

# Wisconsin Public Psychiatry Network Teleconference (WPPNT)

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# WPPNT Reminders

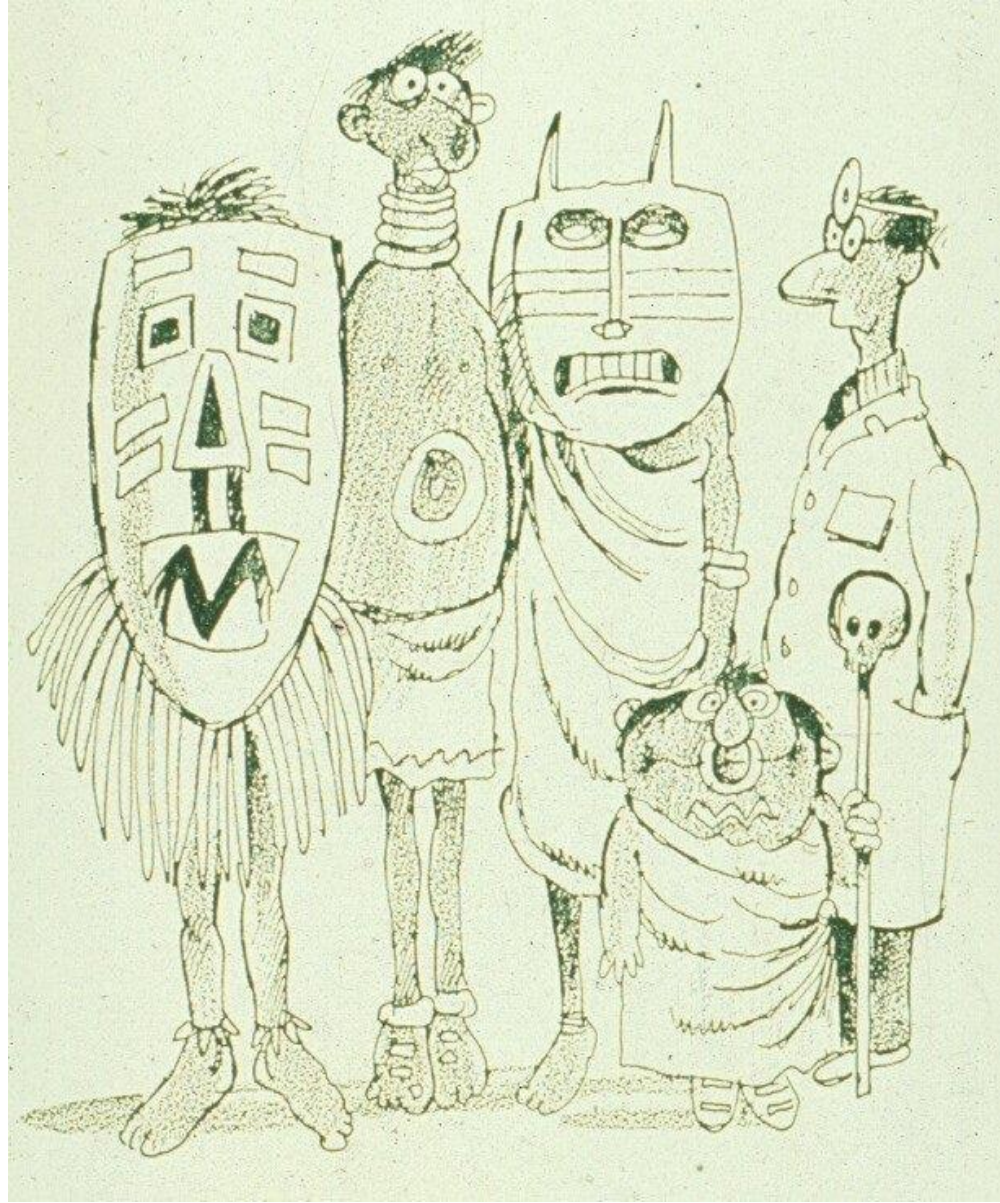
- Call 877-820-7831 before 11:00 a.m.
- Enter passcode 107633#, when prompted.
- Questions may be asked, if time allows.
- To ask a question, press \*6 on your phone to un-mute yourself. Please \*6 to re-mute your line.
- Ask questions for the presenter, about their presentation.
  
- The link to the evaluation for today's presentation is on the WPPNT webpage, under today's date:  
<https://www.dhs.wisconsin.gov/wppnt/2020.htm>. Complete the evaluation to receive the CEH.

# Antipsychotic Medications Update

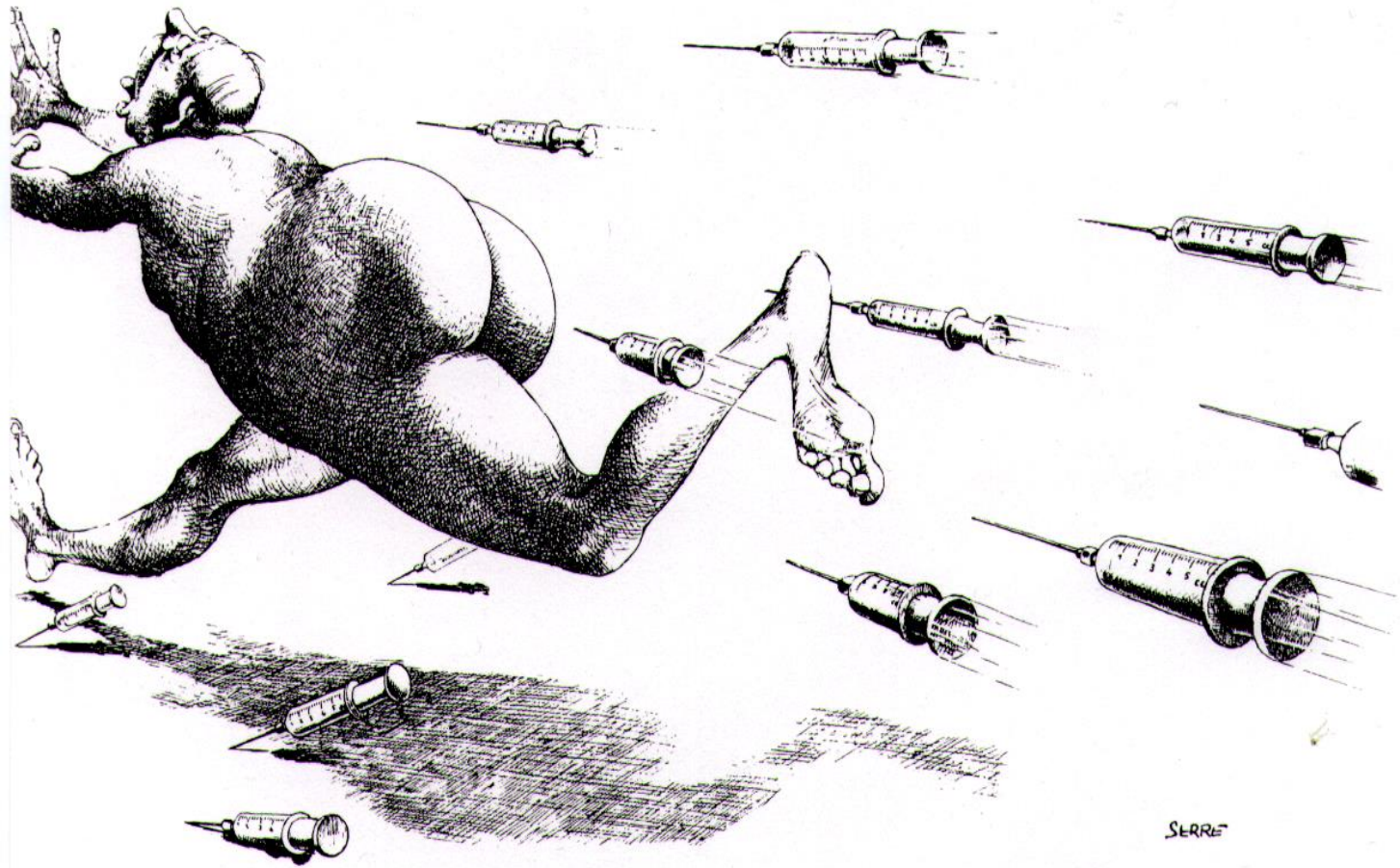
7/23/20

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**Four out of five doctors  
recommend. . .**



# Evidence Based Practice (Modified from PORT Recommendations)

- Family psycho-education
- ACT and Clubhouse psychosocial programs
- Integrated supported work programs
- Skill training
- Integrated Mental Health and AODA Treatment
- Cognitive Behavioral Therapy
- Cognitive Remediation

Dixon L, et al. *Schizophr Bull.* 2010;36:48-70.

