

**Weight Gain and the Metabolic Syndrome in Youth Treated with Atypical Antipsychotic Medications**

**Michael W. Naylor, M.D.**  
Director, Clinical Services in  
Psychopharmacology

**Disclosures**

None

**Objectives**

- **The participant will:**
  - be aware of the risks of a child or adolescent developing obesity and metabolic complications with second generation antipsychotics (SGAs).
  - know how to monitor for the development of metabolic abnormalities associated with the use of SGAs.
  - learn effective strategies for managing weight gain due to the use of SGAs.

**Outline**

- **Background**
- **Weight gain**
  - magnitude
  - comparison between atypical antipsychotics

**Outline**

- **Metabolic syndrome**
  - definition
  - pathophysiology
- **Treatment**
  - pharmacological
  - nutritional

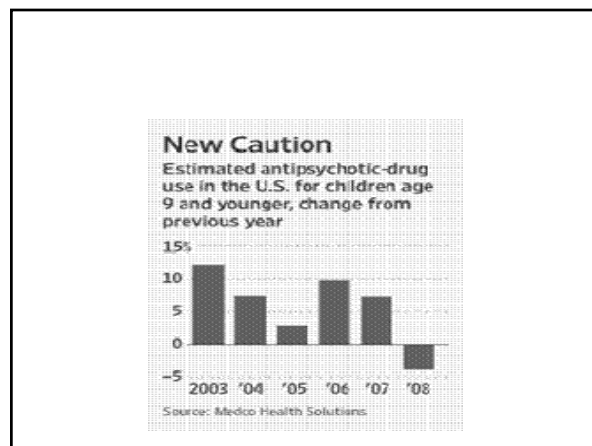
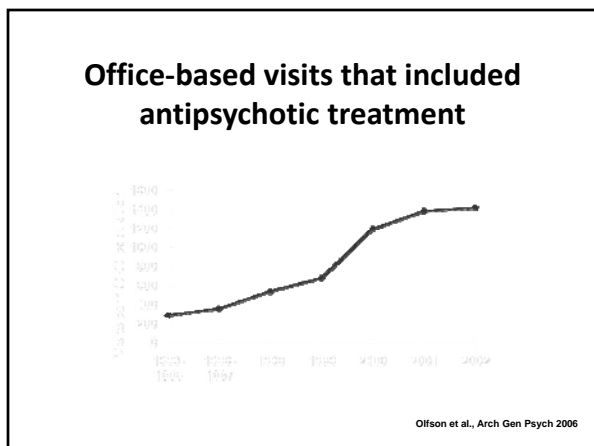
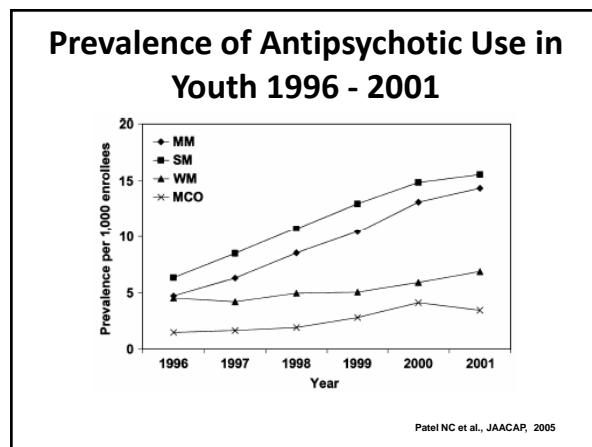
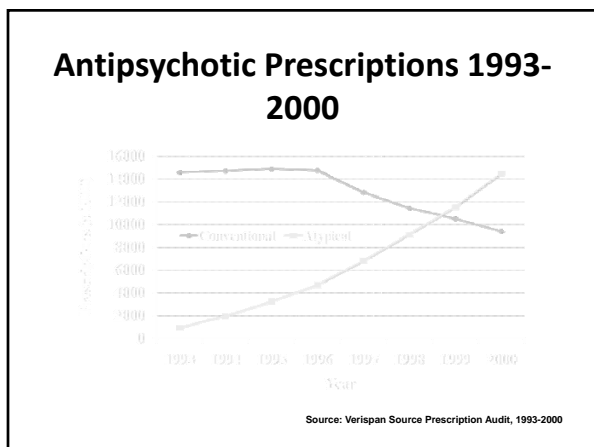
**The New York Times**

