

Antipsychotic Medications

2nd Edition

Fully Revised & Updated

Instant Psychopharmacology

Up-to-date information about the most commonly
prescribed drugs for emotional health

Ronald J. Diamond

Smoking

Induced CYP 1A2

- Can decrease clozapine levels by up to 50%, and may also decrease olanzapine to some extent

de Leon J. Atypical antipsychotic dosing: the effect of smoking and caffeine. *Psychiatr Serv.* 2004;55:491-493.

Pan L, Vander Stichele R, Rosseel MT, Berlo JA, De Schepper N, Belpaire FM. Effects of smoking, CYP2D6 genotype, and concomitant drug intake on the steady state plasma concentrations of haloperidol and reduced haloperidol in schizophrenic inpatients. *Ther Drug Monit.* 1999;21:489-497.

Race and Ethnicity: CYP2D6

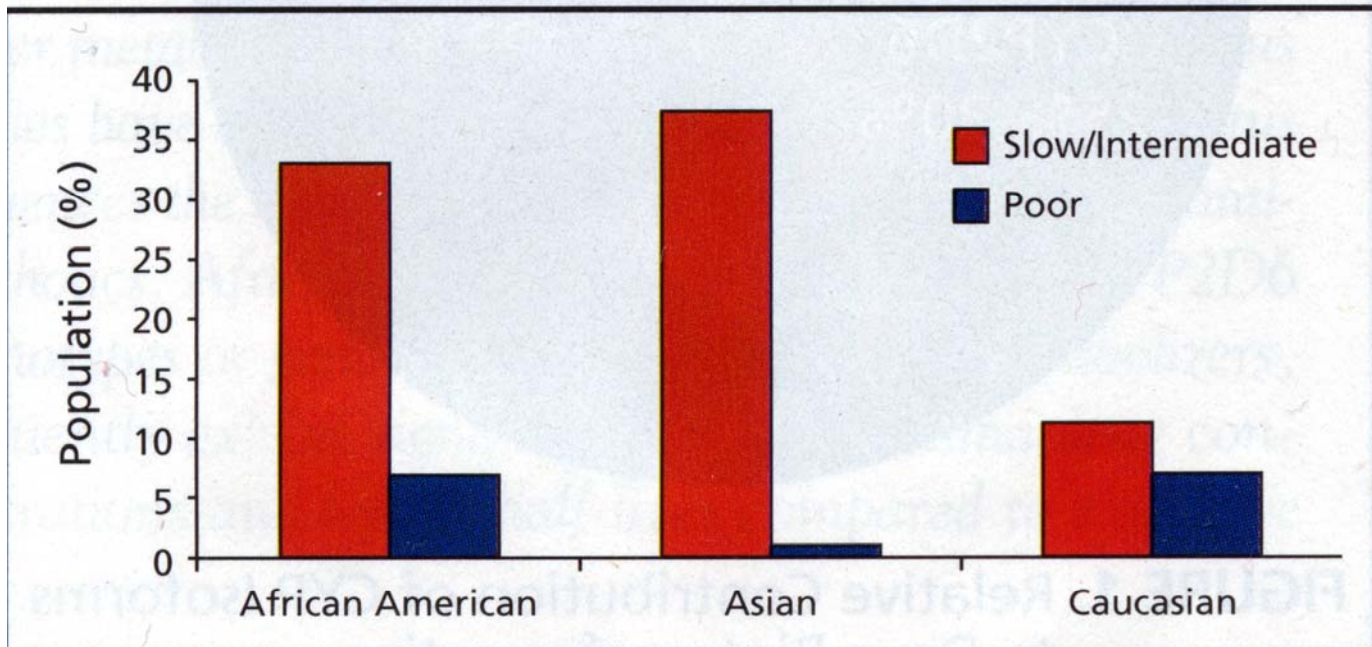


FIGURE 2. Frequency of Slow/Intermediate and Poor Metabolizers of CYP2D6-Mediated Drugs^{9,17,18}

CYP=cytochrome P450.

Bradford LD. *CNS Spectr.* Vol 10, No 3 (Suppl 2). 2005.

antipsychotics

- Asians have higher level of haloperidol levels that Asians Lin et al 1988
 - Highest, foreign born Asians
 - Medium US born Asians
 - Lowest American born caucasions
- Asians had higher clozapine level on same dose of clozapine

Cultural Issues in Medication Response

Smoking 45% of Egyptians smoke

- Ave cig 1201 in egypt
- Greece 3230
- Norway 739

Caffeine; people from middle east prefer tea rather than coffee

Tarek A. Okasha Egypt

Impact of culture on Psychopharmacology

- Relationship to prescriber and to illness influenced by cultural beliefs
- Placebo response influenced by cultural beliefs and cultural bound syndromes
- Cultural basis in length of time before seeking treatment
- Cultural basis in what counts as “getting better”
- Differences in SES and insurance

