Psychopharmacology of Co-occurring Conditions in Autism Spectrum Disorders

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Disclosures

- In the past 12 months, I have not had a significant financial interest or other relationship with the manufacturer(s) of the product(s) or provider(s) of the service(s) that will be discussed in my presentation.

- This presentation will not include discussion of pharmaceuticals or devices that have not been approved by the FDA.

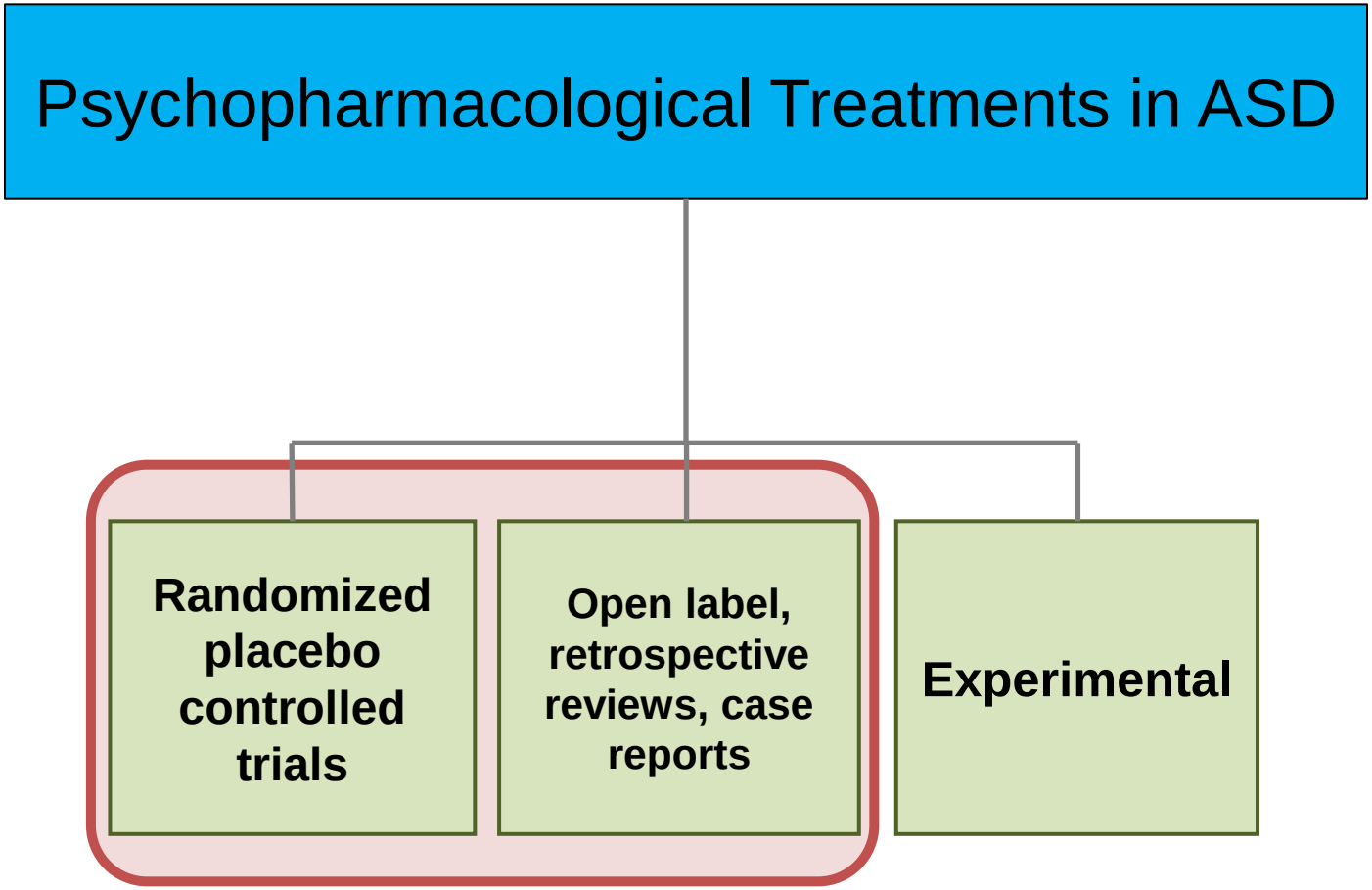
- This presentation will be discussing unapproved or “off-label” uses of pharmaceuticals or devices.

Objectives

- Medications to treat 3 classes of symptoms

  - Hyperactivity, impulsivity, inattention: STIMULANTS
  - Aggression, self-injury, irritability: ATYPICAL ANTIPSYCHOTICS
  - Anxiety, repetitive behaviors: SELECTIVE SEROTONIN REUPTAKE INHIBITORS

- Review efficacy, side effects, monitoring plan


Psychopharmacological Treatments in ASD
Randomized placebo controlled trials
Open label, retrospective reviews, case reports
Experimental

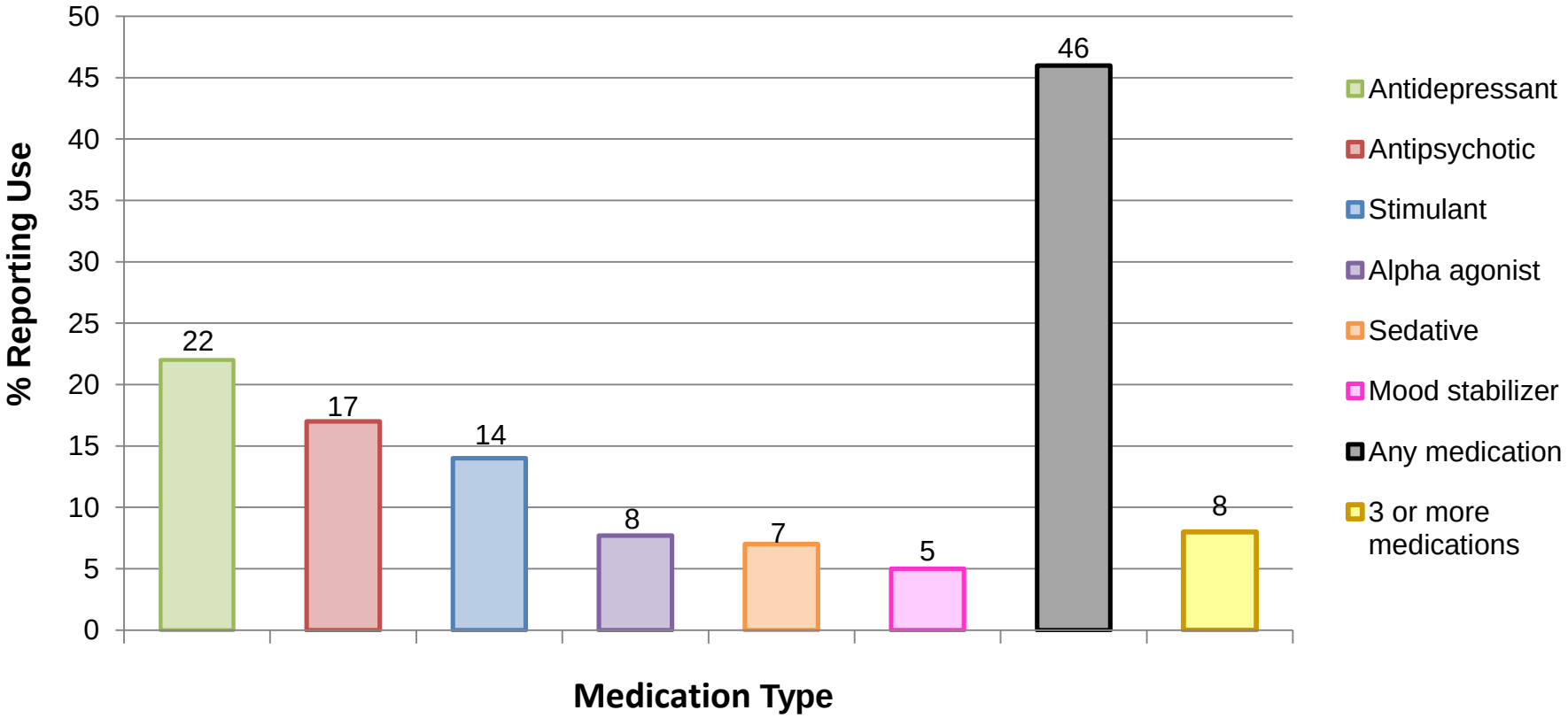
Interventions

- Speech and language services
- Educational programming
- Behavioral interventions
- Social skills training
- Sensory integration
- Medical treatments
- **Psychopharmacological treatments**
- Complementary and alternative medicines

The goal of intervention is to maximize adaptation.

