Pharmacodynamics of Antipsychotic Drugs

Donald C. Goff, MD

Harvard University

Shitij Kapur, MD

Univesity of Toronto

Conventional (Typical) Antipsychotics or "Neuroleptics"

- Dopamine D2 blockers
- Produce extrapyramidal symptoms (EPS)
- Elevate prolactin (PRL) levels
- All conventional agents are equally effective but differ in potency and side effects

Conventional Neuroleptics: Activity at Other Receptors

- Alpha-adrenergic (hypotension)
- Histaminergic (sedation)
- Muscarinic anticholinergic (dry mouth, etc.)

"Low-potency" agents have relatively higher affinities for these receptors

Atypical Antipsychotics: Shared Characteristics

Share D2 and 5HT2A antagonism in common.

Addition of 5HT2A blockade may:

- reduce EPS
- improve efficacy for negative symptoms

Additional Receptor Activities of Atypical Antipsychotics

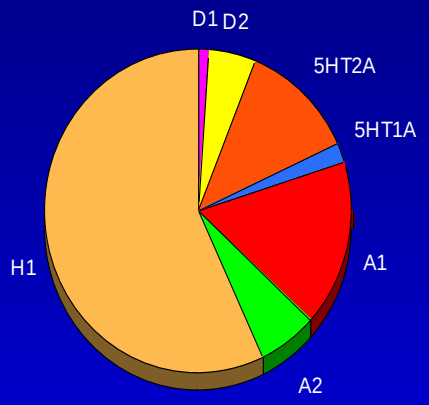
Clozapine also binds to:

- Other dopamine subtypes (D1, D3, D4)
- Alpha adrenergic (alpha 1&2)
- Histaminergic (H1)
- Muscarinic anticholinergic (M1)
- Other serotonergic subtypes (5HT1A, 2C, 6 & 7)

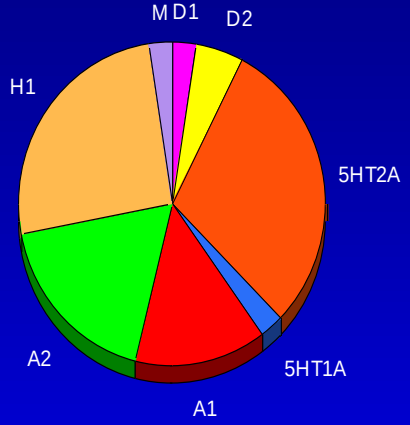
Other atypicals vary in activity at these receptors

