Psychosis in Youth and Antipsychotic Side Effects

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Pre-Lecture Exam Question 1

1. **Antipsychotics are not used in the pharmacotherapy of which of the following conditions:**

A. Manic Depressive Illness

B. ADHD and aggression

C. ADHD without aggression

D. PDD-NOS with self-injurious behaviors

E. Tourette Syndrome

Question 2

2. Which one of the following statements is true about Childhood Onset Schizophrenia (COS)?

A. More girls than boys have the condition

B. It is a common disorder

C. It has a good prognosis

D. It has a dramatic onset

E. More boys than girls have the condition

Question 3

3. The diagnosis of Multidimensional Impaired Syndrome (Atypical Psychosis) should be considered when one of the following is present:

A. No evidence of ADHD

B. Evidence of high intelligence

C. Presence of an imaginary friend

D. Hallucinatory experiences

E. Docile temperament

Question 4

4. **A child with COS is treated with risperidone. Which one of the following statements is true?**

A. Children are less sensitive to the development of EPS

B. Children are less sensitive to weight gain when compared to adults

C. Children may not have a potential for the development of hyperprolactinemia

D. Because of their age, children have a low potential to develop hyperprolactinemia

E. Children are more vulnerable to develop EPS at lower doses

Question 5

5. Which one of the following statements about haloperidol and children is true?

A. Teenaged girls are more likely than boys to develop acute dystonia

B. Teenaged boys are more likely to develop akathisia than adults

C. There are no case reports of the development of NMS in childhood

D. Teenaged boys are not likely to gain weight

E. Mortality in NMS in childhood is higher than in adults

Question 6

6. A teenager with treatment resistant schizophrenia has been tried on two atypical antipsychotics. Clozapine usage is being considered. Which one of the following statements is true?

A. The clinician should carefully watch for the development of seizures

B. The clinician should carefully watch for the development of substantial weight loss

C. The clinician should carefully watch for development of tics

D. The clinician should carefully watch for the development of increased WBC's

E. The clinician should watch for the development of polycystic ovaries

Question 7

7. **Which of the following statements is true?**

A. The differential diagnosis of COS should not include organic psychosis

B. The differential diagnosis of COS should not include PTSD

C. The differential diagnosis of COS should not include delerium

D. The differential diagnosis of COS should not include PDD-NOS

E. The differential diagnosis of COS should not include ADHD

Antipsychotic Agents

- Used in as many as 50% of child inpatients
- Psychosis (COS) an actually *rare* indication for their use
- Other common target diagnoses
  - Disruptive, Mood, Personality Disorders
  - PDD, MR, TS, OCD
- Other common target symptoms
  - Irritability, self-injury, repetitive behaviors
  - Aggression, mania

Childhood Psychosis I

- Childhood Onset Schizophrenia (COS)
  - Onset before age 12 (VEOS)
  - Rare disorder (~ 1/5000, *vs* 1/100 adult onset)
  - M:F ratio 2-3:1
  - Insidious onset
  - Poor prognosis
  - Criteria same as for adult disorder
    - Positive and negative sxs,
    - Decline in function, 6+ months of sxs

Childhood Psychosis II

- Developmental Continuity: NIMH Studies
  - Clinical presentation / phenomenology
  - Premorbid function
  - Neuropsychology
  - Smooth pursuit eye tracking
  - Structural MRI
  - MRS
  - Genetic studies, including VCFS (22q11)
    - More common in VEOS?
    - VEOS ~6%; Schiz ~2%; Control ~0.2%

Childhood Psychosis III

- Differential Diagnosis COS/VEOS
  - Affective Disorders (MDD, MDI)
  - Schizophreniform dz and acute psychotic sxs
  - Trauma/dissociation/PTSD/reactive attach.
  - OCD
  - PDD Spectrum
  - Multiplex (Multidimensionally Impaired Syn.)
  - Organic psychoses/delirium

Multidimensional Impaired Syndrome (Atypical Psychosis)

- Must be seriously disturbed by 7 years
- Hallucinatory experiences that do not meet DSM3-R criteria for schizophrenia (e.g., brief hallucinations lasting a few minutes or distorted perceptions)
- Affective instability e.g. tantrums, mood swings .
- Poor social skills in spite of wishing to relate to peers
- Excessive age-inappropriate fantasy, magical thinking, (e.g., 11-year who checked under sewer plates for Ninja Turtles)
- Moderate to severe neuropsychologic deficits
- Originally normal intelligence now thought to be borderline range
- ADHD 84%
- Is it forme fruste of schizophrenia?

(McKennen 1994,1997, 1998)

Typical Antipsychotics I
Pediatric Considerations

- Low potency: chlorpromazine, thioridazine
  - Anticholinergic < EPS
  - Sedation, hypotension
- Mid Potency: Trilafon, Navane
- High potency: Haldol, Orap, Prolixin
  - EPS: acute dystonia inc. teen boys, NIPs ?30% akathisia: less common (Sachdev 1995)
  - NMS: mortality up to 9% in children (Silva 1999)

Typical Antipsychotics I
Pediatric Considerations

- Dyskinesias
  - Withdrawal (WD): More common in children (34%, transient, Campbell 1989)
  - Tardive (TD): females, perinatal insults, MDI
- Pretreatment screen: AIMs, liver,kidney, CBC and EKG Monitoromg with pimozide (e.g., in TS); higher-dose perphenazine; concurrent TCA or alpha-2 use (Gutgusell 1999)
- Concurrent anticholinergic use
  - Rarely needed if dose increase gradual
  - Added risk of cavities in chronic use (⇓saliva)

Atypical Antipsychotics I
Pediatric Considerations

- Clozapine (Clozaril)
  - Double Blind: COS (better than HAL)
- Risperidone (Risperdal)
  - DB: Autism & CD study- ongoing
  - Open: PDD, TS, OCD augmentation,MDI, COS
- Olanzapine (Zyprexa)
  - Open: PDD, COS, MDI
- Quetiapine (Seroquel)
  - Open: PDD (-), COS
- Ziprasidone (Zeldox)
  - Very preliminary experience: PDD, TS

Atypical Antipsychotics II
Pediatric Considerations

Promises and Limitations

- ⇓ EPS / TD?
- ⇓ Prolactin Elevation?
- ⇑ Targeting of Negative Symptoms?
- 5HT2 / D2
- Mesolimbic > Nigrostriatal
- ? Efficacy in OCD / TS / PDD
- ⇑ Weight gain liability

Clozapine I
Pediatric Considerations

- Controlled haloperidol comparison study
- Kumra, Rapport et al (NIMH)
  - COS, 6 - 18 yrs of age; symptom onset < 12
  - Non-response to 2+ previous agents
  - Taper (2wk), medication-free (4wk), then:
  - Clozapine / haloperidol 6 weeks
  - Followed by crossover

Clozapine II
Pediatric Considerations

- Starting doses
  - 12.5 clozapine + placebo
  - 0.5 haloperidol + benztropine
- Mean doses at six weeks: mean (SD)
  - Clozapine 176.3 (149.1)
  - Haloperidol 15.9 (7.9)
  - Benztropine 2.2 (0.8)
- C > H Improvement: BPRS*, SANS***, SAPS**

Clozapine III
Pediatric Considerations

- Common and limiting side effects
  - Sedation
  - Appetite / weight gain
  - Hypersalivation / sialorrhea
  - Seizure liability
    - Abnormal EEG and seizures
    - Need for concurrent valproate
  - Neutropenia liability
    - Weekly (6mos), or bimonthly (6+) WBC monitoring

Risperidone
Pediatric Considerations

- "Atypical" only at low doses (< 3mg / d)
- Monitor weight, lipids / GL, LFTs, EKG, AIMS
- Weight gain common (~20 lbs/6 months)
  - Direct somatic effect? Increased appetite?
  - Treatment-naïve and prepubertal at higher risk?
  - Monitor weight, height, growth chart
- Children may be more sensitive to EPS
- Potential for hyperprolactinemia - inquire
- Subgroup vulnerable to QTc prolongation?

