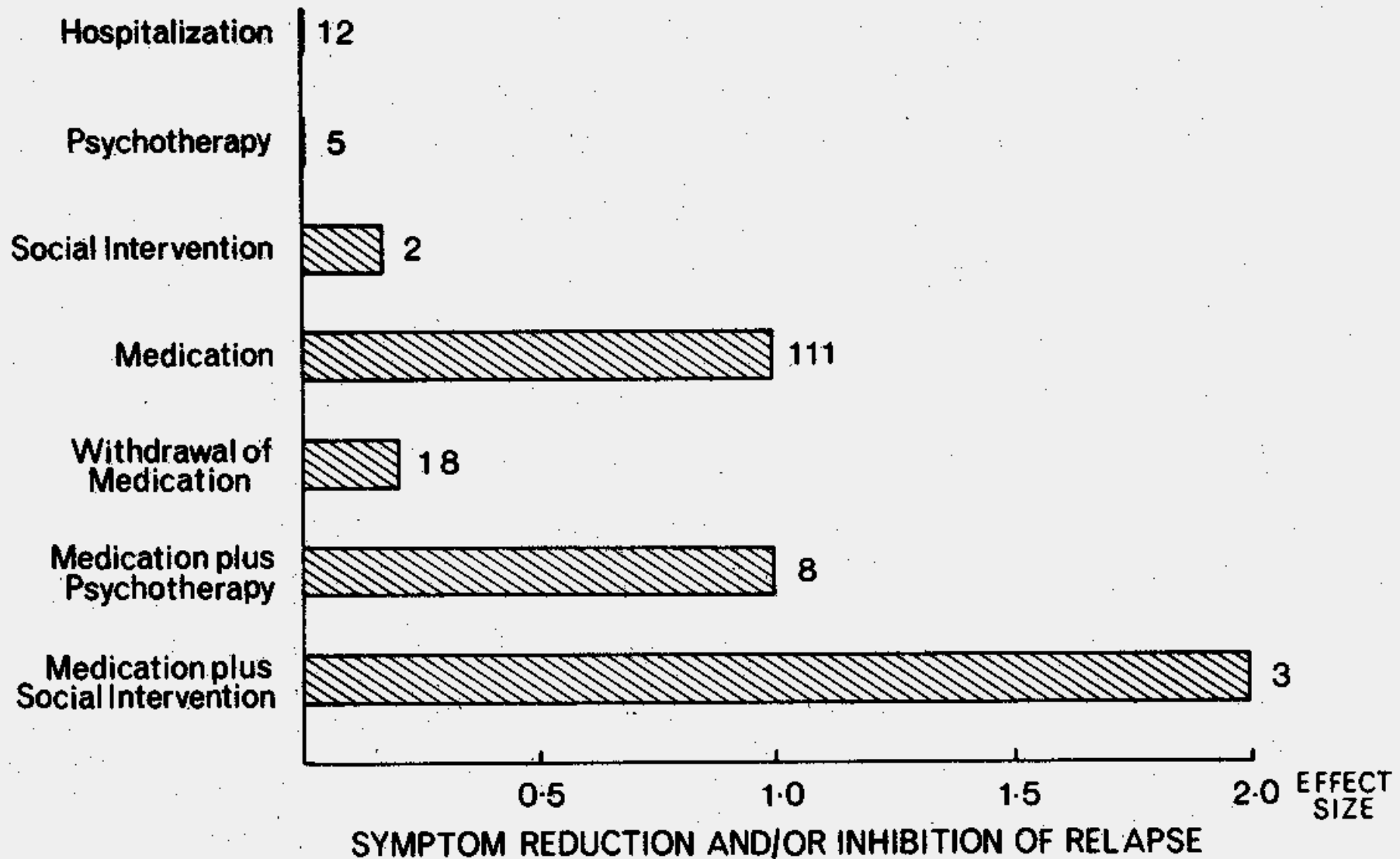
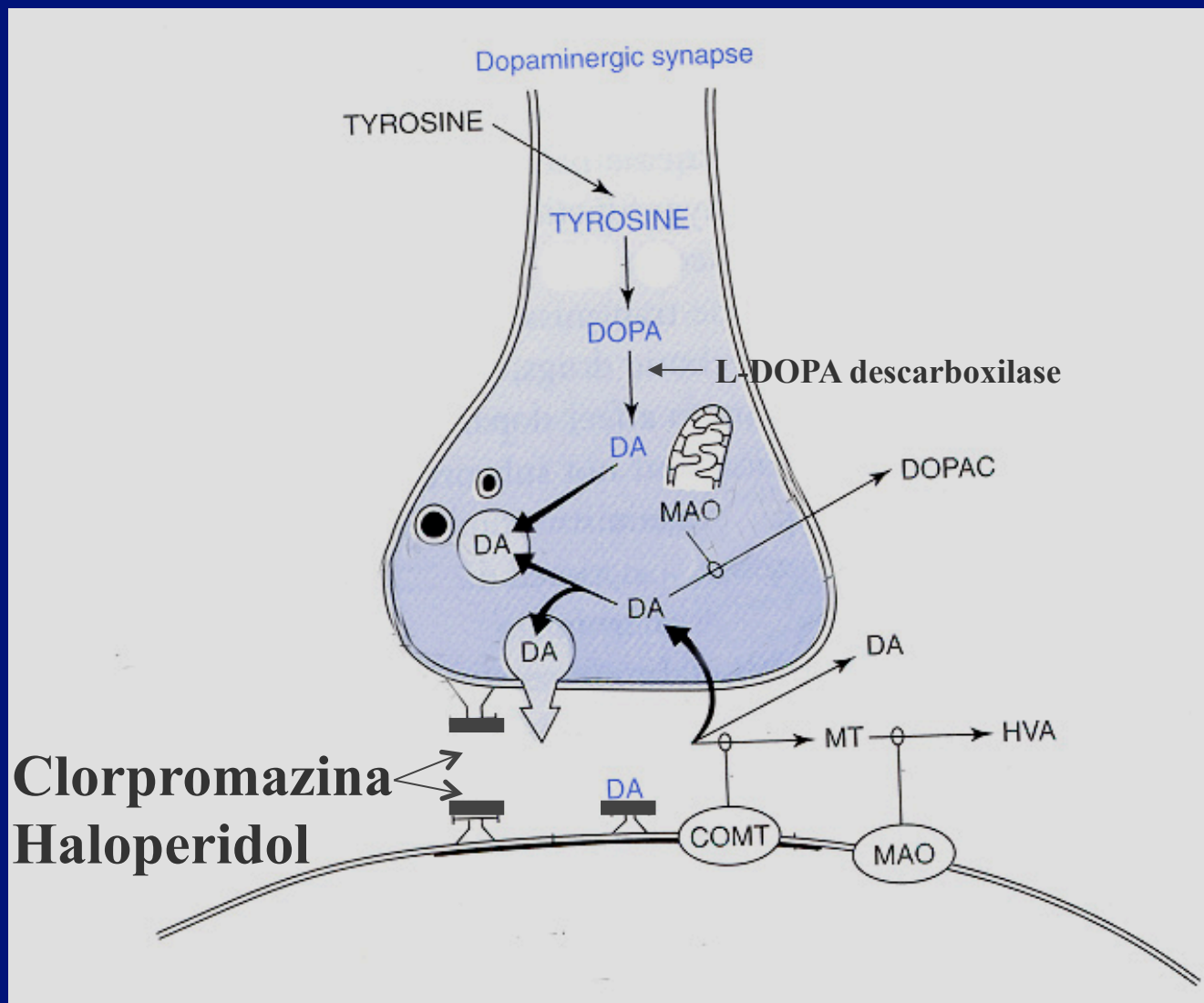