Comparative Receptor Binding Profiles

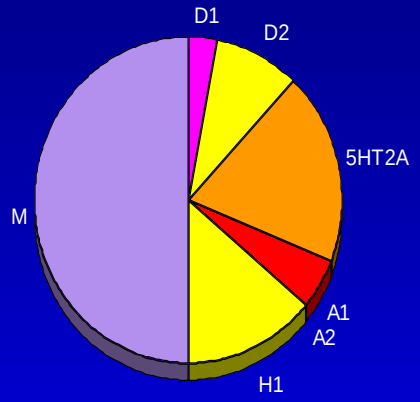
Quetiapine



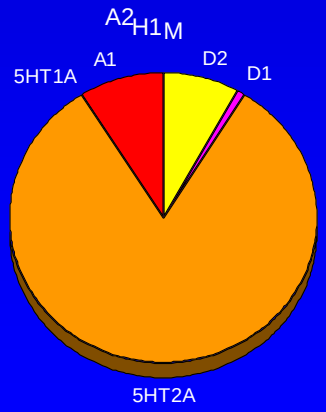
Clozapine



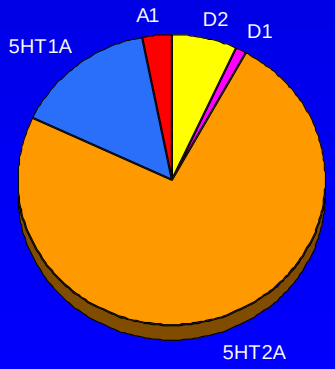
Olanzapine



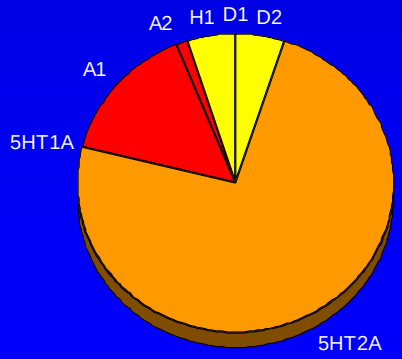
Sertindole



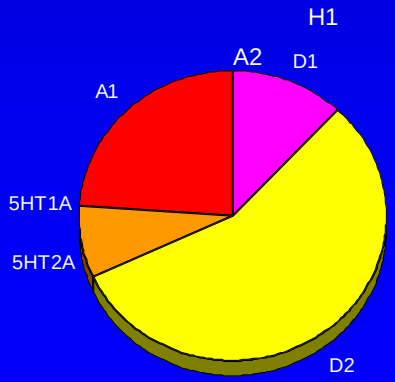
Ziprasidone



Risperidone



Haloperidol



Acute effects on dopamine systems

- Conventional agents block 65-90% of D_2 receptors-- certain atypicals are effective with much lower D_2 occupancy
- Blockade of presynaptic D_2 autoreceptors increases neuronal electrical activity and release of dopamine

Delayed effects (4-6 weeks)

- Conventional agents increase density of post-synaptic D_2 receptors (supersensitivity)
- Conventional agents produce depolarization blockade in A9 (substantia nigra) and A10 (ventral tegmental) dopamine neurons
- Atypical agents produce depolarization blockade in A10 neurons only
- All agents increase c-fos in nucleus accumbens; conventionals increase c-fos in striatum