DROPERIDOL IN CHILDREN

Butyrophenone (Inapsinea)

- Onset 3-12 mins after IM
- Duration 2-4 hrs
- Dosing 1 cc=2.5mg

  <75 lbs--->1/4 cc

  75-125 lbs--->1/2 cc

  125-150 lbs---> 3/4 cc

  >150---> 1 cc
- EPS, use benztropine
- IM injections may be painful, gluteal region best ? Use in kids with abuse
- Must know legal issues of involuntary sedation

(Joshi 1998)

Side Effects With Atypical Agents

Relatively Common	Relatively Uncommon	Rare
Sedation Weight gain	Confusion Impotence Enuresis Dizziness EPS	Gynecomastia Galactorrhea Amenorrhea Diabetes TD NMS

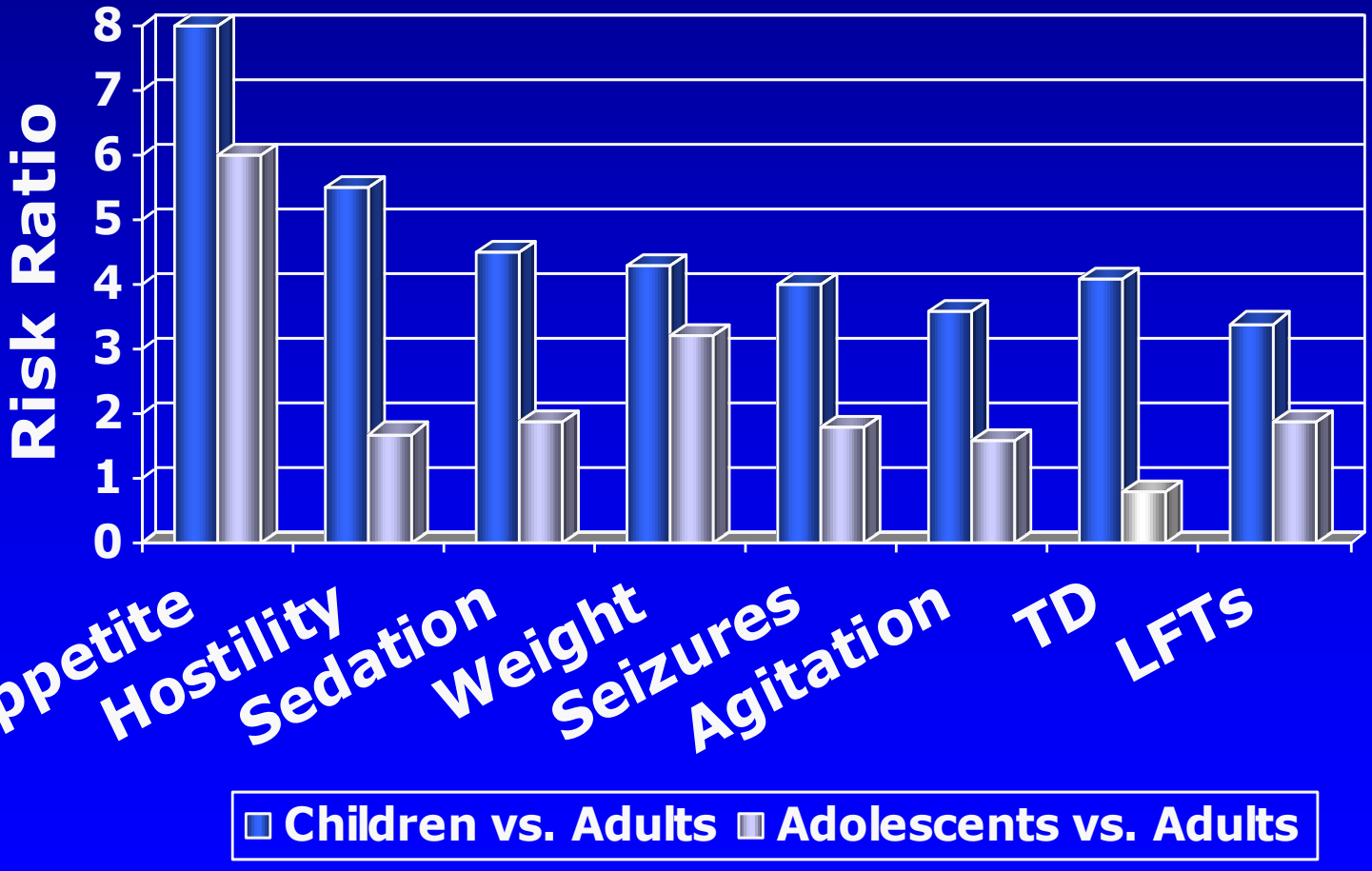
EPS = extrapyramidal symptoms; TD = tardive dyskinesia
NMS = neuroleptic malignant syndrome

Does Development Have an Impact on Atypical Antipsychotic Related Adverse Events?

- Pharmacovigilance data for 20 AE categories on olanzapine suggest so:
- *Numerator:*
  - FDA Post-Marketing surveillance
  - AERS (Adverse Event Reporting System)
  - Through 3/31/2000
- *Denominator:*
  - Lilly's worldwide exposure estimates
  - categorized by age group

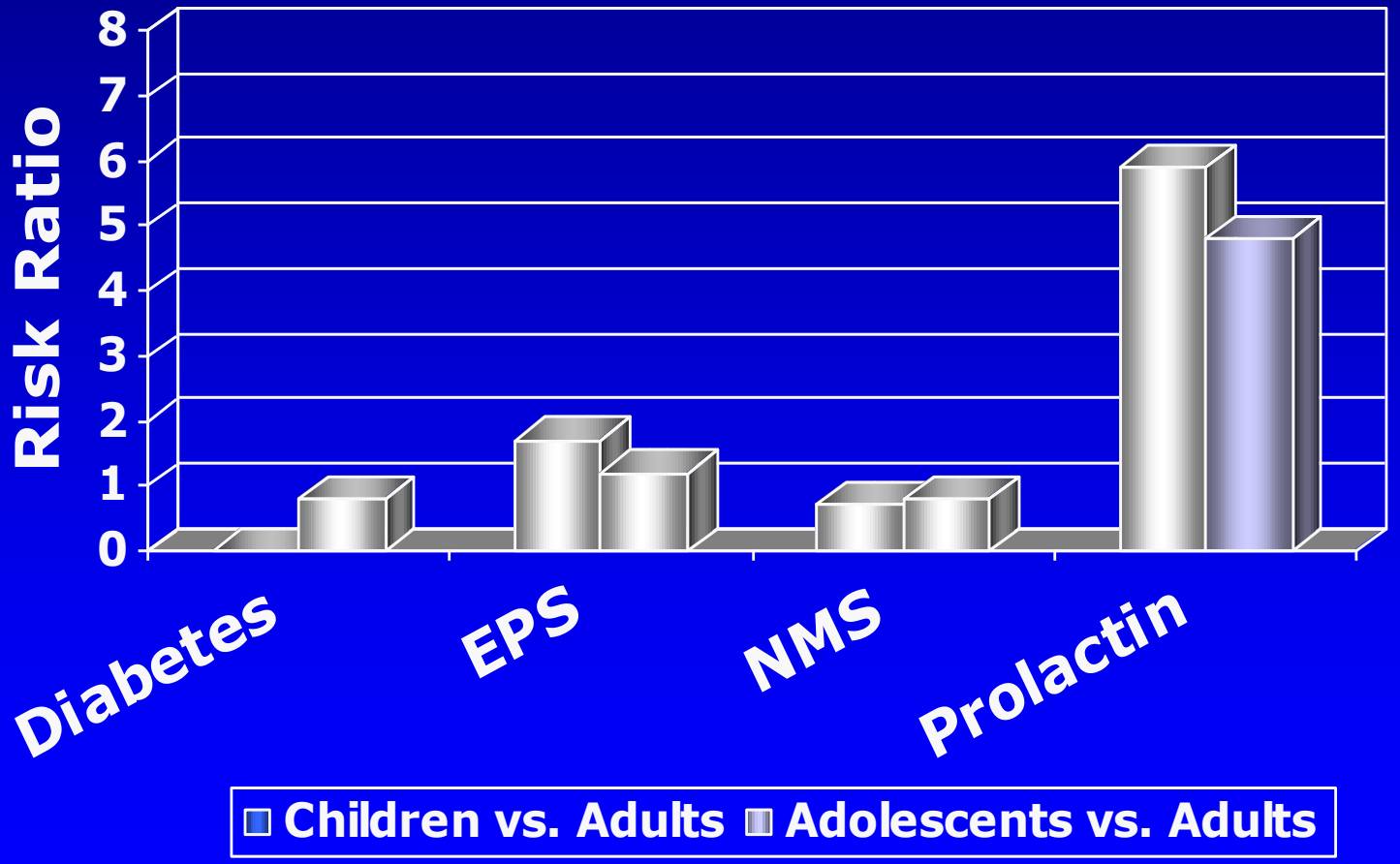
Woods S, et al. *JAACAP.* 2002;41:1439-1446.