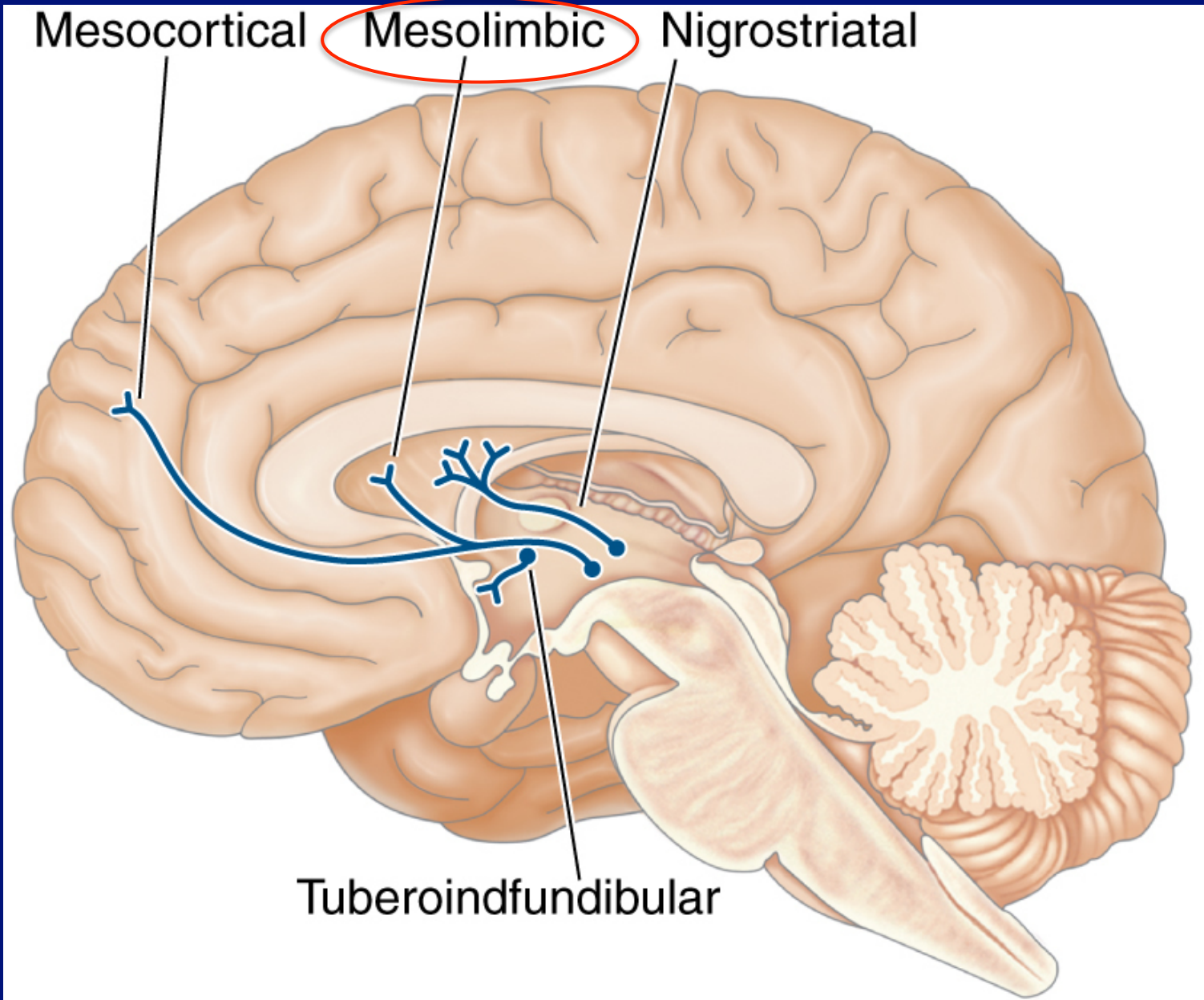
Eficácia dos neurolépticos



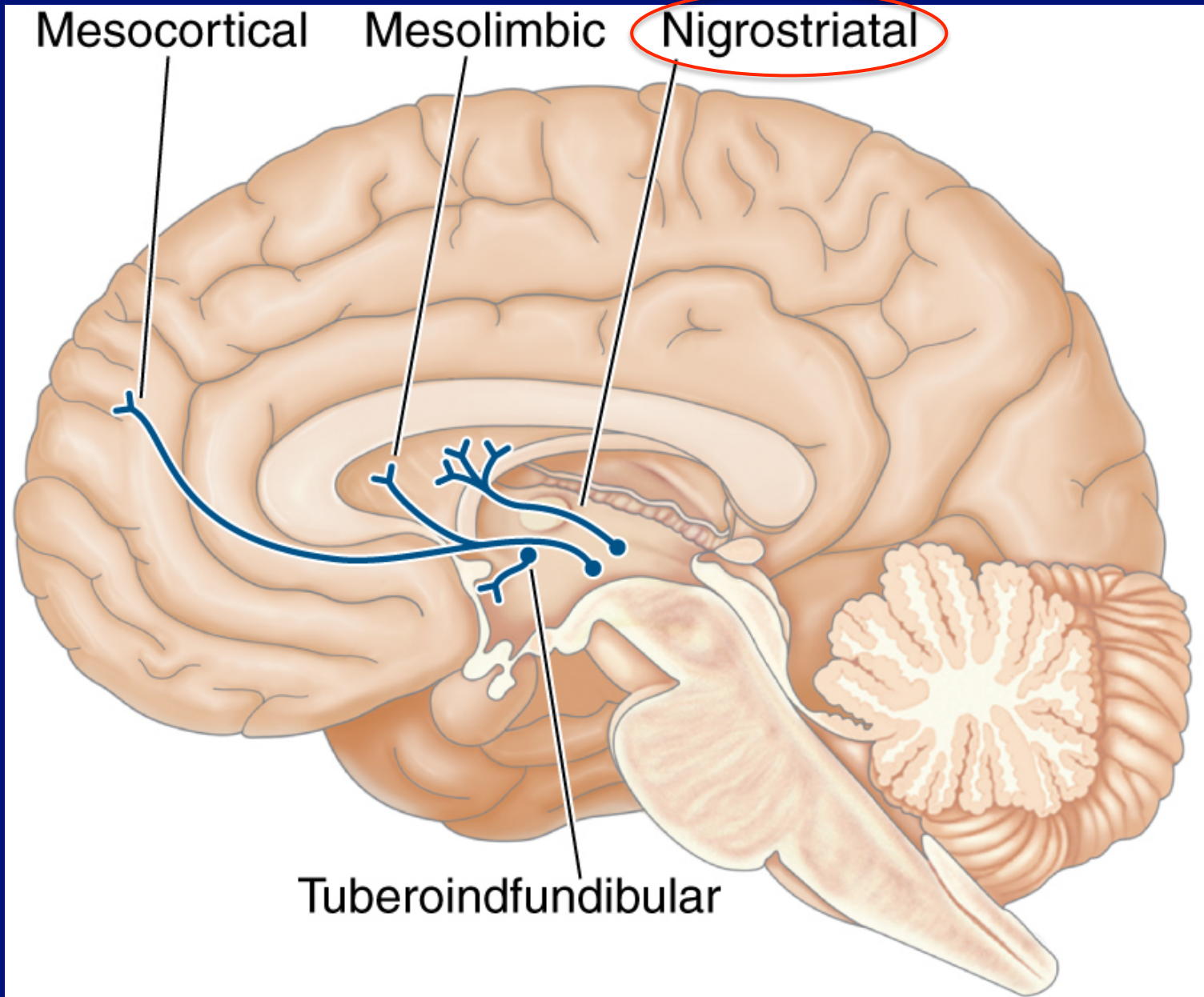


Antipsicóticos (neurolépticos) são antagonistas superáveis de receptores de dopamina de tipo D2