North Carolina Survey, N = 1,538

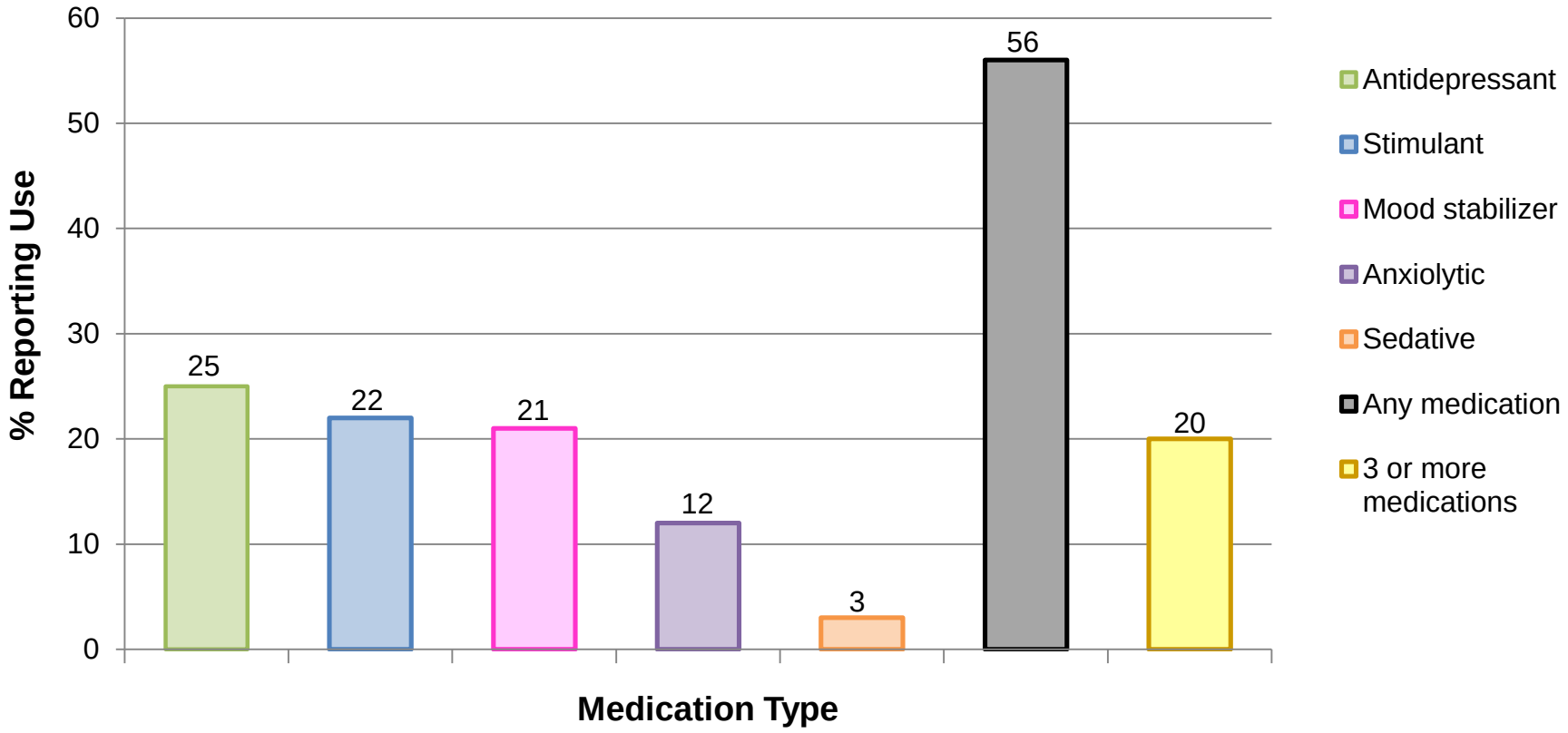
3 to 56 years
Autism Society of North Carolina



J Child Adolesc Psychopharmacol, 2002

National Medicaid Sample, N = 60,641

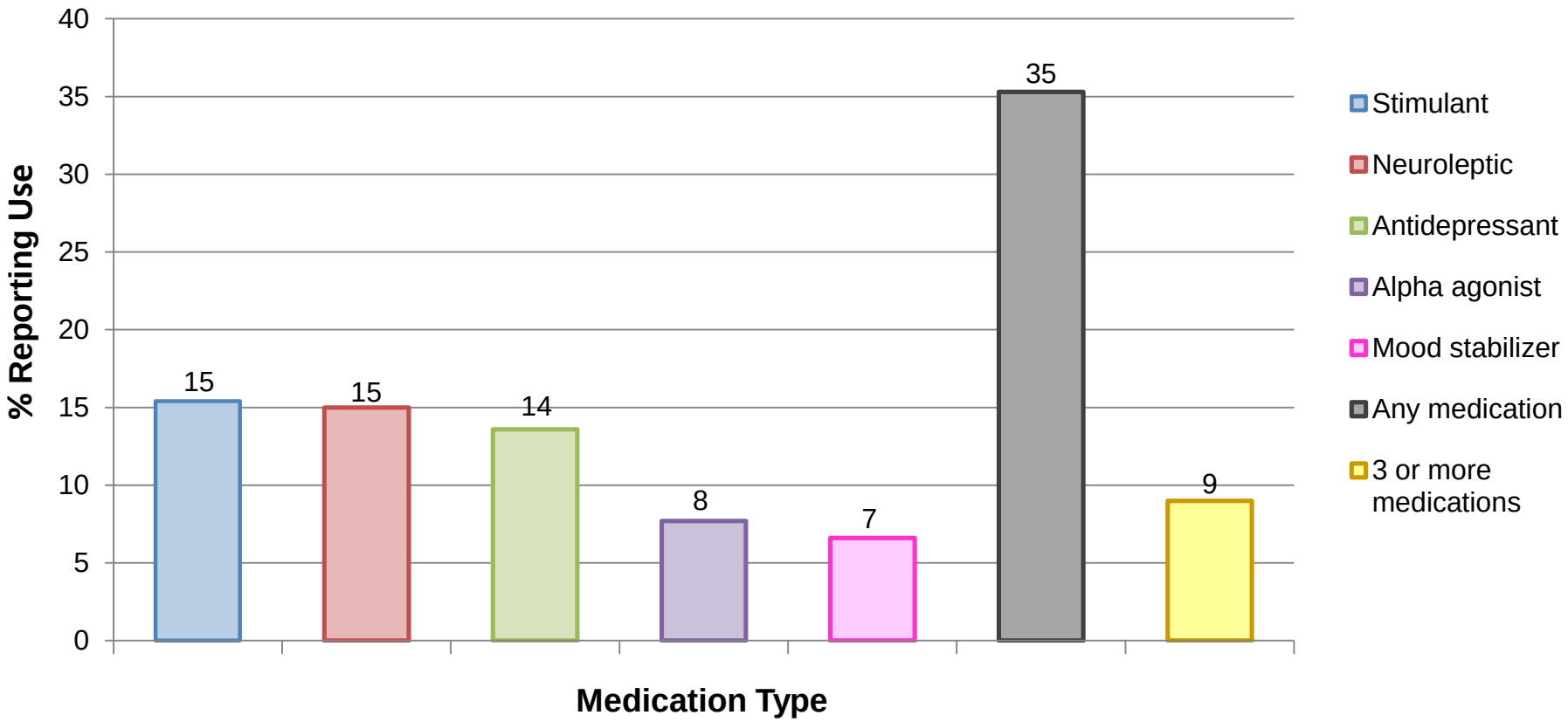
0 to 21 years
All 50 states plus Washington DC