Developmental Impact on Adverse Events



Woods S, et al. *JAACAP.* 2002;41:1439-1446.

Developmental Impact on Adverse Events

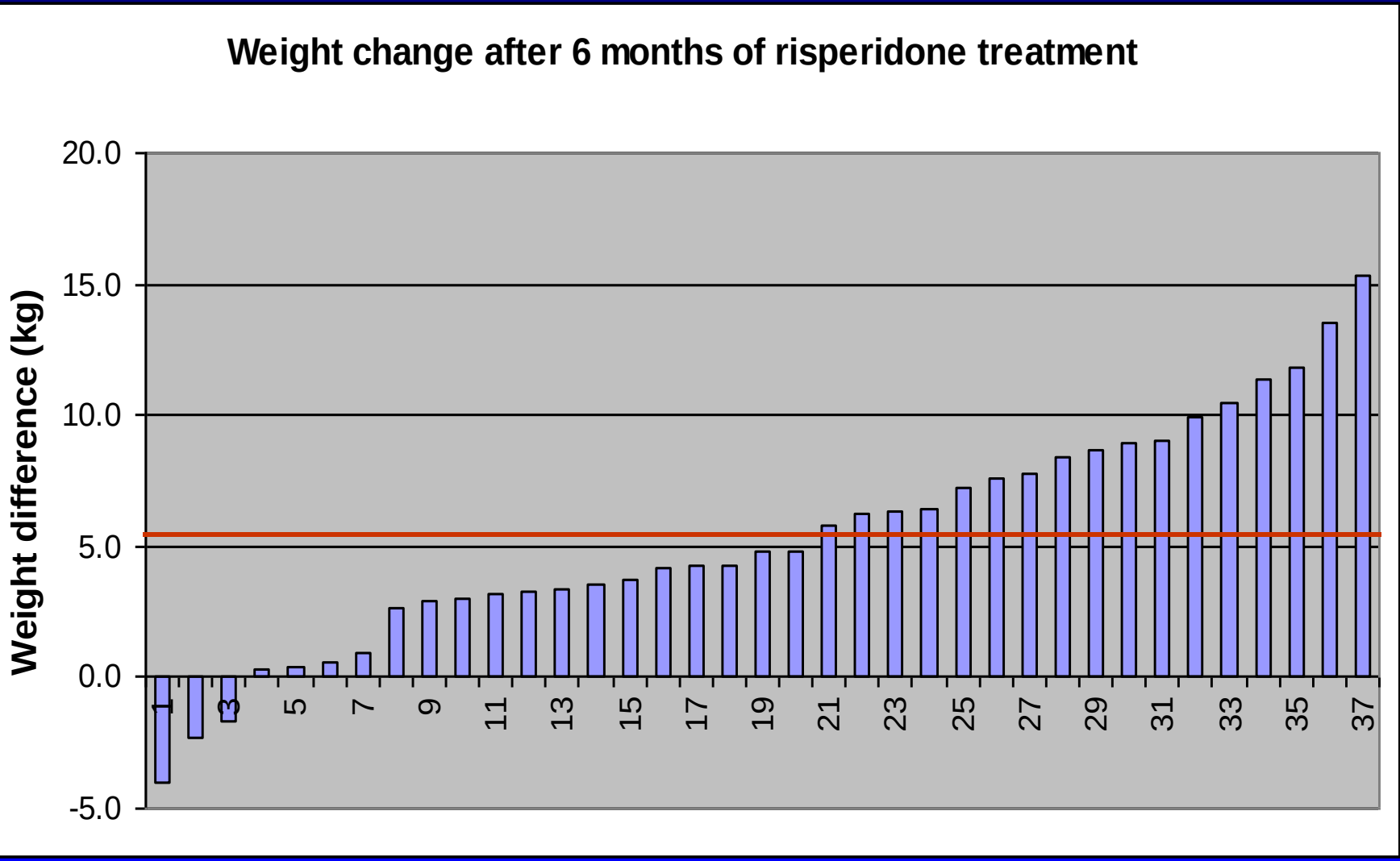


Woods S, et al. *JAACAP.* 2002;41:1439-1446.

Weight gain: long-term consequences

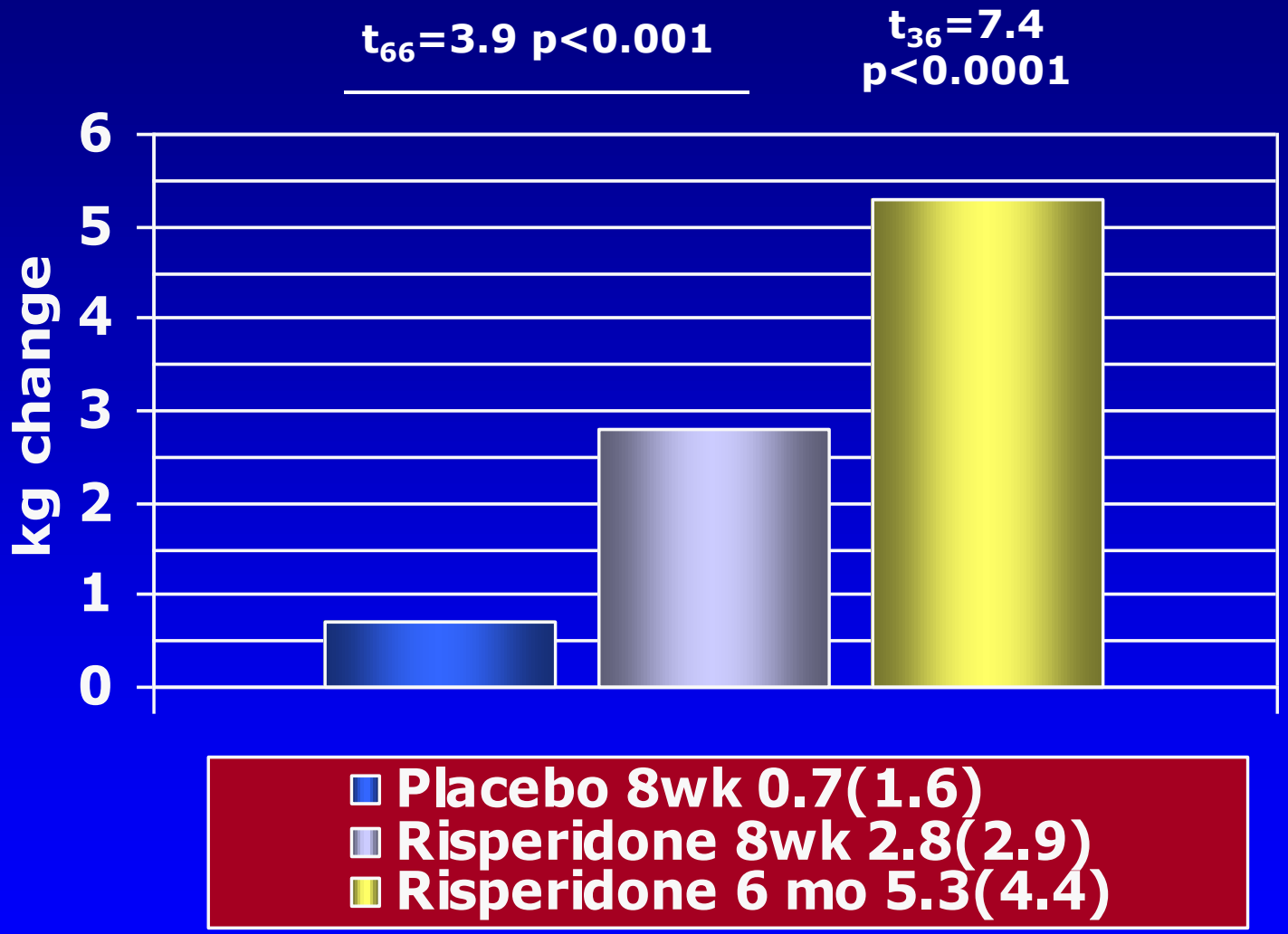
- Risk of adult obesity and attendant consequences *(Dietz 1998)*, e.g.:
  - Cardiovascular illness
  - Hypertension
  - Osteoarthritis
- Psychological effects
  - Including further isolation
- Cholesterol and triglyceride increases *(Martin & L'Ecuyer, 2002)*
- Association with NIDDM