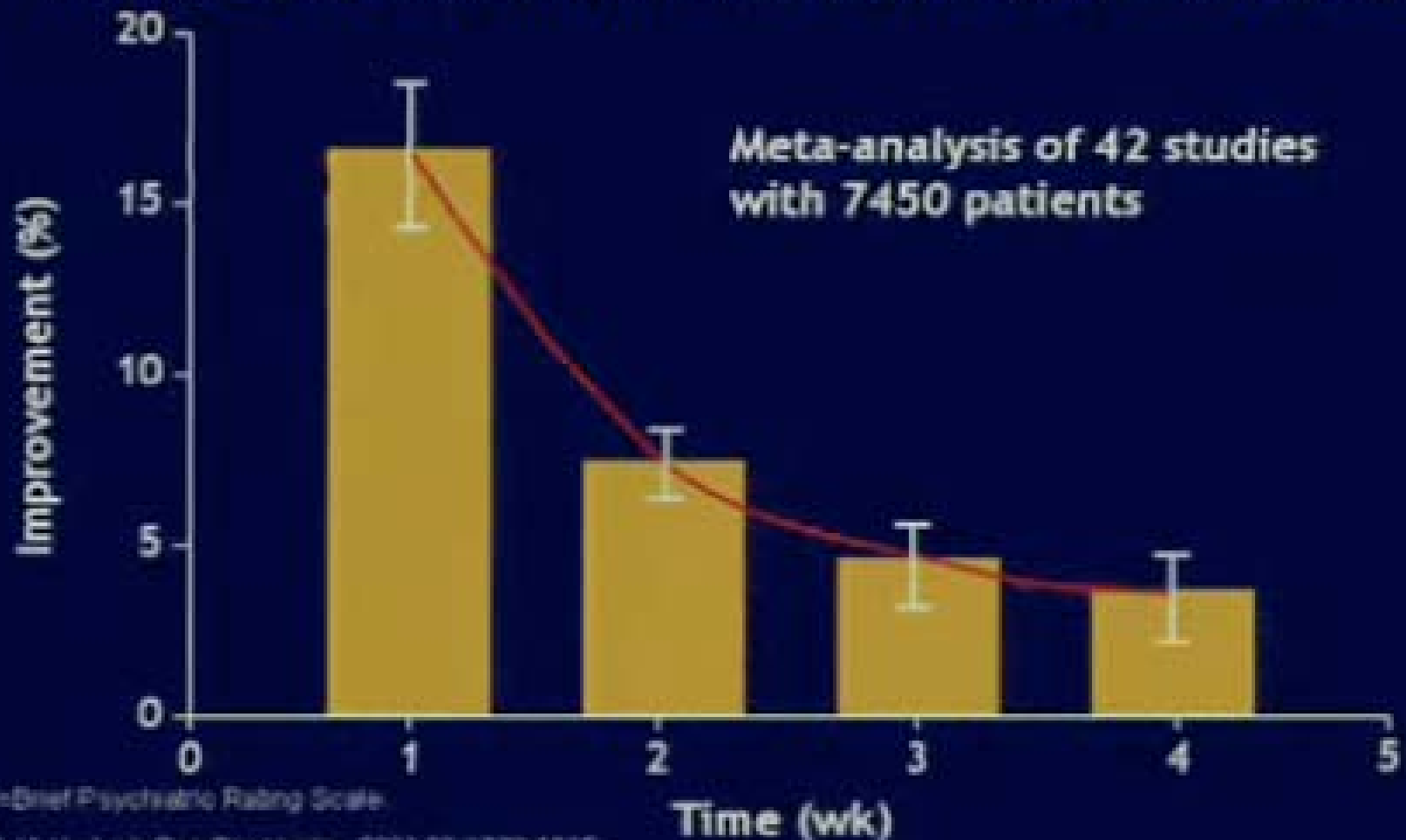
A Brief Discussion about Money

- clozapine (Clozaril)*100 mg x 4/day \$ 499 \$ 202
- olanzapine (Zyprexa)15 mg/day \$ 388 —
- quetiapine (Seroquel) 300 mg x 2/day \$ 487
- risperidone (Risperdal)4 mg x 1/day \$ 273 —
- aripiprazole (Abilify) 15 mg x 1/day \$ 303
- Ziprasidone (Geodon) 80 mg x 2/day \$ 318

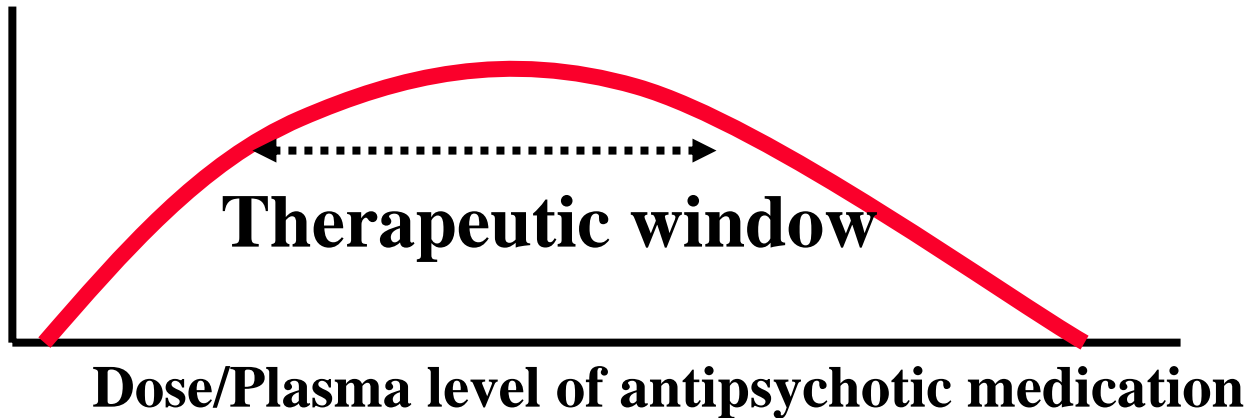
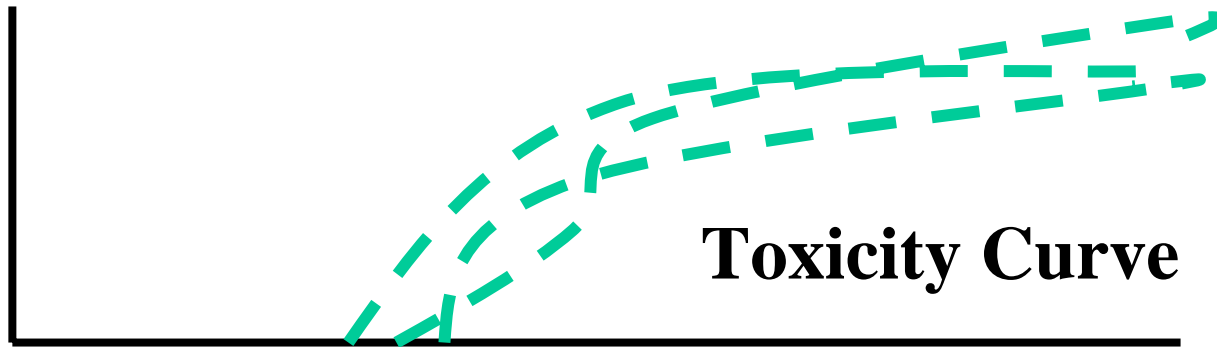
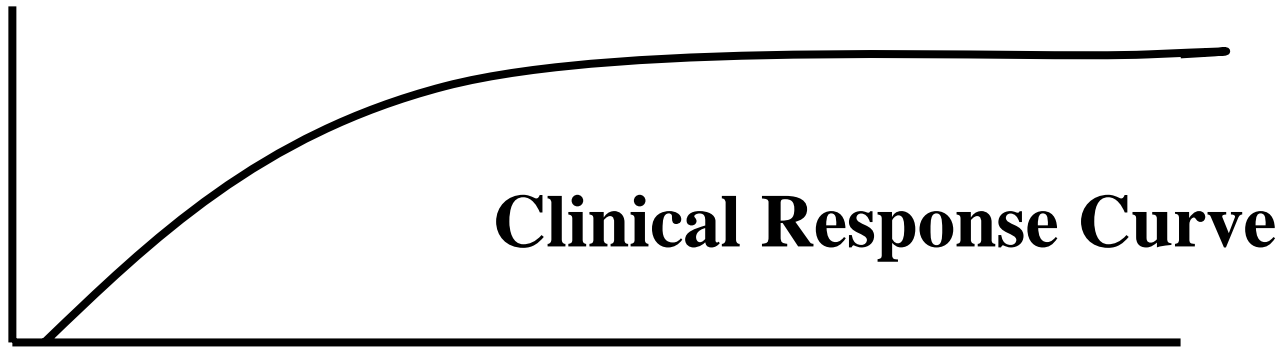
- fluphenazine (Prolixin)10 mg/day \$ 76 \$ 12
- haloperidol (Haldol)10 mg/day \$ \$ 33
- loxapine (Loxitane)25 mg x 4/day \$ 325 \$ 89

Time Course of Antipsychotic Effect

Psychotic Symptoms (PANSS Positive or BPRS Thought Disorder Scores)