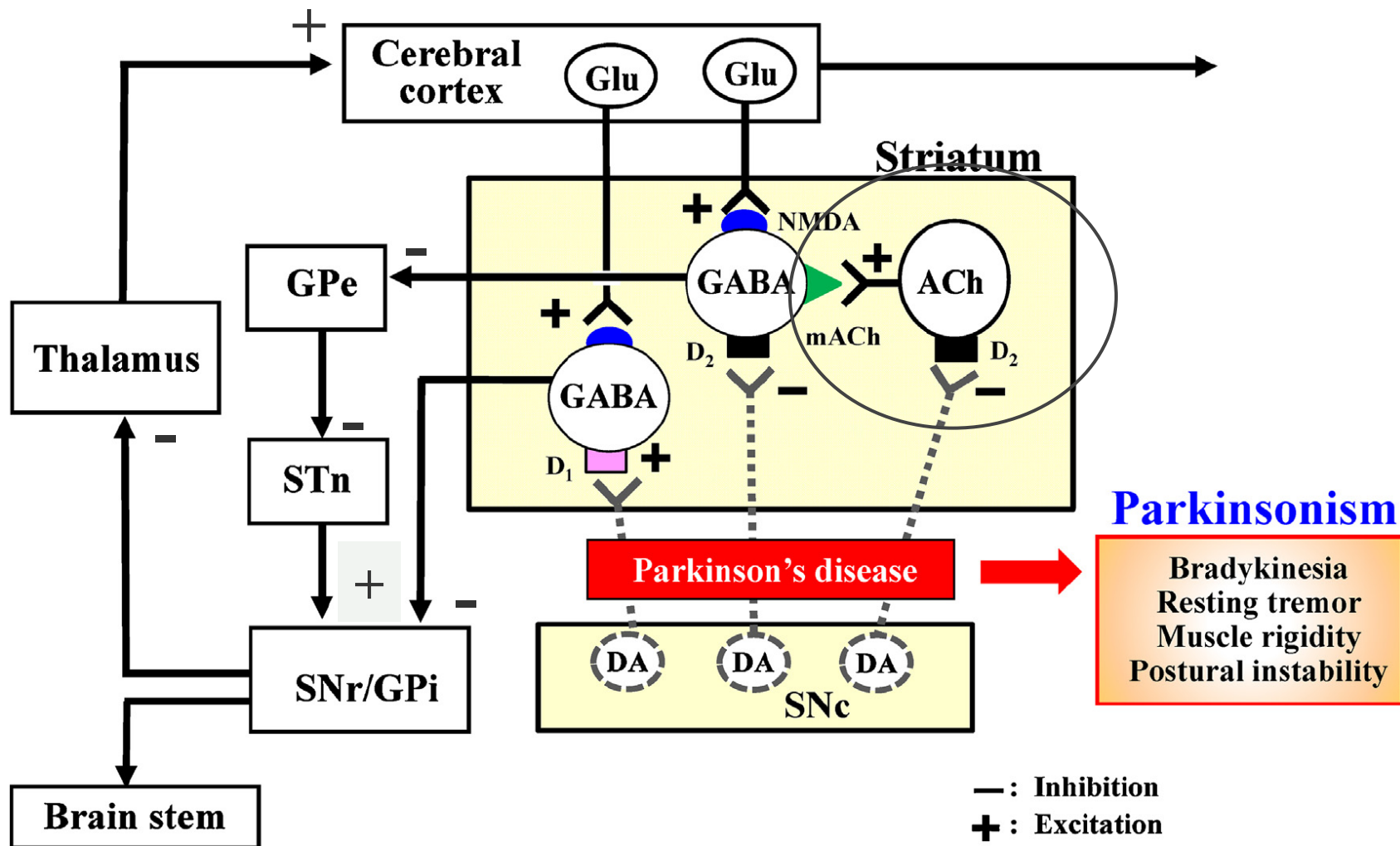
Vias Dopaminérgicas



Aonde: vias Dopaminérgicas



Efeito motores de antipsicóticos



Parkinsonism

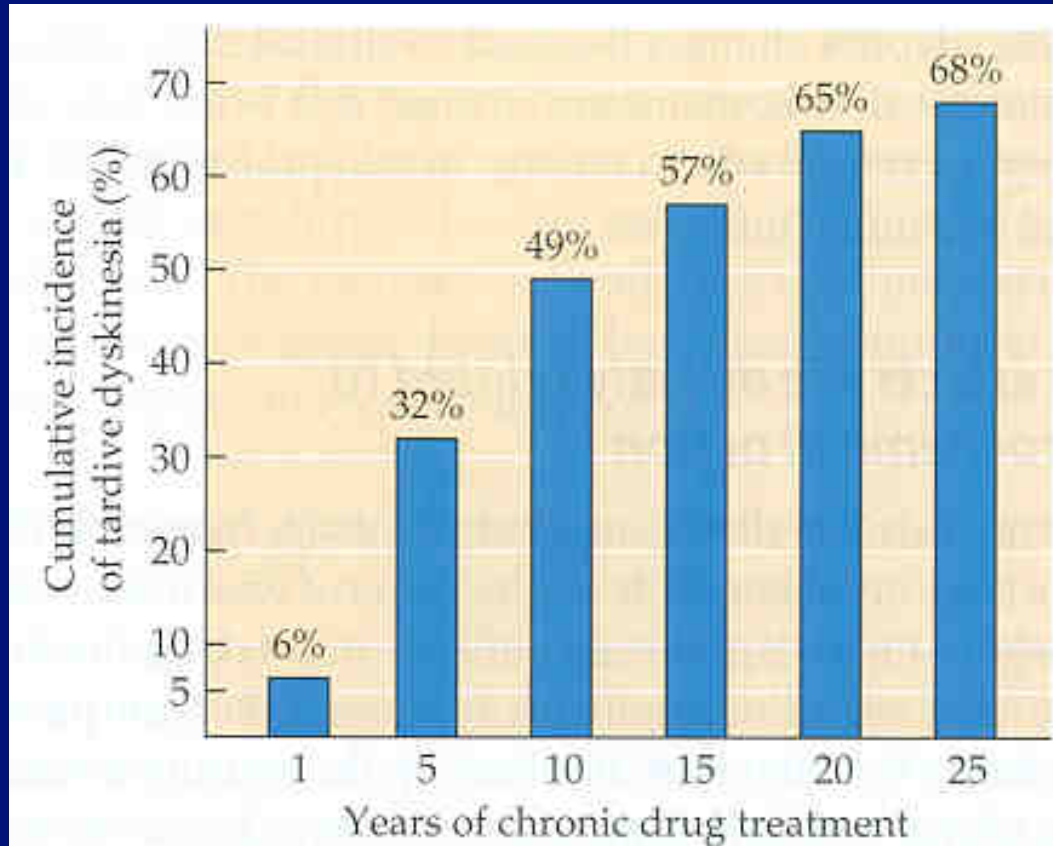
- Bradykinesia
- Resting tremor
- Muscle rigidity
- Postural instability

Efeitos motores agudos de antipsicóticos: Parkinson, Dystonia aguda, acatisia (em humanos) e catalepsia em roedores