Pediatrics, 2008

Interactive Autism Network, N = 5,181

3 to 17 years



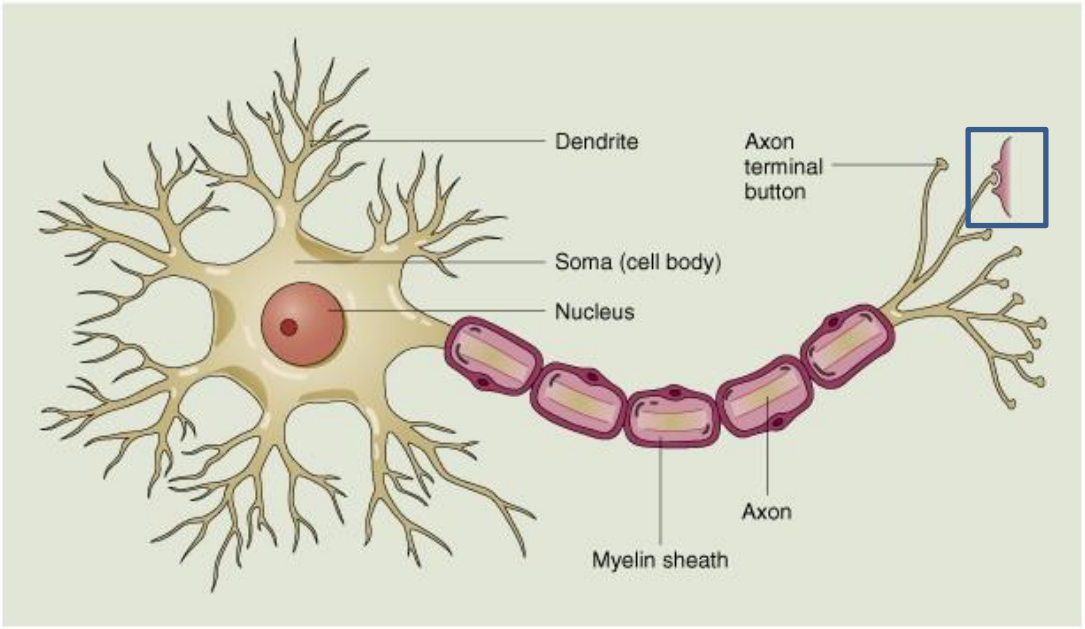
JADD, 2010

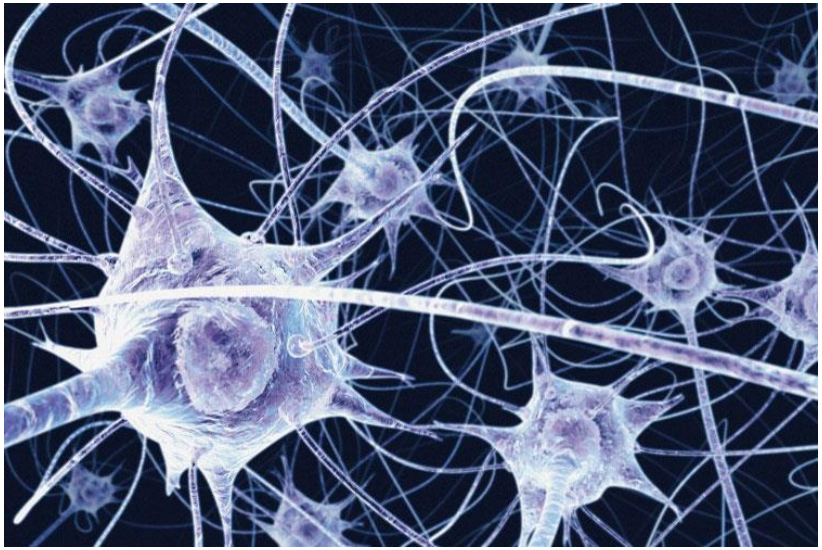
Assessment

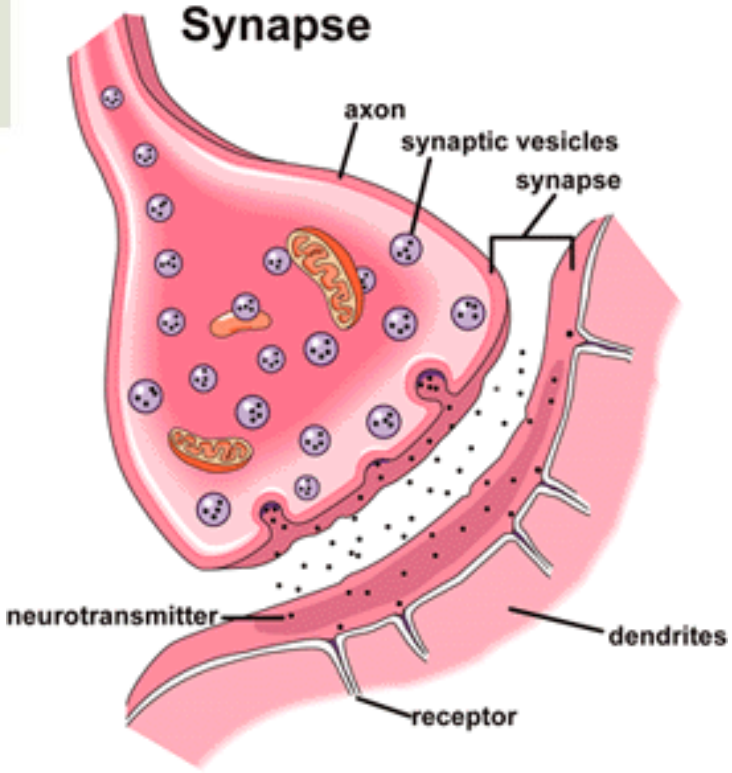
- 1 - 2 visits
- Multi-informant
- Family history
- What is the primary behavior of concern?
- What might be the cause?
- Do symptoms interfere with functioning?
- Do the parents want to try medications?
- Are other providers aware?

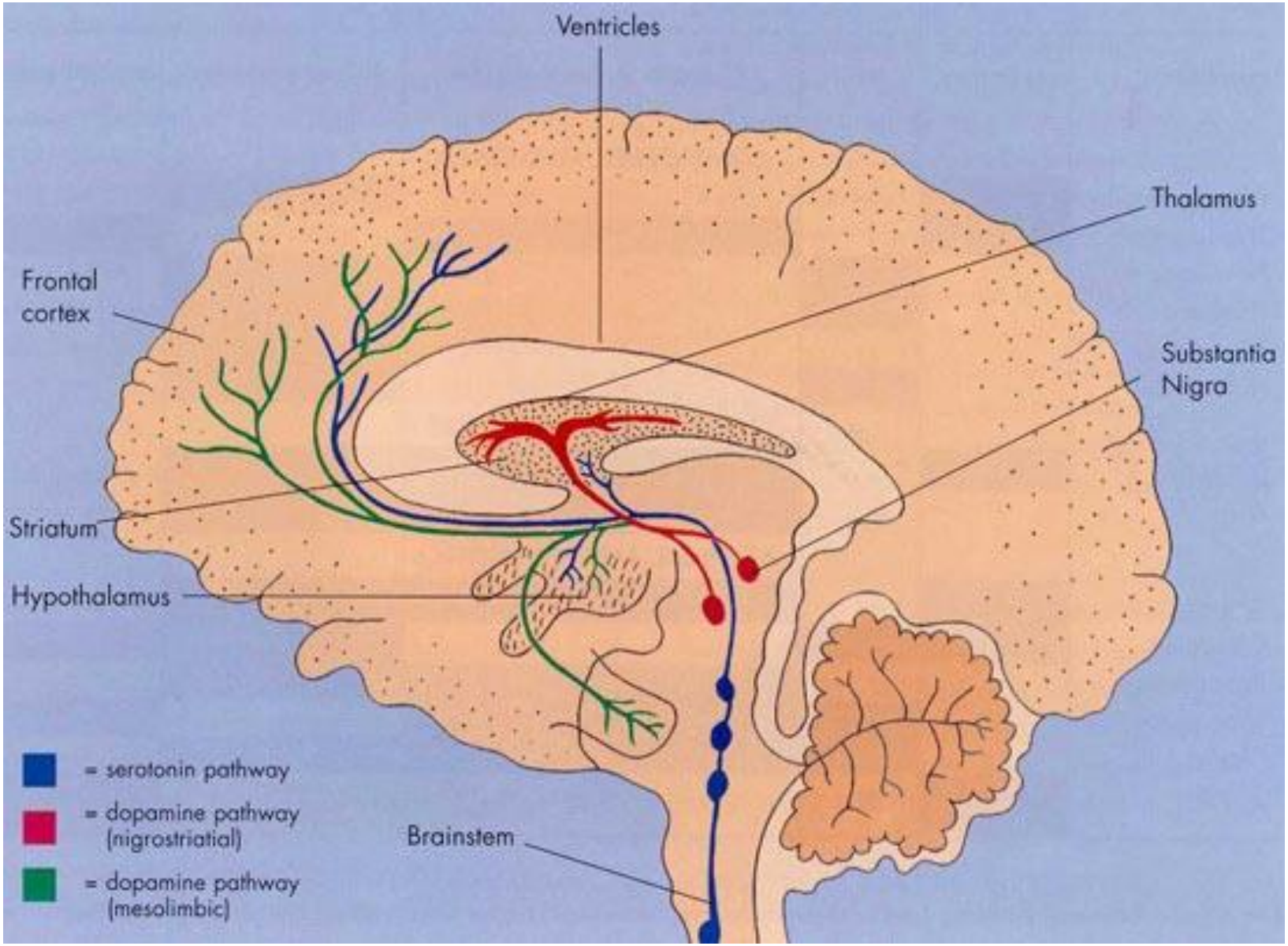
Discussion

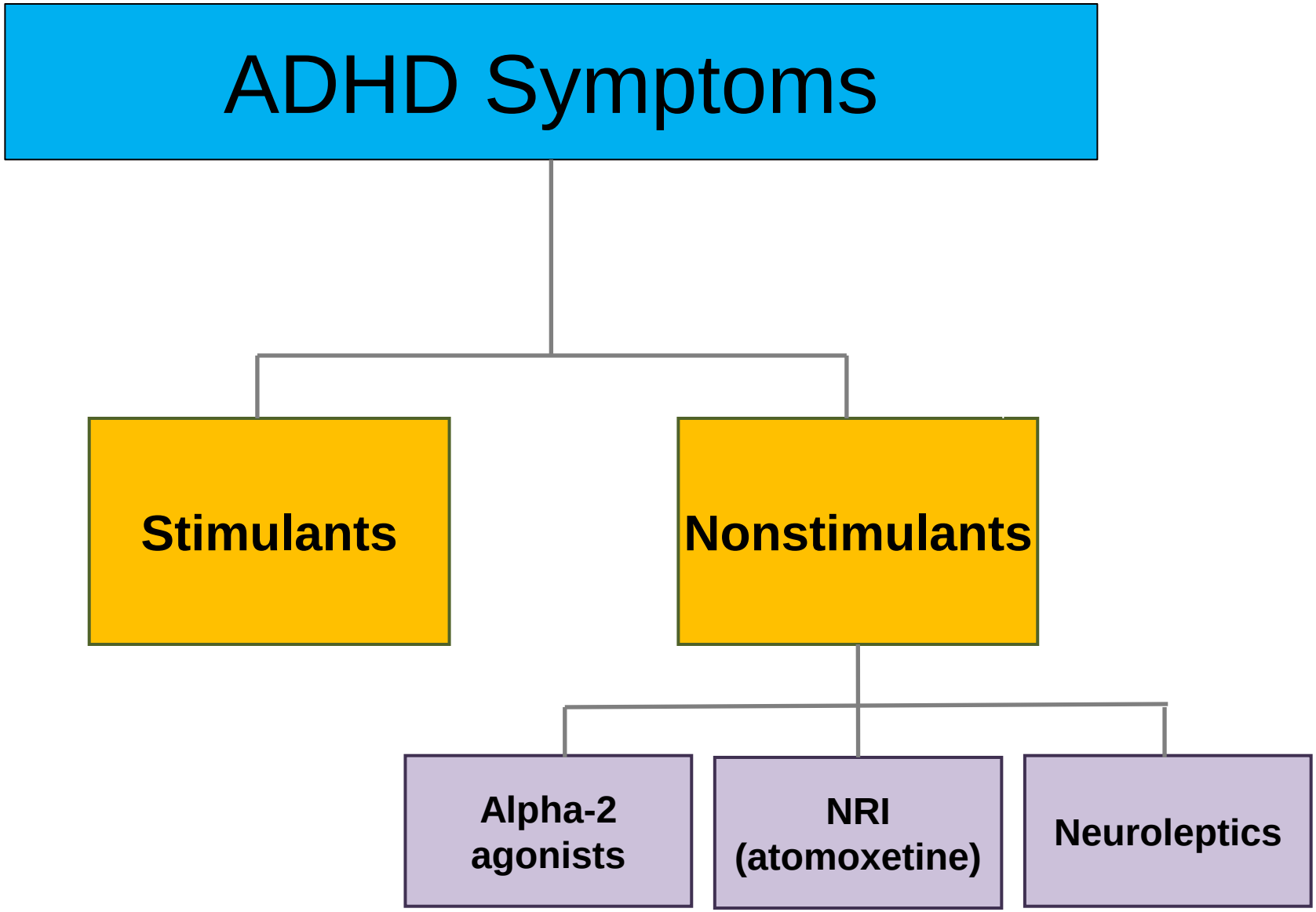
- Evidence (sometimes trial and error process)
- Factors to consider
  - risks/benefits of each medication
  - swallow pills/liquid preparation
  - tolerate blood draw/EKG
  - timing
- Plan
  - measurable goals
  - start with well-studied medication
  - ‘start low and go slow’
  - compliance
  - duration of treatment
  - monitoring plan
  - future medication trials
  - polypharmacy
  - coordination of care