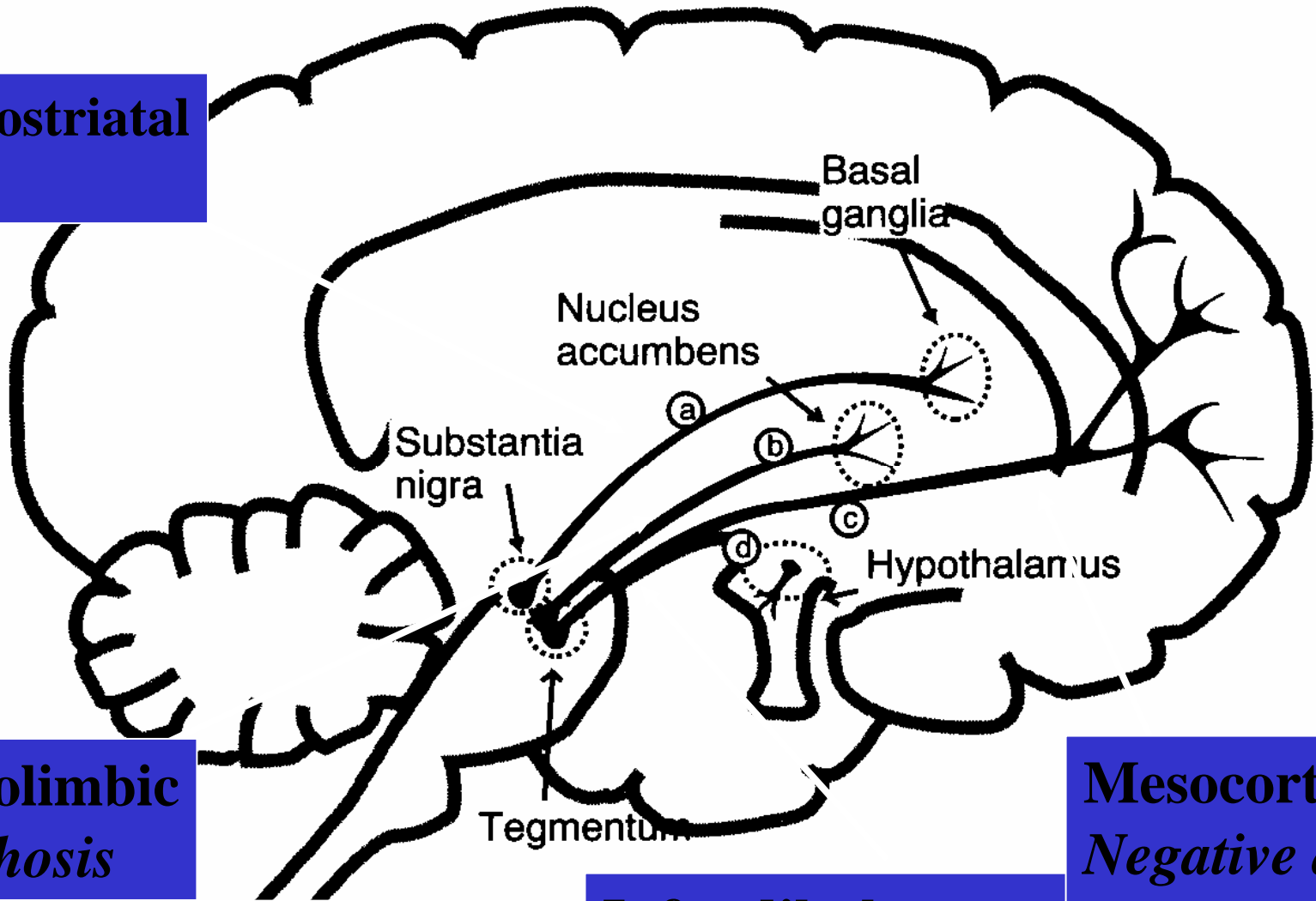


Antipsychotic Dose-Response Curve



Dopamine Pathways

**Nigrostriatal
*EPS***

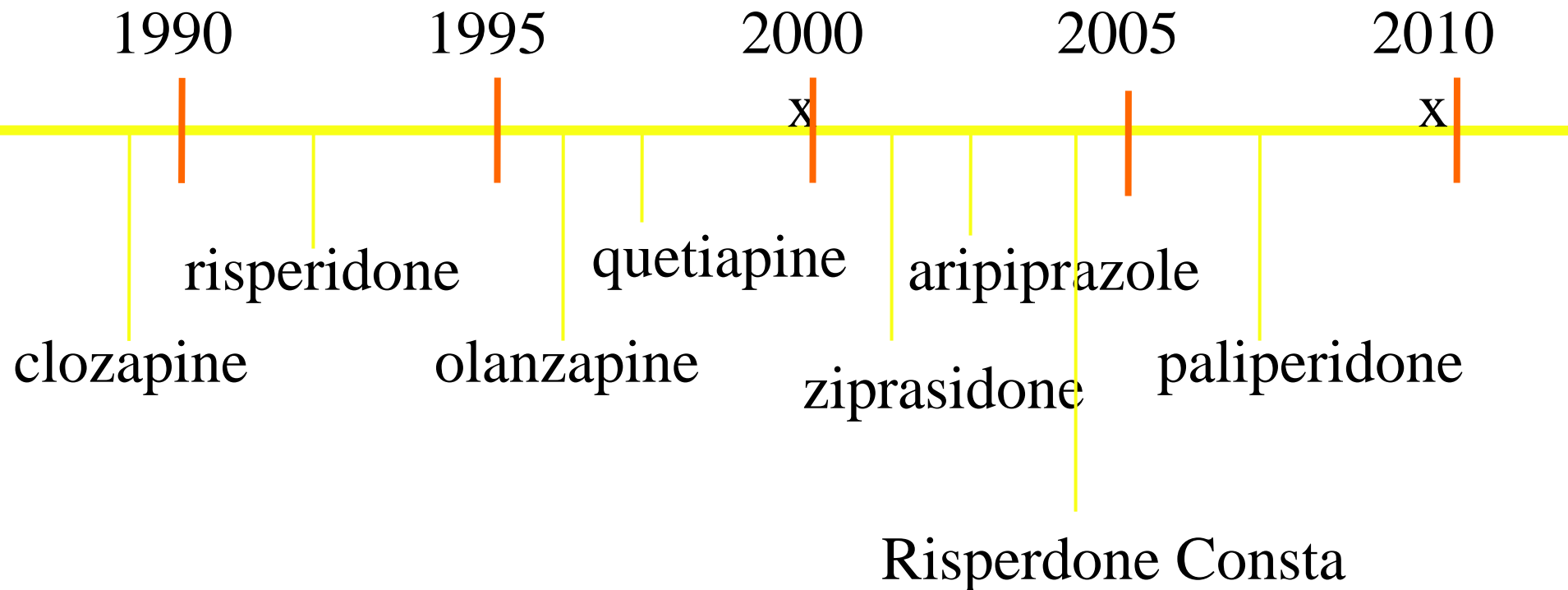


**Mesolimbic
*psychosis***

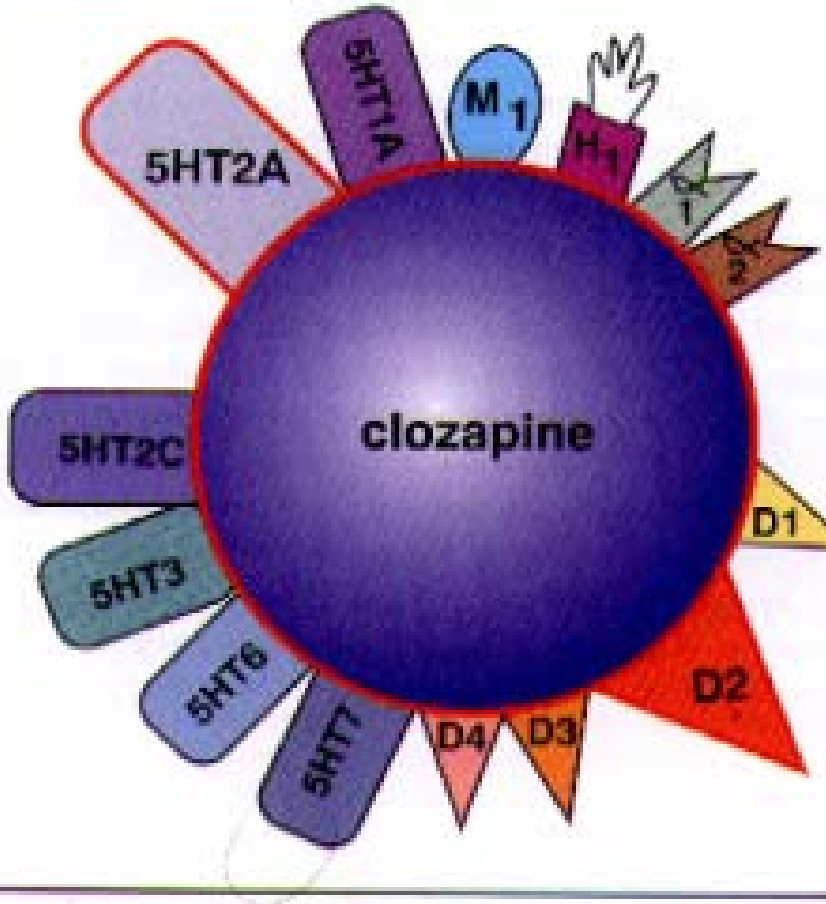
**Infundibular
*Prolactin elevation***

**Mesocortical
*Negative and
cognitive sx***

History of Second Generation Antipsychotic Medications



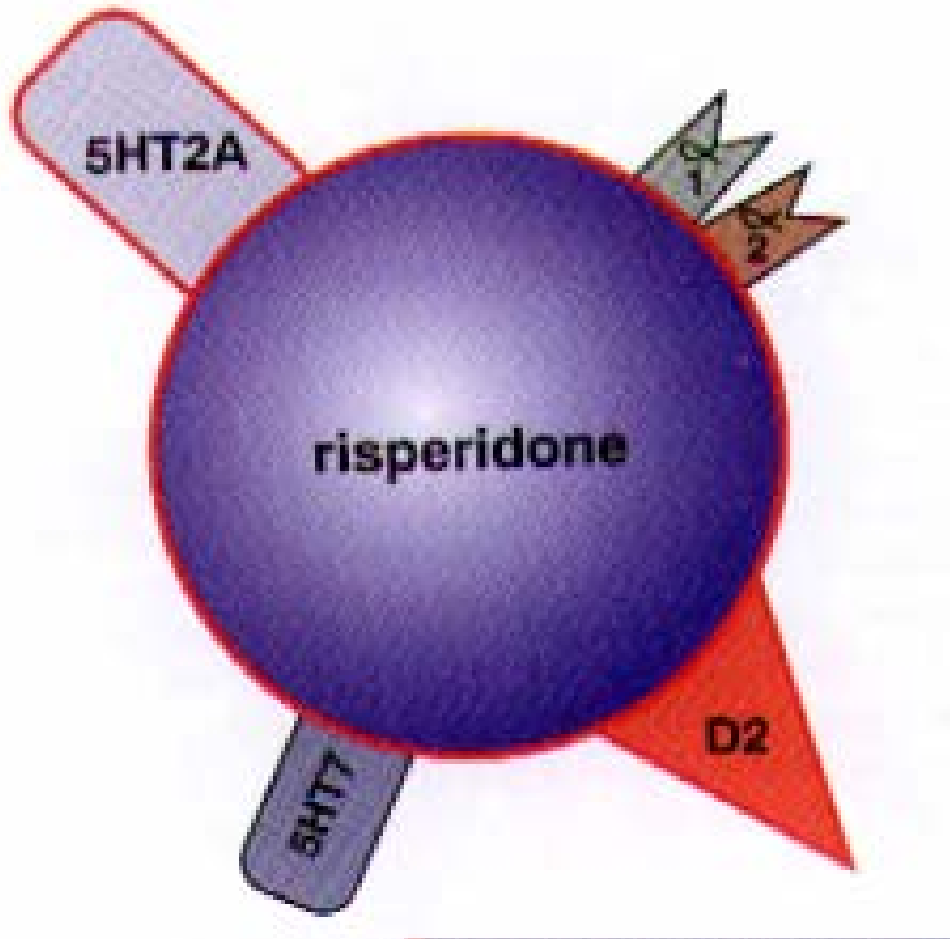
Clozapine



Very complicated pharmacology

- **Many side effects**
 - **Weight Gain**
 - **Anticholinergic**
 - **Sedation**
 - **Seizures**
 - **Agranulocytosis**
 - **Heat Related Deaths**
- **Very effective**
 - **positive and negative**
 - **good mood stabilizer**
 - **very low EPS**
 - **very low TD**

Risperidone (Risperdal)



- **Dose related EPS**
- **Less is better**