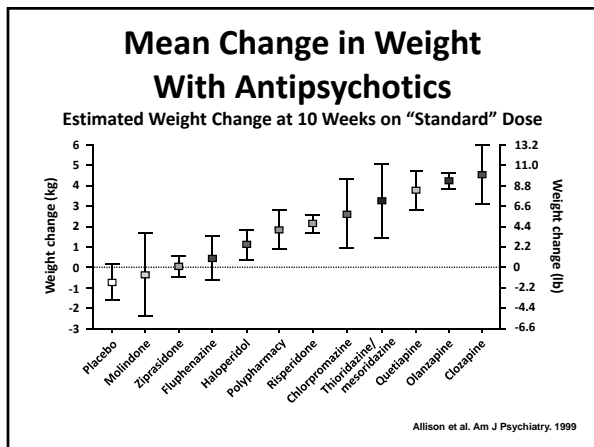
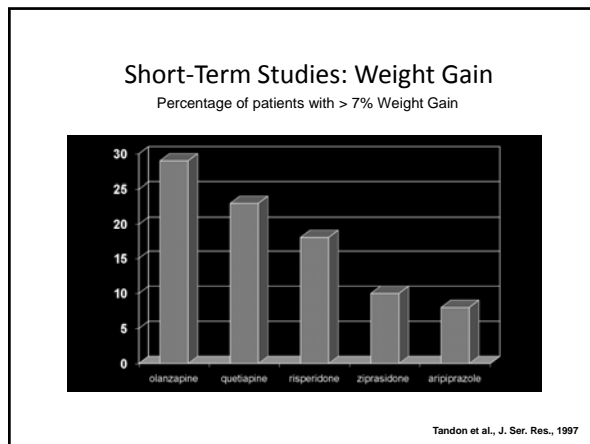
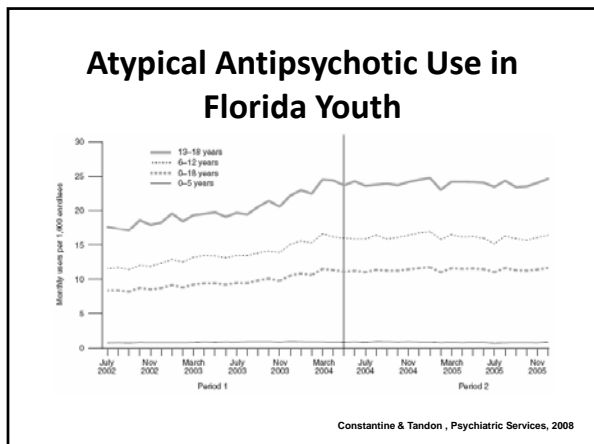
June 6, 2006

**Use of Antipsychotics by Youth Rose**

**Fivefold**

By BENEDICT CAREY

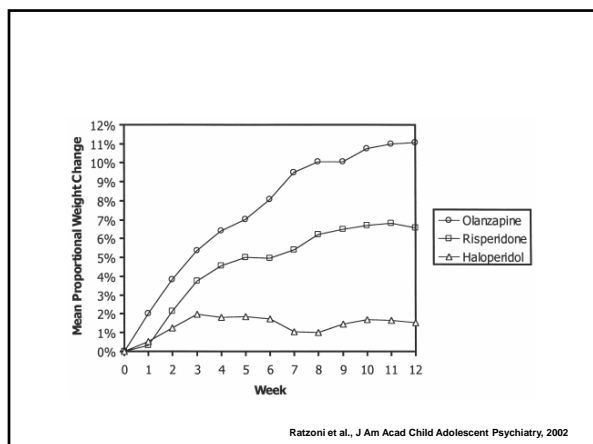




- ### SGAs and Weight Gain
- 50 hospitalized adolescents
    - 12 weeks of antipsychotic treatment
      - olanzapine (n = 21)
      - risperidone (n = 21)
      - haloperidol (n = 8)
    - Wt, BMI monitored weekly
- Ratzoni et al., J Am Acad Child Adolescent Psychiatry, 2002

- ### SGAs and Weight Gain
- Results
    - olanzapine, risperidone groups had significant weight gain ( $p < .01$ )
    - no significant weight change in haloperidol group
    - average weight gain olanzapine ( $7.2 \pm 6.3$  kg) > risperidone ( $3.9 \pm 4.8$  kg,  $6.6\% \pm 8.6\%$ ) and haloperidol ( $1.1 \pm 3.3$  kg)
- Ratzoni et al., J Am Acad Child Adolescent Psychiatry, 2002