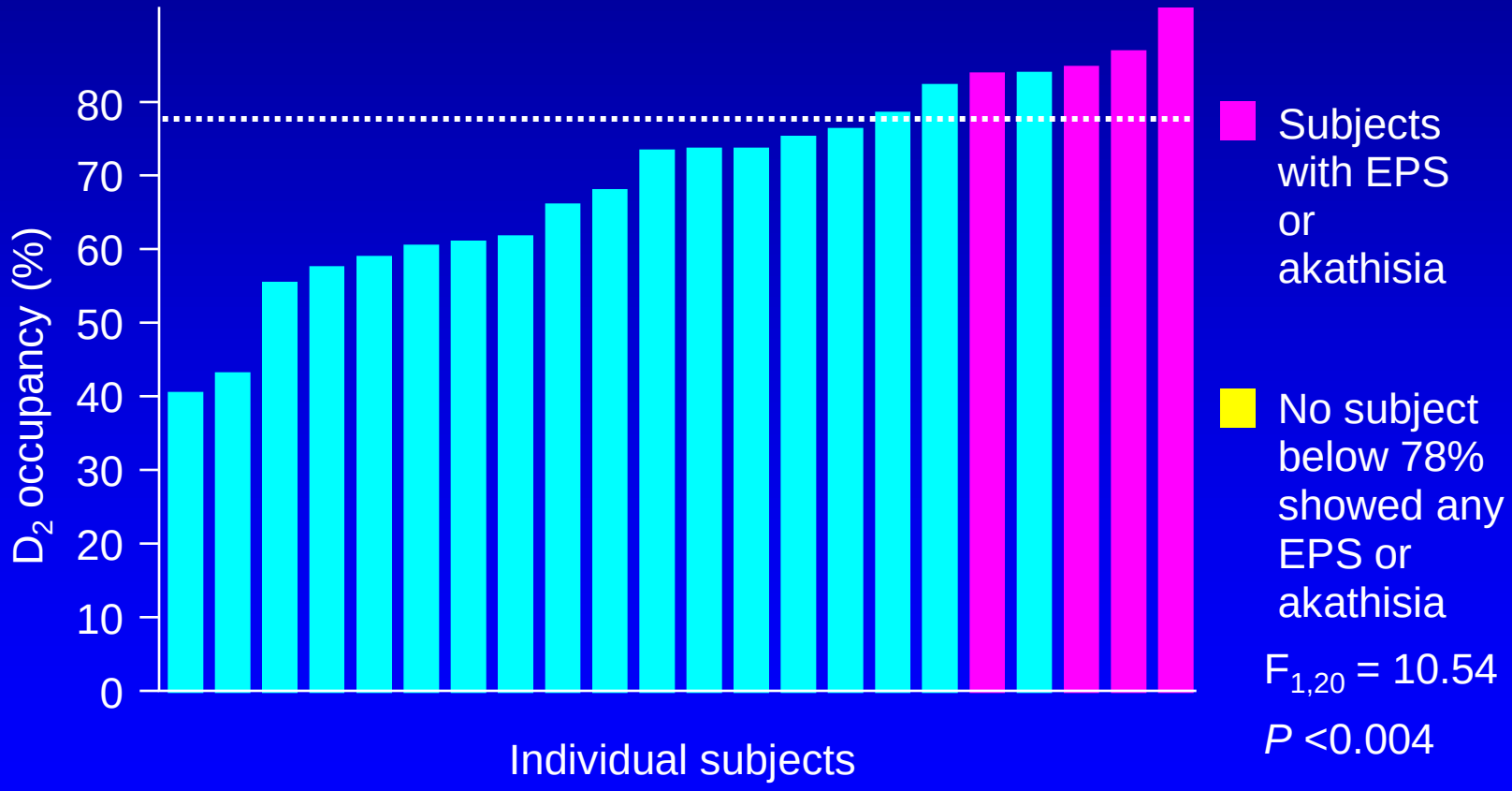
Dopamine Neurons/ Pathways

- A9/ Nigrostriatal (midbrain to neostriatum), blockade responsible for EPS
- A10/ Mesolimbic (midbrain to limbic structures) blockade possibly associated with antipsychotic effect?
- A10/ Mesocortical (midbrain to frontal and temporal cerebral cortex) possibly associated with negative symptoms?

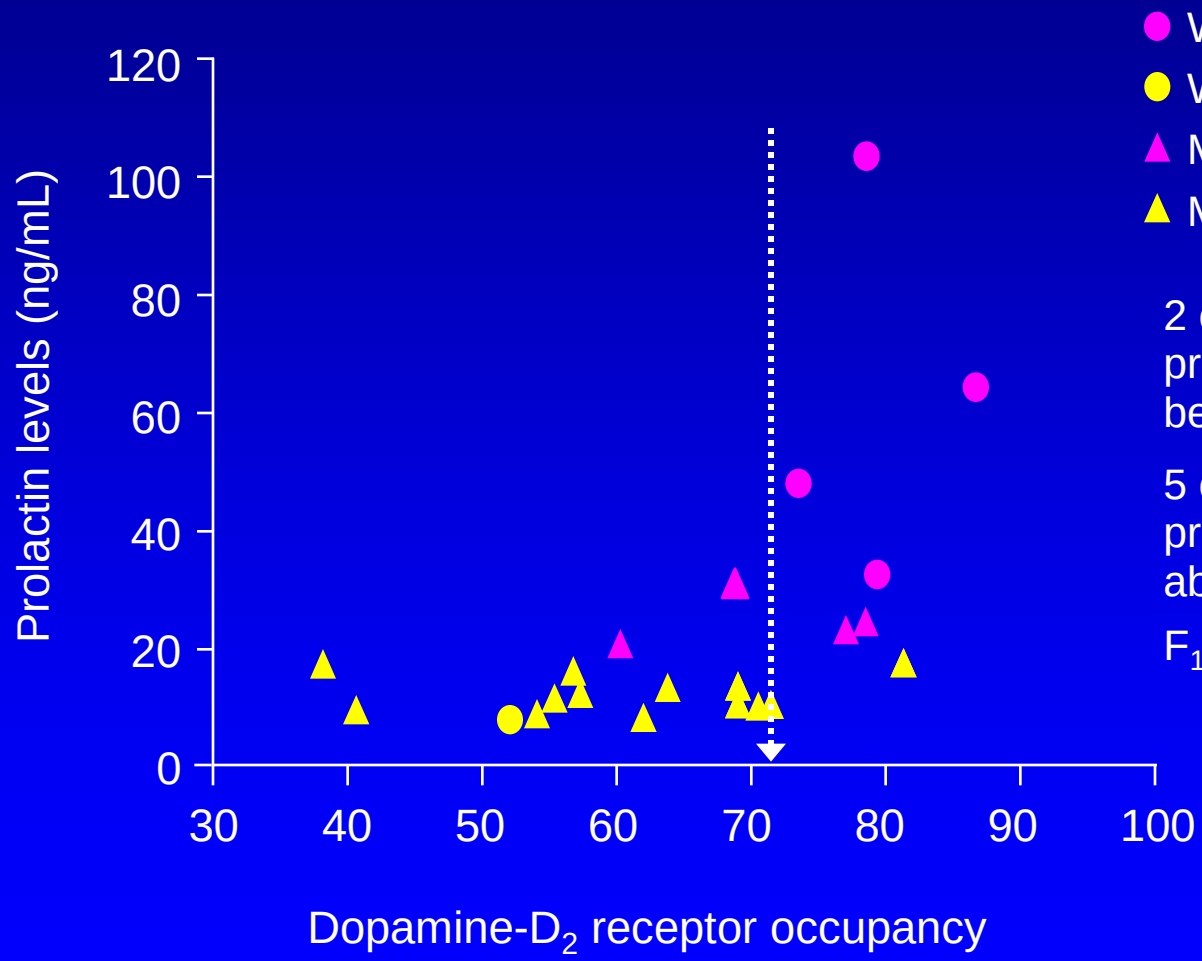
Dopamine blockade and clinical effects of conventional agents