Ventricles
Thalamus
Frontal cortex
Substantia Nigra
Striatum
Hypothalamus
= serotonin pathway
= dopamine pathway (nigrostriatial)
= dopamine pathway (mesolimbic)
Brainstem


ADHD Symptoms
Stimulants
Nonstimulants
Alpha-2 agonists
NRI (atomoxetine)
Neuroleptics

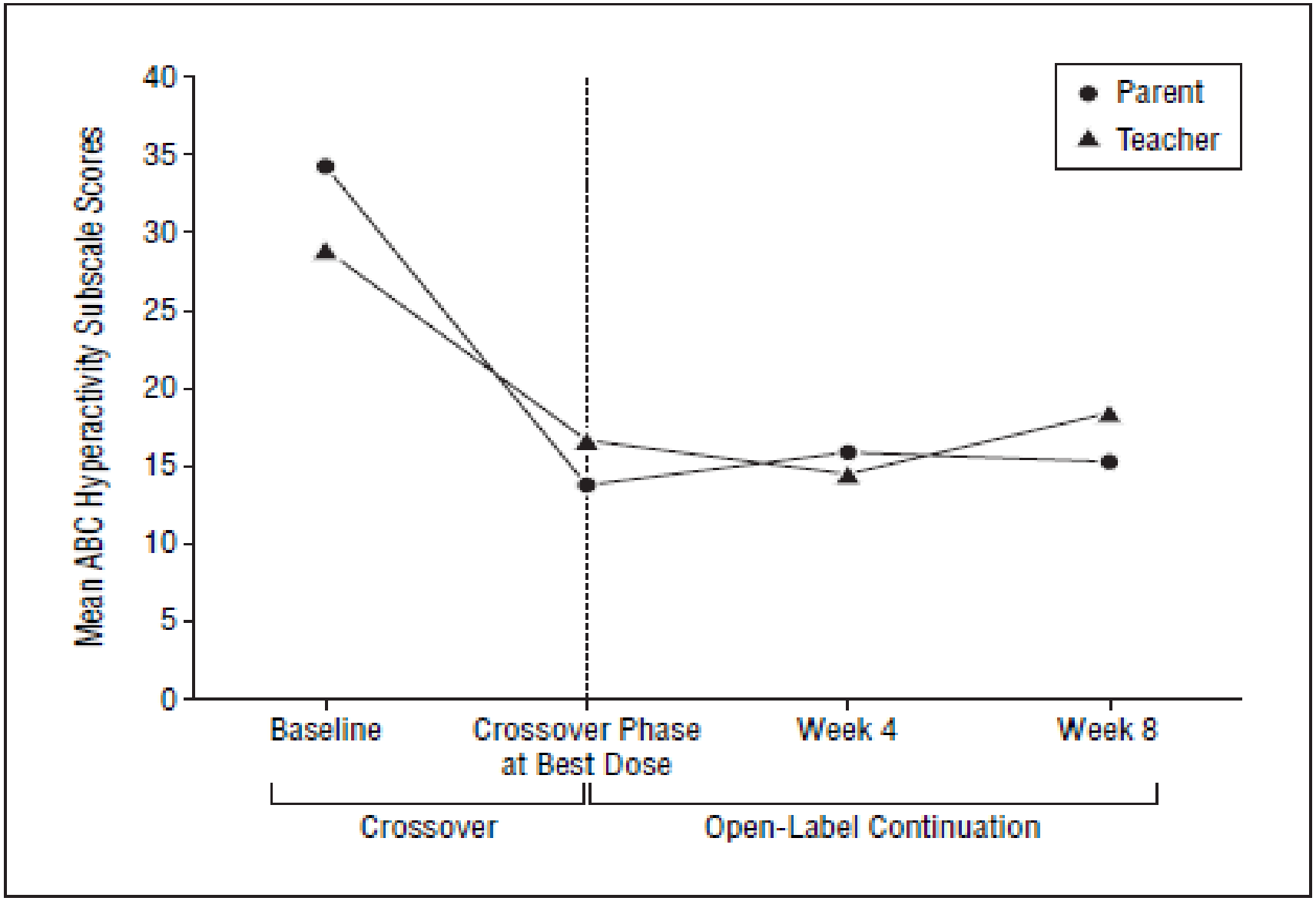
Methylphenidate (MPH) - Ritalin

- 72 subjects, 5 to 14 years
- Double blind placebo cross over trial
- MPH: Low (0.125mg/kg), medium (0.25mg/kg), high (0.5mg/kg)
- Outcome measures: Aberrant Behavior Checklist (ABC)
  Clinician Global Impression Scale

Results: 49% - Improved attention, decreased hyperactivity (versus 69% in typically developing children)

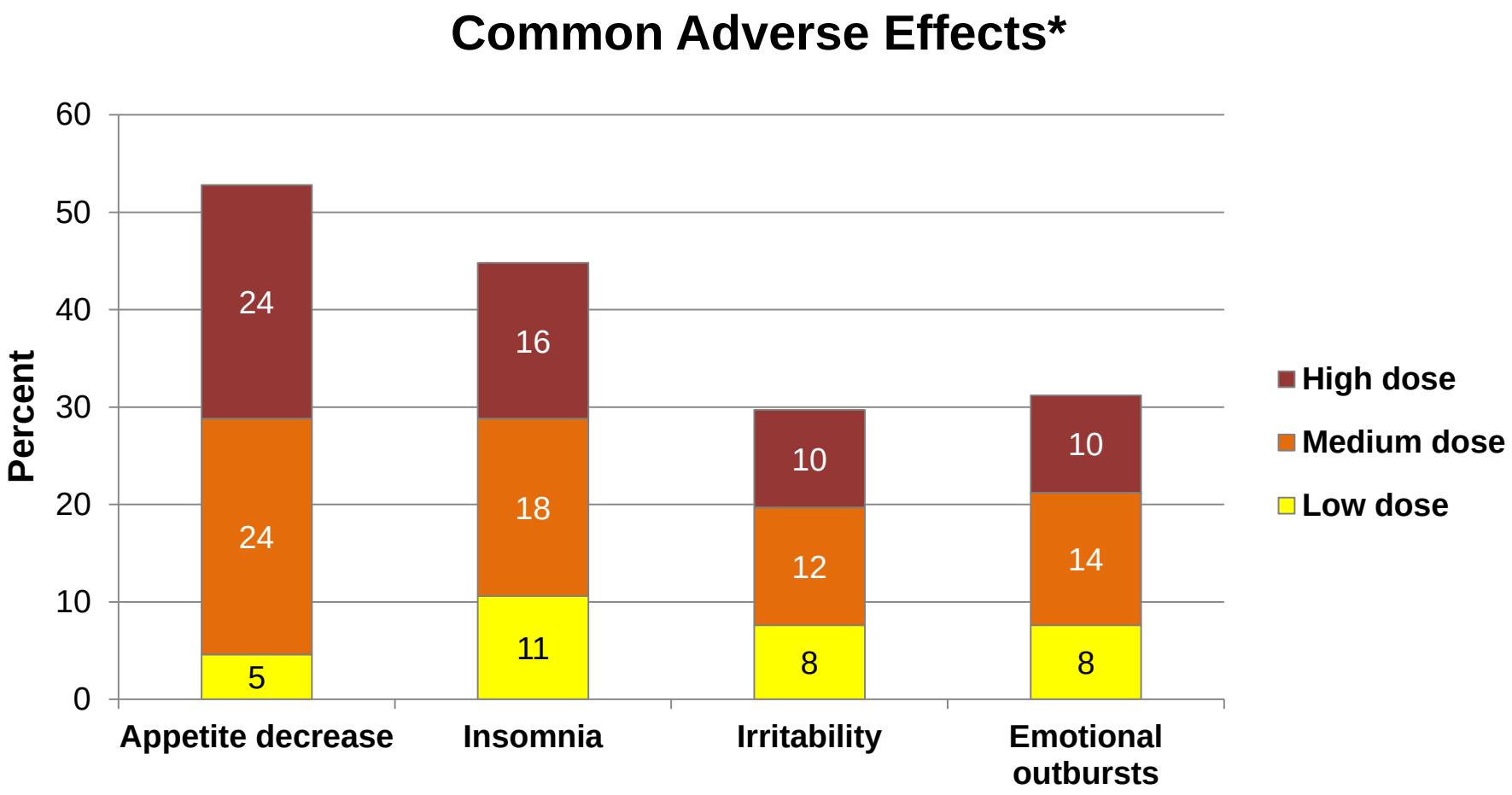
Arch Gen Psychiatry, 2005

MPH



Arch Gen Psychiatry, 2005

MPH



*** 18% drop out (versus 1.4% in children without ASD) due to irritability**

Arch Gen Psychiatry, 2005

Stimulant Side Effects

- Appetite suppression
- Negative mood
- Flat affect
- Worsening anxiety, repetitive behaviors
- Elevated blood pressure/pulse
- Insomnia
- Psychosis
- Disorganizing effects

