SSRIs- I

SSRIs used for transition anxiety or OC symptoms- but there is little research support

- 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)

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 AspS

SSRIs- III

Flouoxetine-case reports and open studies

- Cook et al 1992-15/23 child and adult responders
- DeLong et al 1998- children 22/37 responders

Serotonergic Agents

- Unresolved Issues: 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?

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

- 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

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

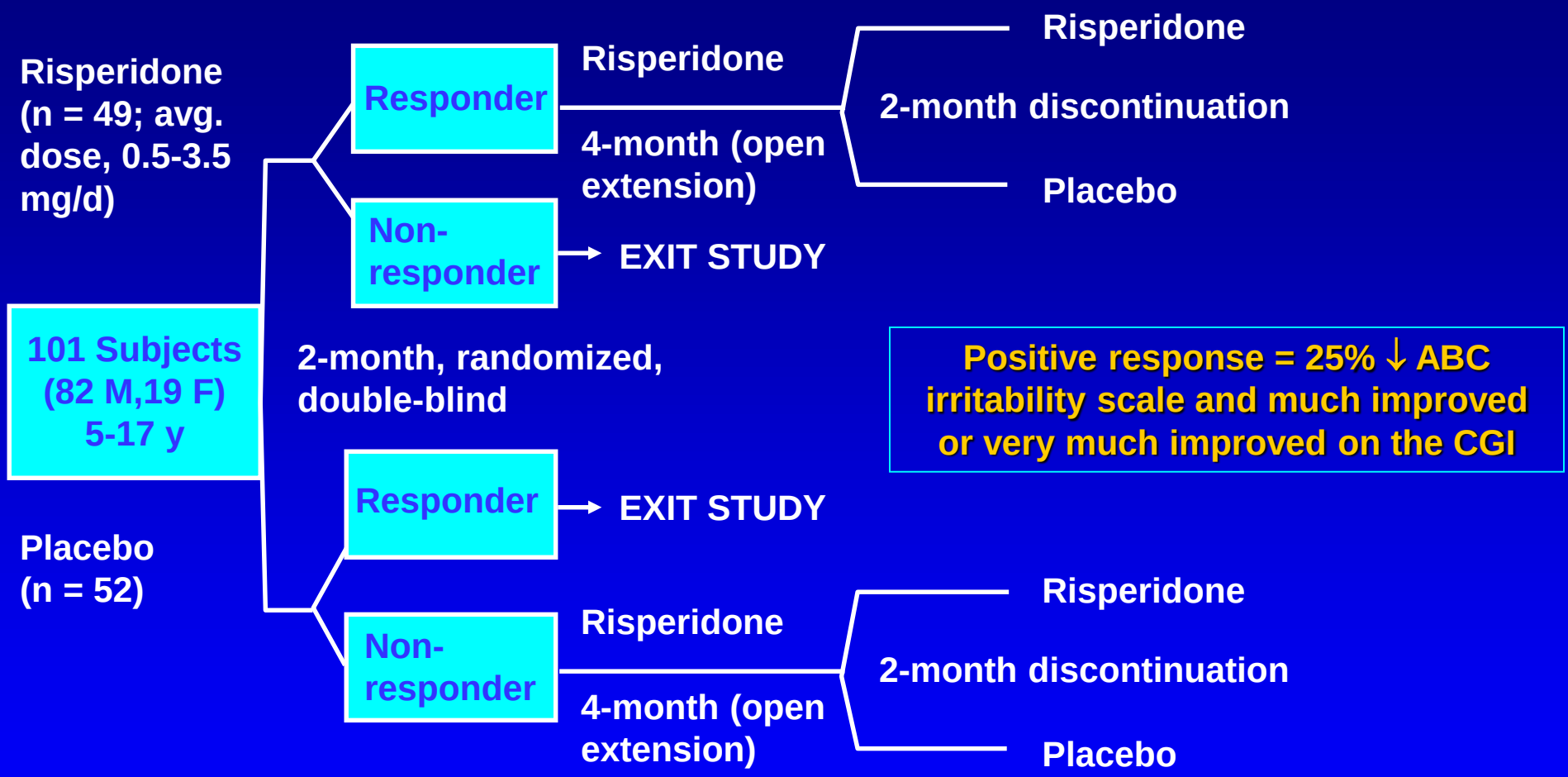
- RISP 0.5-3.5mg range

(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.