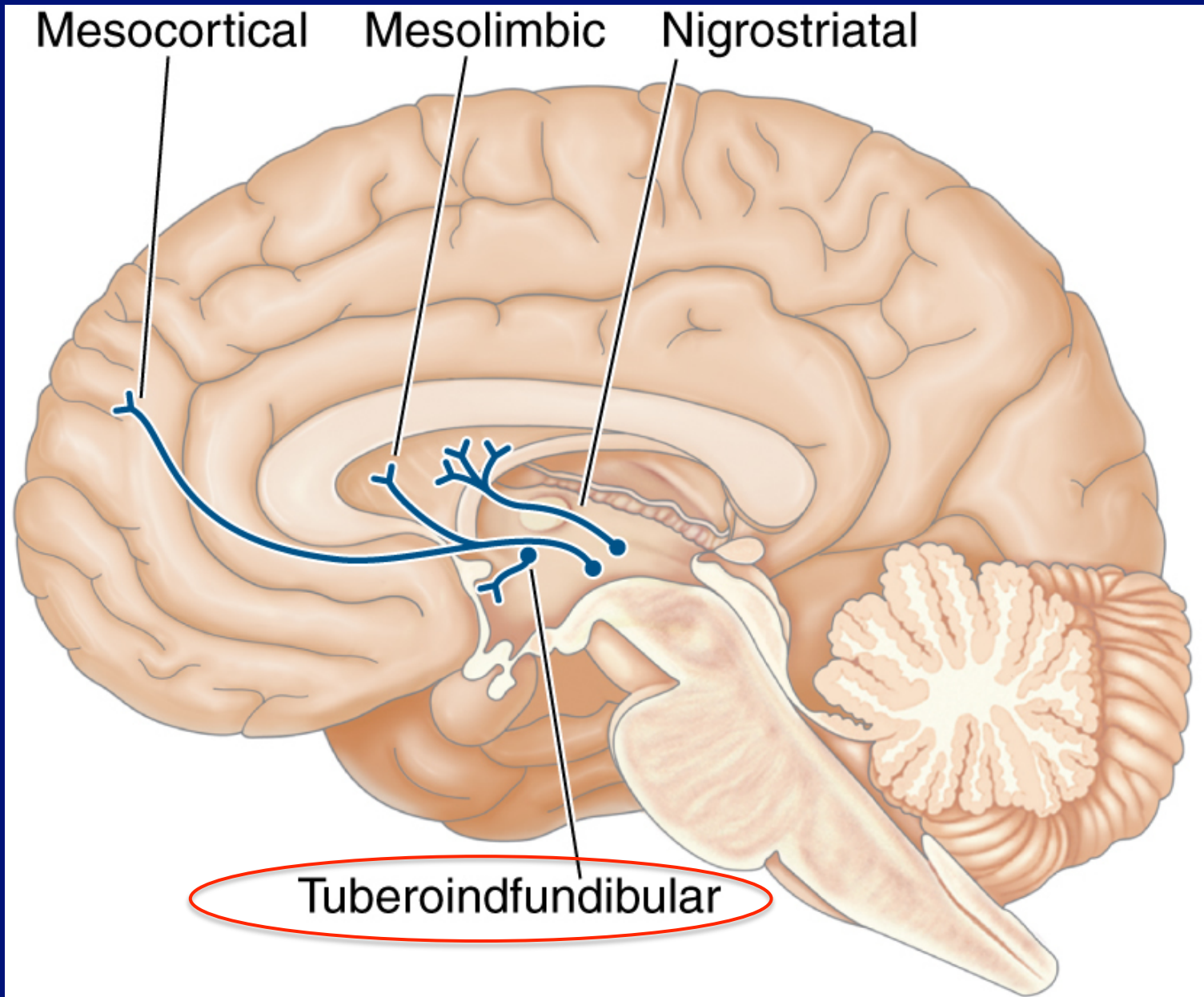
Efeitos motores crônicos de antipsicóticos: discinesia tardia



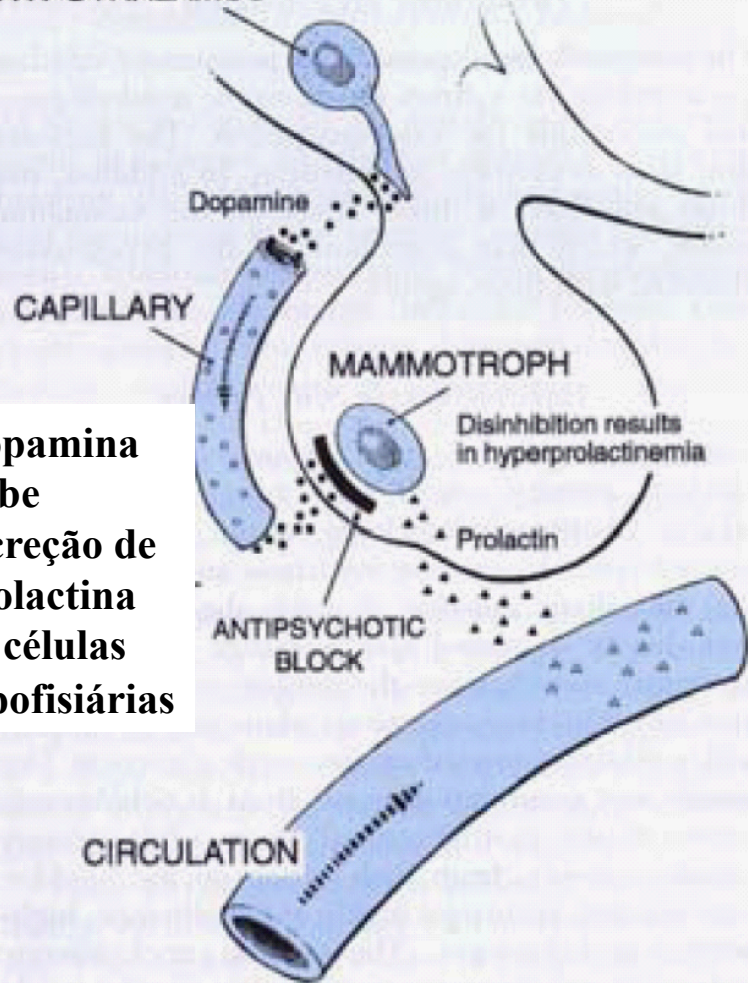
Discinesias tardias



Vias Dopaminérgicas



DOPAMINE-RELEASING
NEURON IN
HYPOTHALAMUS



Dopamina
inibe
secreção de
prolactina
de células
hipofisiárias

Figure 28-11. Mechanism of production of hyperprolactinemia by antipsychotics.