Stimulant Monitoring

- BP/Pulse
- Appetite suppression
- Height/Weight
- Sleep
- Mood/Anxiety
- Thought processes
- Repetitive behaviors/Tics

Alpha-2 Agonists

- Hyperactivity/impulsivity > Inattention
- Clonidine (Kapvay) – can be sedating, shorter acting, frequent dosing, liquid preparation
- Guanfacine/Tenex (Intuniv) - binds preferentially to postsynaptic 2A-adrenoreceptors in the prefrontal cortex
- Other: aggression, outbursts (prn), anxiety
- Side effects: Low BP, pulse, sedation, mood change
- Consider as first line agent

Clonidine and Guanfacine

Study	Dose	Subjects	Design	Results	Adverse effects
Jaselskis et al., 1992	Clonidine 0.15 – 0.2 mg/day (tid)	n = 8, 5 to 13 yrs	DBPC 6-week crossover	**Clonidine > PBO** by parent and teacher report	Hypotension, sedation, irritability
Fankhauser et al., 1992	Transdermal clonidine 5 µg/kg/day	n = 9 5 to 33 yrs	DBPC 4-week crossover	**Clonidine > PBO** by clinician report	Fatigue, sedation
Scahill et al., 2006	Guanfacine 1.0 – 3.0 mg/day	n = 25 6 to 9 yrs	8 week open trial	**Guanfacine > PBO** by parent and teacher report	Mood change, sedation, sleep problems, constipation
Posey et al., 2004	Guanfacine 0.25 – 9 mg/day	n = 80 3 to 18 years	Retrospective analysis	**Improvement with guanfacine** by clinician report	

Atomoxetine (ATX) - Strattera

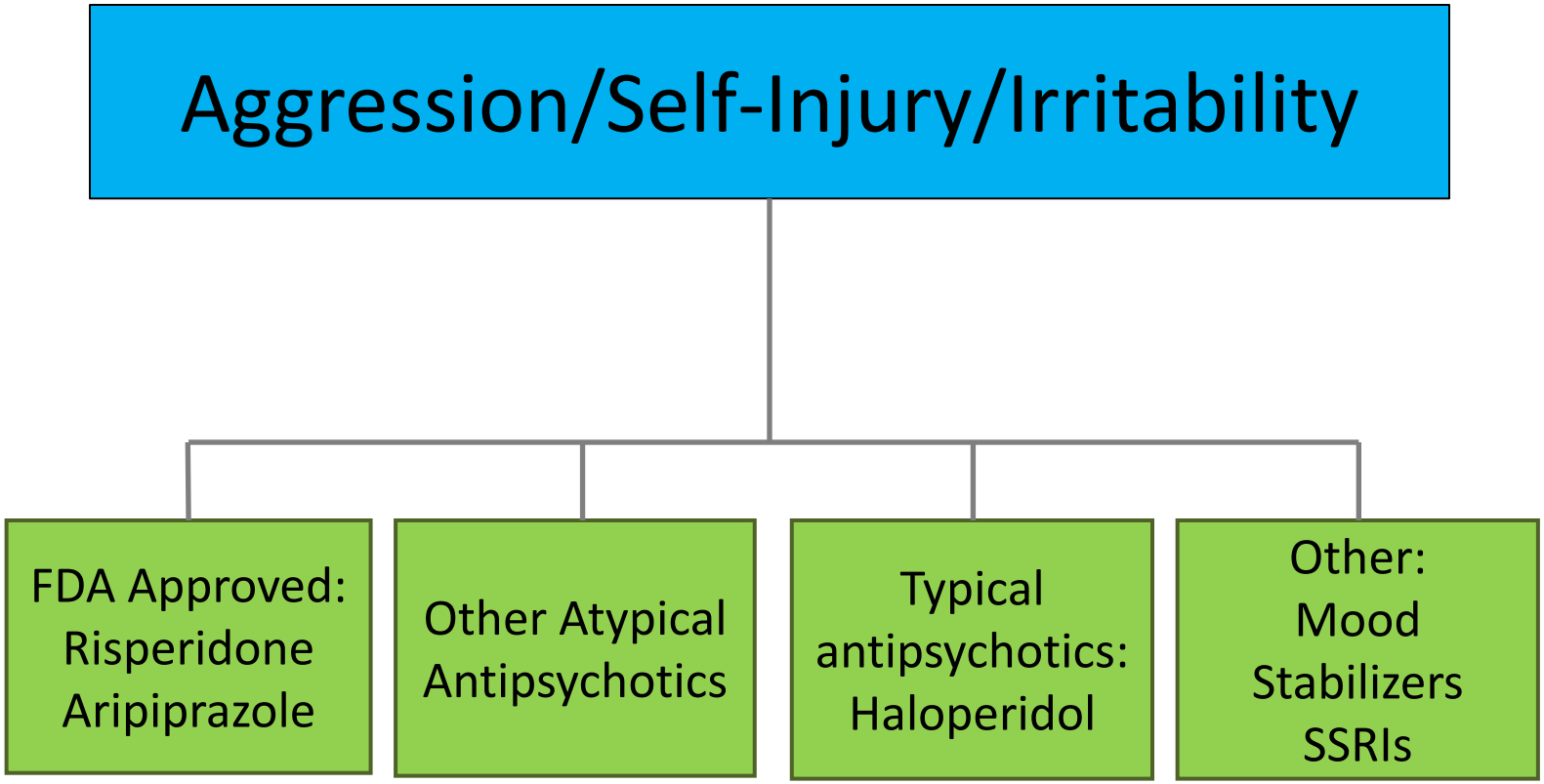
- 16 subjects, 5 to 15 years
- Design: PBO-controlled crossover trial
- ATX: 2.5-40 mg/day
- Outcome: ABC-hyperactivity - 25% improvement
  CGI-I - “very much improved” or “much improved”

Results: 9 subjects (57%) on drug improved

4 subjects (25%) on PBO improved

Appetite suppression (75%), moodiness (88%)

JAACAP, 2006


Aggression/Self-Injury/Irritability
FDA Approved:
Risperidone
Aripiprazole
Other Atypical
Antipsychotics
Typical
antipsychotics:
Haloperidol
Other:
Mood
Stabilizers
SSRIs

Risperidone

- 101 subjects, 5-17 years, mental age >18 mos.
- Multi-site double blind placebo controlled trial – 8 weeks
- Mean dose = 1.8 mg/day (range 0.5-3.5 mg/day)
- Outcome measures: ABC-irritability, CGI-I

Results: Reduction in irritability cluster
69% Risperidone versus 12% Placebo
30% nonresponders

NEJM, 2002

Risperidone

Effect size = 1.2

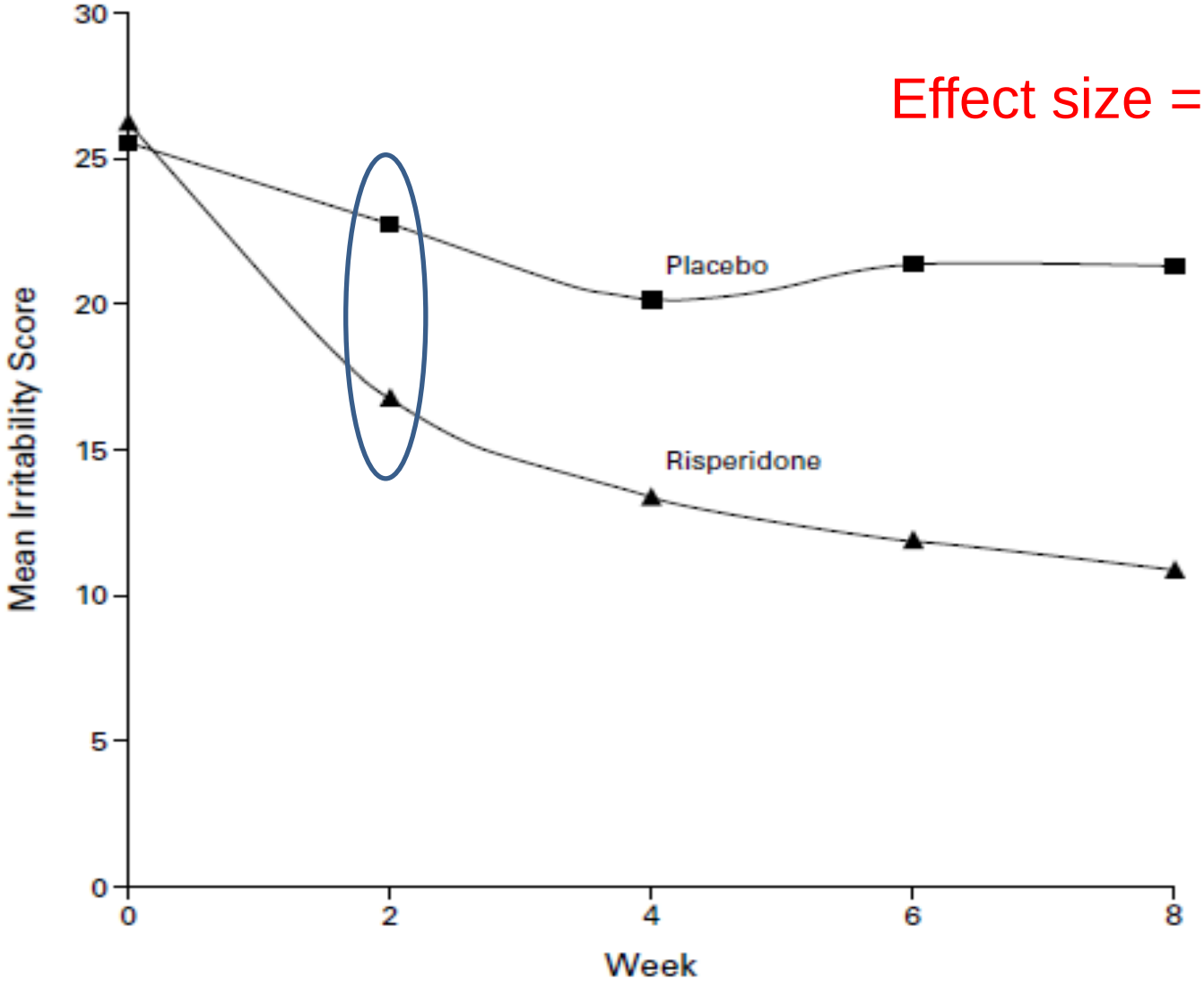


Figure 1. Mean Scores for Irritability in the Risperidone and Placebo Groups during the Eight-Week Trial. Data are for all 101 children (49 assigned to the risperidone group and 52 assigned to the placebo group). Higher scores indicate greater irritability.

