Atomoxetine

- Open study showed 60% response of inattention and hyperactivity with a few much worse… (Jou et al 2005)

Buspirone

- Case reports (McCormick 1997, Hillbrand and Scott 1995,Realmuto et al 1989, Buitelaar et al 1998) for anxiety, aggression and hyperactivity

Serotonergic Agents I

- Serotonin in autism: background
  - Hyperserotonemia (Schain & Friedman 1961)
  - mCPP and fenfluramine challenges
    - Blunted neuroendocrine response
  - Tryptophan depletion (McDougle et al 1996)
  - Serotonin transporter (HTT)
    - *l / s* polymorphisms - (Cook et al 1997)
  - Clomipramine and SSRIs

Serotonergic Agents II

- Fenfluramine
  - Early enthusiasm, no replication
  - Toxicity concerns: neural death, valvulopathy
- Clomipramine
  - Controlled and crossover studies >PLA >DMI
  - Concern about side effects especially in younger children (e.g., sedation or agitation, tachycardia, QTc prolongation, seizures)

*SSRIs- I

SSRIs used for transition anxiety, reduction in rituals, sterotypies, repetitive behaviors

Fluvoxamine

- 30 adults, mean age 30, mean dose 276 mg/d
  - Double blind, placebo-controlled study
  - Responders: 8/15 (53%) active *vs* 0/15 placebo
  - YBOCS, aggression, maladaptive behaviors, social relatedness (McDougle et al 1996)
- ***0/15 children*** responders in attempt at study replication - behavioral activation (McDougle et al 1998)
- Open label study of 18 subjects with a mean age of 11.3
  - 78% completed the 10 week trial (3 paticipants experienced behavioral activation)
  - 8 subjects were at least partial responders (Martin et al 2003)

SSRIs- II

Sertraline- 2 cases series

- Steingaard et al 1997 children n=9, 8 responders with transition anxiety; 3 “poop-outs”: no doses above 50 mg;
- McDougle et a1 1998- adult responders:
  - 15/22 (68%) of AD
  - 9/14 (64.4%) of PDD-NOS
  - 0/15 (0%) of AspD

*SSRIs- III

Fluoxetine-case reports and open studies

- Cook et al 1992-15/23 child and adult responders
- DeLong et al 1998- children 22/37 responders
- Hollander et al 2005.
  - Double blind, placebo controlled crossover trial with liquid fluoxetine.
  - Doses were low> Mean final dose around 10 mg daily
  - Two 8 week phases with 45 children and adolescents randomized into 2 groups
  - Low dose liquid fluoxetine was was superior to placebo in the short term treatment of repetitive behaviors by CY-BOCS compulsion scale; not on speech or social impairment
  - Low incidence of AEs

*Serotonergic Agents

- Unresolved Issues: how well do they work?
  - Developmental differences to explain age-related response patterns?
  - CNS maturation, hormonal and pubertal changes?
  - AD and AspS different neurobiological characteristics?
  - Difficulties with measurement and instruments?
  - Lack of change *vs* ability to detect change?
  - Use LOW doses; watch for activation (Posey 2005)

Other Antidepressants

- Venlafaxine-only retrospective case series-6/10 response (Hollander 2000)
- Mirtazapine -adult open label-9/26 response (Posey et al 2001)

Dopaminergic Agents

- Dopamine in autism: background
  - Elevated CSF HVA
  - Symptoms sometimes exacerbate with stimulants
  - Neuroleptic efficacy
    - Traditional agents: haloperidol
    - Atypical agents

Haloperidol in Autism I

- Campbell et al 1978
  - Double blind, placebo controlled study
  - 40 children, mean age 4.5
  - Mean dose 1.65 mg /day
- Anderson et al 1984
  - Improved learning
  - Direct attentional effect
  - Not only decrease in maladaptive behaviors

Haloperidol in Autism II

- Withdrawal (WD) and Tardive (TD) Dyskinesias - Campbell et al 1997
  - 118 children treated between 1979 and 1994
  - 6 month haloperidol / 4 week placebo cycles
  - 34% of subjects developed dyskinesias
    - 86 episodes (12 TD, 74 WD)
  - Putative risk factors:
    - Female gender / perinatal complications / dose and cumulative drug exposure