Clubhouse not part of current PORT recommendations

# What is the purpose of taking this antipsychotic medication?

- May increase stability
- May decrease positive symptoms
- May help people improve function and quality of life

Medication can be part of a solution to a problem, but first we need to be very clear about the consumer's goal, the nature of the problem, and how medication may help

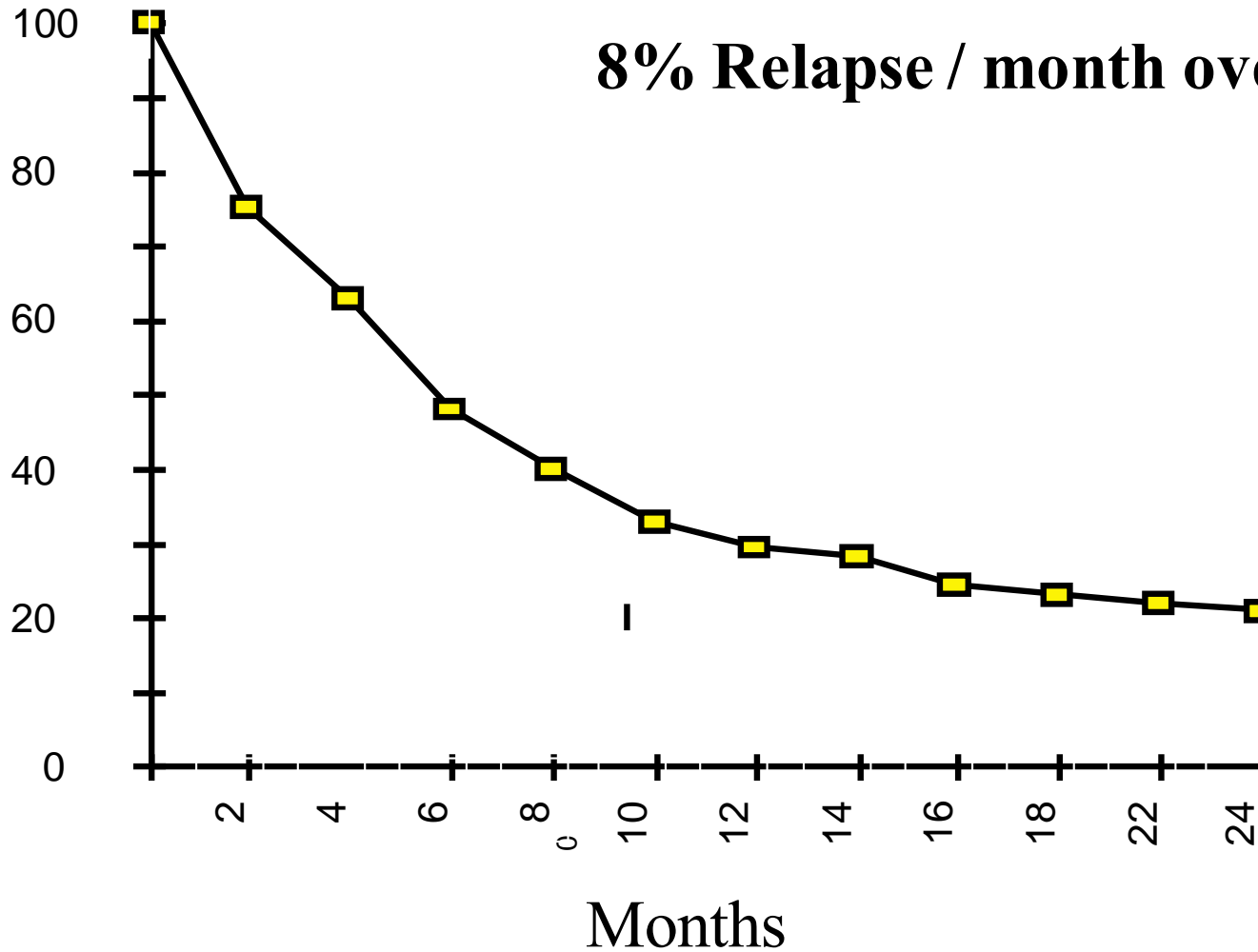
# Cost of Antipsychotic Medication

Cost of 30 tabs (from drugs.com)

- Aripiprazole 15 mg (generic): \$ 21
- Abilify 15 mg (branded form): \$ 940
  
- Olanzapine 20 mg (generic) \$ 7.50
- Zyprexa (branded form) \$ 1,370

# Relapse Rate on Placebo: Schizophrenia

Cumulative Percent Unrelapsed







“Paper or plastic?”

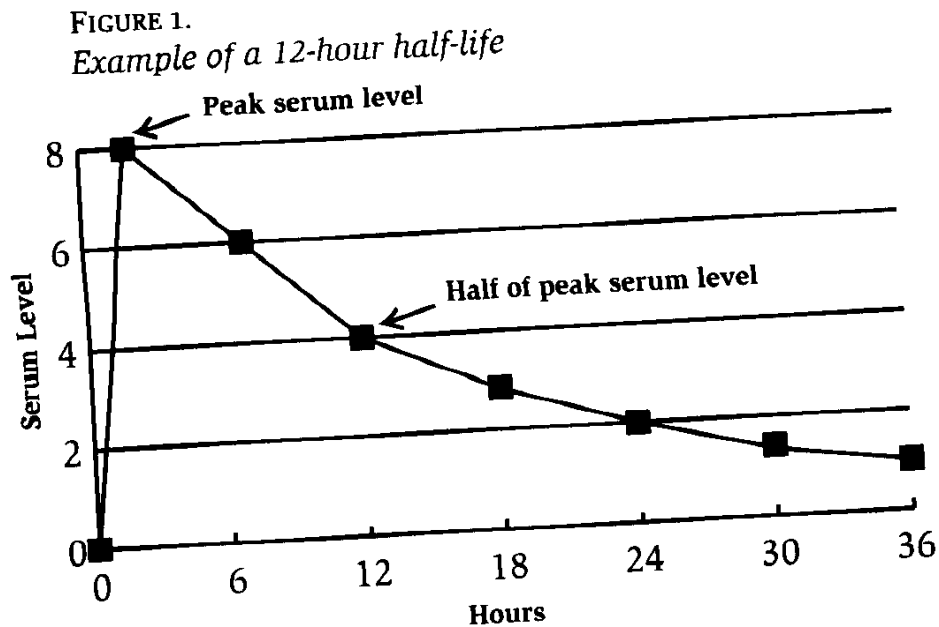
# A brief discussion about time:

Absorption

Half-life

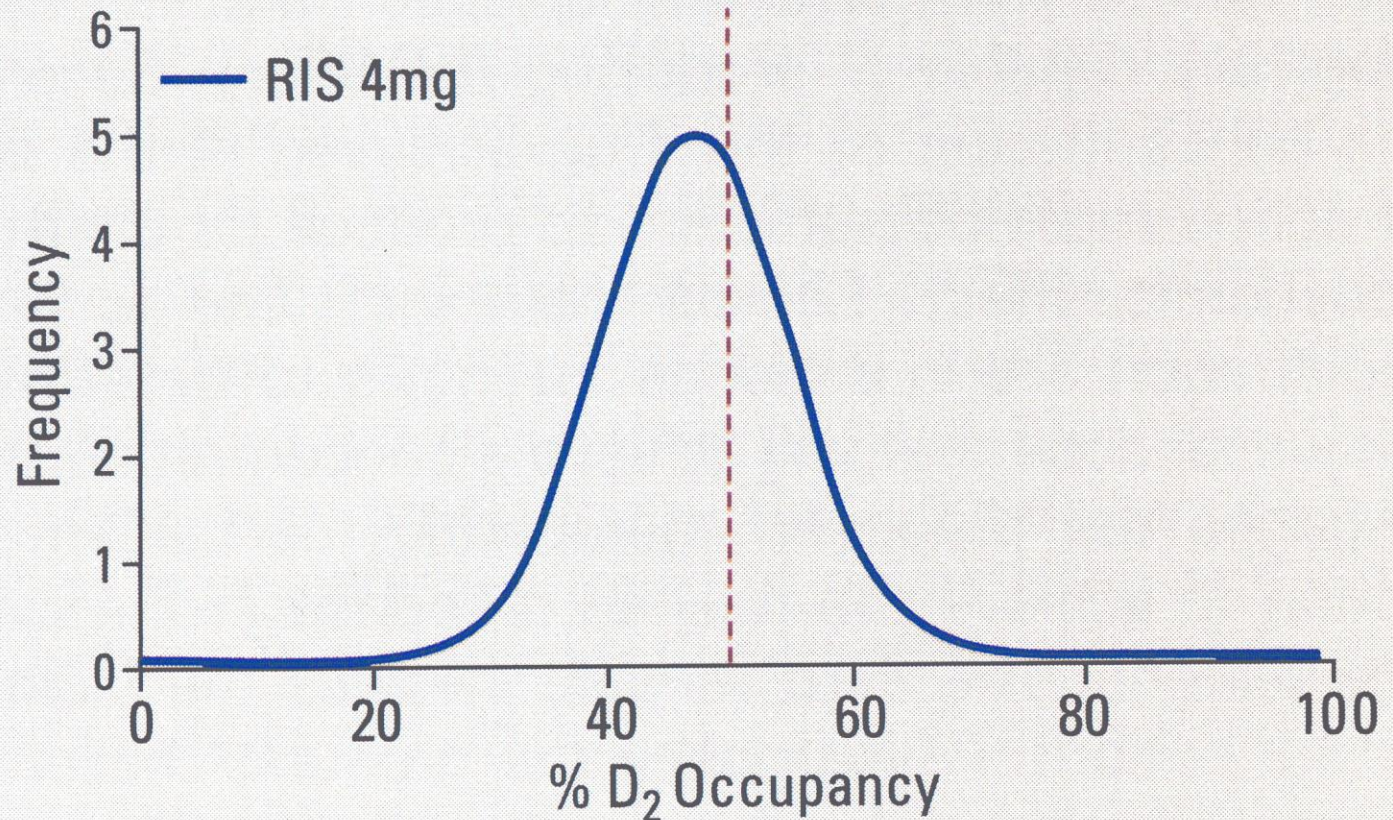
Crossing blood-brain barrier

Time to take Effect



# Same Dose $\neq$ Same Serum Level

*Distribution Curve of Dopamine Receptor Occupancy in 100 Patients Treated with Risperidone 4 mg<sup>10</sup>*



RIS=risperidone; D=dopamine.