- ### SGAs and Weight Gain
- Results (cont.)
    - extreme weight gain recorded in 90.5% - olanzapine, 42.9% - risperidone, 12.5% - haloperidol
    - risk factors – male sex, low baseline BMI
- Ratzoni et al., J Am Acad Child Adolescent Psychiatry, 2002



## SGAs and Weight Gain

- Weight gain associated with SGAs in youth
  - clozapine (n = 15)
  - olanzapine (n = 15)
  - risperidone (n = 15)
- All 3 had significant weight gain ( $p < 0.0001$ )
  - olanzapine (4.6 kg +/- 1.9) > risperidone (2.8 kg +/- 1.3) = clozapine (2.5 kg +/- 2.9)
  - olanzapine and risperidone - disproportionately > weight gain in youth than adults

Fleischhaker et al., J Neural Transmission, 2007

## TEOSS Study

- Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS) Study
- Design
  - 116 youth aged 8 – 19 years
  - randomly assigned to treatment with molindone, olanzapine, or risperidone
  - 8 week, double-blind trial
  - schizophrenia, schizoaffective d/o, or schizophreniform d/o
  - KID-SCID, PANSS

Sikich et al., Am J Psychiatry, 2008

## TEOSS Study

- Dosage
  - molindone – 59.9 ± 33.5 mg
  - olanzapine – 11.4 ± 5.0 mg
  - risperidone – 2.8 ± 1.4 mg
- Response
  - molindone – 50%
  - olanzapine – 34%
  - risperidone – 46%

Sikich et al., Am J Psychiatry, 2008

## TEOSS Study

- Weight gain
  - molindone – 0.3 ± 2.9 kg
  - olanzapine – 6.1 ± 3.6 kg (> risp, mol)
  - risperidone – 3.6 ± 4.0 kg (> mol)
- Insulin change
  - molindone – 1.2 ± 7.1
  - olanzapine – 15.7 ± 38.1 (>mol)
  - risperidone – -2.4 ± 19.4

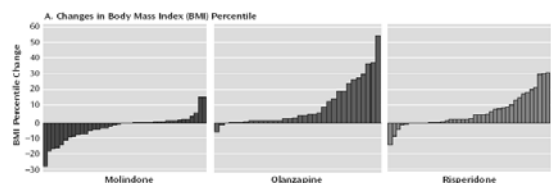
Sikich et al., Am J Psychiatry, 2008

## TEOSS

- NIMH's Data and Safety Monitoring Board discontinued random assignment to olanzapine:
  - greater increase in weight
  - no greater efficacy

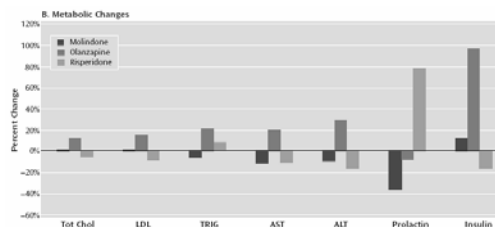
Sikich et al., Am J Psychiatry, 2008

## TEOSS Study



Sikich et al., Am J Psychiatry, 2008

## TEOSS



Sikich et al., Am J Psychiatry, 2008

## SGAs and Weight Gain

- Literature review
- Risk for weight gain associated with SGAs in youth:
  - clozapine and olanzapine – substantial
  - risperidone and quetiapine – moderate
  - ziprasidone and aripiprazole – low

Stigler et al., Paediatric Drugs, 2004

## Metabolic Syndrome

- International Diabetes Federation
  - Age 6 - < 10 years
    - Obesity  $\geq 90^{\text{th}}$  (waist circumference)
    - Metabolic syndrome should not be diagnosed, further evaluation if child has a family history of:
      - metabolic syndrome
      - type 2 diabetes mellitus
      - dyslipidemia
      - cardiovascular disease
      - hypertension
      - obesity

## Metabolic Syndrome

- International Diabetes Federation
  - Age 10 - < 16 years
    - Obesity  $\geq 90^{\text{th}}$  (waist circumference)
    - Two or more of the following:
      - Triglycerides  $\geq 1.7$  mmol/l
      - HDL-cholesterol  $< 1.03$  mmol/l
      - BP  $\geq 130$  mm Hg systolic or  $\geq 85$  mm Hg diastolic
      - Glucose  $\geq 5.6$  mmol/l\* or known type 2 diabetes mellitus