  (Sernyak et al, 2002)


Weight change after 6 months of risperidone treatment
Weight difference (kg)
20.0
15.0
10.0
5.0
0.0
-5.0
1
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
37

(SD) = (4.4) kg

Weight Gain: RUPP Autism Study



Mean Baseline Weight: 33.0(17.0)

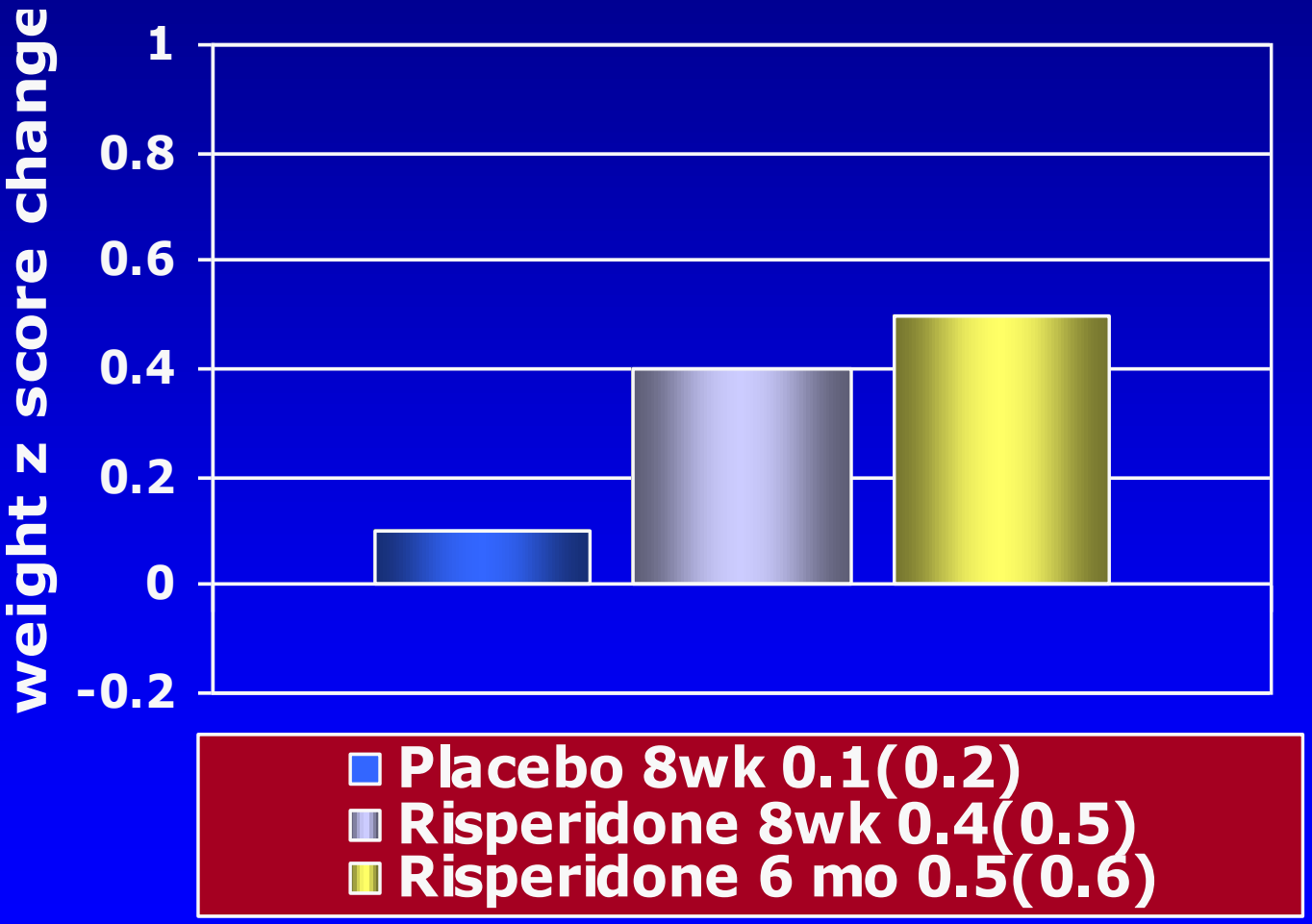
RUPP Autism Network: NEJM 2002 347:5, 314-321

Is a Kilogram Always a Kilogram?