- **Prolactin Elevation**
- **Weight Gain**

- **Positive and negative efficacy**
- **Mood stabilizer**
- **Decreased TD**

Paliperidone (Invega)

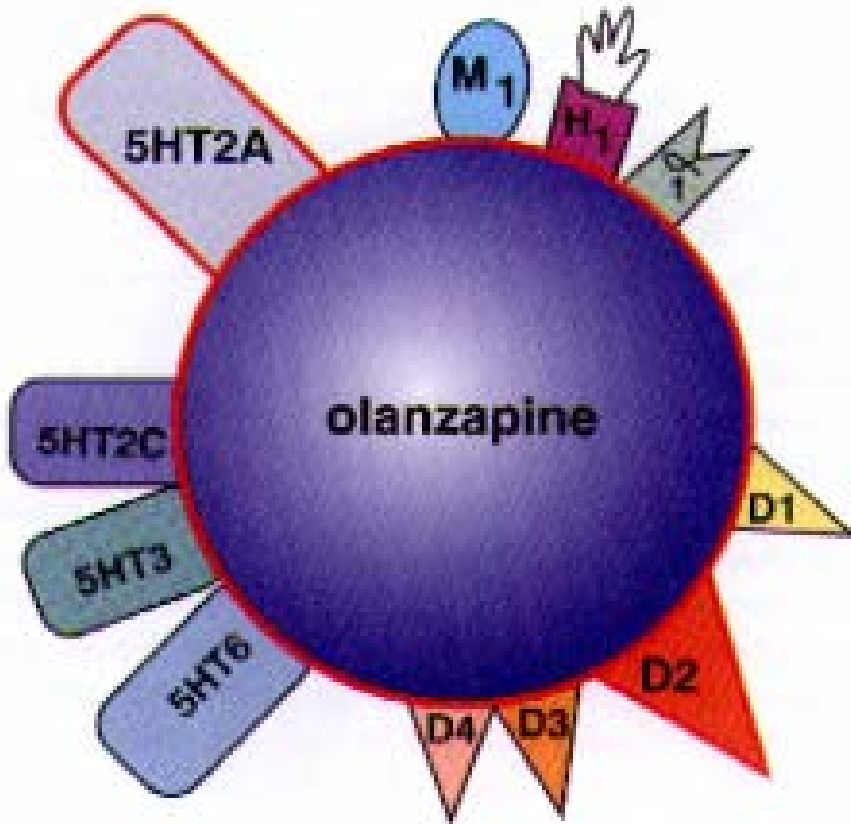
- Major metabolite of risperidone
- More gradual release than risperidone [but risperidone converted into paliperidone]
- Fewer drug-drug interactions (metabolized primarily in kidneys, little P450 interaction)
- More QTc prolongation [not significant]
- Similar prolactin elevation to risperidone
- ? Similar weight gain

Paliperidone Vs Risperidone

	Risperidone	Paliperidone
T_{max}	R: 1 hr 9-OH-R: 3 hrs	24 hrs
Peak to Trough Ratio (%)	38	125
T 1/2	3 hrs	23 hrs
Steady State	R: 1 day 9-OH-R: 5 days	4-5 days
CYP450 enzyme	2D6 - extensive	4 enzymes <10 % each

Docherty JP 2007 U.S. Psychiatric Congress

Olanzapine (Zyprexa)