NEJM, 2002

Risperidone

- Risperidone > Placebo (effect sizes) – BROADER COVERAGE

  Irritability – 1.2
  Hyperactivity – 1.0
  Stereotypy – 0.8

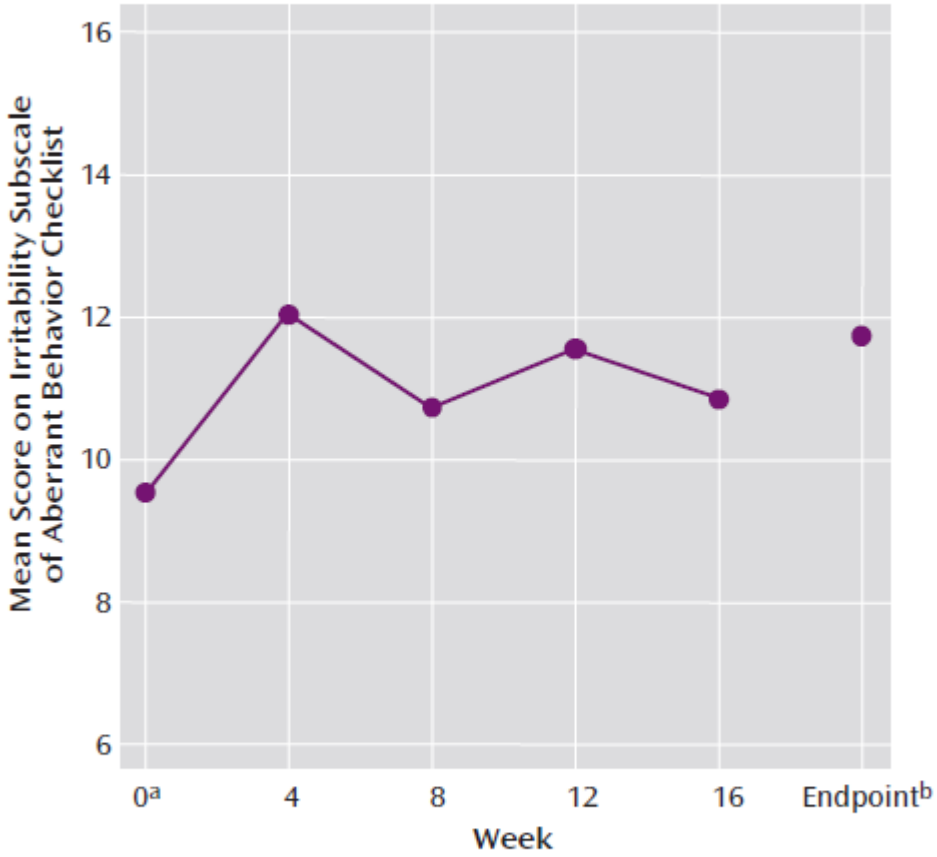
- No drop out

- Side effects: Increase in appetite and weight (2.7kg versus 0.8kg), drowsiness, dizziness, and drooling were greater in the drug compared to placebo group.

NEJM, 2002

Risperidone

FIGURE 1. Scores on the Irritability Subscale of the Aberrant Behavior Checklist for 63 Children With Autism Who Responded to Risperidone in an 8-Week Trial and Participated in a 4-Month Open-Label Extension



[a] Week 0 corresponds to the end of the initial 8 weeks of medication exposure.

[b] For patients who discontinued treatment, the last observation was carried forward.

Risperidone + Parent Management Training

- 124 children, 4 to 13 years, 24 weeks
- Two groups: Medication + Parent Training
  Medication alone

Results:

Combo > Meds - irritability, stereotypy, hyperactivity

Combo (1.98mg) versus Medication alone (2.26mg)

JAACAP, 2009

Aripiprazole

- 218 subjects, age 6-17 years
- 8 week double-blind, PBO- controlled, parallel-group
- 3 drug groups (fixed dose: 5, 10, or 15 mg/day), PBO
- Outcomes: ABC-Irritability; CGI-I

Results: **Irritability: Drug (49-56%) > PBO (35%) (about 50% nonresponders)**

Also reduction in hyperactivity, stereotypies, inappropriate speech, compulsions

JAACAP, 2009

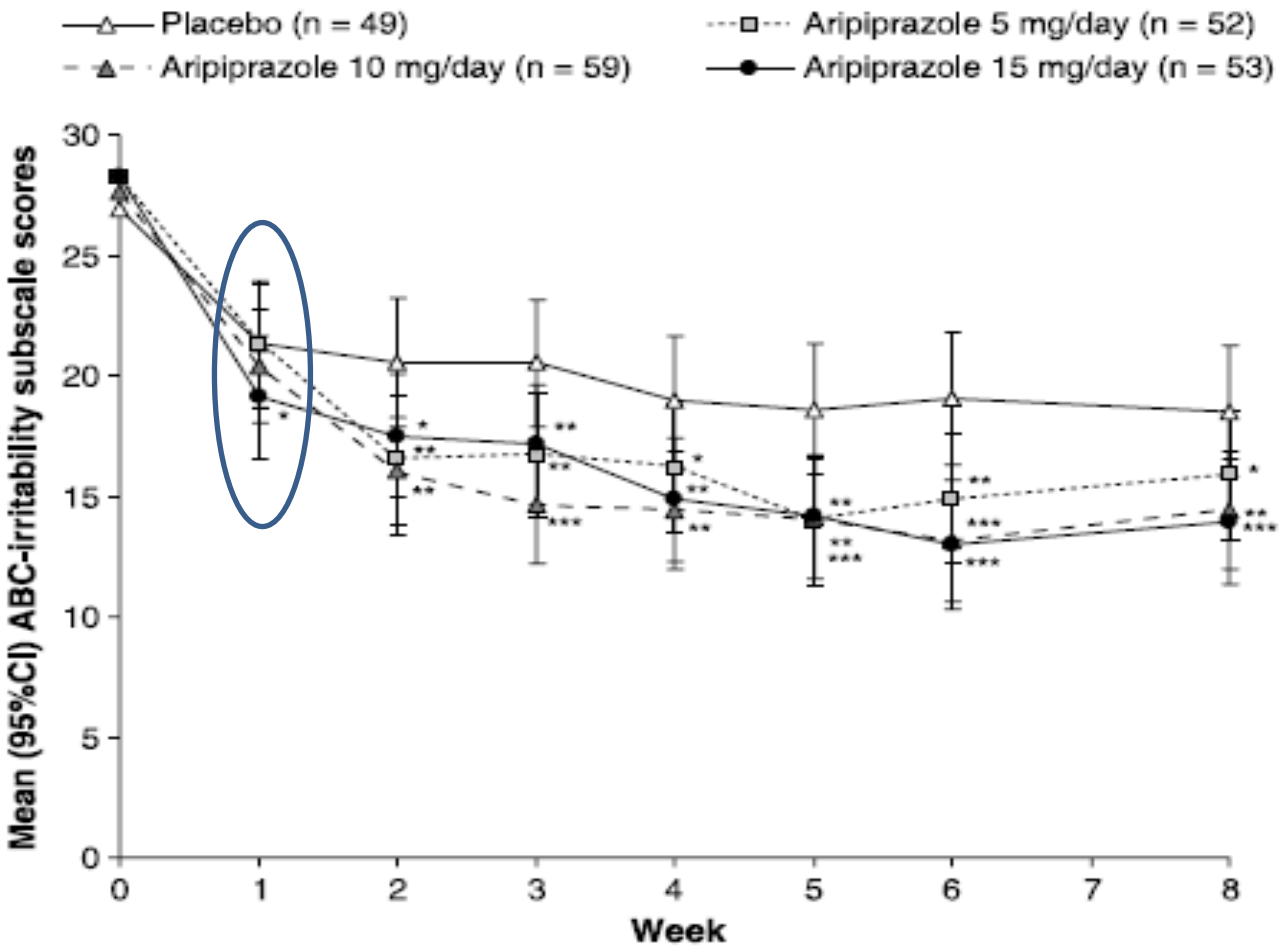


Fig. 2 Mean (95% CI) ABC-Irritability subscale score by week (LOCF; efficacy sample). Treatment difference (95% CI) (aripiprazole–placebo): aripiprazole 5 mg/day, –4.0 (–7.7, –0.4); aripiprazole 10 mg/day, –4.8 (–8.4, –1.3); aripiprazole 15 mg/day, –6.0 (–9.6, –2.3). ABC = Aberrant Behavior Checklist; LOCF = last observation carried forward; CI = confidence interval. $^{*}p < .05$; $^{**}p < .01$; $^{***}p \leq .001$ versus placebo.