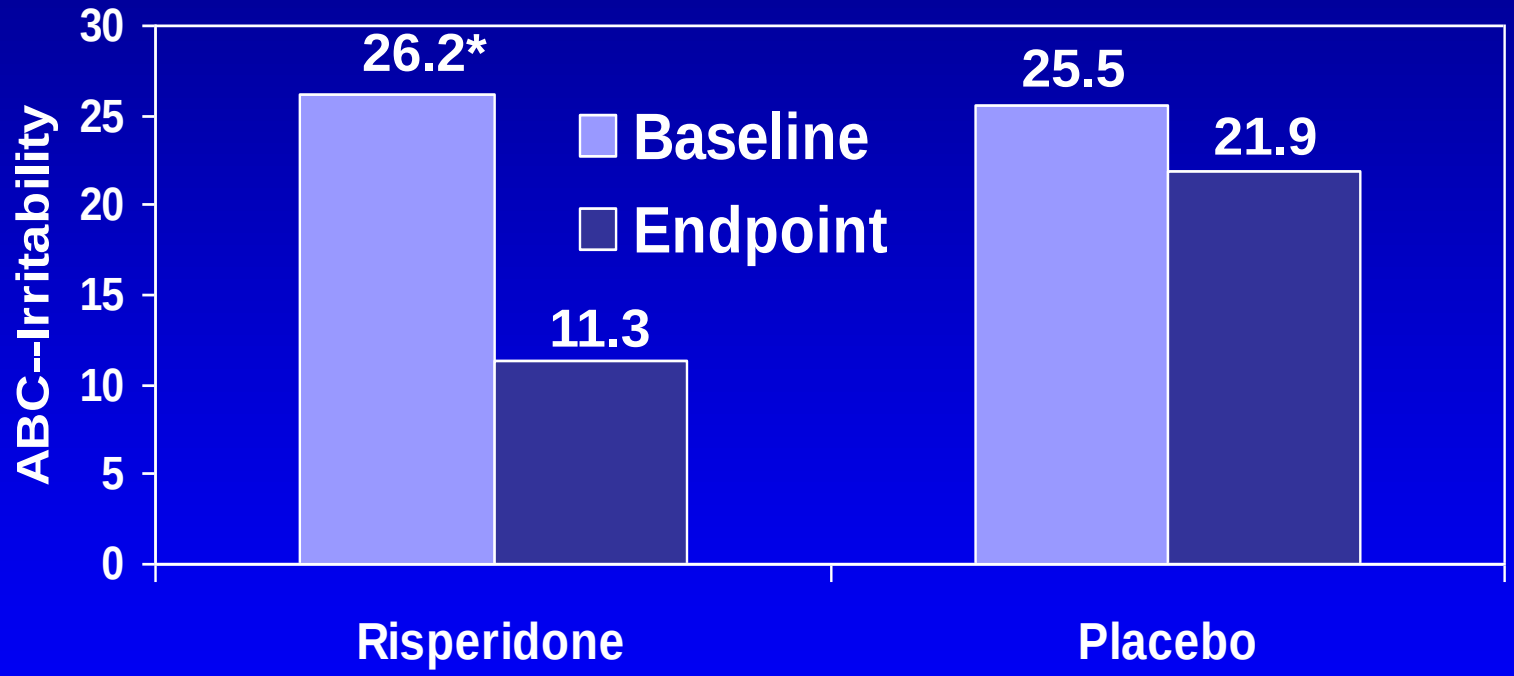
Risperidone in Children with Autism: Primary Outcomes