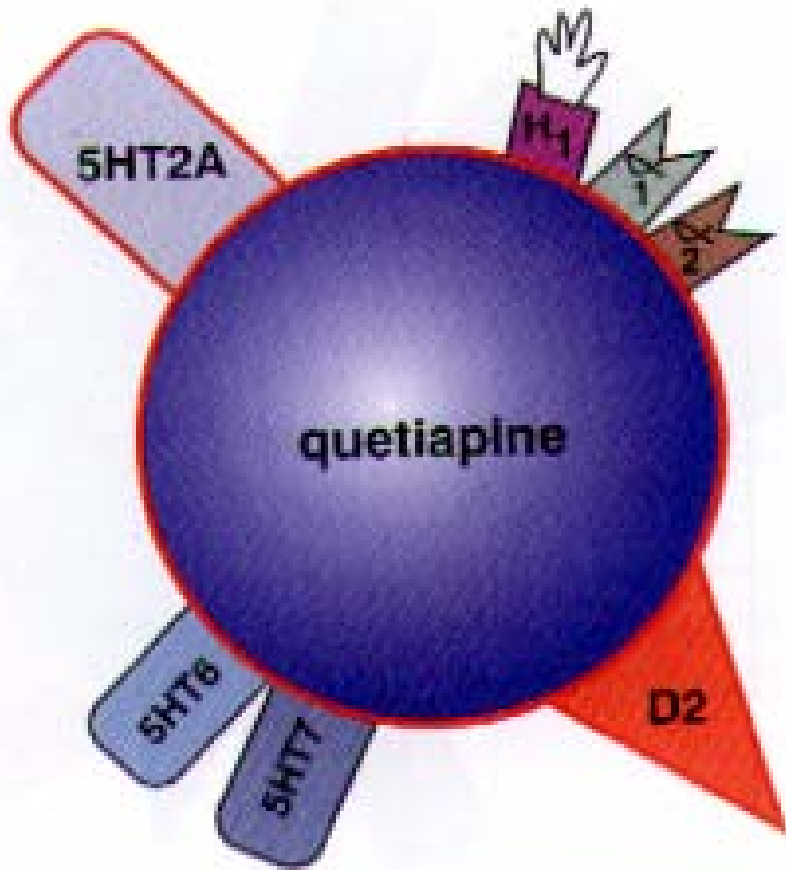


- Some dose related EPS
- Slight prolactin Elevation
- Big Weight Gain
- Diabetes (?)
- Somewhat sedating

- Positive and negative efficacy
- Mood stabilizer
- Decreased TD

Adapted from Stahl
Essential Psychopharmacology

Quetiapine (Seroquel)



- **More is Better**
- **400 mg up to 1200 mg**
- **Very low EPS**
- **Very low TD risk**
- **Some weight gain**
- **Sedating**
- **Needs dose titration to decrease dizziness**

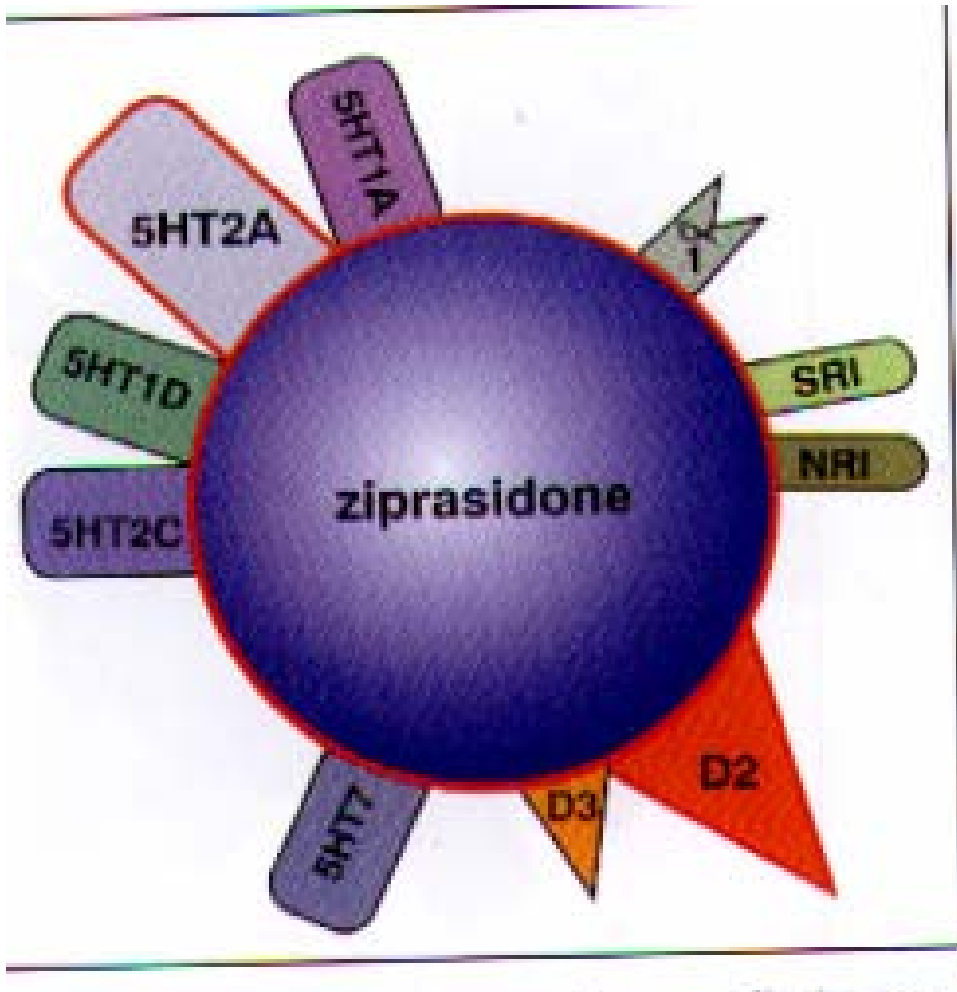
- **Low dose may be useful in people with borderline disorder**

Adapted from Stahl
Essential Psychopharmacology

Quetiapine and bipolar depression

- 2 trials support efficacy in bipolar depression [Boulder I and Boulder II]
- Norquetiapine (metabolite of quetiapine) potent inhibitor of norepinephrine transporter
- Blocks alpha-2 autoreceptors (as does mirtazapine)
- Stimulates 5-HT_{1A} receptors

Ziprasidone (Geodon)



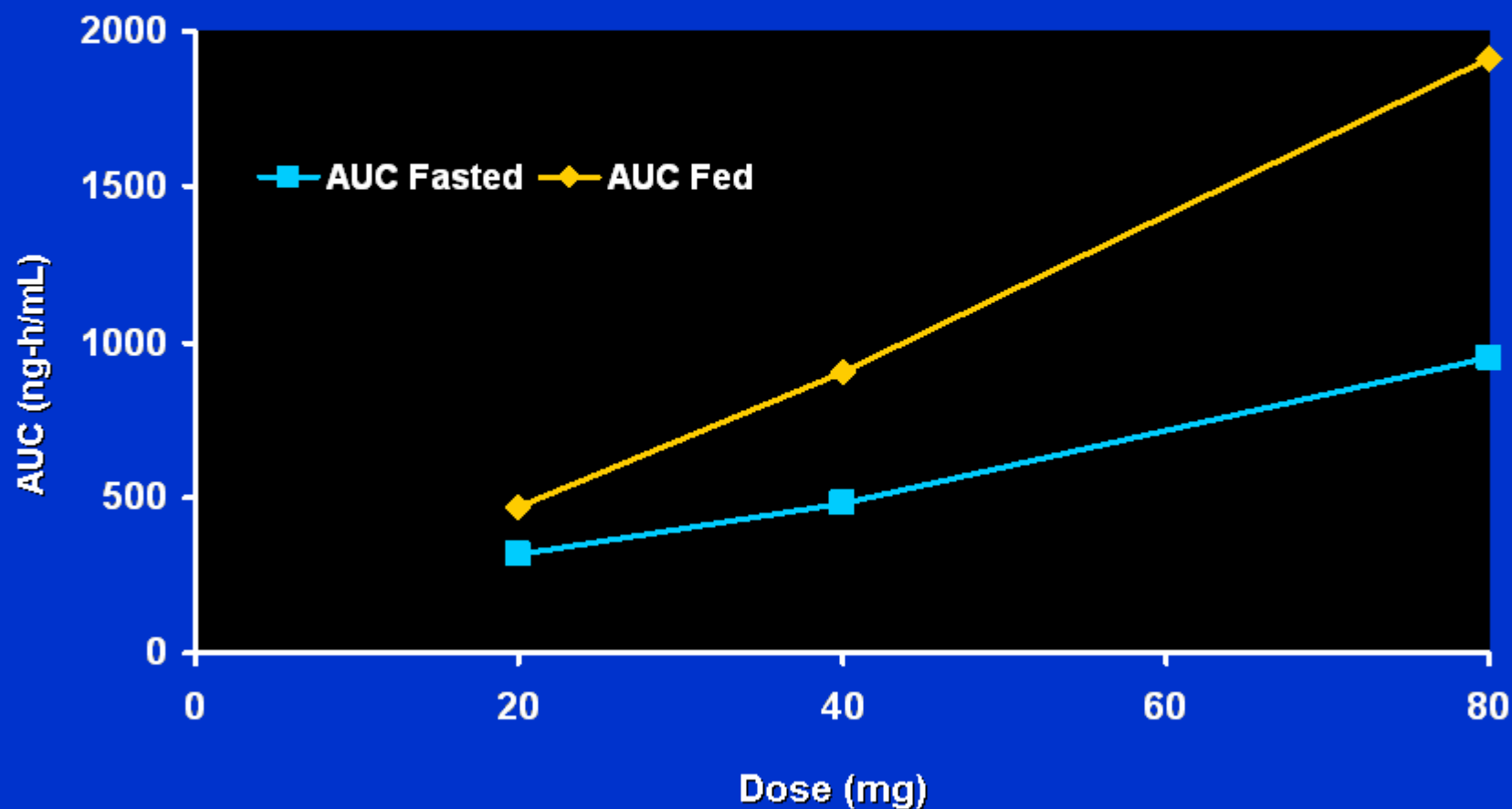
Adapted from Stahl
Essential Psychopharmacology