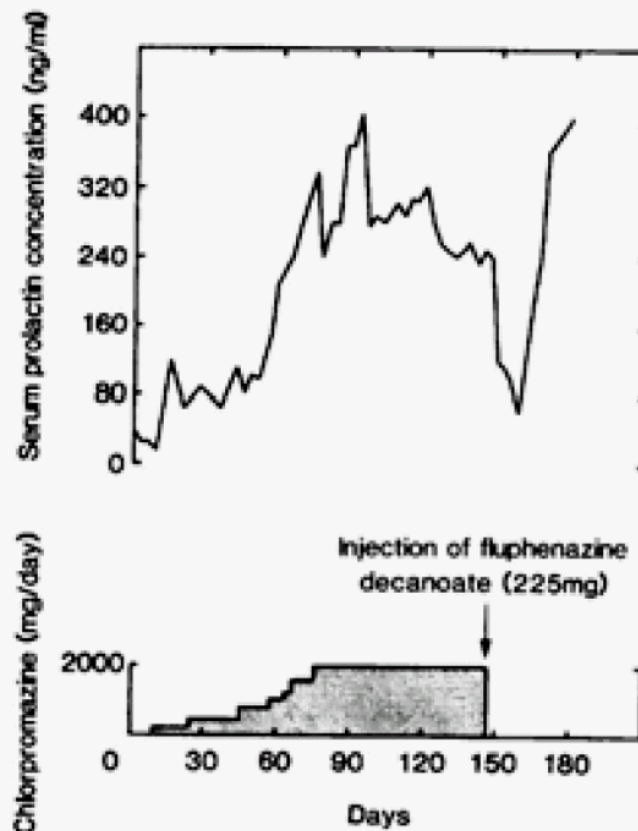


Fig. 28.4 Effect of neuroleptics on prolactin secretion in a schizophrenic patient. When daily dosage with chlorpromazine was replaced with a depot injection of fluphenazine the plasma prolactin initially dropped, because of the delay in absorption, and then returned to a high level. (From: Meltzer H Y et al. 1978 In: Lipton et al. (eds) Psychopharmacology. A generation of progress. Raven Press, New York)

Afinidade de antipsicóticos por receptores (K_i em nM)

	<u>D₂</u>	<u>Muscarínico</u>	<u>α₁</u>	<u>H₁</u>
<u>Clorproma- zina</u>	19,0	6,0	0,60	9,1
<u>Haloperidol</u>	4,0	> 2000,0	6,2	1890,0
<u>Clozapina</u>	180,0	7,0	9,0	2,7

$$K_i = \frac{IC_{50}}{1 + [L]/K_d}$$

↓
Efeitos
ansipsicó-
ticos, etc.

↓
Efeitos anticolinérgi-
cos

↓
Hipotensão
postural

↓
Sedação, ganho
de peso

Afinidade de antipsicóticos por receptores D2 (Ki em nM)

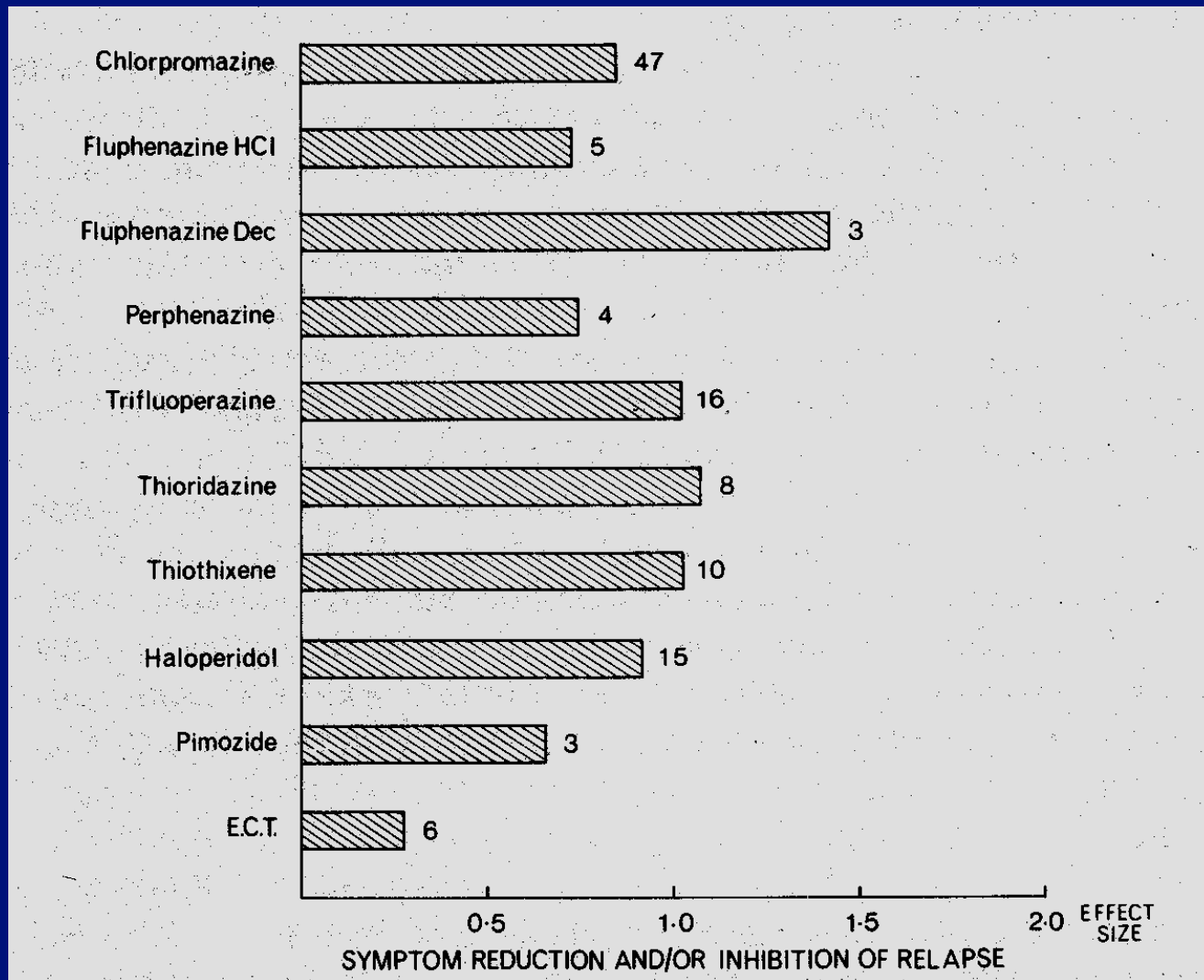
Qual o mais eficaz?

	<u>D2</u>
<u>Clorproma- zina</u>	19,0
<u>Haloperidol</u>	4,0
<u>Clozapina</u>	180,0

$$K_i = \frac{IC_{50}}{1 + [L]/K_d}$$

↓
Efeitos
ansipsicó-
ticos, etc.