- 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

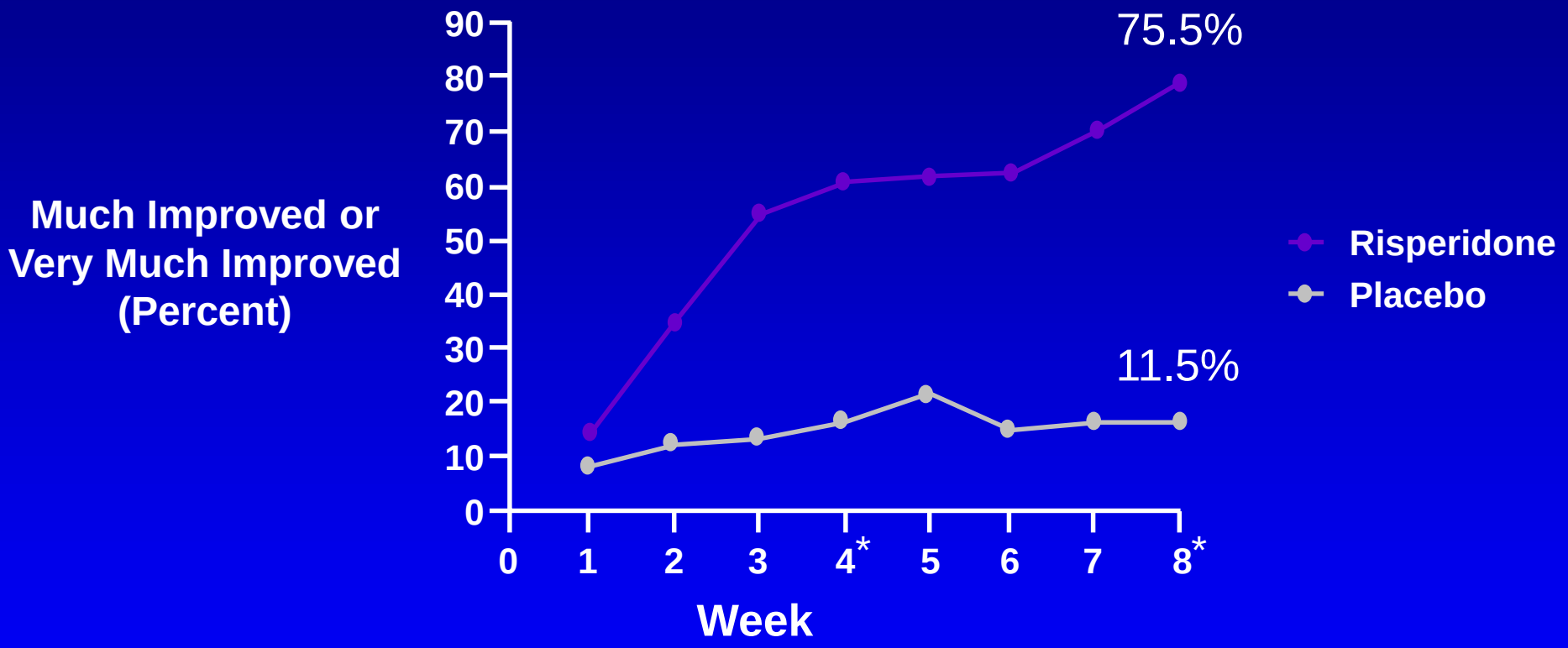
4= No Change

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)
- Quetiapine-case report (n=6, negative report, ? 1 seizure, Martin et al 1999)
- Clozapine-1case report: blood draw and seizure limitations
- Ziprasidone-open study (n=12) 50% responders (McDougle et al 2002)

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

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
- Remember: lobotomy won Moniz the Nobel Prize

Post Lecture Exam Question 1

1. **A child of age 2-1/2 years is not yet speaking single words. He has no imaginative plan, but pulls his mother's hand to show what he wants. He does not shake his head to indicate "yes" or "no". Which one of the following statements is true?**