Newest antipsychotic
NO WEIGHT GAIN
Very low diabetes risk
Higher dose often better than low

QTc prolongation
Activating/agitating
Antidepressant activity

Nausea, sleep disturbance
EPS dose related

Dose Ziprasidone With Food to Maximize Absorption

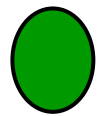


Aripiprazole (Abilify)

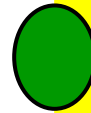
- Dopamine agonist/antagonist
- Appears to cause little or no weight gain, little EPS, little sedation and little effect on heart function

Intrinsic Activity: Ability to Stimulate Receptors

D₂ receptor



Full agonist (dopamine)



Full receptor activity



Antagonist (haloperidol, etc.)



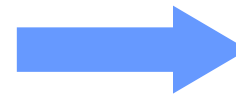
No receptor activity



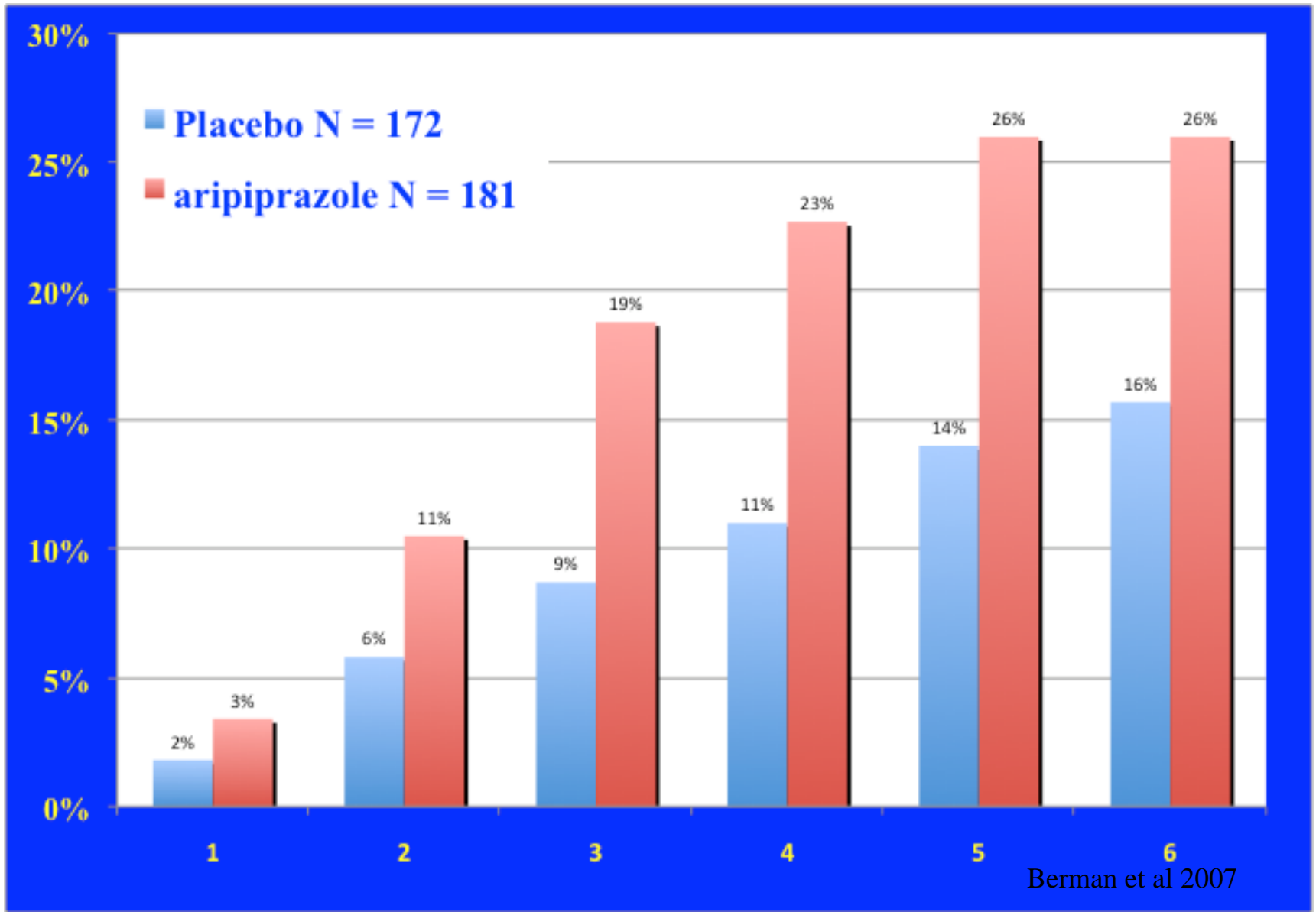
Partial agonist (aripiprazole)