- 65% occupancy associated with efficacy
- 70% occupancy associated with hyperprolactinemia
- 80% occupancy associated with EPS and akathisia

D_2 Occupancy Predicts EPS/Akathisia



D_2 Occupancy Predicts Prolactin Elevation



- Women – elevated
- Women
- Men – elevated
- Men

2 of 15 show prolactin elevation below 72% D_2

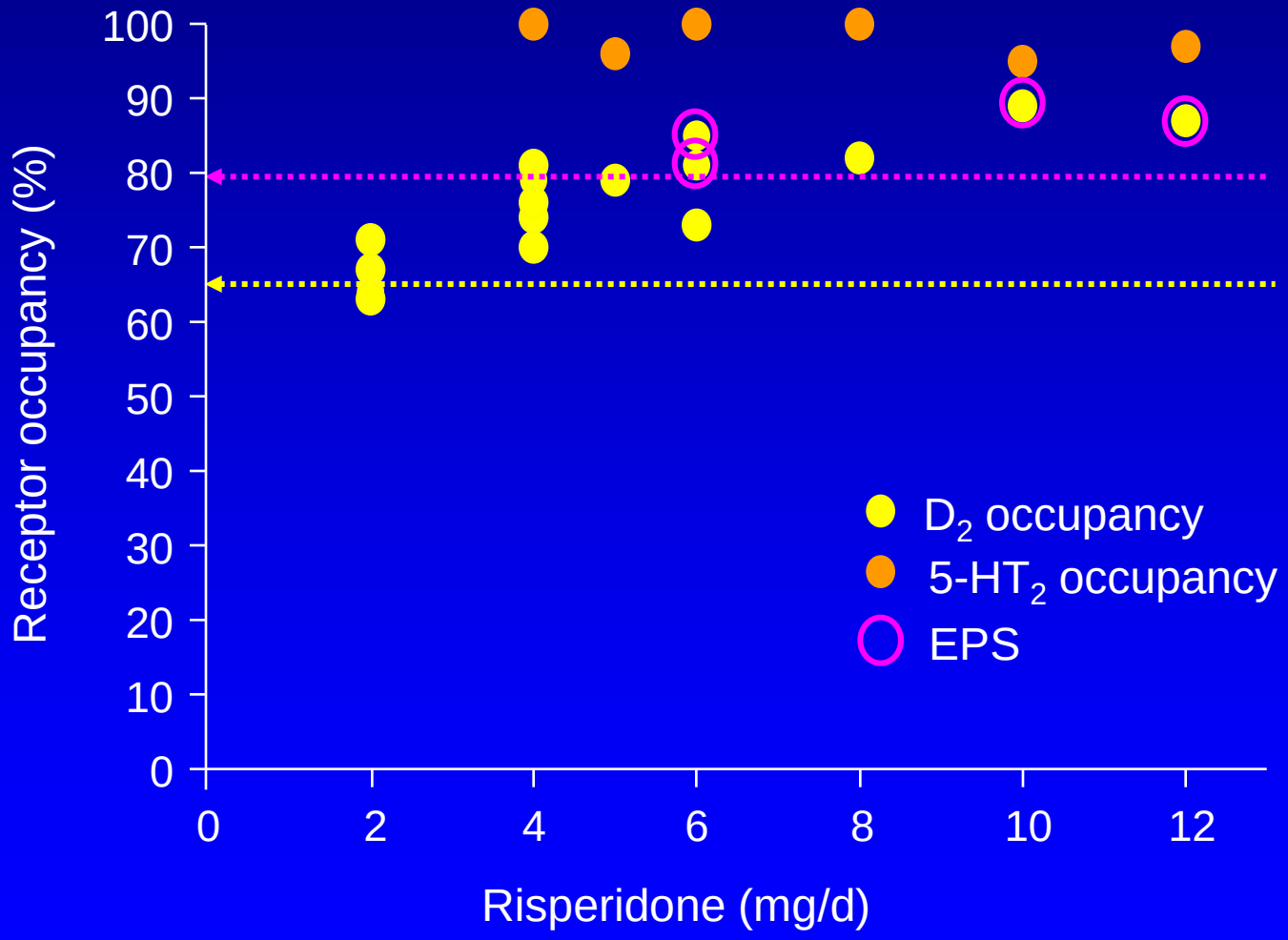
5 of 6 show prolactin elevation above 72% D_2