Studies of Risperidone in Autism I

- Positive open study in children and adolescents (Malone et al 2002)
- McDougle et al 1997, 1998
  - 18 minors, mean age 10.2 (1997)
    - 12 week open-label study, mean dose 1.8 mg/d
  - 31 adults, mean age 28 (1998)
    - 12 week double blind, mean dose 2.9 mg/d
  - Repetitive behaviors, self/other aggression, anxiety, depression
  - Mild sedation

Studies of Risperidone in Autism II

- Troost et al (JAACAP Nov 2005)
  - 36 children (5-17 yo) with autism spectrum disorders and tantrums, aggression and SIB
  - 8 week open label trial with the 26 responders continuing a further 16 weeks followed by double blind discontinuation (=24)
  - Risperidone was superior to preventing relapse than placebo. 3 of 12 who continued on risperidone vs 8 of 13 on placebo

*RUPP Study: Hypothesis

Risperidone will be superior to placebo for:

- Aggressive behavior
- Agitation
- Tantrums (e.g., in response to routine environmental demands or change)
- Self-injurious behavior

Risperidone: RUPP Study- I

- Research Units in Pediatric Pychopharmacology (RUPP) study n=101
  - Randomized, double-blind, placebo-controlled, parallel groups, AD ages 5-18
  - 8wk DB phase: RISP or PLA (Study I)
  - 4mo open follow-up option
  - 8wk DB discontinuation for 6mo RISP completers (Study II)

Risperidone: RUPP Study-II

Targets: aggression, tantrums, SIB using ABC irritability subscale (25% decrease) and CGI (much improved or very much improved) as response: positive in 34/49 and maintained over 8 weeks