Partial receptor activity



Remission rates of depression with aripiprazole augmentation

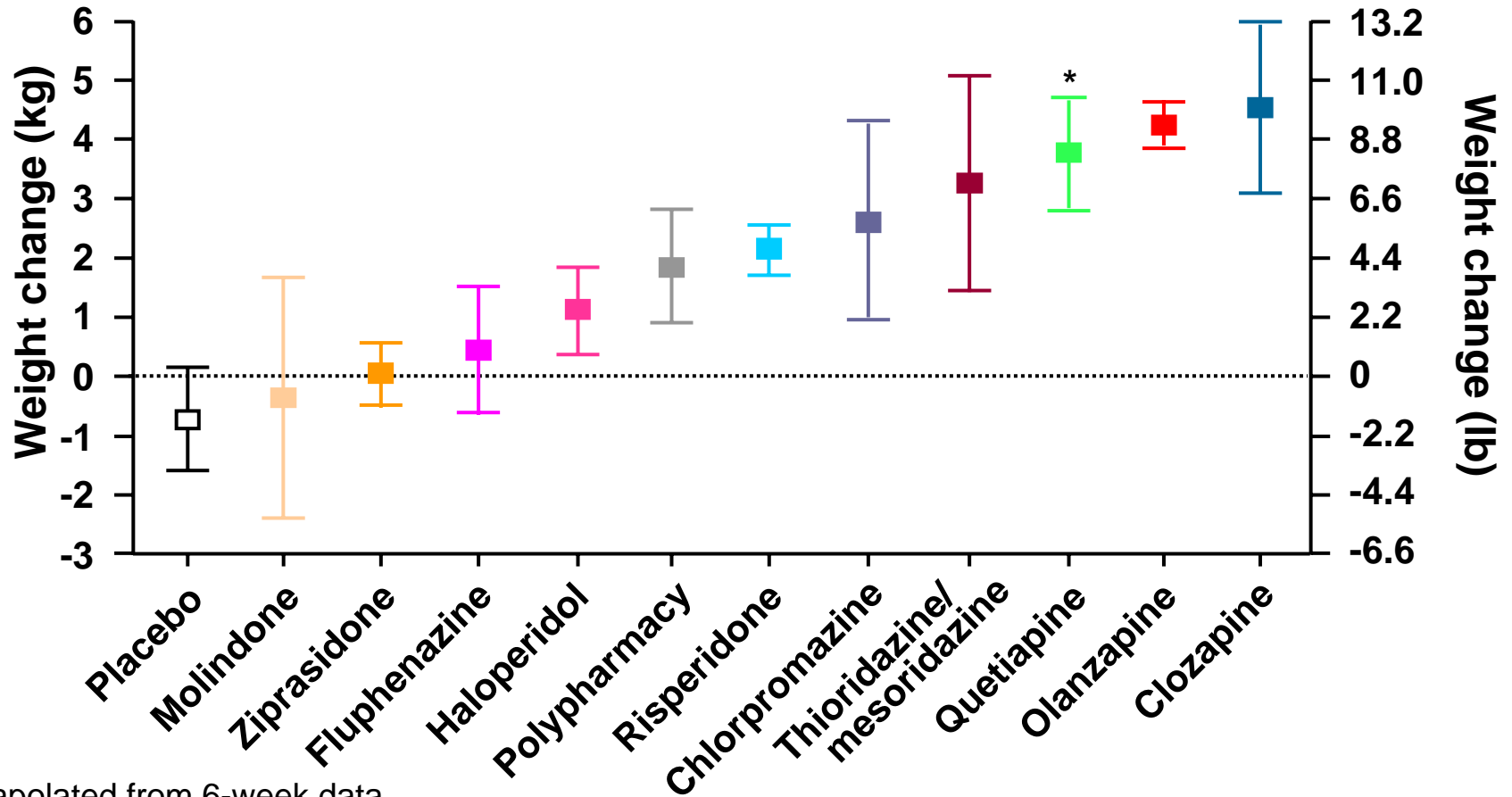


Side Effects of Antipsychotic Medications

	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole	haloperidol
Weight gain	+++	++	+++	++	0	0	0
dyslipidemia	+++	+	+++	+	0	0	0
Diabetes	+++	++	+++	++	+	+	+
Sedation	+++	+	++	+++	±	±	±
EPS	±	++	+	±	+	+	++
↑ Prolactin	0	+++	+	0	0	0	+++

Mean Change in Weight With Antipsychotics

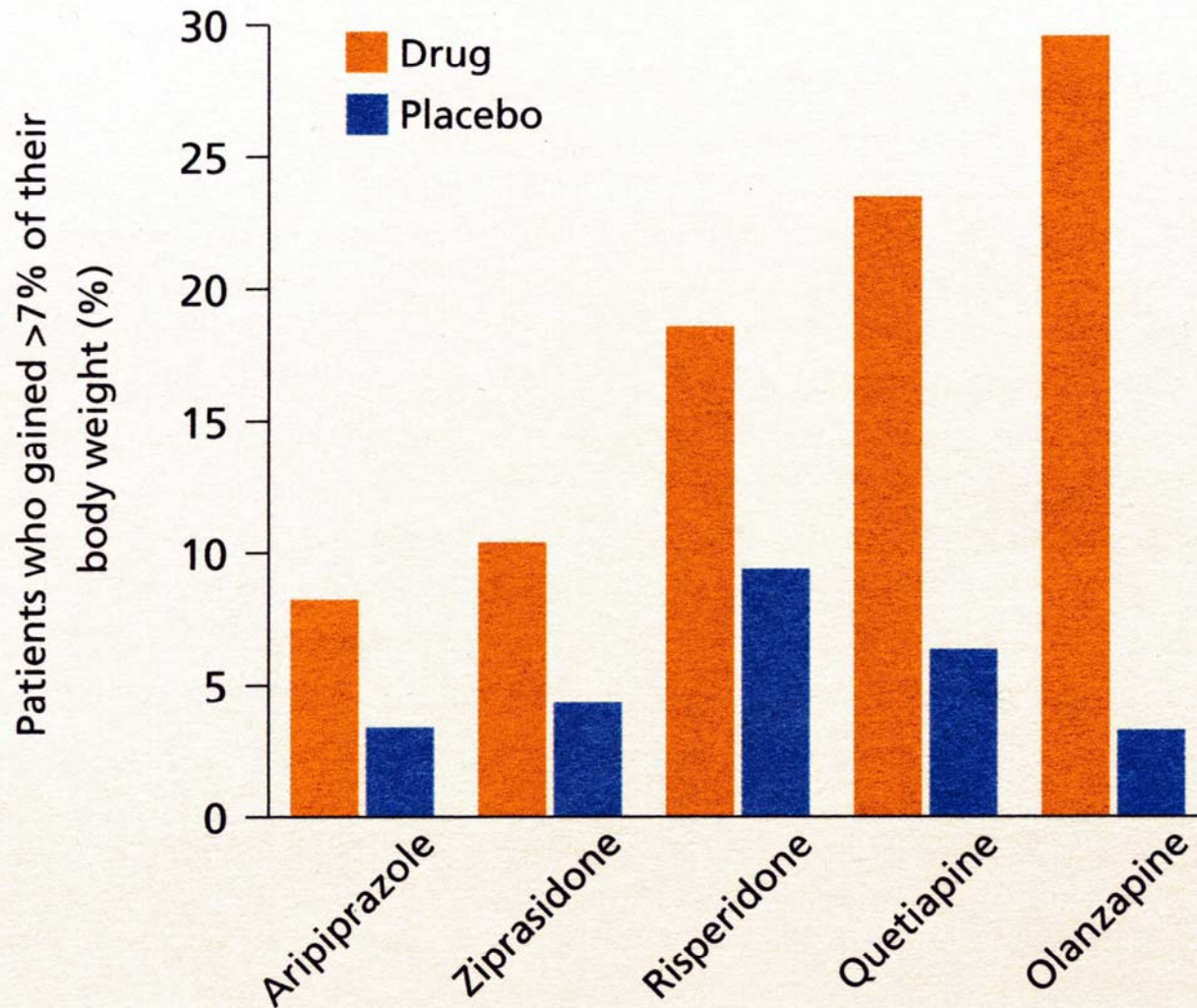
Estimated Weight Change at 10 Weeks on "Standard" Dose



*Extrapolated from 6-week data.

Allison et al. *Am J Psychiatry*. 1999;156:1686.