Comparação de eficácia entre diferentes neurolépticos



Afinidade de antipsicóticos por receptores (K_i em nM): outros efeitos adversos

	<u>D₂</u>	<u>Muscarínico</u>	<u>α₁</u>	<u>H₁</u>
<u>Clorproma- zina</u>	19,0	6,0	0,60	9,1
<u>Haloperidol</u>	4,0	> 2000,0	6,2	1890,0
<u>Clozapina</u>	180,0	7,0	9,0	2,7

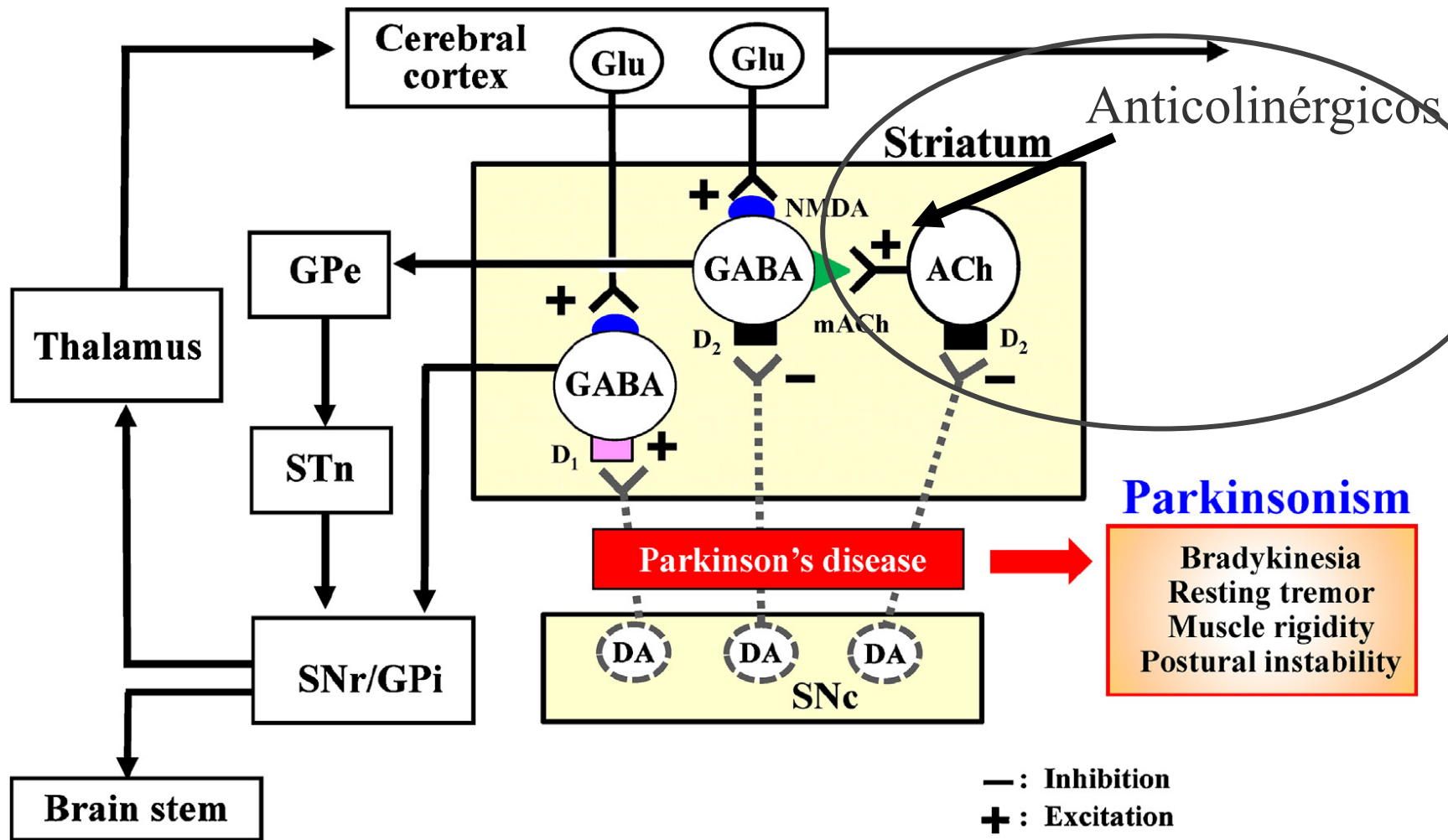
$$K_i = \frac{IC_{50}}{1 + [L]/K_d}$$

↓
Efeitos
ansipsicó-
ticos, etc.

↓
Efeitos anticolinérgi-
cos

↓
Hipotensão
postural

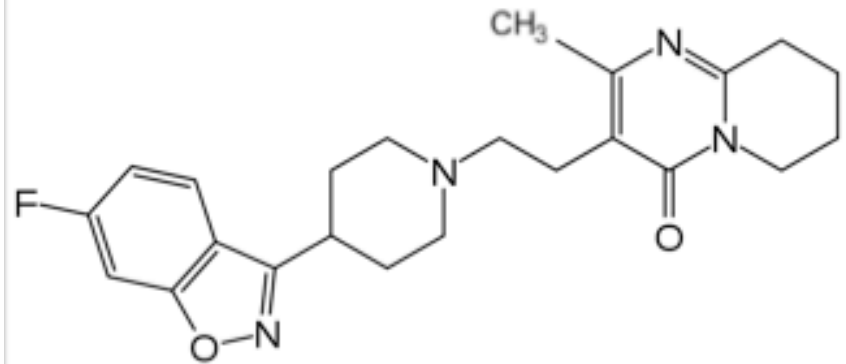
↓
Sedação, ganho
de peso



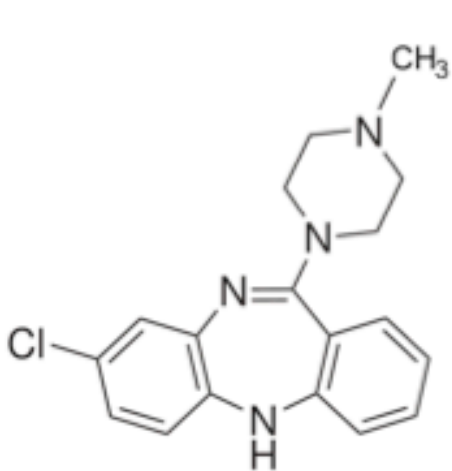
: D₁ receptor
 : D₂ receptor
 : mACh receptor
 : NMDA receptor