A. One of the Pervasive Developmental Disorders is unlikely because he has no imaginative play.

B. One of the Pervasive Developmental Disorders is unlikely because he uses his mother's hand as a tool.

C. One of the Pervasive Developmental Disorders is unlikely because he does not shake his head.

D. One of the Pervasive Developmental Disorders is likely because he is not able to do any of the above.

E. One of the Pervasive Developmental Disorders is unlikely because he is too young to make a diagnosis.

Question 2

2. **If a child has a diagnosis of Autistic Disorder, which one of the following statements is true?**

A. He is likely to have normal intelligence.

B. He is unlikely to have any coexistent medical condition.

C. It is very likely that a sibling will have the same condition.

D. If he learns to speak, he is likely to have a better outcome.

E. He has a “refrigerator mother”.

Question 3

3. **The "gold standard" for diagnosis of Pervasive Developmental Disorders is which of the following?**

A. Childhood Autism Rating Scale and Aberrant Behavior Checklist.

B. WISC or WIPPSI

C. Childhood Autism Rating Scale and Leiter

D. Autism Diagnostic Interview and Autism Diagnostic Observation Schedule

E. WIPPSI and Childhood Autism Rating Scale

Question 4

4. **A child of 9 years has a confirmed diagnosis of Autistic Disorder. He is non-verbal. Which one of the following statements is true?**

A. He has a 1 of 3 chance of developing seizures as an adolescent.

B. He has 1 of 10 chance of developing seizures as an adolescent.

C. There is no reason to give him speech and language interventions since he is non-verbal.

D. He should be treated with fenfluramine to improve his IQ.

E. He should be placed in a residential treatment facility.

Question 5

5. **Which one of the following statement is true about pharmacotherapy in childhood Autistic Disorder?**

A. Drug studies show that fluvoxamine is the drug of choice in the treatment of aggression in children with Autistic Disorder.

B. Drug studies show that risperidone can improve aggression and increase IQ in children with Autistic Disorder.

C. Drug studies show that risperidone can improve repetitive behaviors and self-injurious behaviors in children with Autistic Disorder.

D. Drug studies show that fluvoxamine can improve aggression in children with Autistic Disorder.

E. There are no clinical studies that show that risperidone is useful in the treatment of repetitive behaviors in children with Autistic Disorder.

Question 6

6. **A child of 8 years has a diagnosis of Autistic Disorder. He is very aggressive and you are considering the use of risperidone. You are discussing the possibility of using this drug with his parents. Which one of the following statements is true?**

A. He is very unlikely to gain weight.

B. He is unlikely to gain weight since he is not yet a teenager.

C. He is unlikely to gain weight because he has Autistic Disorder.

D. He is likely to gain weight because he has Autistic Disorder.

E. He is likely to gain weight because he is in a high risk group because of his age.

Question 7

7. **A parent of a child with normal intelligence, normal language development, but poor social skills asks if it is possible that their children has Asperger Syndrome. You reply:**

A. Definitely not, since children with Asperger do not have normal intelligence.

B. Definitely not, since children with Asperger do not have normal language development.

C. Definitely not, since children with Asperger do not have poor social skills.

D. Possibly, since children with Asperger have normal intelligence, normal language development, and poor social skills.

E. Possibly, since children with Asperger have normal intelligence and poor social skills but abnormal language development.

Question 8

8. **A parent of a child with Pervasive Developmental Disorder NOS is concerned about the fact that their child is receiving clomipramine (CMI) because of possible side effects. They ask you which side effects they should be concerned about. Which one of the following statements is true?**

A. Children who take CMI have a high incidence of pancreatitis.

B. Children who take CMI are at special risk to develop Stevens-Johnson syndrome.

C. Children who take CMI frequently develop polycystic ovaries.

D. Children who take CMI frequently develop mitral valve prolapse.

E. Children who take CMI are at risk for the development of seizures.

Answers to Pre & Post Competency Exams

1. D
2. D
3. D
4. A
5. C
6. E
7. D
8. E