Standardized Weight Gain – and Its Interpretation

$t_{62}=4.8$ $p<0.001$

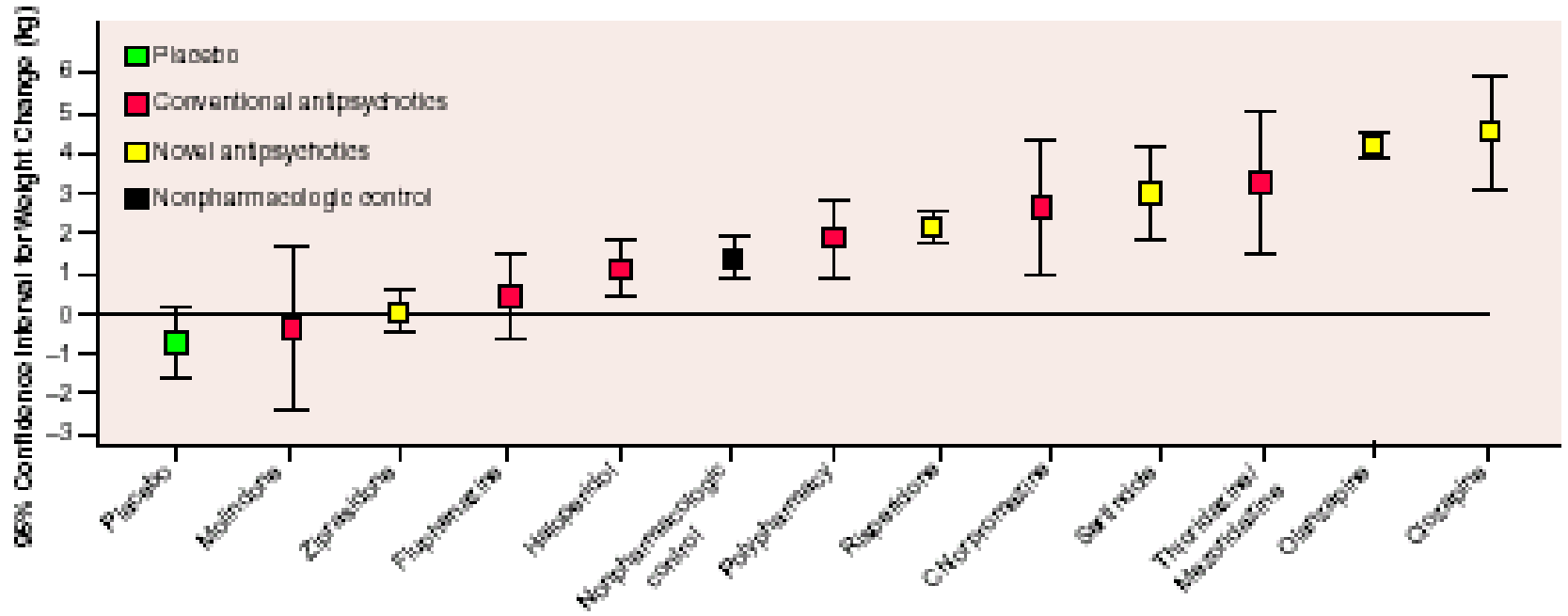
$t_{36}=5.3$
$p<0.0001$



RUPP Autism Network: NEJM 2002 347:5, 314-321

Antipsychotics and Weight Gain
Different Liabilities?

FIGURE 1. 95% Confidence Intervals for Weight Change After 10 Weeks on Standard Drug Doses, Estimated From a Random Effects Model



Adult meta-analysis results

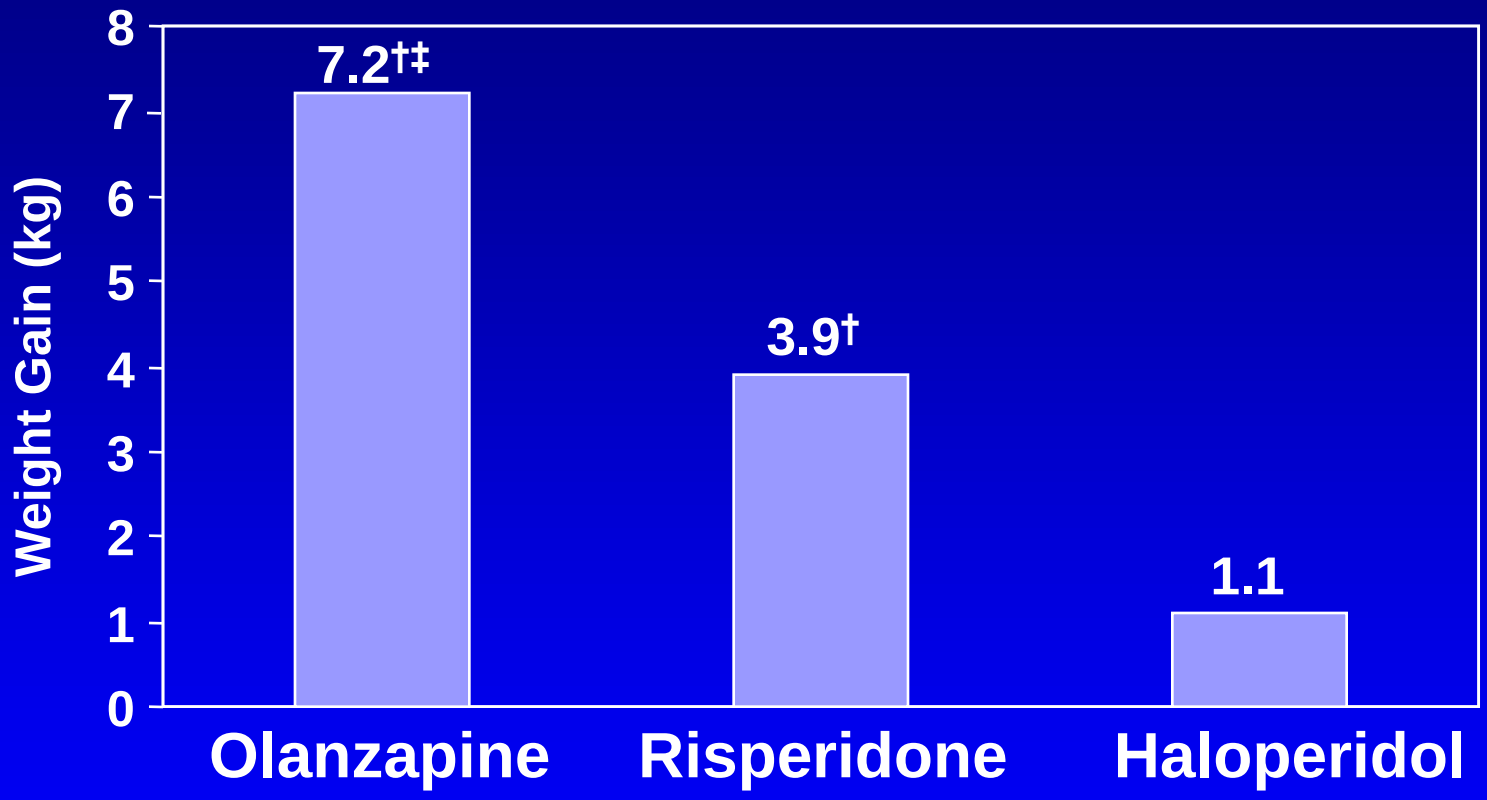
(Allison et al, AJP 1999)

Weight Gain in Adolescents Receiving Antipsychotic Therapy

- Comparative, prospective study
- 50 adolescent patients
  - 21 receiving olanzapine
  - 21 receiving risperidone
  - 8 receiving haloperidol
- Body weight and body mass index monitored for 12 weeks of hospitalization

Ratzoni G, et al. *J Am Acad Child Adolesc Psychiatry.* 2002;41:337–343.

Weight Gain* in Adolescents Receiving Antipsychotic Therapy



*Average weight gain over first 12 weeks of treatment

†*P*<0.01 between atypicals (olanzapine and risperidone) and haloperidol

‡*P*<0.001 between olanzapine and risperidone

Ratzoni G, et al. *J Am Acad Child Adolesc Psychiatry.* 2002;41:337–343.