# Smoking

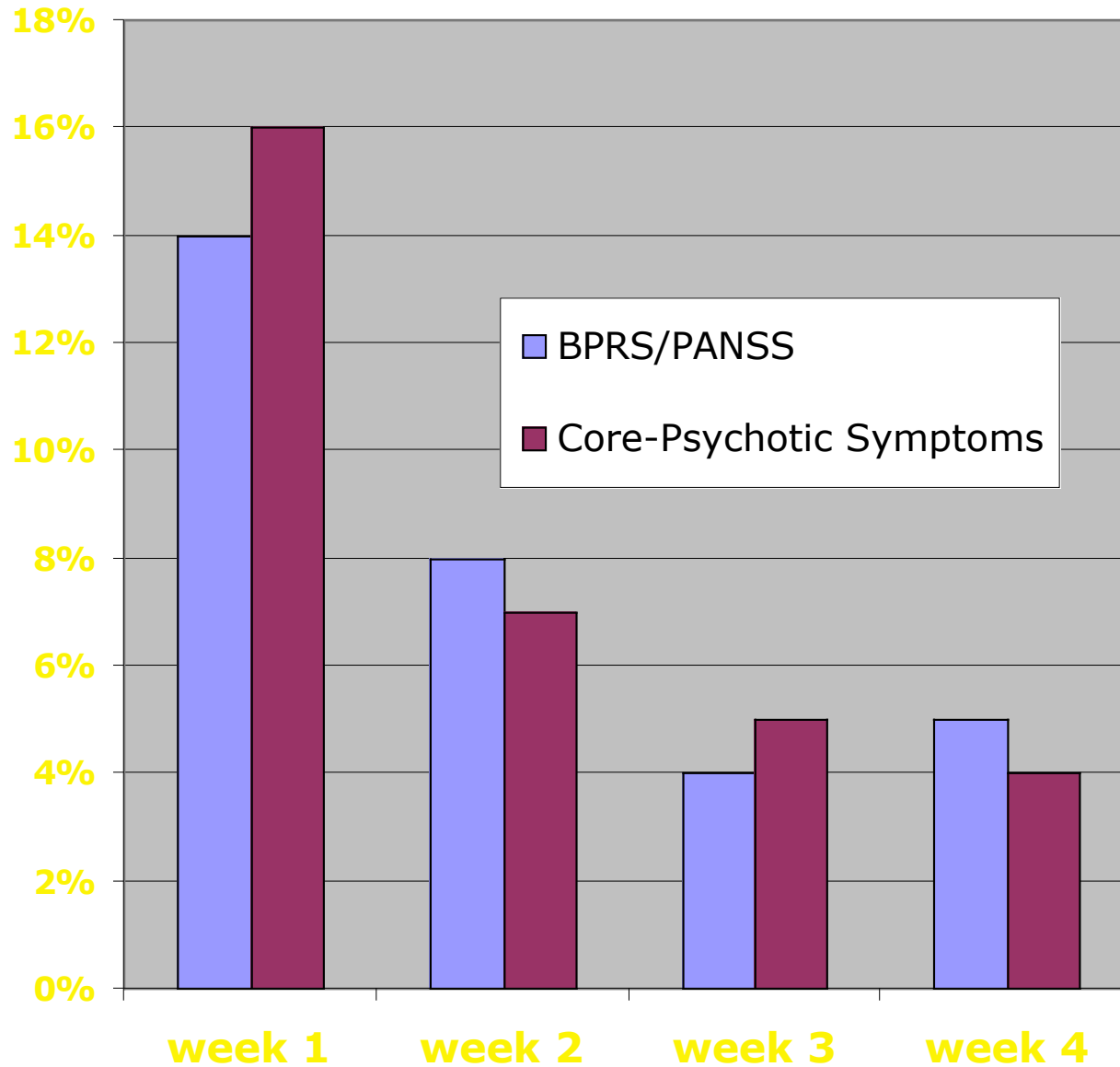
## Induced CYP 1A2

- 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.

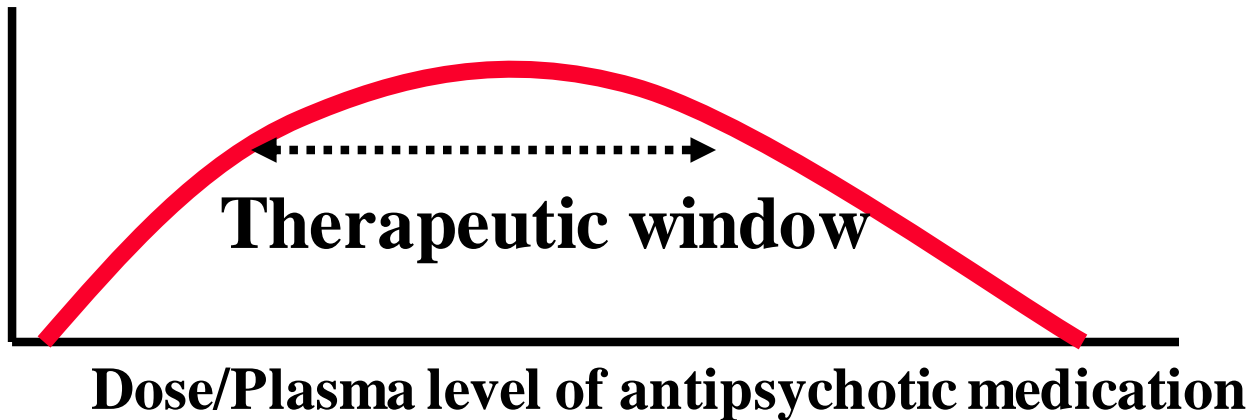
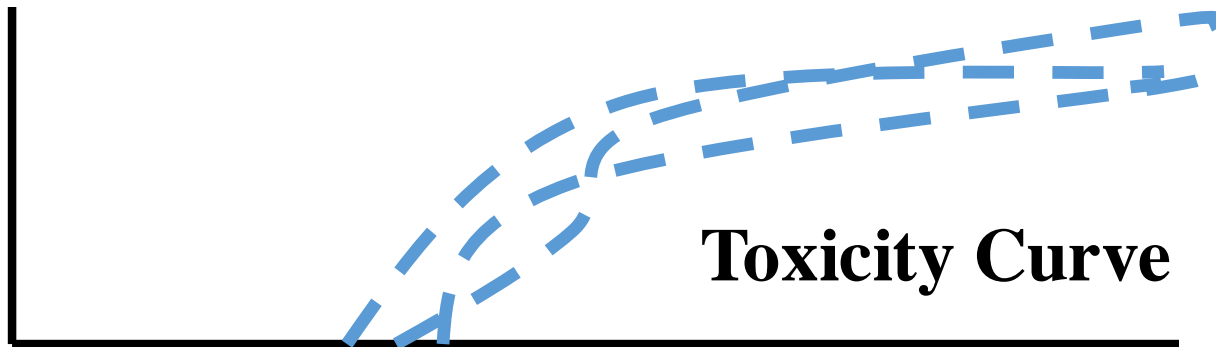
# Improvement Per Week



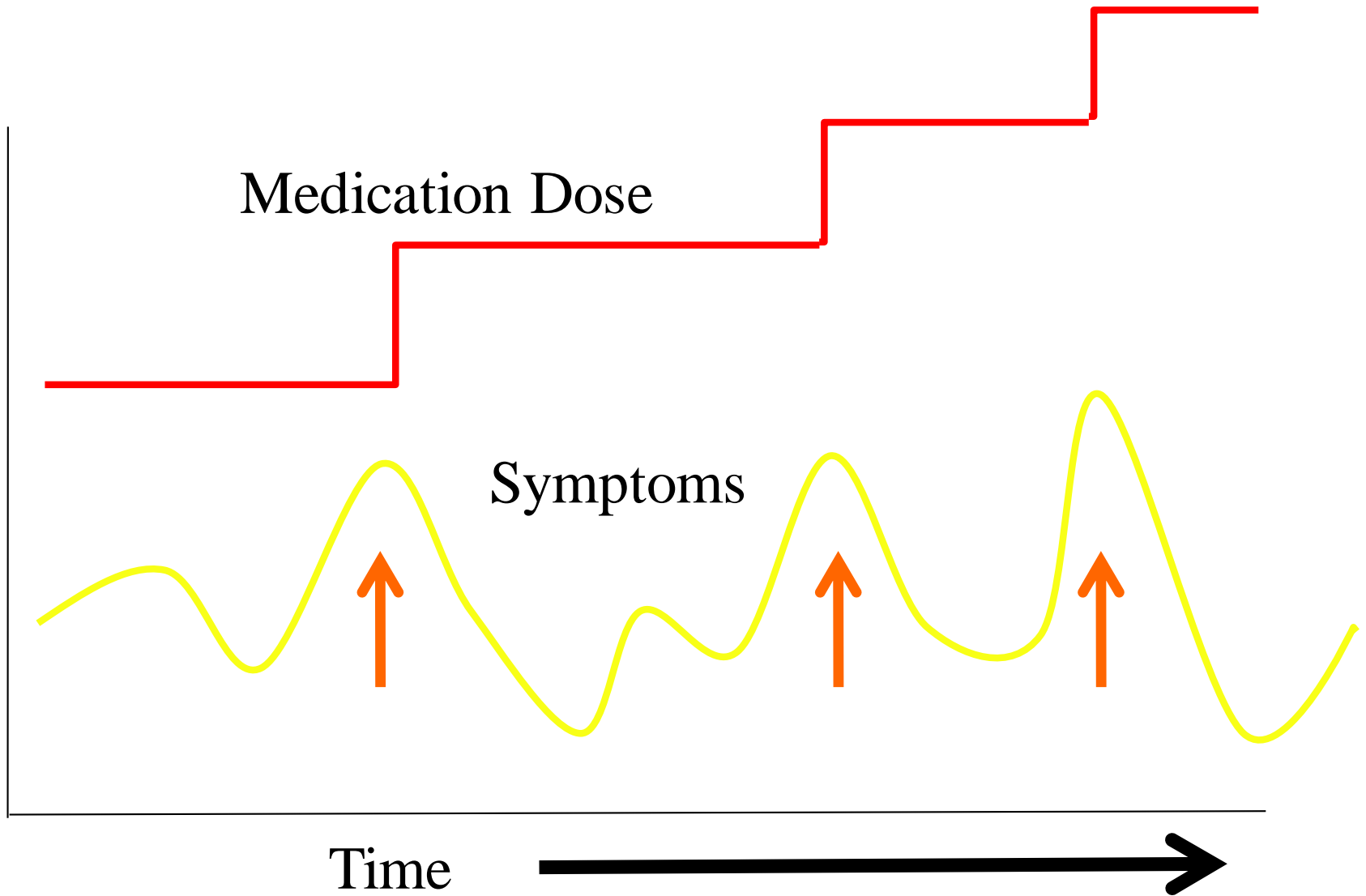
**Meta-analysis of  
114 trials with >  
8000 patients**