$F_{1,20} = 7.3$, $P < 0.01$

Atypical agents and D2 blockade

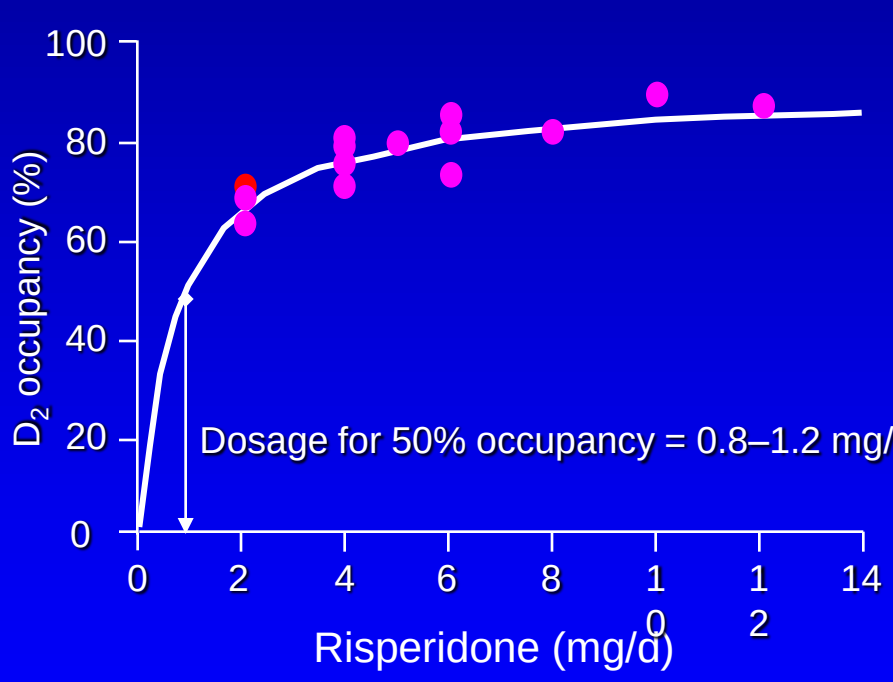
- Risperidone achieves 70% occupancy at approx 5 mg/d
- Olanzapine achieves 70% occupancy at approx 20 mg/d
- Clozapine and quetiapine do not exceed 60% occupancy
- Quetiapine is rapidly displaced from D2 receptors