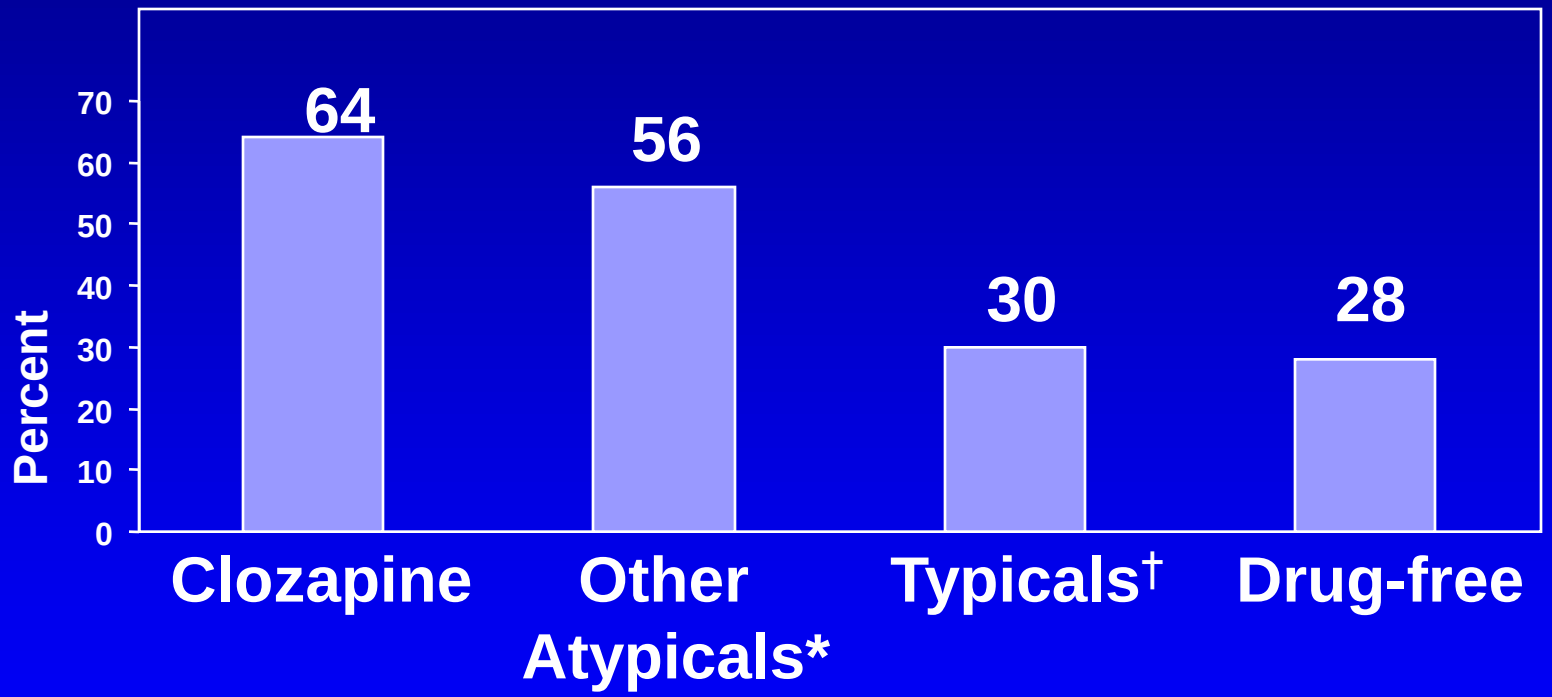
Prevalence of Obesity in Young Patients on Antipsychotic Therapy

- Cross-sectional naturalistic study
- 151 inpatients, mean age: 19.5 yr
- In whole study population, obesity (BMI ≥90th percentile) occurred in
  - Half of all patients
  - 45% of male patients
  - 59% of female patients

BMI = Body mass index

Theisen FM, et al. *J Psychiatr Res.* 2001;35:339–345.

Obesity Associated With Antipsychotic Therapy



*Includes olanzapine, risperidone, sulpiride
†Typical antipsychotics include haloperidol, flupentixol, perazine

Theisen FM, et al. *J Psychiatr Res.* 2001;35:339–345.

Extrapyramidal Symptoms in Patients Using Antipsychotic Agents

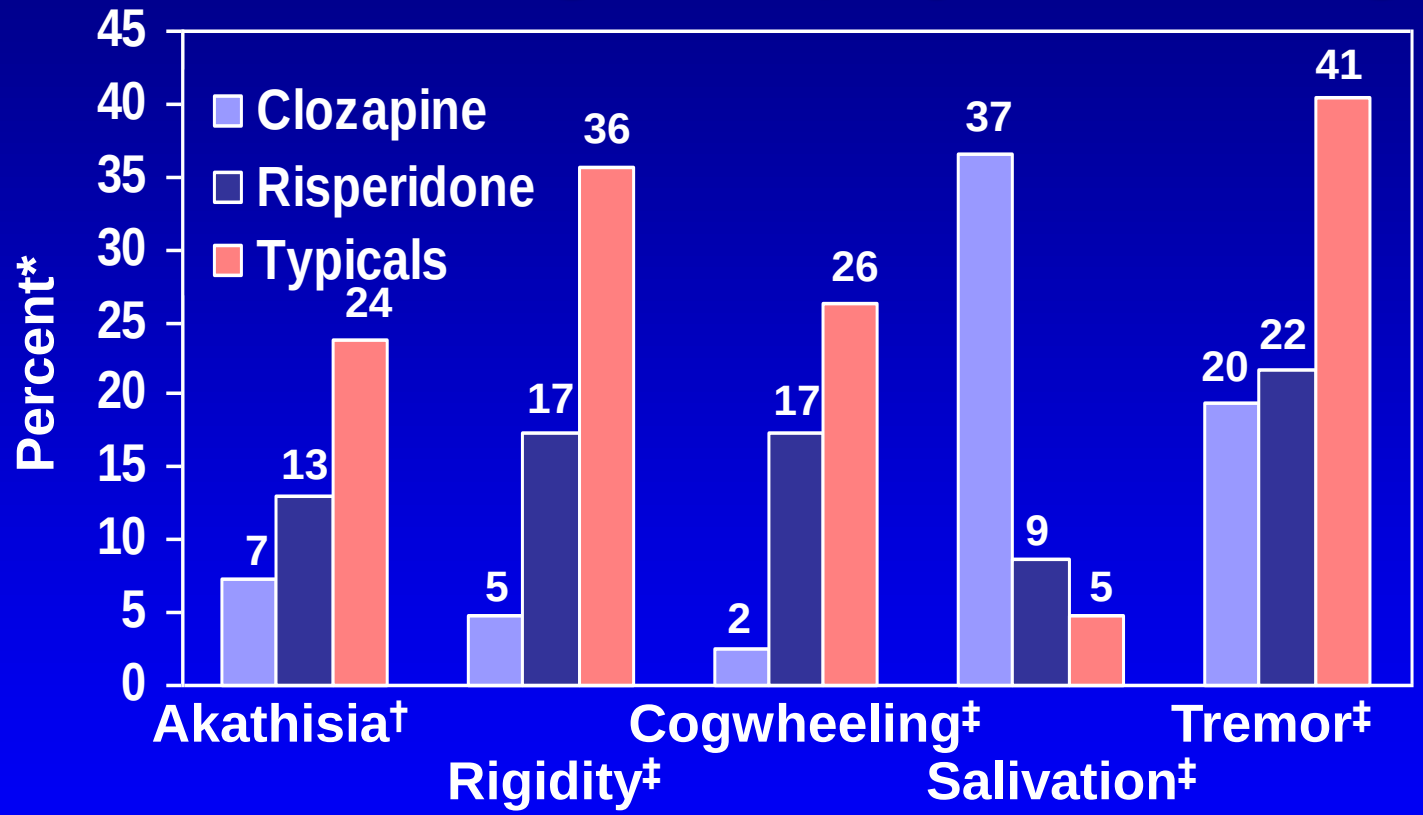
- 106 patients from ongoing study of TD
  - 41 using clozapine
  - 23 using risperidone
  - 42 using typical antipsychotics
- Mean dose*
  - Clozapine: 425.6 mg/day
  - Risperidone: 4.7 mg/day
  - Typical antipsychotics: 476.5 mg/day

TD = tardive dyskinesia

*Calculated in chlorpromazine equivalents.

Miller CH, et al. *J Clin Psychiatry.* 1998;59:69–75.