**Refractory patients  
and acute  
emergency patients  
excluded**

# Antipsychotic Dose-Response Curve



# Dose Escalation:



# Antipsychotic Medications: Indications

- **Schizophrenia:**
  - + **positive symptoms**
  - x **Negative symptoms**
  - x **Cognitive dysfunction**
- **Depression**
  - + **psychotic depression**
  - + **Some (quetiapine)**
- **Bipolar disorder** + **mood stabilizer (some)**
- **OCD**
- **Autism related behaviors**
- **Aggression**



# Antipsychotic Medications: other uses (NOT FDA indicated)

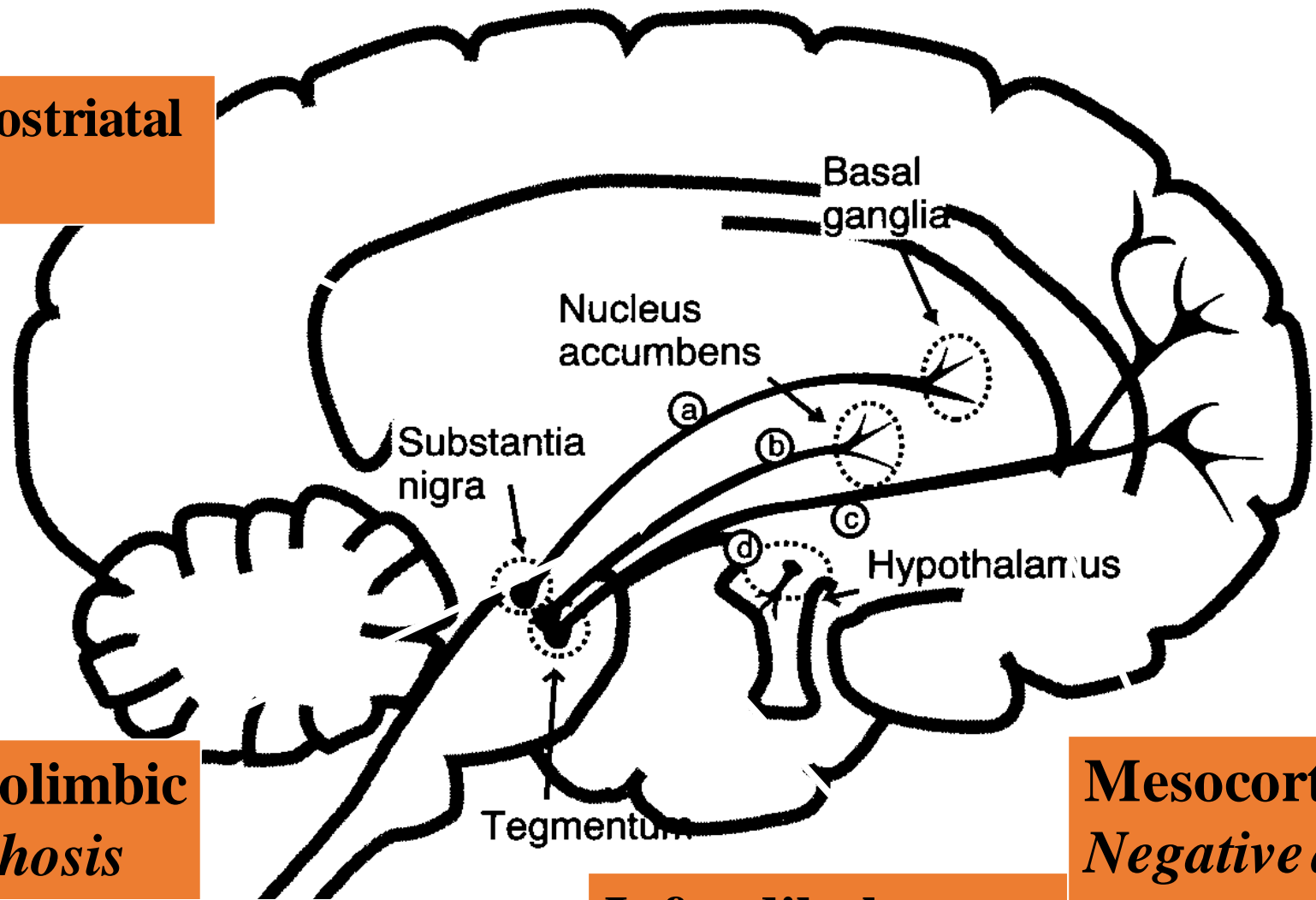
- Psychosis associated with dementia
  - Black Box warning when used in people with dementia
- Borderline Personality Disorder
- Conduct disorder/childhood aggression
- Anti-anxiety
  
- Hiccups
- Nausea

# Antipsychotic Medications: What do we really know?

- All are much more effective for positive sx than for negative sx
- Clozapine is more effective than any other antipsychotic
- None of the others is clearly more effective than any other, but they are different and different people respond differentially
- They are equally effective, but have very different side effect risks.
- The data on lifetime need is problematic and may be wrong, at least for some patients