\* - Oral GTT recommended but is not necessary to define presence of syndrome

## Metabolic Syndrome

- International Diabetes Federation
  - Age > 16 years (adult criteria)
    - Central obesity (waist circumference corrected for ethnicity)
    - Two or more of the following:
      - elevated triglycerides
        - »  $\geq 150$  mg/dL (1.7 mmol/L)
        - » treatment for hypertriglyceridemia
      - reduced HDL-cholesterol
        - »  $\leq 40$  mg/dL (1.03 mmol/L) in men
        - »  $\leq 50$  mg/dL (1.29 mmol/L) in women
        - » treatment for this lipid abnormality

### Metabolic Syndrome

- International Diabetes Federation
  - Age > 16 years (adult criteria)
    - Two or more of the following:
      - elevated blood pressure
        - » systolic  $\geq$  130 mm Hg
        - » diastolic  $\geq$  85 mm Hg
        - » treatment of previously diagnosed hypertension
      - elevated fasting plasma glucose
        - » fasting plasma glucose  $\geq$  100 mg/dL (5.6 mmol/L)\*
        - » previously diagnosed type 2 diabetes

\* - Oral GTT recommended but is not necessary to define presence of syndrome

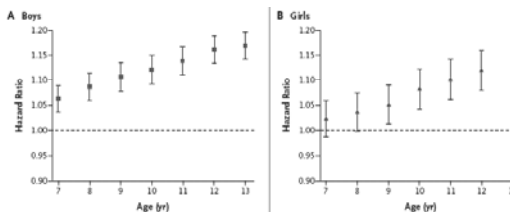
### Insulin Resistance

- Impaired ability of plasma insulin to:
  - promote peripheral glucose disposal
  - suppress hepatic glucose
  - metabolize triglycerides

### Metabolic Syndrome

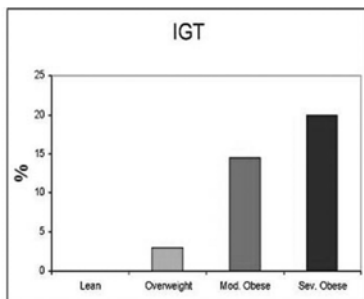
- Consequences
  - glucose abnormalities
    - impaired glucose tolerance
    - type 2 diabetes mellitus
  - hypertension
  - dyslipidemia
  - early onset atherosclerotic coronary vascular disease

### Age of Onset of Obesity and Risk of Adult Heart Disease



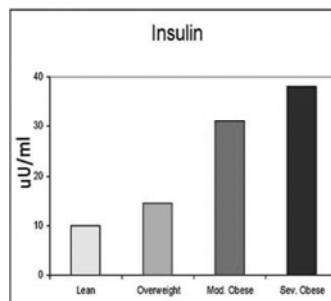
N Engl J Med, 2007

### Obesity and Cardiometabolic Risk Factors

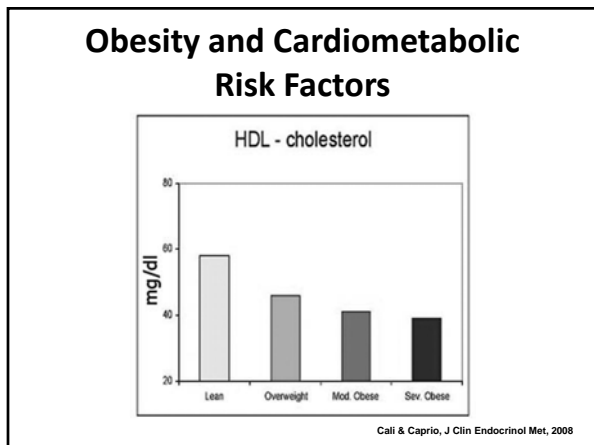
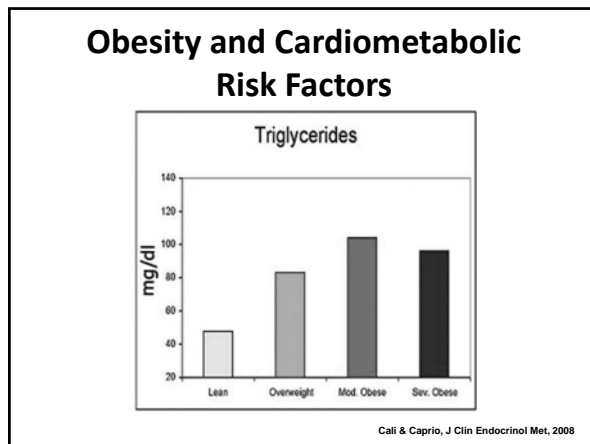
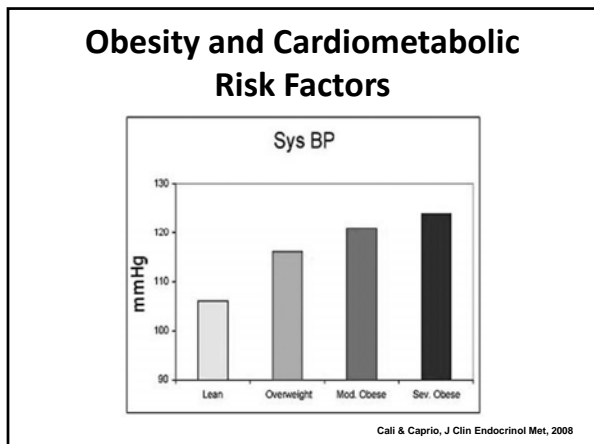