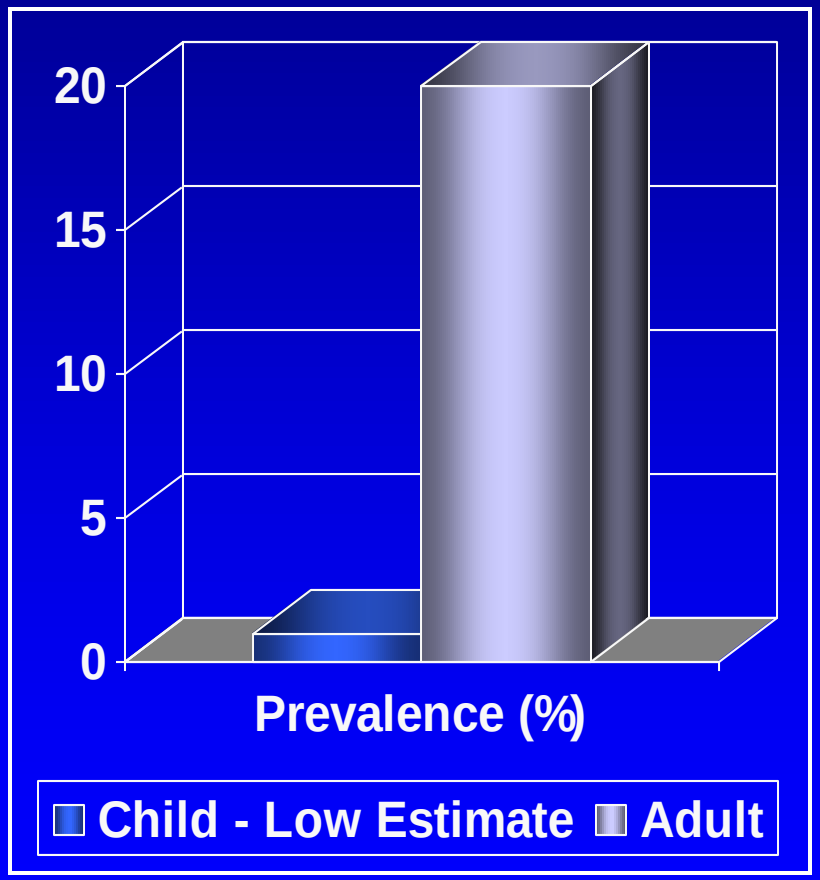
Extrapyramidal Symptoms in Patients Using Antipsychotic Agents

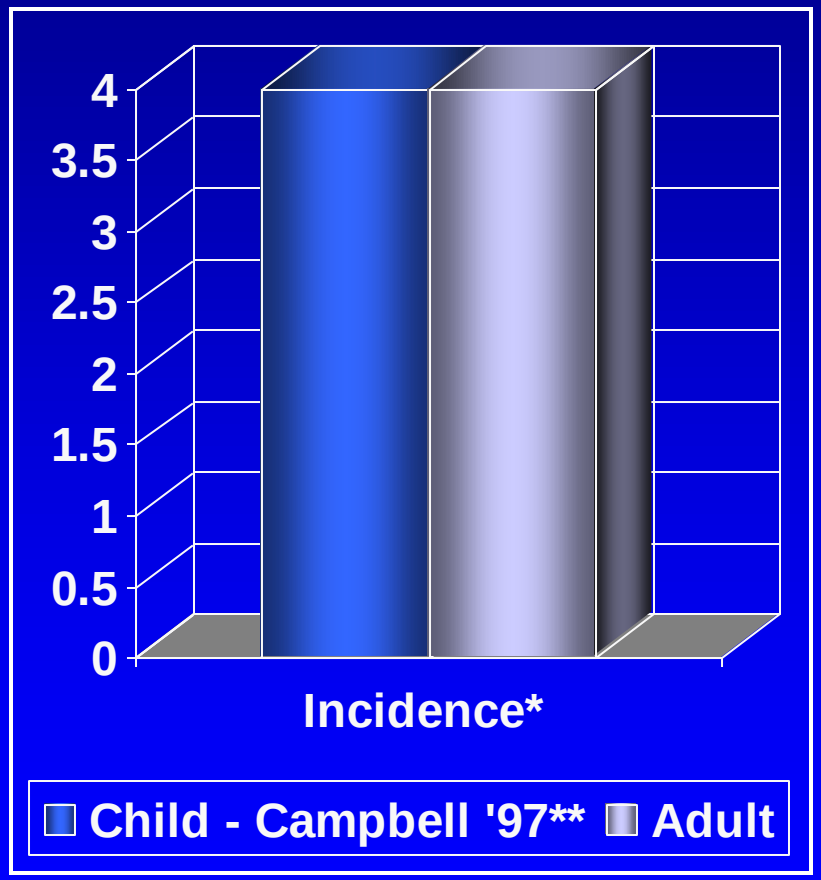


*Point-prevalence; †Barnes Akathisia Scale >1; ‡Simpson-Angus Scale >0

Miller CH, et al. *J Clin Psychiatry.* 1998;59:69–75.

Tardive Dyskinesia:
What do we know from traditional agents?





* Per 100 patients / year

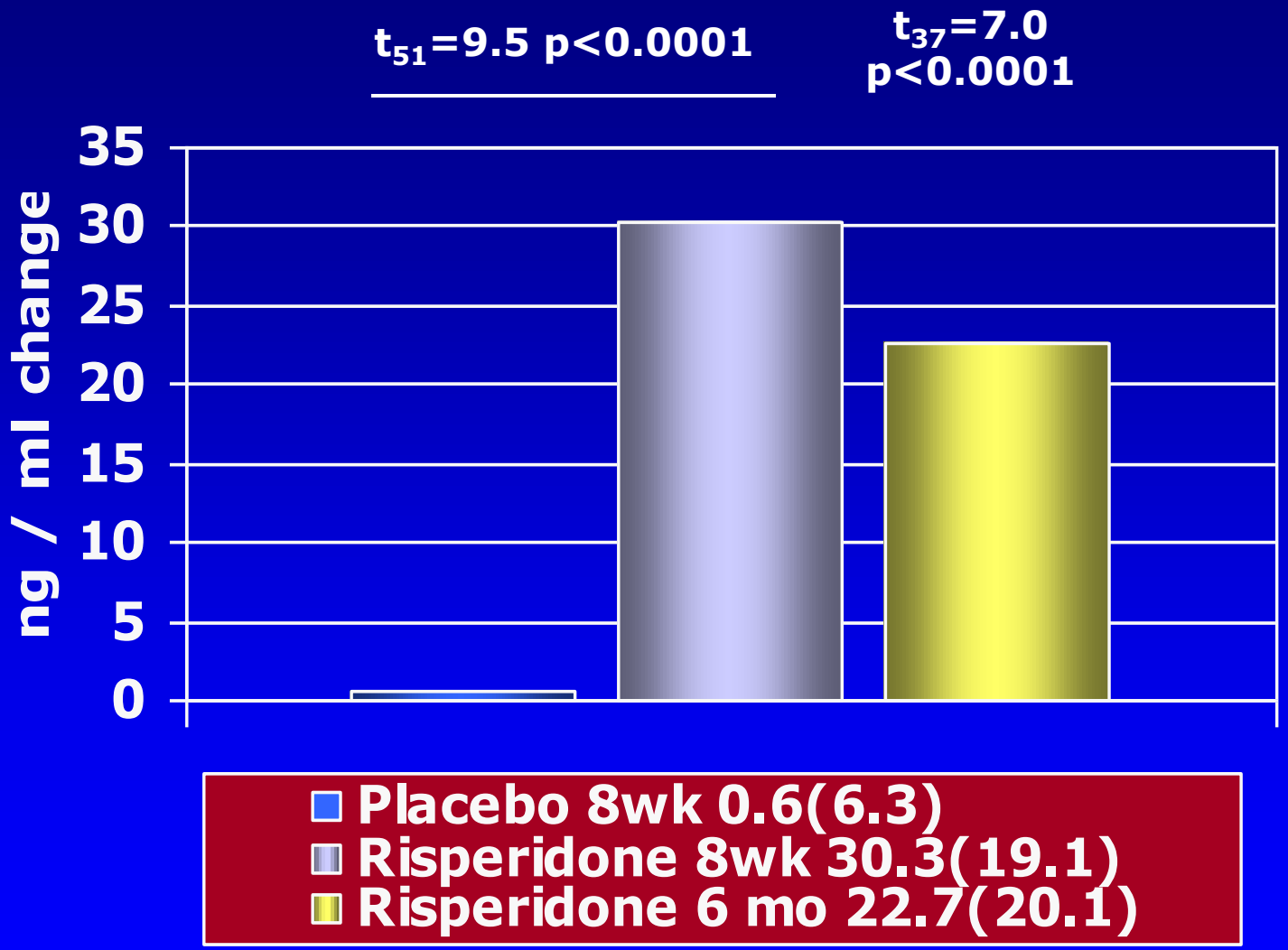
** *Note:* Includes TD and WD

Prolactin Elevation in Children/Adolescents

- 6-week open or double-blind studies in 35 patients (aged 9–19 yr) with schizophrenia or psychotic disorder (not otherwise specified)
- Regimens
  - 10 on haloperidol
  - 15 on clozapine
  - 10 on olanzapine
- Results at 6 weeks
  - All three elevated mean prolactin concentration
  - Prolactin above upper normal limit for all on haloperidol, 70% on olanzapine, and none on clozapine