# Dopamine Pathways

**Nigrostriatal**  
*EPS*

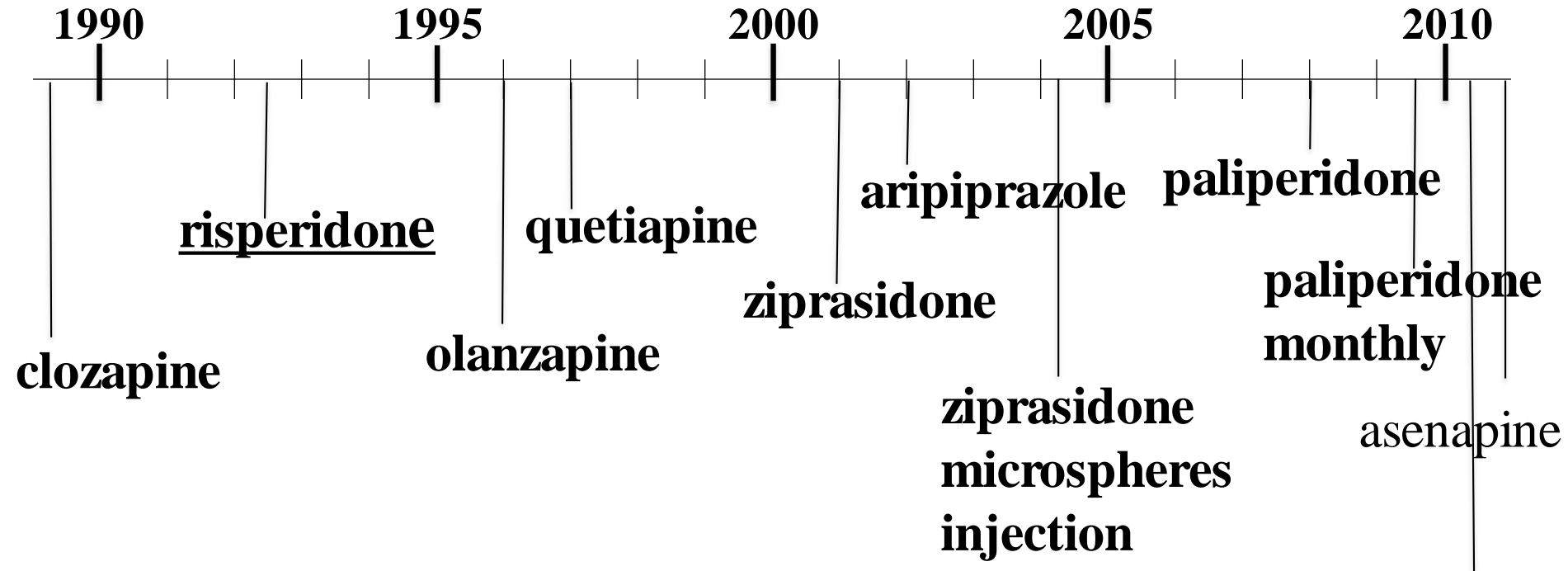


**Mesolimbic**  
*psychosis*

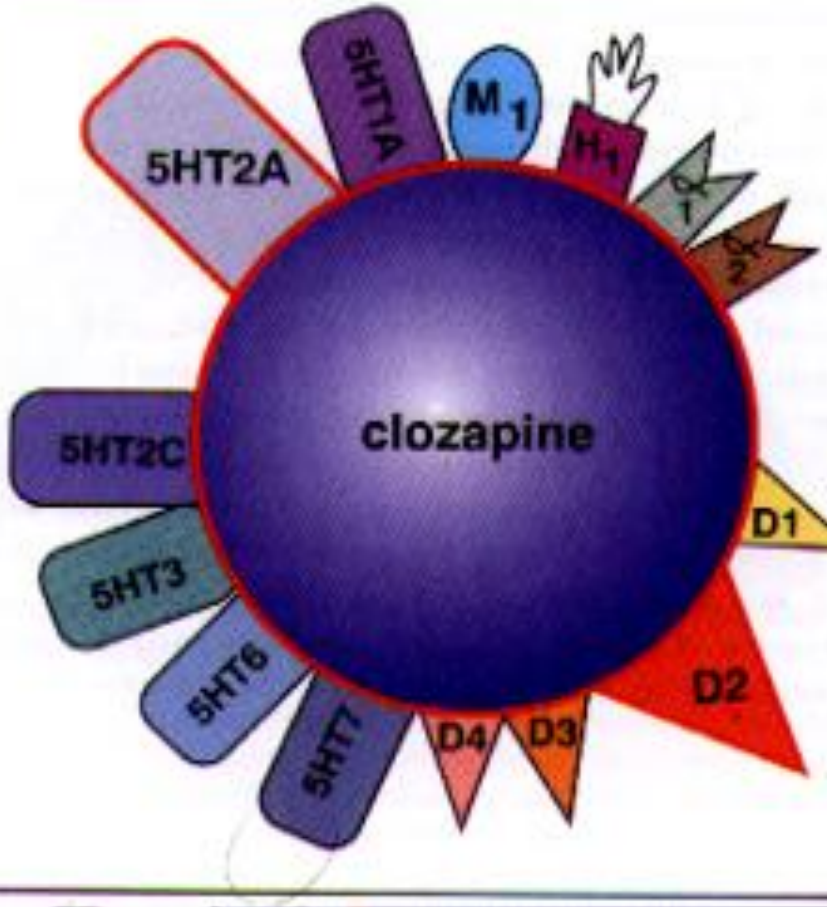
**Infundibular**  
*Prolactin elevation*

**Mesocortical**  
*Negative and cognitive sx*

# Second Generation Antipsychotic Medications

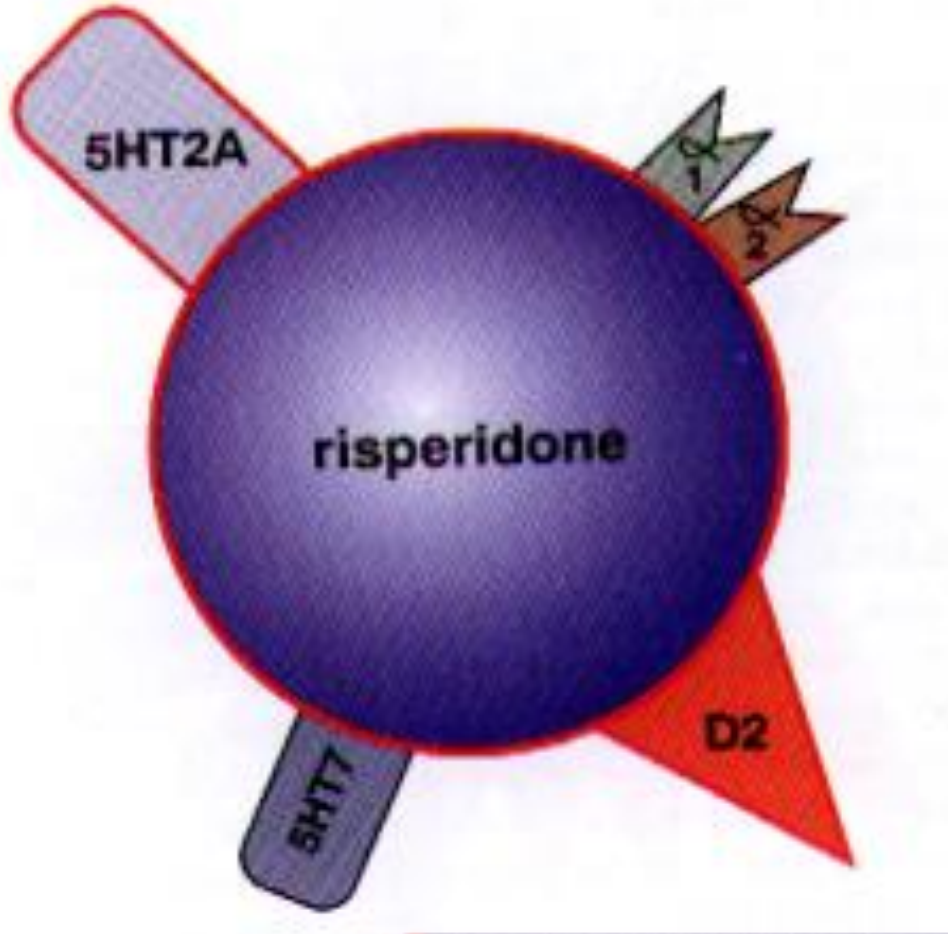


# Clozapine



- Other side effects
  - Severe neutropenia
  - Heat Related Deaths
  - Cardiomyopathy
  - Pulmonary embolism
  - Gastric hypomotility
  - Diabetes
  - Diabetic ketoacidosis
  - Drooling
  - Seizures
- Very effective
  - positive and negative
  - good mood stabilizer
  - very low EPS
  - very low TD

# Risperidone (Risperdal)



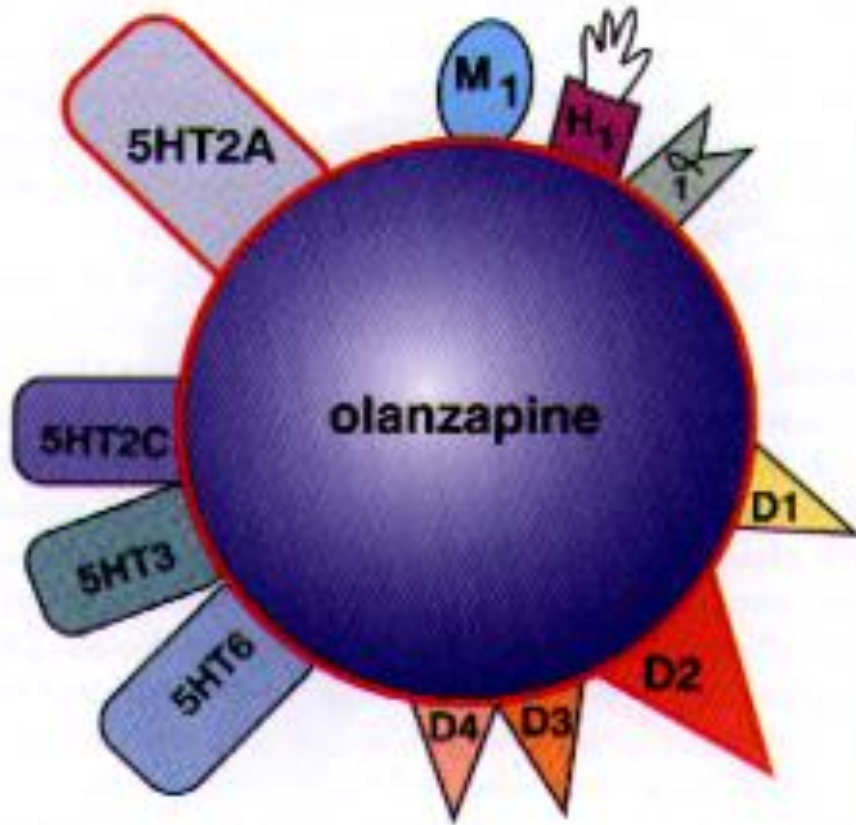
- **Dose related EPS**
- **Less is better**
- **Prolactin Elevation**
- **Weight Gain**
  
- **Positive and negative efficacy**
- **Mood stabilizer**
- **Decreased TD**

Adapted from Stahl  
Essential Psychopharmacology

# 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

# Olanzapine (Zyprexa)

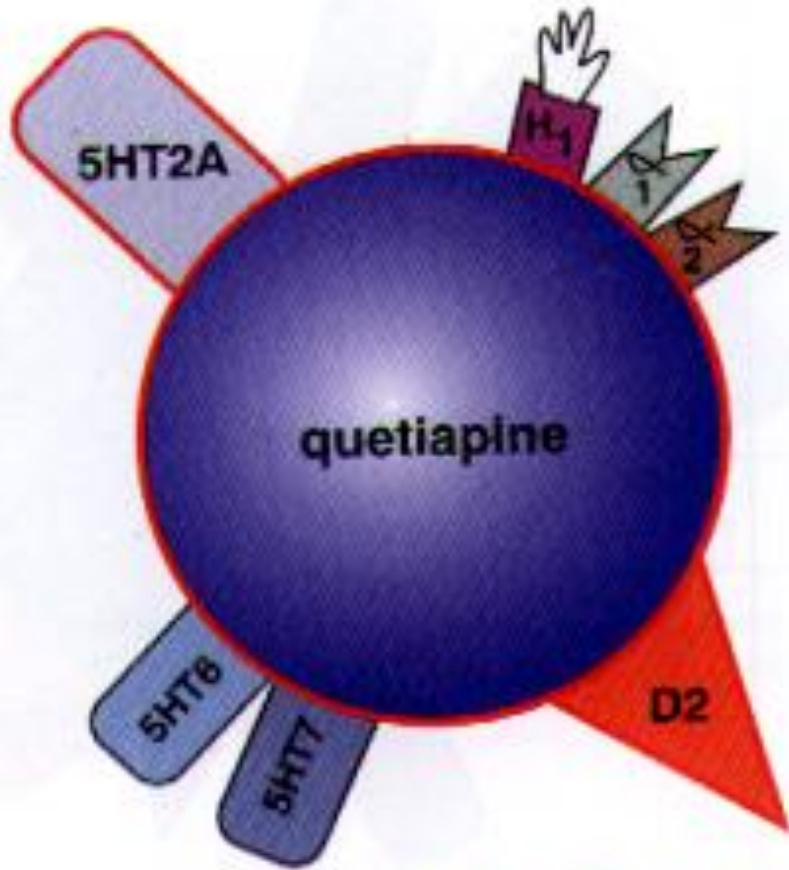


- Some dose related EPS
- Slight prolactin Elevation
- Big Weight Gain
- Diabetes (?)
- Somewhat sedating
  