Call & Caprio, J Clin Endocrinol Met, 2008

### Obesity and Cardiometabolic Risk Factors



Call & Caprio, J Clin Endocrinol Met, 2008



### Metabolic Syndrome

Drug	Weight gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole	+/-	-	-
Ziprasidone	+/-	-	-

+ = increased effect, - = no effect, D = discrepant Diabetes Care, 2004

### Monitoring Protocol for SGAs

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	x					x	
Weight (BMI)	x	x	x	x	x	x	x
Waist circumference	x					x	
BP	x			x		x	
Fasting blood glucose	x			x		x	
Fasting lipid profile	x			x			x

Diabetes Care, 2004

- ### Managing SGA Induced Weight Gain and Metabolic Syndrome
- Psychoeducation
  - Dietary intervention and exercise
  - Cognitive behavioral therapy
  - Behavioral therapy
  - Family-based interventions
  - Motivational interviewing

### Managing SGA Induced Weight Gain and Metabolic Syndrome

- Motivational interviewing
  - <http://www.alleninteractions.com/>
  - HOME >CASE STUDIES&DEMOS>DEMOS>Motivating Change for Pediatric Weight Management

### Managing SGA Induced Weight Gain and Metabolic Syndrome

- Healthy lifestyle behaviors:
  - replace all drinks containing sugar , diet drinks, and whole milk with  $\geq 2$  L of water and unsweetened tea or low-fat milk
  - eat every 3 - 4 hours, with  $\leq 2$  meals in evening or at night
  - eat small portions at meals
  - eat breakfast every morning
  - eat slowly, drink plenty of water between bites, and take second helpings only after a delay

Correll and Carlson, JAACAP, 2006

### Managing SGA Induced Weight Gain and Metabolic Syndrome

- Healthy lifestyle behaviors:
  - $\leq$  one fast food meal/week
  - replace refined white flour and processed sugar products with whole-grain and foods with low glycemic index
  - do not snack when full, replace high-fat, high-calorie snacks with fruits or vegetables
  - limit saturated fat intake

Correll and Carlson, JAACAP, 2006

### Managing SGA Induced Weight Gain and Metabolic Syndrome

- Healthy lifestyle behaviors:
  - eat at least 25 - 30 g/day of soluble fiber
  - limit screen time to  $< 2$  hours/day
  - moderate to vigorous physical activity 30 - 60 minutes/day

Correll and Carlson, JAACAP, 2006

### Managing SGA Induced Weight Gain and Metabolic Syndrome

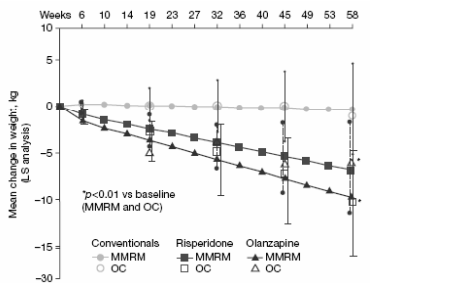
- Pharmacologic interventions
  - discontinuing the medication
  - switching to another medication

### Managing SGA Induced Weight Gain and Metabolic Syndrome

- 14 youth treated with risperidone:
  - treatment noncompleters
  - weight checked at baseline, termination, and 3, 9-12, and 24 months after termination
- 12 and 24 month post-termination standardized weights indistinguishable from standardized weight before risperidone
- Risperidone induced weight gain is reversible