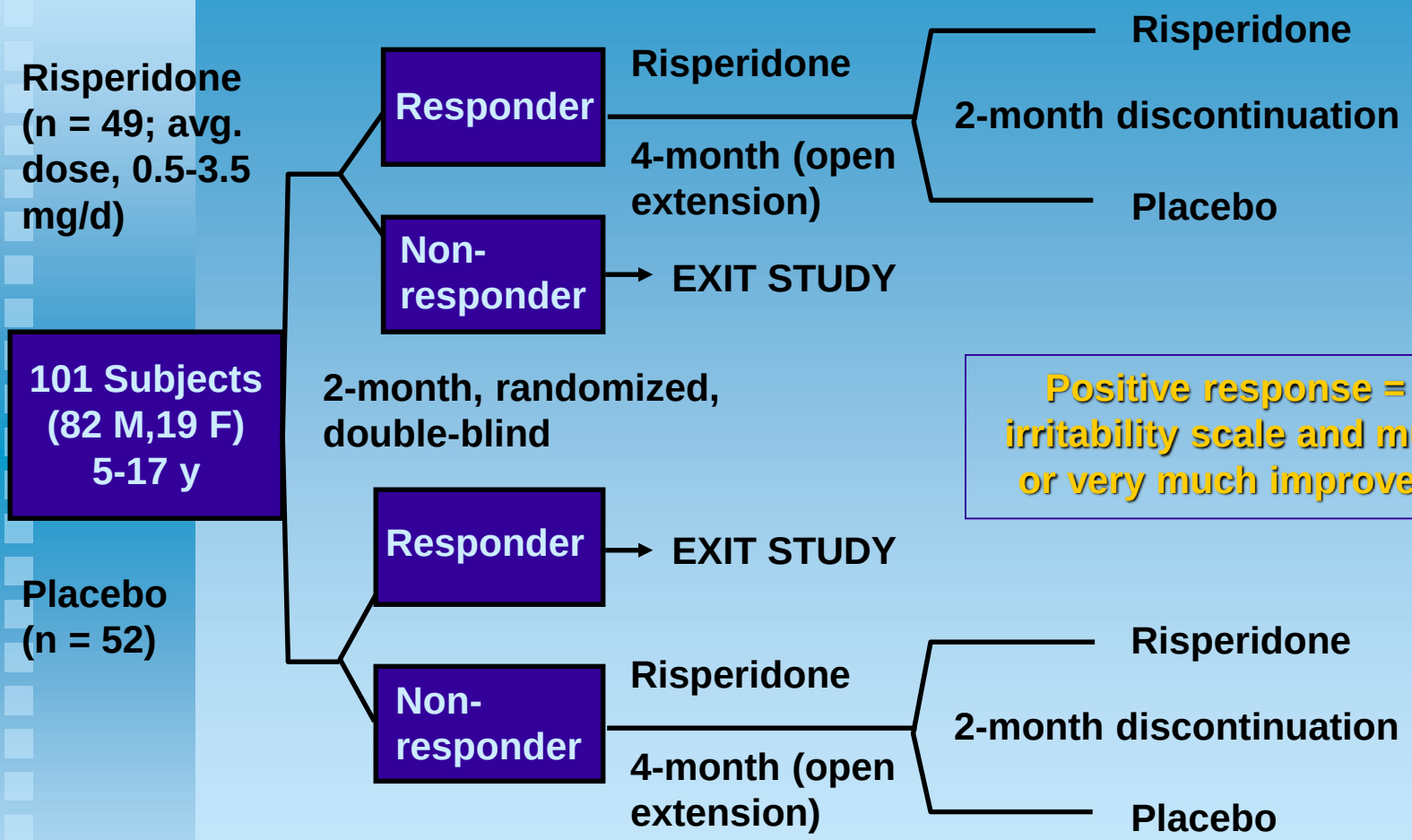
- RISP 0.5-3.5mg range

(McCracken et al 2002)

Risperidone in Children with Autism: Inclusion Criteria

- Autism
- Age 5 to 17
- Irritability subscale score $\geq$ 18
  - (approx. 1.3 SD units above mean in developmentally disabled population)
- CGI-Severity $\geq$ 4
- Mental age $\geq$ 18 months
- Medication free
  - (14 to 28 days depending on drug)