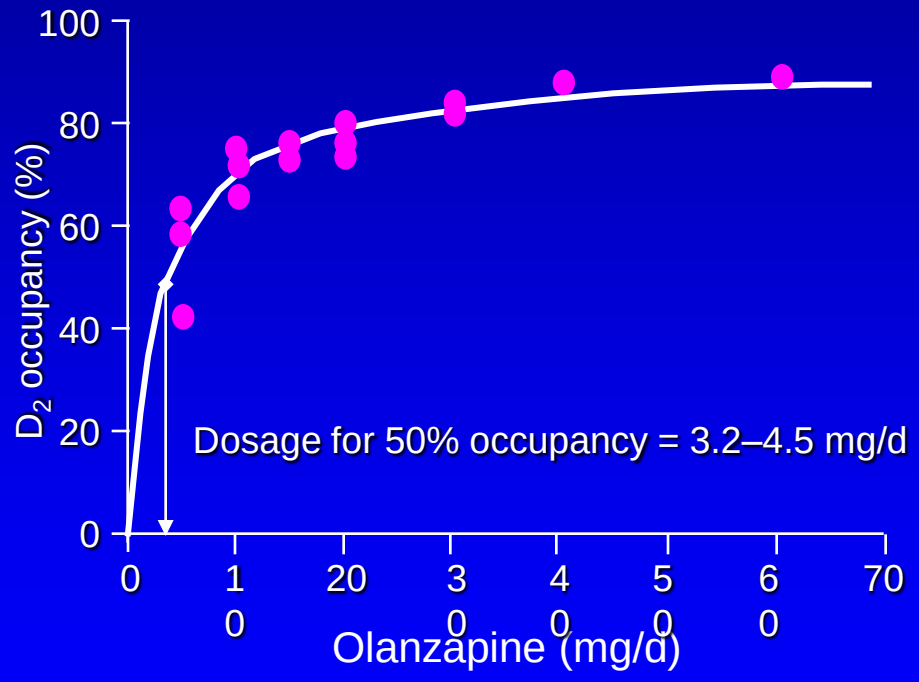
Risperidone 5-HT_2 and D_2 Occupancy



Risperidone and Olanzapine

D_2 Occupancy

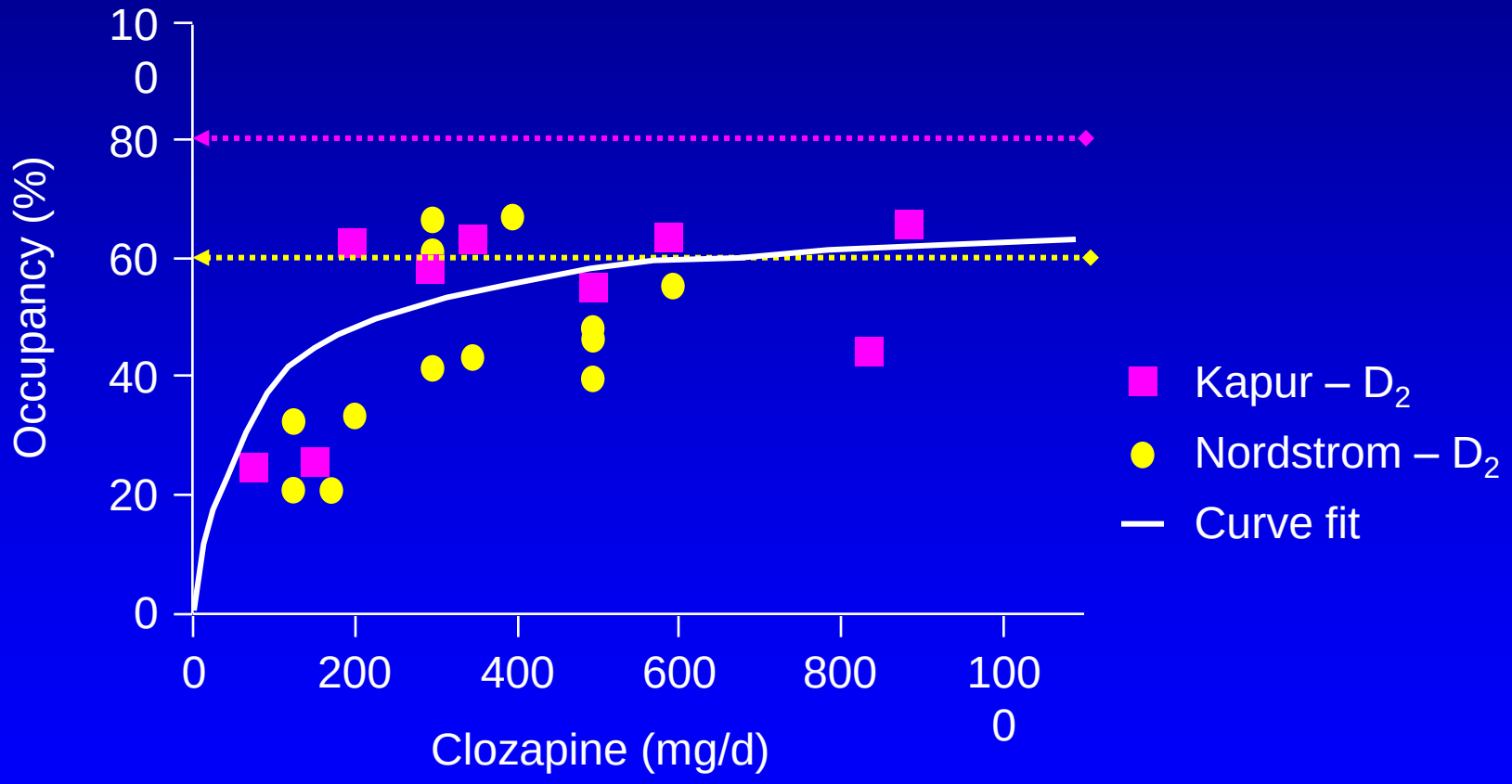




D_2 equipotent doses: 2.5–3.0 mg/d risperidone vs 10 mg/d olanzapine

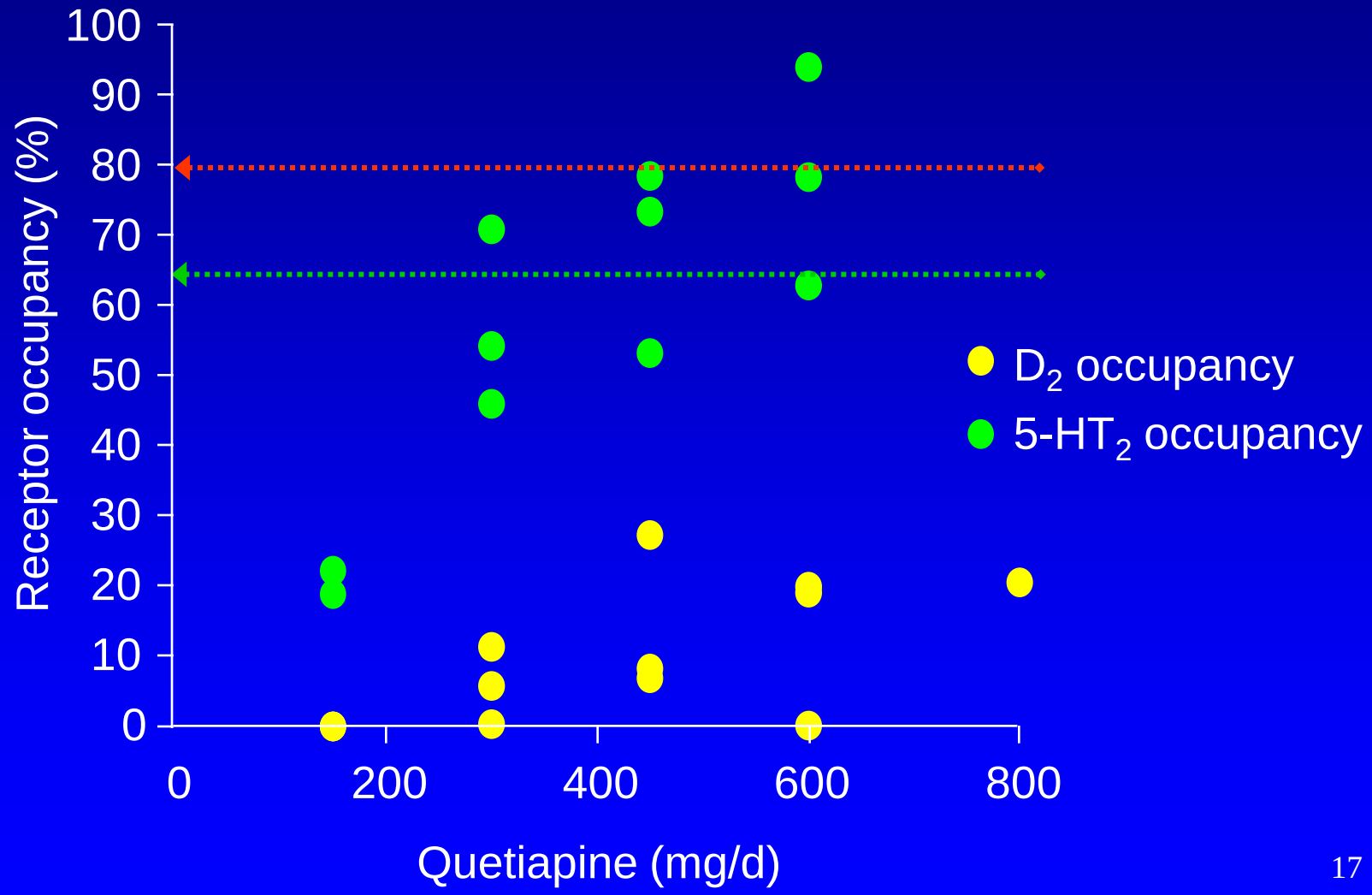
Clozapine D_2 Occupancy

Never Crosses the EPS Threshold



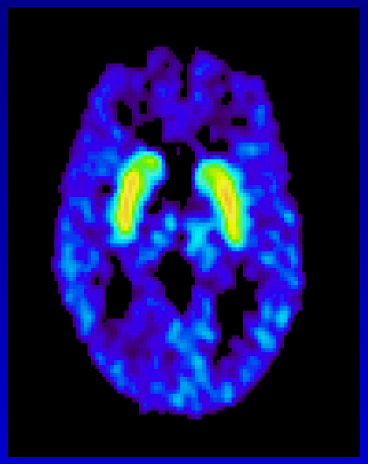
Kapur, Remington, and Zipursky. 1999.
Data from Nordstrom et al. *Am J Psychiatry.* 1995.