JAACAP, 2009

Aripiprazole

- 98 subjects, age 6-17 years
- 8 week double-blind, randomized, PBO-controlled
- Flexible dosing (target: 5, 10, 15mg)
- Outcome measures: ABC-Irritability and other subscales

Results: **Irritability: 52% on drug vs 14% on PBO**

Also reduction in hyperactivity, stereotypies, inappropriate speech, compulsive behavior

Pediatrics, 2009

Effect size = 0.9

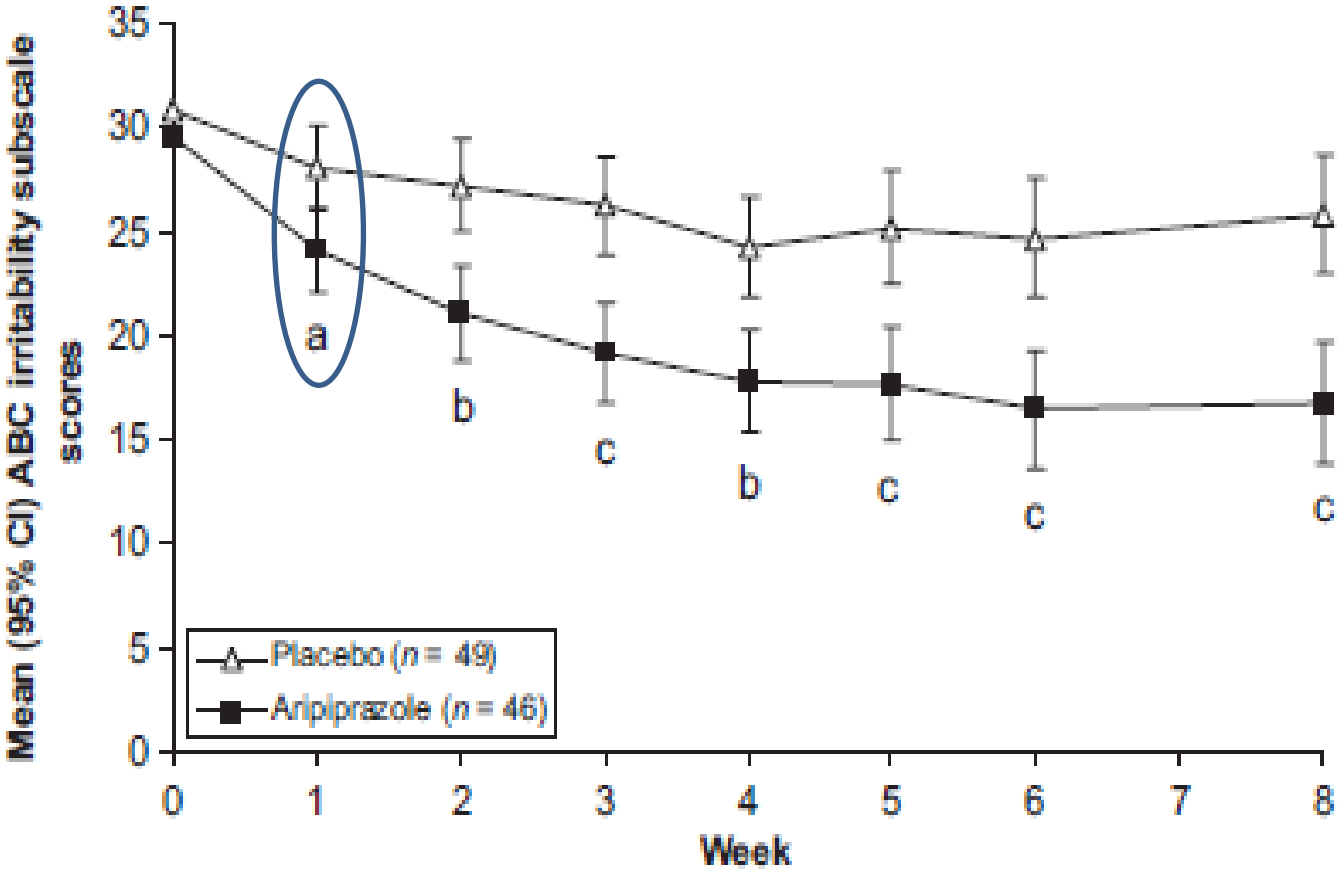
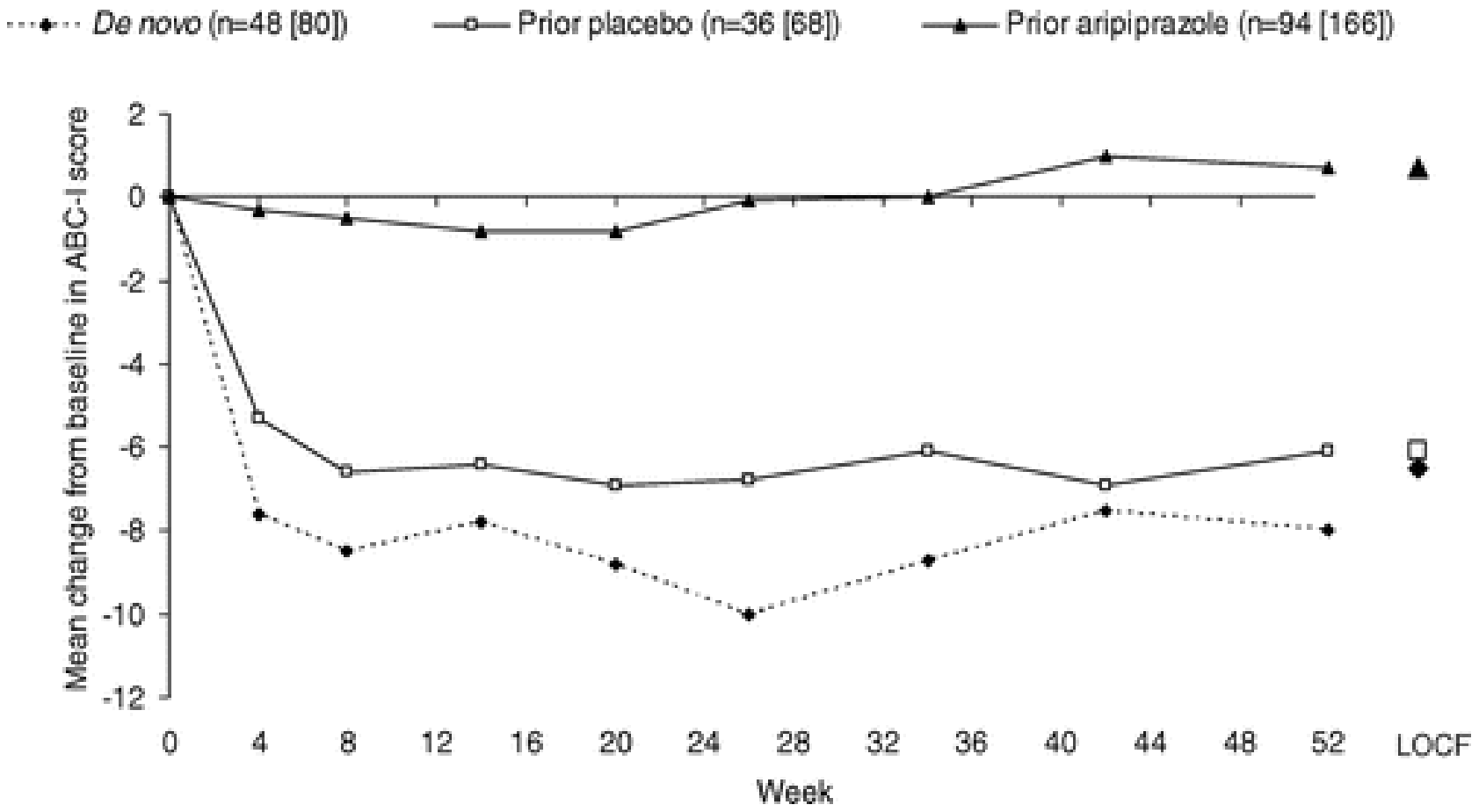


FIGURE 2

Mean ABC irritability subscale score according to week (LOCF; efficacy sample). [a] $P < .05$, [b] $P < .005$, and [c] $P < .001$ versus placebo.

Pediatrics, 2009

Aripiprazole



J Clin Psychiatry, 2011

Other Atypical Neuroleptics

Promising	Not suitable
Olanzapine (Malone et al., 2001; Hollander et al., 2006)	**Quetiapine** (Martin et al., 1999; Corson et al., 2004)
Ziprasidone (McDougle et al., 2002; Cohen et al., 2004)	**Clozapine** (e.g., Beherec et al., 2011; Lambrey et al., 2010; Chen et al., 2001; Zuddas et al., 1996)