  - (except anticonvulsants)

NIMH RUPP Autism Network: Risperidone in Children With Autism and Serious Behavioral Problems



ABC = Aberrant Behavior Checklist.
RUPP = Research Units on Pediatric Psychopharmacological Autism Network.

RUPP Autism Network. *N Engl J Med.* 2002;347:314-321.

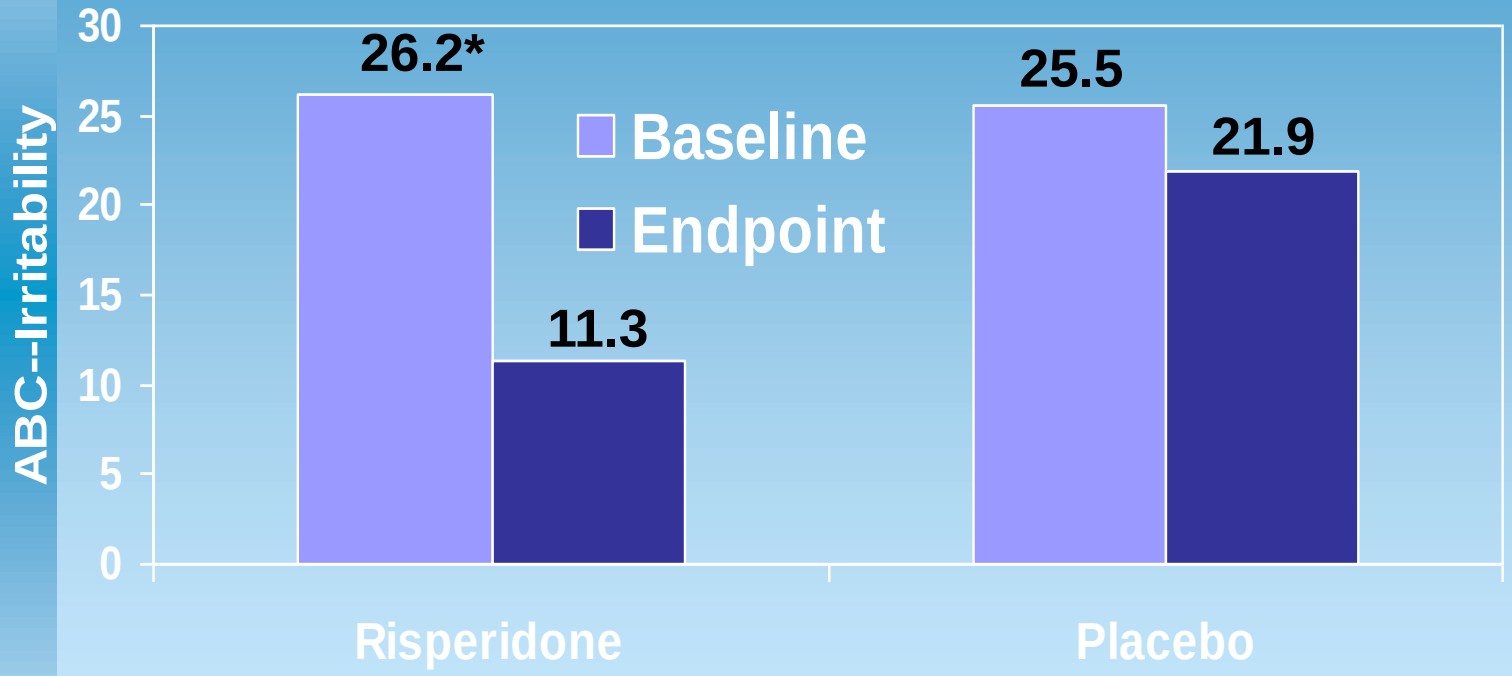
Risperidone in Children with Autism: Primary Outcomes