- Positive and negative efficacy
- Mood stabilizer
- Decreased TD

Adapted from Stahl  
Essential Psychopharmacology



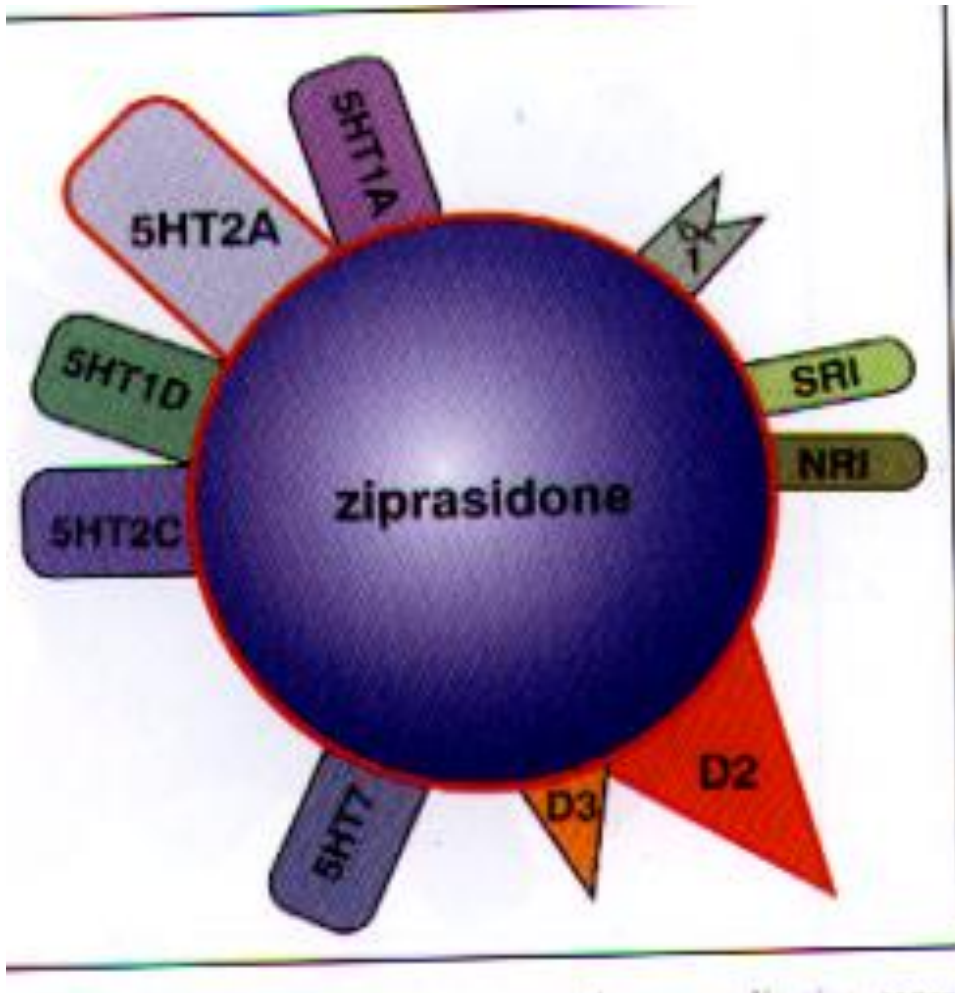
# Quetiapine (Seroquel)



Adapted from Stahl  
Essential Psychopharmacology

- **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**

# Ziprasidone (Geodon)



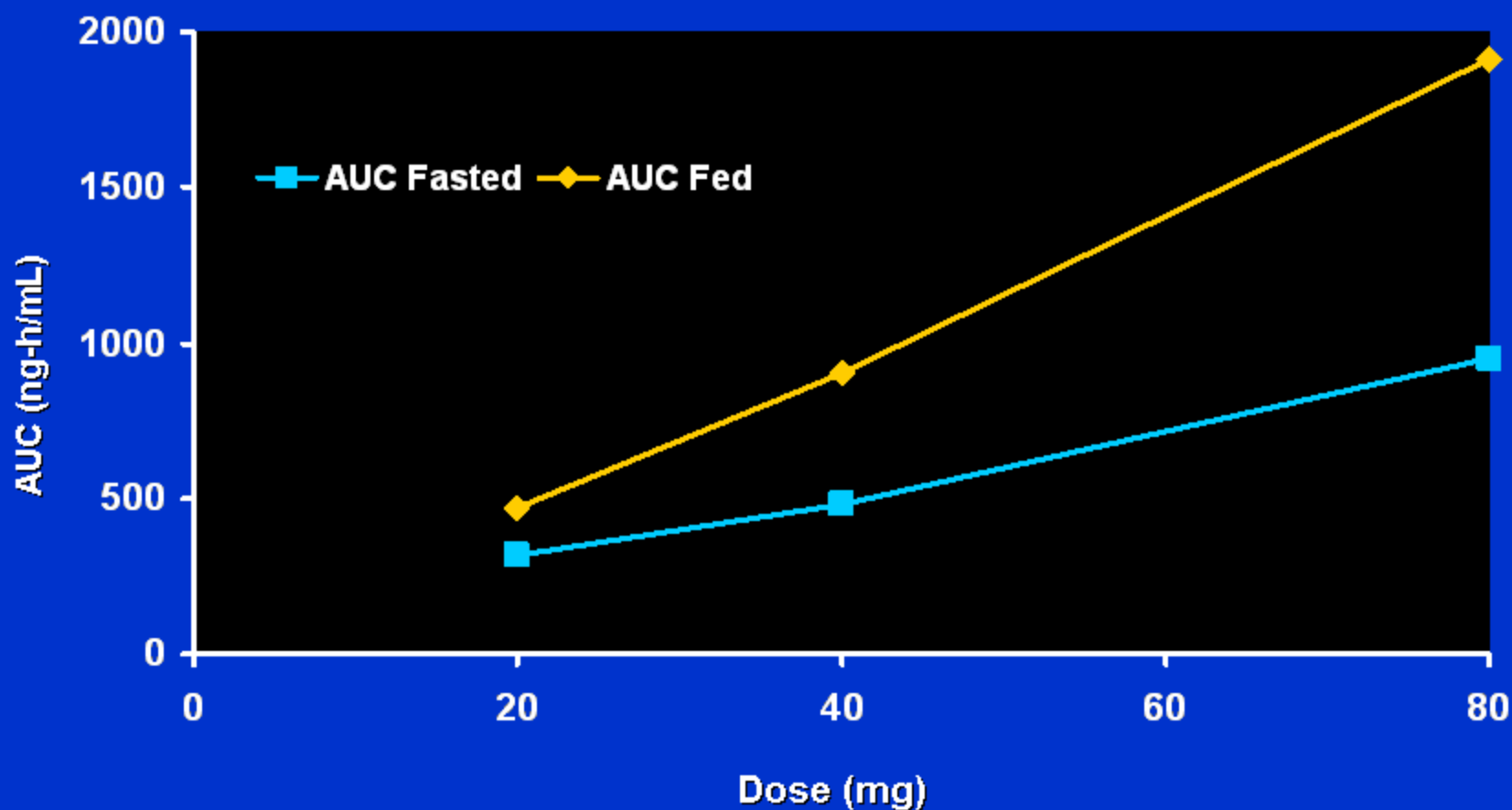
Adapted from Stahl  
Essential Psychopharmacology

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

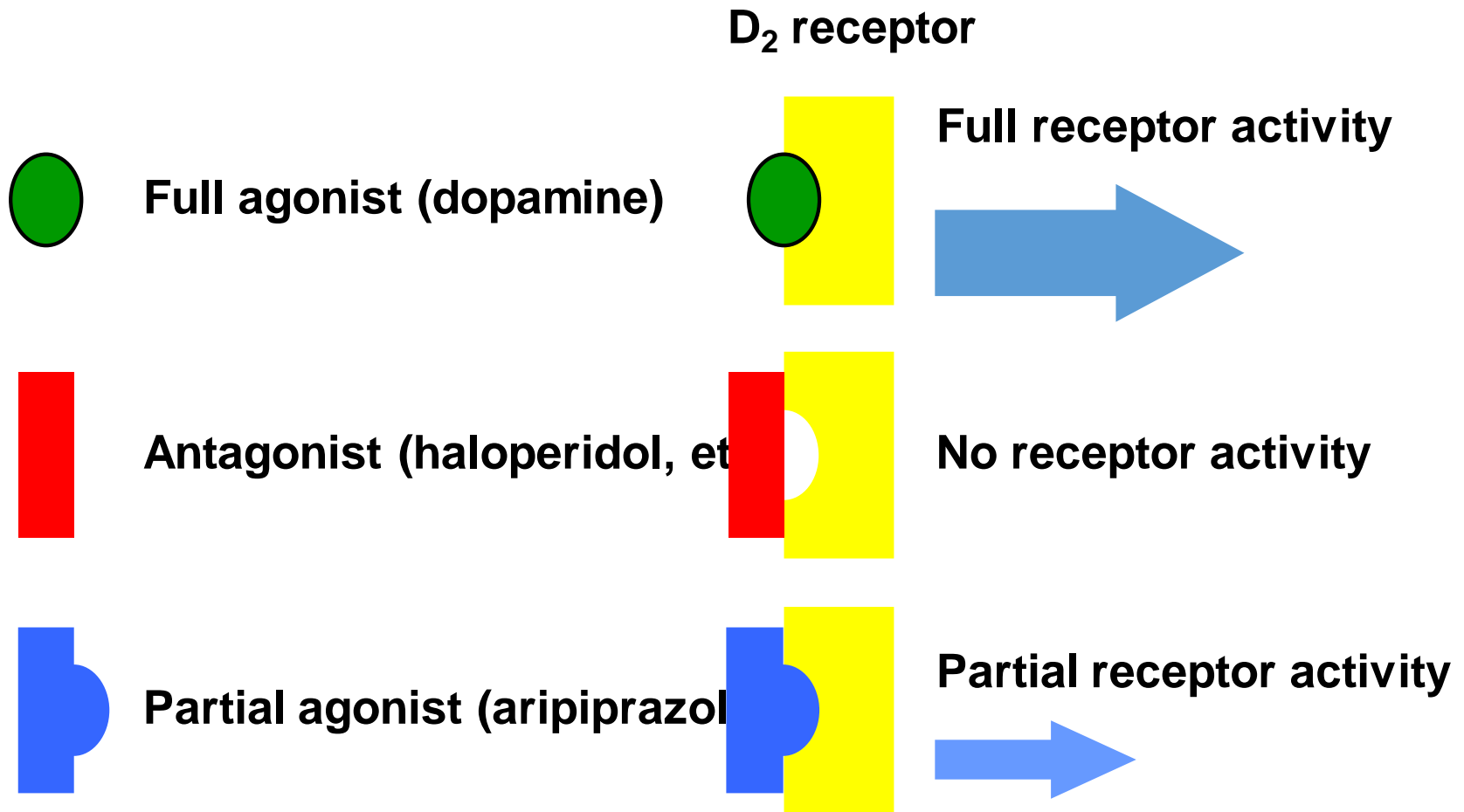
**QTc prolongation**  
**Activating/agitating**  
**Antidepressant activity**