Quetiapine 5-HT_2 and D_2 Occupancy



Transient D_2 Receptor Occupancy with Quetiapine

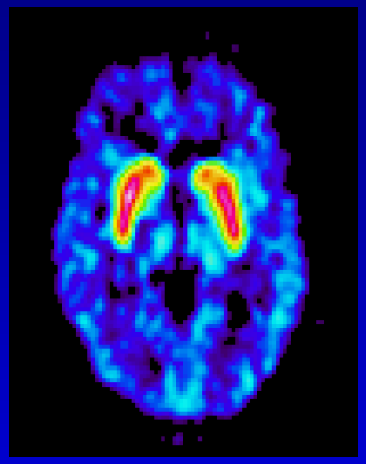
400 mg → 3 hours



57% D_2 occupancy

PRL 19 ng/mL elevated

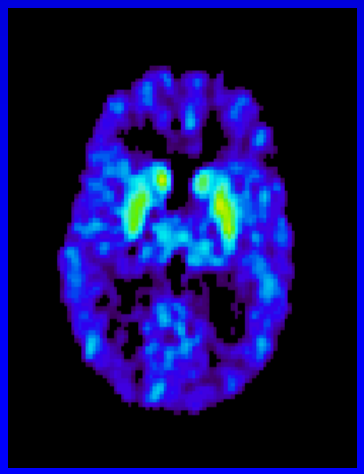
9 hours →



20% D_2 occupancy

PRL 4 ng/mL normal

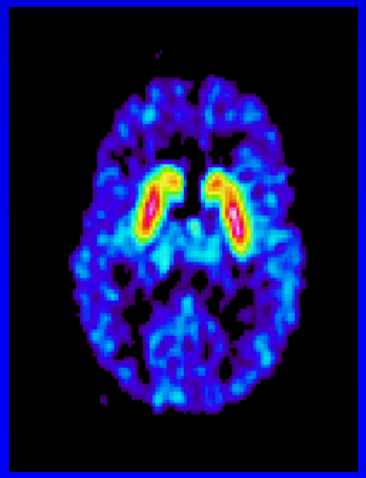
450 mg → 2 hours



64% D_2 occupancy

PRL 27 ng/mL elevated

24 hours →



0% D_2 occupancy

PRL 2 ng/mL below normal

Effects on glutamatergic systems

- No evidence of direct activity at glutamate receptors
- Clozapine (and possibly other atypicals) differ from conventionals in blockade of behavioral and cognitive effects of NMDA antagonists (PCP, ketamine)
- This may be a delayed effect

Atypical Antipsychotic Effects in NMDA Models

	Clozapine	Olanzapine	Quetiapine	Risperidone
Block Ketamine Effects in Schiz Pts	+	+	?	?
Block PCP Effects on Prepulse Inhibition	+	+	+	?
Block PCP-Induced Isolation	+	+	?	?