- ABC* Irritability scale
  (15-item parent-rated measure containing aggression, SIB, tantrums)

- CGI-Improvement
  (Clinician rating of change)

* *ABC=Aberrant Behavior Checklist*

Aberrant Behavior Checklist—Irritability Subscale



*P<0.0001 change from baseline
ABC = Aberrant Behavior Checklist

McDougle CJ, et al. ACNP, December 9–13, 2001, Waikoloa, Hawaii: #172.

Clinical Global Impression-Improvement

7-point index of overall response to treatment

1=Very Much Improved

2=Much Improved

3=Minimally Improved

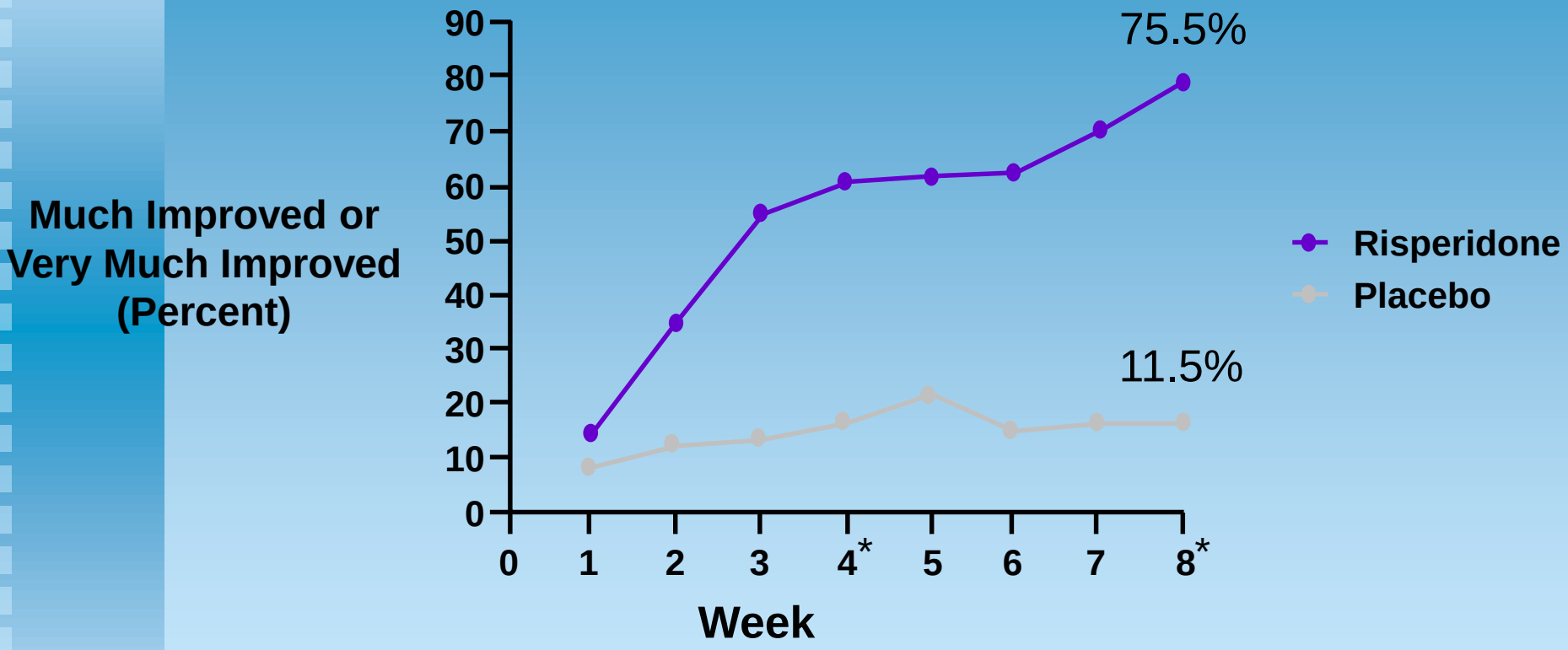
4= No Change

5=Minimally Worse

6=Much Worse

7=Very Much Worse

*RUPP Autism Study: CGI-I



CGI-I, Clinical Global Impressions Improvement Scale.
Data for all 101 children (n = 49, risperidone group; n = 52, placebo group).
Higher scores are indicative of greater irritability.
*$P < 0.001$ between groups.

RUPP Autism Network. *N Engl J Med.* 2002;347:314-321.

*Adverse effects in RUPP Autism Study

Adverse event	Risperidone n = 49 n (%)	Placebo* n = 51 n (%)	*P* value†
↑ appetite			
Mild	24 (49)	13 (25)	0.03
Moderate	12 (24)	2 (4)	0.01
Fatigue	29 (59)	14 (27)	0.003
Drowsiness	24 (49)	6 (12)	<0.001
Constipation	14 (29)	6 (12)	0.06
Drooling	13 (27)	3 (6)	0.02
Dizziness	8 (16)	2 (4)	0.05
Tremor	7 (14)	1 (2)	0.06
Tachycardia	6 (12)	1 (2)	0.06
Weight gain in kg	2.7 ± 2.9	0.8 ± 2.2	<0.001

RUPP Autism Network. *N Engl J Med.* 2002;347:314-321.

*Other Atypical Antipsychotics in PDD

- Olanzapine-case reports, case series (n=7,dose 5-20 mg), open study(n=25, only 3 responders (Kenner 2002)-associated with high incidence of weight gain
- Quetiapine-case report (n=6, negative report, ? 1 seizure, Martin et al 1999. Findling et al 2004: n=9 concluded quetiapine "may not be a particularly effective agent in the treatment of adolescents with autism"); 2 open label studies ?? response
- Clozapine-case reports: blood draw and seizure limitations
- Ziprasidone-open study (n=12) 50% responders (McDougle et al 2002)
- Aripiprazole-case series 5/5 response (Stigler et al 2004)

  DBPC trial is underway

*Dopaminergic Agents

- Limitations
  - Traditional agents: TD/ WD
  - Atypicals: Weight gain liability
    - ~60% of minors gain >7% by 6 months (Risp)
    - Prepubertal children may be at greater risk
    - CLZ > OLZ > RISP > QUET likelihood
    - Ziprasidone/Aripiprazole - promising weight gain SE profile
  - Clozapine
    - Blood monitoring a challenge / seizure liability

Mood stabilizers

- VPA-retrospective study-10/14 response (Hollander 2001) Negative study (Helllings 2005)
- Lamotrigine-DBPC trial-no more than placebo (Belsito et al 2001)

*Secretin and Autism I

- Initial enthusiasm (Horvath, 1998)
  - Secretin infusion during routine EGD
  - 3 non-verbal children improve at 5wks
  - Dateline show: instant public awareness
- Careful studies ensue
  - Several completed DB studies following single dose and q 4 weeks
  - No evidence of improvement (Corbett et al 2001,Carey et al 2002, Kern et al 2002, Unis et al 2002, Sponheim et al 2002)

*Secretin and Autism II

- Desperate solutions to desperate conditions
- Is secretin the late-90's autism fad?
- Long tradition of "cures" for autism
  - Facilitated communication
  - Megavitamins
  - Dolphin therapy
  - Sheep brain injections
  - Gluten free diet/casein free diet
  - Ketogenic diet
- Remember: lobotomy won Moniz the Nobel Prize

What is possible? No current evidence but worth further study- Posey 2005?