**Nausea, sleep disturbance**  
**EPS dose related**

# Dose Ziprasidone With Food to Maximize Absorption



# Intrinsic Activity: Ability to Stimulate Receptors



Tamminga. *J Neural Transm.* 2002;109:411.

# Iloperidone (Fanapt): Problems

- Dose dependent increase in QTc (9.1 msec at 20-24mg/day) which may or may not be an issue
- Must be titrated gradually to prevent dizziness
- Start 1 mg BID, then increase 2mg/day til 12-24 mg
- 2D6 inhibitors can increase serum level (fluoxetine, paroxetine)
- Several negative effectiveness studies

# Asenapine (Saphris)

- Sublingual tablet
  - 35% bio-available sublingual <2% oral
  - Bid dosing-- sublingual tablet
  - Avoid food 10 min after dose
- 5HT 2D2 antagonist
- Also antagonist at D1,D3,D4, 1-HT1A, 5-HT2A,5-HT2C, alpha 1 and H1
- Less wt gain than olanzapine
- VERY LITTLE data published

# Lurasidone (Latuda) (FDA approved Oct 2010)

- **Weight Neutral**
- FDA indications for schizophrenia and Bipolar depression
- High Affinity for:  $D_2$ ,  $5-HT_{2A}$ ,  $5-HT_7$ ,  $5-HT_{1A}$   
 $NE_{\alpha 2c}$
- Low Affinity for:  $NE_{\alpha 1}$  and  $\alpha 2a$ ,  $H_1$ ,  $M_1$
- EPS similar to risperidone
- 160 mg had better clinical outcomes than 80 mg
- **[MORE IS BETTER]**

# New antipsychotic medications

All are very expensive, have no long-term data, and no data demonstrating better efficacy than older better known medications.

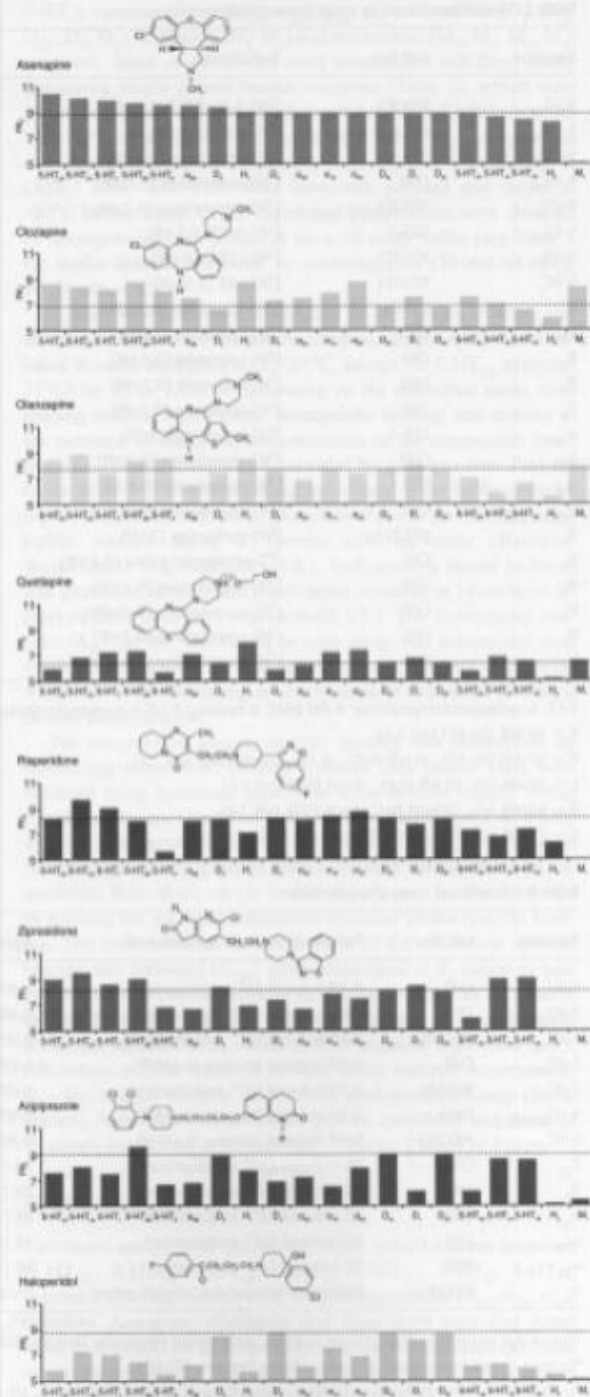
- Brexpiprazole (Resulti): D2 partial agonist, in some ways similar to aripiprazole
- Cariprazine (Vraylar): D2 and D3 partial agonist with preferred binding to D3
- Lumateperone (Caplyta): much more serotonin rather than D2 binding



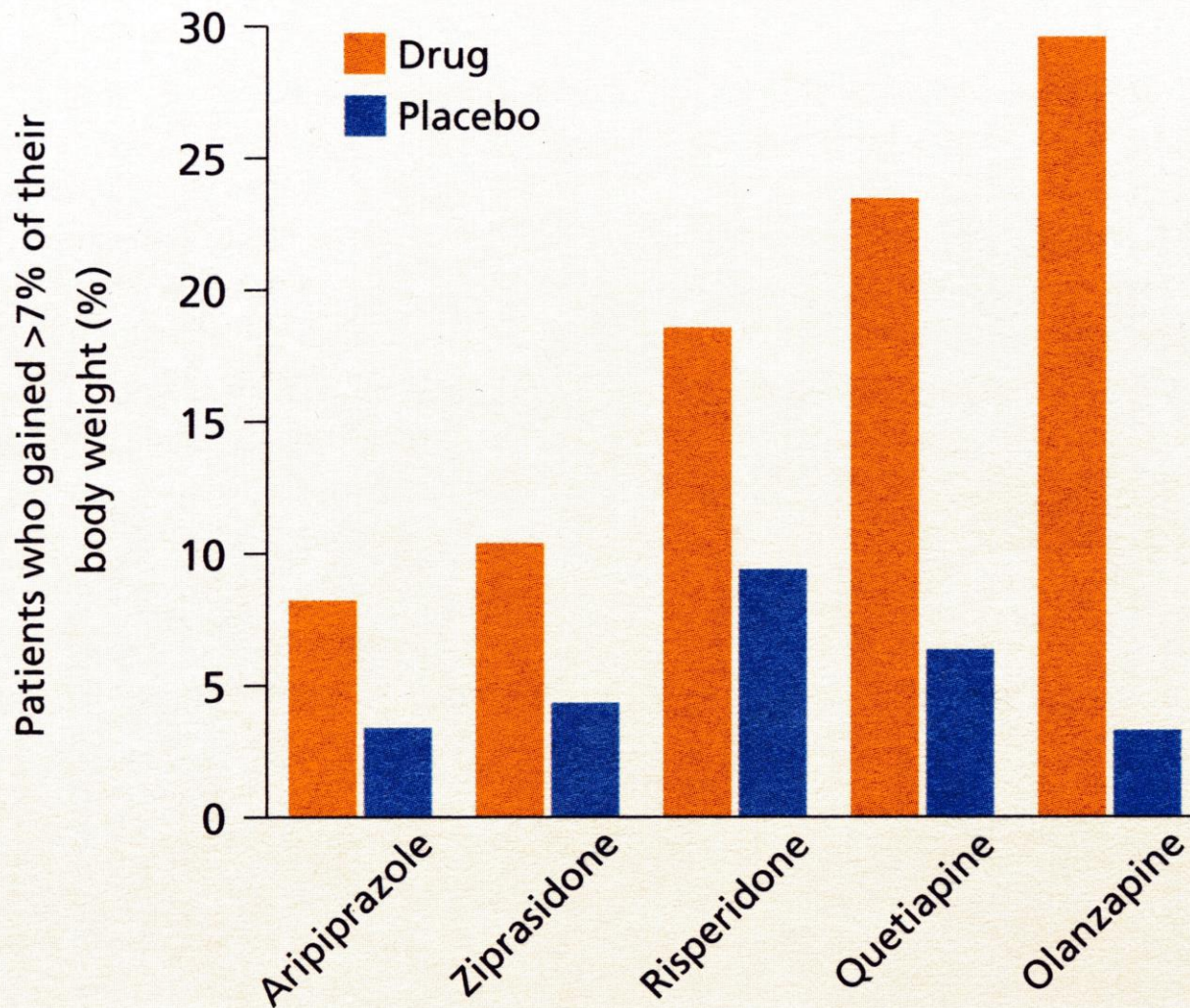
# 1<sup>st</sup> Generation Antipsychotic Meds

