td>
<td>FDA Schedule II</td>
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<tr>
<td>Lisdexamfetamine</td>
<td>Vyvanse</td>
<td>Metabolized to D-</td>
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<td>Amphetamine, Not FDA Sch. II</td>
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<tr>
<td>Atomoxetine, Attentin</td>
<td>Strattera</td>
<td>Norepinephrine reuptake inhibitor (NRI), not FDA Schedule II</td>
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References

(Stimulants)


**Alpha-2 Agonists**

<table>
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<tr>
<th>Generic Name</th>
<th>Brand Name(s)</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>Catapres</td>
<td>More sedating than guanfacine</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>Tenex, Intuniv</td>
<td></td>
</tr>
</tbody>
</table>

- Frontal cortex / Locus Ceruleus: post-synaptic alpha-2 receptors
- Sympathetic outflow (autonomic nervous system): Pre-synaptic autoreceptors

**Alpha-2 Agonists**

- Pre-synaptic α2 receptors ➔ release of dopamine & norepinephrine ➔ BP
- Post-synaptic α2 receptors (Locus Ceruleus & Frontal Cortex) ➔ Attention

**Alpha-2 agonists**

- (clonidine, guanfacine)

(provided from Stahl, Essential Psychopharmacology, fig. 12.6)

**Benefits**
- Agitation
- Hyperactivity
- Attention Span
- No exacerbation of anxiety / rigidity

**Side Effects**
- Sleepiness: Common
- Emotional Lability (crying) - occasional
- Hypotension (low BP) - rare

**References**


**Clinical Pearl**

- Beware of anxiety or perseveration masquerading as inattention
  - Perseveration on inner stimuli: “Inattentive”
  - Perfectionism: “Problems w. task completion”
  - Anxiety: “Rushes through work”
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Abnormal regulation of arousal

Abnormal regulation of attention
- (Perseveration)
- (Inattention)

Abnormal regulation of sleep
- (Hypo-arousal)
- (Hyper-arousal)

Cognitive Rigidity

Atypical neuroleptics
- α-2 agonists
- GABA-ergic drugs

Impulsive

Agitation

Aggression

SIB

Impulsivity

Hyperactivity

Perseverative

Rigid

Routines

Stereotypies

Agitation

Aggression

SIB

Impulsivity

Hyperactivity

Perseverative

Rigid

Regulation of Arousal

Hypoarousal
- Lethargic

Calm & Relaxed

Fight or Flight Response

“Red Alert”
- Adrenaline
- Heart Rate
- Resp. Rate
- Combative

Dopamine
(Dopaminergic; Noradrenergic; Sympathomimetic)

Dopamine
(Nestler, Molecular Neuropharmacology, Fig 8.6)

Substantia Nigra (“black stuff”), Ventral tegmentum, arcuate nucleus

F. O. MRN 06-0208

“He is so hard to calm down when he gets upset….His emotional thermostat doesn’t work”

Parent of an 8 year old with ASD
Atypical Neuroleptics
(Dopamine Blockers)

Side Effects
Sleepiness (initially)
Weight Gain (common)
Diabetes (uncommon)
Movement Disorder (rare)

Atypical Neuroleptics
- Relatively less risk of weight gain
- FDA approved for Rx of ASD

Clozapine (Clozaril)
- Bone marrow suppression

Olanzapine (Zyprexa)
- Greater risk of weight gain

Quetiapine (Seroquel)
- Greater sedation

Risperidone (Risperdal)
- Greater risk of weight gain
- FDA approved for Rx of ASD

Ziprazidone (Geodon)
- Relatively less risk of weight gain

References
(neuroleptics, AEDs, GABA)

Regulation of Sleep - 1
- Melatonin
  - Brain hormone
  - Metabolic rate (Heart, Temp)
  - “You’re sleepy now”
- Suppressed by light
  - 24 hr cycle
  - Seasonal cycle
Regulation of Sleep - 2

- Abnormal melatonin cycling
  - Primary disorders of sleep
  - Blindness
  - ASD
- Symptoms
  - Delayed onset of sleep
  - Shortened duration / frequent wakening

Regulation of Sleep - 3

- Shared genetic control
  - Regulation of sleep
  - Regulation of arousal
- Family history of sleep disorder

References
(Melatonin)

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Sensory Processing

- Subjective Properties
  - Familiar / Unfamiliar
  - Pleasant / Unpleasant
  - Strong / Weak
  - Internal / External
- Sensory Input ➔ Self-awareness
- Mirror Neurons ➔ Empathy


The whole is greater than the sum of its parts
Max Wertheimer

Summary

- Why this child?
  - What is this child’s developmental Level?
  - Is this stage-appropriate behavior?
  - Does the behavior serve a social function?
  - Escape, access, attention
  - Is the classroom placement appropriate?
  - Language level?
  - Does this behavior occur in other settings?
  - Family factors?
    - Parents consistent at home?
    - Parental psychopathology? (Anxiety, Depression, Alcohol)
Summary

• Why this child?
  – Neuropsychological factors?
    • Cognitive Rigidity
    • Dysregulation of attention
    • Dysregulation of arousal
    • Sensory Seeking / Sensory Overload

• Behavioral Intervention – Usually
• Change in classroom setting – sometimes
  – Shift from rote to inferential learning (2nd - 3rd grade): challenge
• Medication: Sometimes

Clinical Pearl

• Beware of anxiety or perseveration masquerading as inattention
  – Perseveration on inner stimuli: “Inattentive”
  – Perfectionism: “Problems w. task completion”
  – Anxiety: “Rushes through work”

An ounce of prevention....

• Identify internalizing behaviors before they lead to externalizing behaviors
  – Behavior Management Plan that proactively seeks to avert or dissipate anxiety

Summary

Directions for future research:

• Better phenotyping of ASD
  – Clinical
  – Genetic

• Better drug studies
  – Drug vs. Behavioral Therapy vs. Combination
  – Drug vs. Drug (not just drug vs. placebo)
  – Drug combinations (not just monotherapy)
  – Stimulant + SSRIs, e.g.
  – Better outcome measures
    • Quality of Life
    • Long-term outcome

• Brain / Behavior / Drug imaging

Thank you