- SSRIs for social interaction improvement?
- AAPs- near significance for social interaction in RUPP study
- Placebo-controlled study donepezil-total score on CARS not improved, now ongoing studies
- Glutaminergic agents

Lamotrigine- negative DBPC

Amantadine-DBPC- no global improvement

D-cycloserine-pilot study-reduction in social w/d

Aggression in Autism

Aggression in Autism Antidepressants

- Fluvoxamine-1 study-poor results 1/18 in children but n=30 DBPC 12 wks. Positive for repetitive thoughts and behaviors and aggression s/e mild sedation and nausea (McDougle 1996)
- Other open label SSRI studies- perhaps 25% response
- One open study with mirtazapine-35% response

Aggression in Autism- Mood stabilizers

- VPA- retrospective- 768 mg/dy n=10/14
- In a double blind placebo controlled study of valproic acid in 30 subjects 6-20 years of age no statistical difference was found between placebo and VPA (Hellings et al, J Child Adolesc Psychopharm 2005 15 (4) 682-92)
- DBPC study of lamotrigine-negative
- Case reports of lithium for manic like symptoms

Aggression in Autism Psychostimulants

- Inconsistent results which may be modest
- RUPP study in Archives of General Psychiatry Nov 2005
  - 72 children (5-14 yo) with PDD and moderate to severe hyperactivity
  - Double blind crossover study
  - 49% were classified responders on measures of hyperactivity
  - 18% discontinued study due to adverse effects
  - Magnitude of response less than in normally developing children and adverse effects more frequent

Aggression in Autism

- Risperidone- best studied RUPP study n=101: 1.8 mg treated aggression and irritability s/e weight gain, inc app, sedation, tremor and hypersalivation
- In adults, n=32. 12 DBPC 57% responded irritibility, aggression and others; s/e mild sedation
- Olanzapine-open studies: 10.7mg/d with 3/25 considered responder, but weight gain significant (Kemmer 2002);7.9 mg with significant weight gain (Potenza 1999)
- Quetiapine- 2 open studies- poor results (Findling 2004, Martin 1999)
- Ziprasidone- 1 open study 59.2 mg lost about 5 lbs (McDougle 2003)

Aggression in Autism alpha 2 and beta adrenergics

- CND-1 DBPC study of 8- some improvement
- Guanfacine- retrospective study- improvement in tics, hyperactivity, inattention- only 14% improved in aggression; in open label trial of RUPP study 2005, only 25% in a retrospective study stayed on it, Posey 2005)
- Beta blockers- no studies in autism

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 be 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

- Which of the following statements is true
  - A Some children with Asperger's disorder have mental retardation
  - B The gene for autistic disorder is found on chromosome 7q
  - C The evidence supports a link between the MMR (measles/mumps/rubella) vaccination and autism
  - D The chance of having a child with Autistic disorder is 1 in 500
  - E If a couple have a child with autistic disorder the chance of having a second child with that diagnosis is 1 in 100

Question 3

- 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 Aripirazole

Question 4

- Which of the following is a semi-structured interactive assessment that can be conducted with a during an evaluation for an autism spectrum disorder?
  - 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)

Question 5

- All of the following statements about the prognosis for a child with autism are true except?
  - A Seizures effect about 25% of those with a generalized learning disability
  - B The peak age for onset of seizures is 11-14 years of age
  - C About 10% go through a phase in adolescence when they lose some language skills
  - D By adulthood approximately 10% of individuals with full autistic syndrome will be working and able to look after themselves
  - E They are at increased risk for developing schizophrenia in late adolescence and adulthood

Answer key

- 1: Correct answer: B
- 2: Correct answer: D
- 3: Correct answer: D
- 4: Correct answer: A
- 5: Correct answer: E