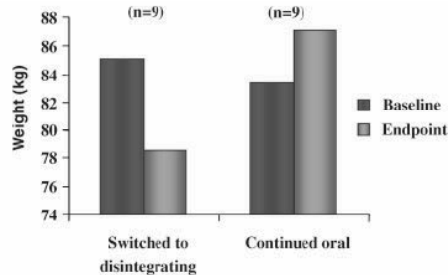
Lindsay et al., Clin Pediatrics, 2004

### Managing SGA Induced Weight Gain and Metabolic Syndrome



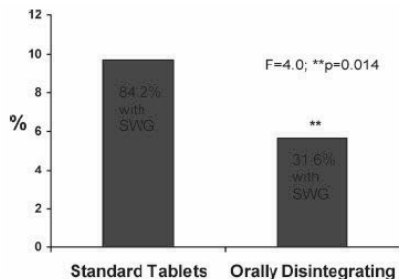
Weiden et al., Neuropsychopharmacology (2008)

### Managing SGA Induced Weight Gain and Metabolic Syndrome



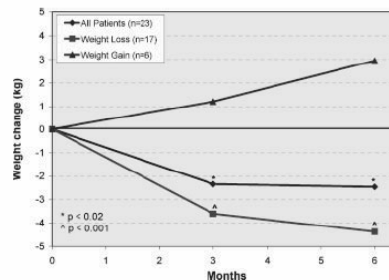
Karagianis et al., Human Psychopharmacology (2008)

### Managing SGA Induced Weight Gain and Metabolic Syndrome



Karagianis et al., Human Psychopharmacology (2008)

### Managing SGA Induced Weight Gain and Metabolic Syndrome



Karagianis et al., Human Psychopharmacology (2008)

### Pharmacologic Interventions

- **Orlistat (Xenical, Alli)**
  - reversible inhibitor of gastric, pancreatic lipases
  - FDA approved for adolescents
  - available OTC
  - 120 mg TID
  - frequent stools, flatus, and steatorrhea

### Pharmacologic Interventions

- **Sibutramine (Meridia)**
  - selective serotonin and NE reuptake inhibitor
  - FDA approved for adolescents
  - sustained increase in resting blood pressure
- **Topiramate (Topamax)**
  - headache, dizziness, sedation, gastrointestinal, and cognitive problems

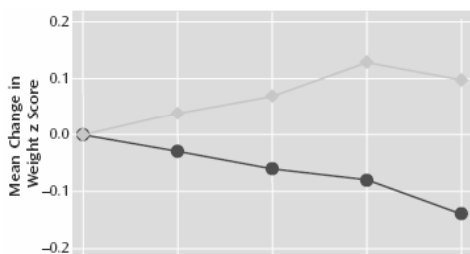
### Pharmacologic Interventions

- **Amantadine**
  - dopamine agonist
  - mixed results
  - decreases effectiveness of the olanzapine
- **Modafinil**
  - decreases GABA levels
  - increased heart rate and blood pressure

### Pharmacologic Interventions

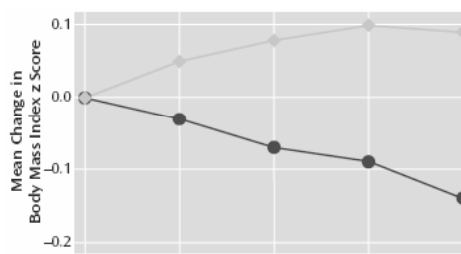
- **Ranitidine**
  - histamine H2 blocker
  - effectiveness is dose related (600 mg/d)

### Metformin



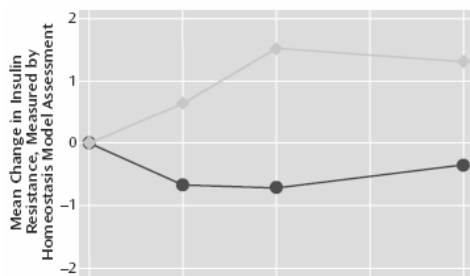
Klein DJ et al, Am J Psychiatry, 163:2072-2079; 2006

### Metformin



Klein DJ et al, Am J Psychiatry, 163:2072-2079; 2006

### Metformin



Klein DJ et al, Am J Psychiatry, 163:2072-2079; 2006