Wudarsky M, et al. *J Child Adolesc Psychopharmacol.* 1999;9:239–245.

Prolactin Changes: RUPP Data



Mean Baseline Prolactin: 9.5(7.5)

Note: **Dampening after 8 weeks**

Reports of Hyperglycemia Associated With Atypical Agents

- Olanzapine
  - FDA received 9 reports of hyperglycemia in adolescents (13–18 yr) between 1996–2001
  - 7 new diagnoses; 2 had exacerbation of existing diabetes
- Clozapine
  - FDA received 11 reports of hyperglycemia in adolescents (13–18 yr) between 1993–2001
  - 8 new diagnoses; 2 had exacerbation of existing diabetes; status of 1 unknown

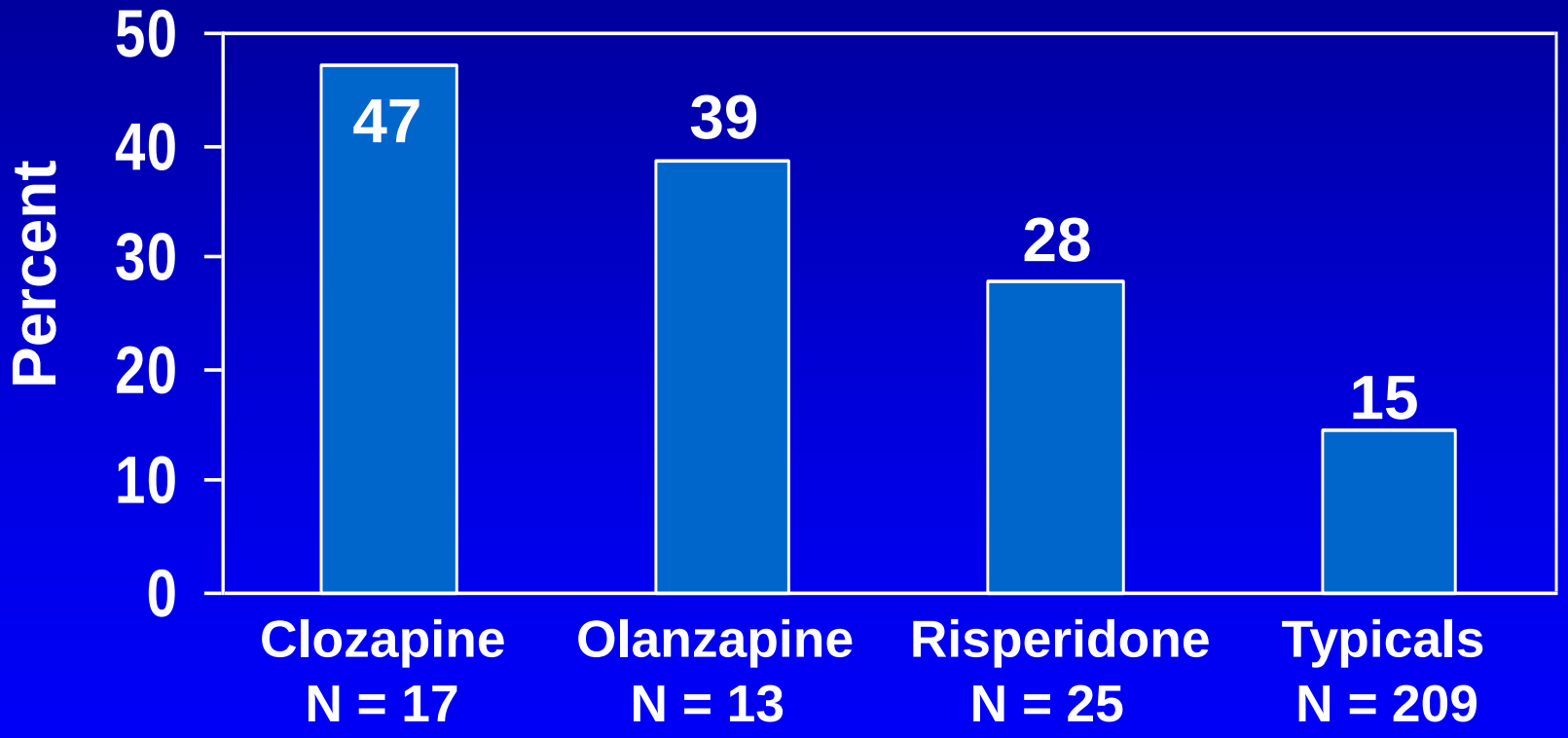
Koller E, et al. *JAMA.* 2001;286:2547–2548.

EEG Abnormalities With Atypical Antipsychotic Use

- Clozapine produces
  - EEG abnormalities
  - Dose-dependent risk of epileptic seizures
- EEG readings from 323 hospitalized psychiatric patients
- Abnormalities
  - 19.1% (56) patients treated with antipsychotics
  - 13.3% (4) patients not treated with antipsychotics

Centorrino F, et al. *Am J Psychiatry.* 2002;159:109–115.

EEG Abnormalities With Atypical Antipsychotic* Use



*No EEG abnormalities were found in the 5 patients receiving quetiapine

Centorrino F, et al. *Am J Psychiatry.* 2002;159:109–115.

Atypical Antipsychotics—Short- and Long-Term Safety: Levels of Evidence

Atypical Antipsychotic	Short-Term Safety	Long-Term Safety
Risperidone	A	B/C
Olanzapine	B	C
Quetiapine	B	C
Ziprasidone	B	C
Clozapine	B	C

A = ≥2 randomized, controlled studies; B = 1 randomized, controlled study; C = clinical experience, eg, open studies, case reports, etc

Adapted from Jobson KO, Potter WZ. *Psychopharmacol Bull.* 1995;31:457–459.

Atypicals and Clinical Monitoring:
What Makes Sense?

- Weight, Height
- Plot Growth Charts
- AIMS
- Baseline ECG
  - TCA-like monitoring?
  - Closer with ZIP, combinations?
- LFTs
- FBG, HBA1C, Lipid Profile
- Prolactin
- EEG

Routine / advisable

Discretionary / clinically based

Electrocardiograph Guidelines with Tricyclic Antidepressants

- UNacceptable indices:
  - QTc > 450-470 ms
  - QRS interval >30% increased over baseline or >120 ms
  - PR interval >200 ms
  - Heart rate >130 bpm at rest
  - WPW and heart blocks are not uncommon
  - When in doubt: consult cardiology / consider Holter
- Be wary of QTc computer printouts.

Adapted from Wilens 1996 and AHA / Gutgessel et al 1999

Post Lecture Exam Question 1

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D. The differential diagnosis of COS should not include PDD-NOS

E. The differential diagnosis of COS should not include ADHD

Answers to Pre & Post Competency Exams

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