- Chlorpromazine ----- Thorazine
- Fluphenazine ----- Prolixin
- Haloperidol ----- Haldol
- Thiothixene ----- Navane
- Perphenazine ----- Trilafon
  
- Loxapine ----- Loxatane
- Molindone ----- Moban

# Receptor Binding of Currently Available Atypical Antipsychotic Meds



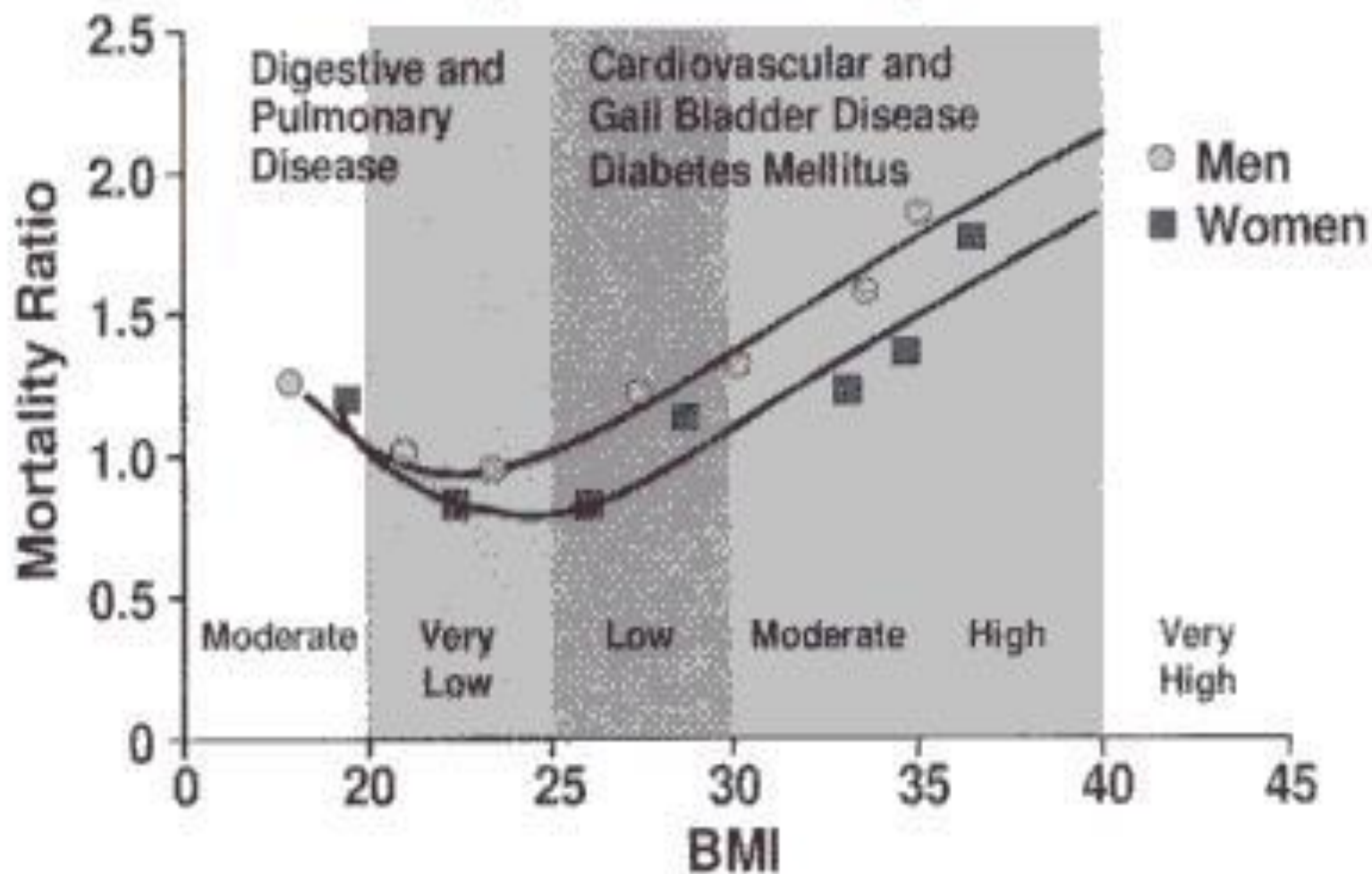
# Percentage of Patients With Clinically Significant Weight Gain in Short-Term Placebo-Controlled Trials



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

# Antipsychotic Side Effects

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

## Metabolic Side Effects:

- Weight gain, diabetes, cardiovascular disease

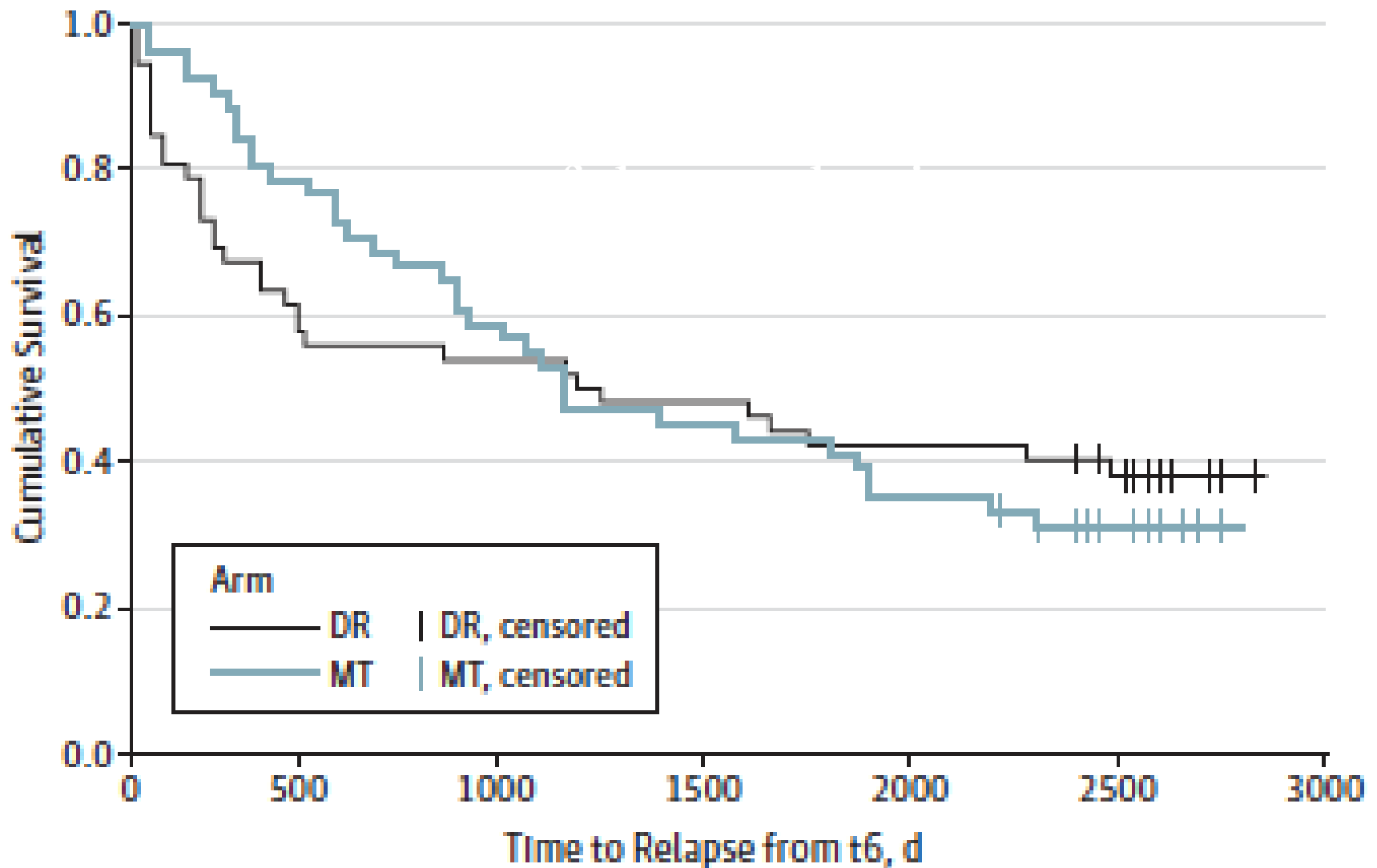
# Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy: Wunderink et al 2013

128 pts remitted on antipsychotic meds for 6 months, then randomized to maintenance dose or slow dose reduction

- Initial relapse rates twice for DR Vs MT in first 2 years
- Relapse = between two groups > 3 yrs
- Recovery (Andreason criteria) all PANSS items 1-3 on 7 point scale
- Function (Groningen Social Disability Schedule (GSDD) all 7 subscales 1 or lower

## Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy: Wunderink et al 2013

- The DR patients experienced twice the recovery rate of the MT patients (40.4% vs 17.6%).
- Logistic regression showed an odds ratio of 3.49 (P =.01).
- Better DR recovery rates were related to higher functional remission rates in the DR group but were not related to symptomatic remission rates.



Time to first relapse after first remission (t6) during 7 years of follow-up in patients assigned to 18 months (547 days) of dose reduction/discontinuation (DR) or maintenance treatment (MT).