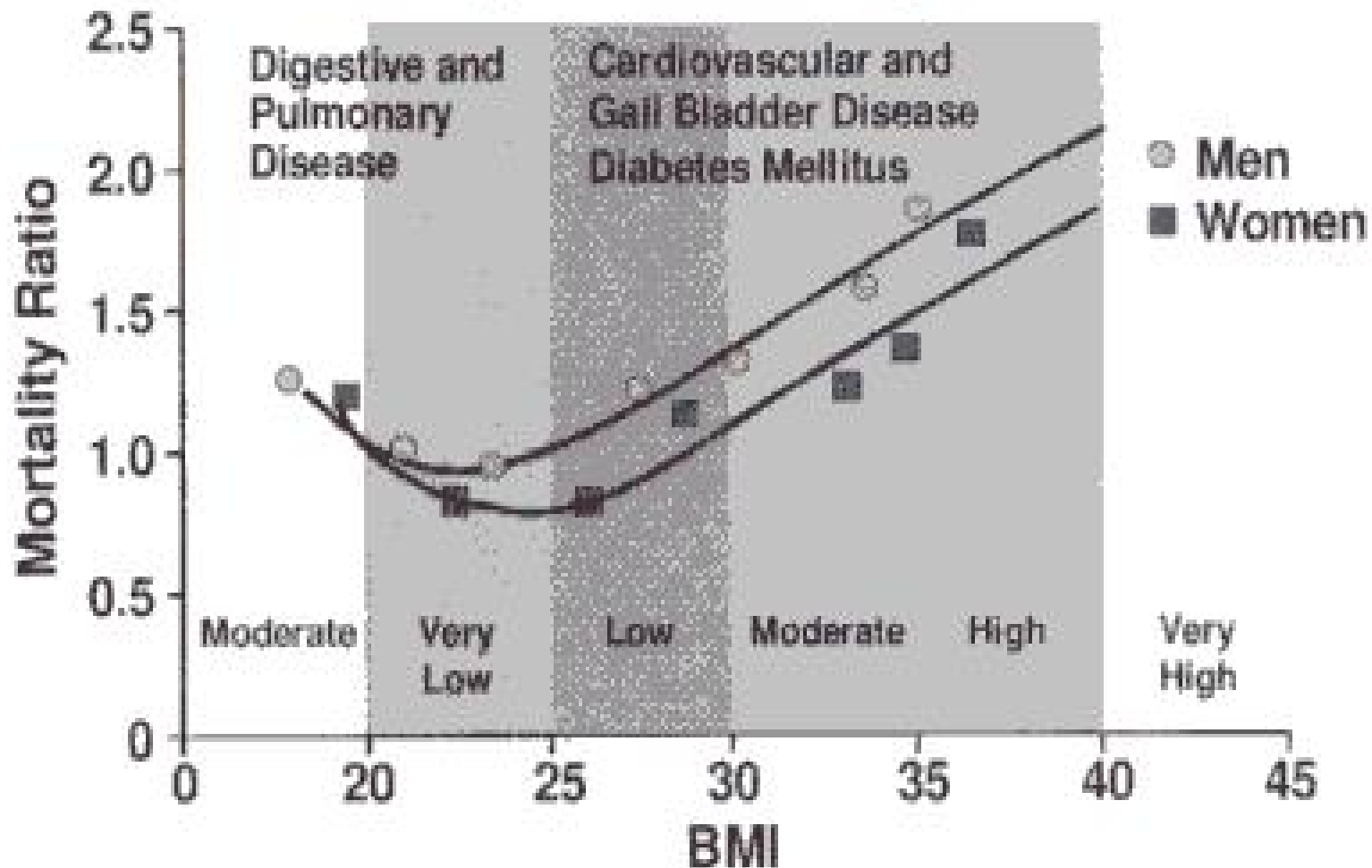
Percentage of Patients With Clinically Significant Weight Gain in Short-Term Placebo-Controlled Trials



Source: Haddad PM. Weight change with atypical antipsychotics in the treatment of schizophrenia. *J Psychopharmacol.* 2005;19(suppl 6):16-27. Reprinted with permission.

Antipsychotics

Obesity and Mortality Risk



Adapted from: Gray. *Med Clin North Am.* 1989;73(1):1-13; Based on data from: Lew EA, Garfinkel L. *J Chron Dis.* 1979;32(8):563-576; American Cancer Society study of 750,000 men and women

Traditional Antipsychotic Medications

Examples

- fluphenazine (Prolixin)
- haloperidol (Haldol)
- Both available as long acting injection
- Traditional D₂ blocker may (??) work better in rare patients
- Much less expensive

“Semi-traditional medications”

- Loxapine (Loxitane)

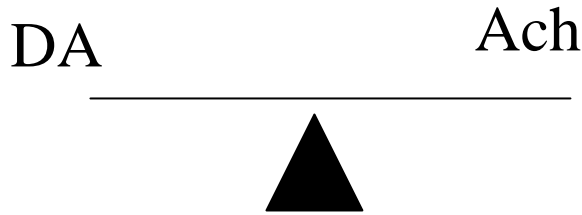
Antipsychotic Side Effects

EPS (Extrapyramidal [muscle] side effects)

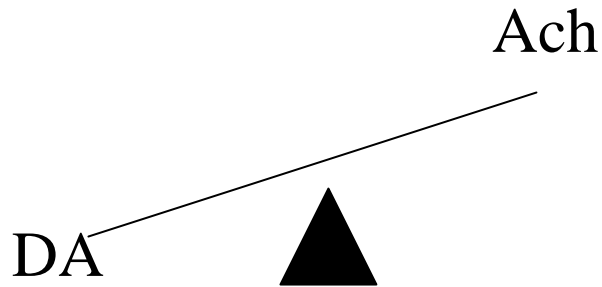
Dystonias (muscle cramps)

- Tremor--coarse Parkinsonian type tremor
- Akinesia--decreased movement/spontaneity
- Akathisia--motor restlessness
- Tardive Dyskinesia: MAY BE PERMANENT

Extrapyramidal Side Effects and Anticholinergic Medications



Dopamine and Acetylcholine
Are normally in balance



When dopamine is blocked,
This system goes out of balance



Blocking acetylcholine with
an anticholinergic medication
puts system back in balance

Antipsychotic Side Effects

common--not life threatening

- Psychotoxic side effects
 - Depression, sedation, confusion, dysphoria
- Anticholinergic
 - Dry mouth, constipation, blurred vision, memory impairment, confusion
- Alpha-adrenergic
 - dizziness
- Increase Prolactin
 - Breast engorgement, sexual side effects

Antipsychotic Side Effects

Rare but dangerous

- Blood dyscrasias: agranulocytosis
- NMS: neuroleptic malignant syndrome
- Temperature regulation: fatal heat stroke
- Cardiovascular effects: sudden death
- Seizures

NMS: Neuroleptic Malignant Syndrome

Usually within 30 days of new medication or dose



- Hyperthermia (fever)
- Muscle rigidity
- Tremor, myoclonus (muscle jerks)
- Confusion, stupor
- Increased heart rate, labile blood pressure
- Rapid breathing, shortness of breath
- Sweating, sialorrhea, incontinence
- Elevated CPK, leukocytosis, metabolic acidosis

Consensus Recommendations on Diabetes Monitoring

	Baseline	4 wks	8 wks	12 wks	3 mos	12 mos	5 yrs
Personal/Family Hx	X					X	
Weight (Body Mass Index)	X	X	X	X	X	X	X
Waist Circumference	X					X	
BP	X			X		X	
Fasting Glucose	X			X		X	
Fasting lipid profile	X						X
Diabetic Care Feb 2004							

Metabolic Syndrome: 3 or more following factors:

☐ Abdominal obesity

Waist circumference of > 40 inches in men

Waste circumference of > 35 inches in women

☐ HDL cholesterol (measured after 12 hours fast)

[LDL = bad cholesterol : low HDL = good cholesterol]

HDL cholesterol < 40 mg/dl in men

HDL cholesterol < 50 mg/dl in women

☐ Elevated triglycerides > 150 mg/dl

☐ Elevated blood pressure $> 130/85$ mm Hg

☐ Fasting blood glucose > 110 mg/dl

Second Generation

Antipsychotics: are they worth
the cost?

- CATIE
- CUTLESS
- Long-term VA study