Atypical Antipsychotic Side Effects

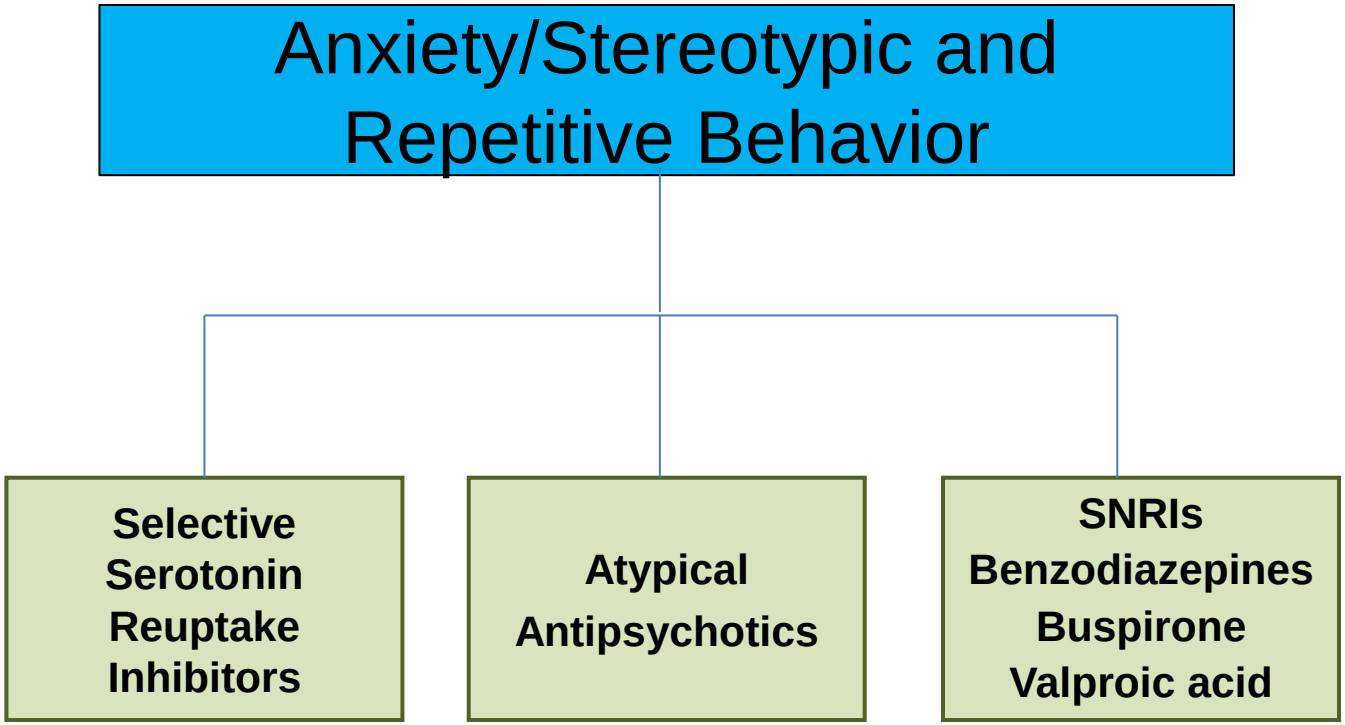
- Weight gain/metabolic sequelae
- Elevated prolactin
- Sedation/fatigue
- Extrapyramidal symptoms/NMS
- Prolonged QTc
- Elevated LFTs
- Blood dyscrasias
- Thyroid dysfunction
- Reduction of seizure threshold

Monitoring Protocol for Patients Taking Atypical Antipsychotics*

Clinical Parameter	Baseline	4 wks.	8 wks.	12 wks.	Quarterly	Annually	Every 5 years
Personal/family history	✓					✓	
Weight (BMI)	✓	✓	✓	✓	✓		
Waist circumference	✓					✓	
Blood pressure	✓			✓		✓	
Fasting plasma glucose	✓			✓		✓	
Fasting lipid profile	✓			✓			✓

*From the Consensus Development Conference on Antipsychotic Drugs and Obesity in Diabetes. Diabetes Care 2004; 27:599.

J Clin Psychiatry, 2004


Anxiety/Stereotypic and Repetitive Behavior
Selective Serotonin Reuptake Inhibitors
Atypical Antipsychotics
SNRIs
Benzodiazepines
Buspirone
Valproic acid

Anxiety

- Steingard et al., 1997 (n = 9)
  - Transition-induced anxiety, separation anxiety, generalized fears
  - Sertraline 25-50mg, one case using 150mg
  - Short term improvement
- Ozbayrak, 1997 (n = 2)
  - Anxiety and repetitive behavior
  - Sertraline 25-50mg
  - Both cases showed improvement
- Buitelaar et al., 1998 (n = 22)
  - Anxiety, irritability
  - Buspirione, mean dose = 29.3mg
  - 76% had reduction in anxiety
- Bhardwaj et al., 2005 (n = 1)
  - Separation anxiety
  - Sertraline 75 mg
  - Improvement in 6 months

Stereotypic and Repetitive Behavior

- Citalopram (Celexa) = Placebo (largest study)
- Fluoxetine (Prozac) > Placebo
- Fluvoxamine (Luvox) = Placebo
- Not studied: Sertraline (Zoloft), Escitalopram (Lexapro), Paroxetine (Paxil)

Fluoxetine

- Benefits in adults and children in reducing repetitive behaviors

- Adolescents/Adults (Hollander et al., 2012)
  - mean dose = 64.8mg
  - superior to PBO

- Children (Hollander et al., 2005)
  - mean dose = 9.9mg
  - superior to PBO
  - side effects comparable in the two groups

Citalopram

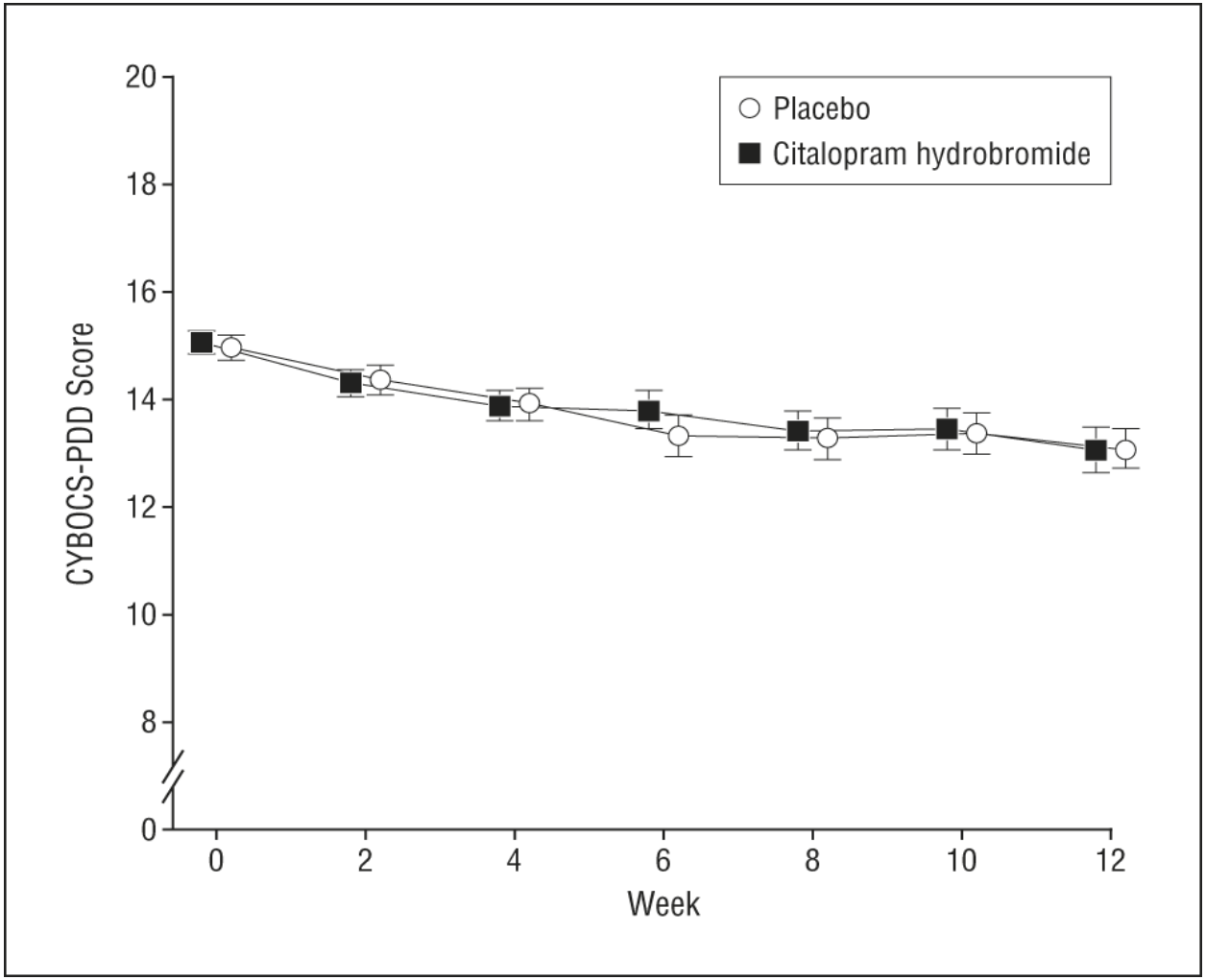
- 12 weeks, double blind placebo controlled
- N= 149 children and adolescents
- Mean dose = 16.5mg
- Outcome measure: CGI-I, CYBOCS

Results: Drug (33%) versus PBO (34%)

More side effects in the drug group: hyperactivity, impulsivity, insomnia, decreased concentration, diarrhea, seizures

Arch Gen Psychiatry, 2009

Citalopram



Arch Gen Psychiatry, 2009

SSRI Side Effects

Somatic	Behavioral
GI disturbance	Activation
Changes in appetite	Manic switching
Headache	Amotivational syndrome
Abnormal bleeding	Suicidal ideation
Hyponatremia	
Toxic serotonin syndrome	
Serotonin withdrawal syndrome	

SSRI Monitoring

- Weekly monitoring for 4 weeks
- Biweekly monitoring for 2 to 4 weeks
- Monthly monitoring thereafter
- Crisis plan
- Avoid abrupt discontinuation

Risperidone and Aripiprazole

- Reduce stereotypies (effect size = 0.8)
- Require metabolic, neurologic, cardiac monitoring

- Atypicals versus SSRIs for repetitive behavior?
  consider symptom severity, blood draw,
  family history (metabolic, bipolar)

Summary

- Some large well-designed studies of psychiatric medications for problematic behavior
- Evidence for the following:

  Inattention/hyperactivity: Methylphenidate
  Clonidine/guanfacine

  Irritability/Aggression/Self-injury: Risperidone, Aripiprazole

  Repetitive behaviors: Fluoxetine

- Low doses and close monitoring of side effects