DA: Dopaminergic neuron, ACh: Acetylcholinergic neuron, Glu: Glutamatergic neuron

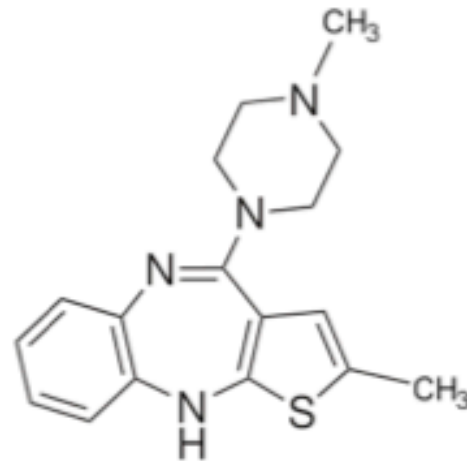
*Antipsicóticos de
Segunda Geração
("atípicos")*



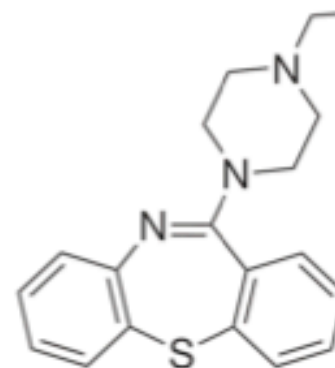
Risperidona



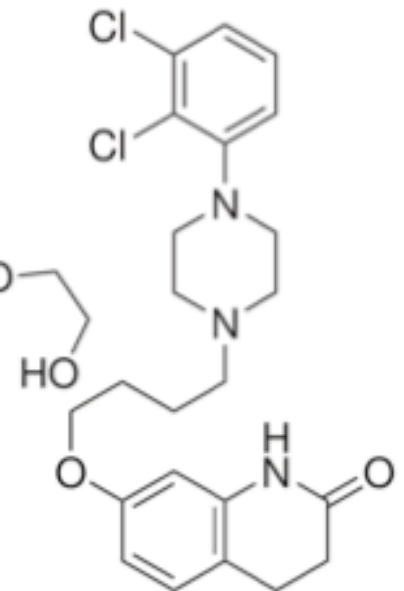
Clozapina



Olanzapina

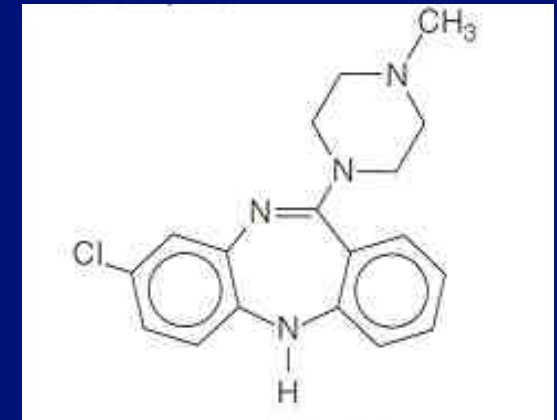
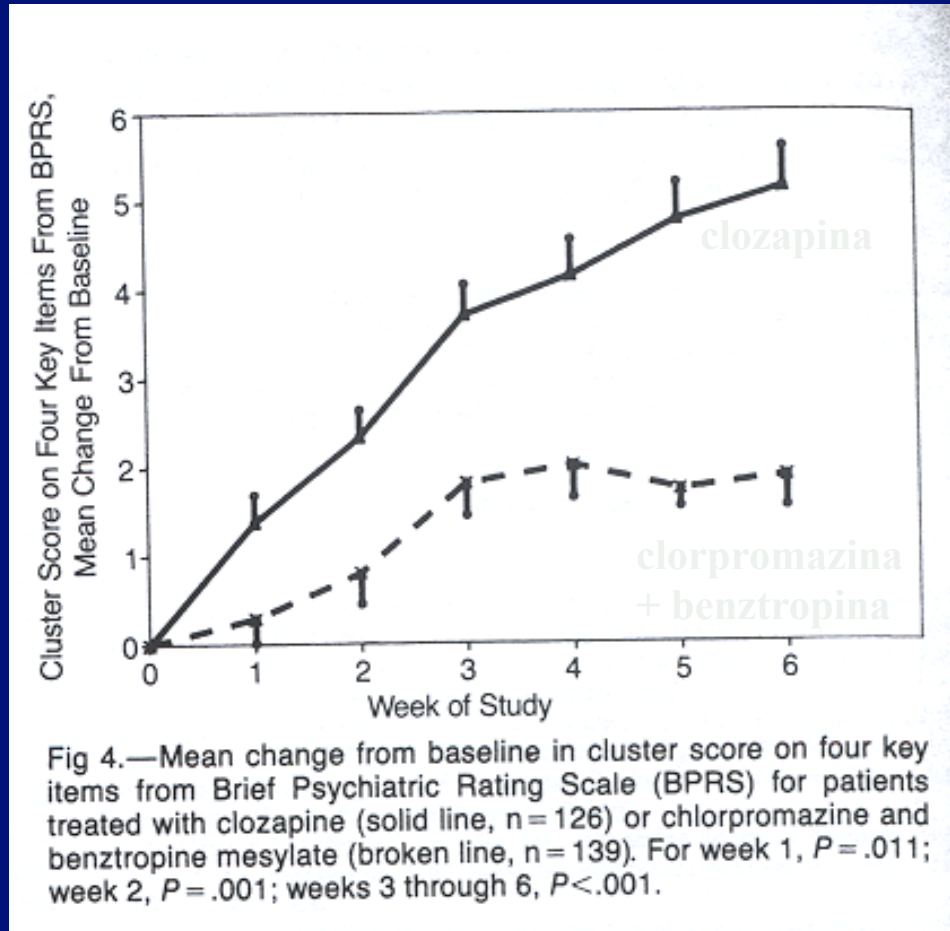


Quetiapina



Aripiprazole

Antipsicóticos atípicos



Kane et al, 1988

Clozapina é mais eficaz que clorpromazina no tratamento de sintomas positivos

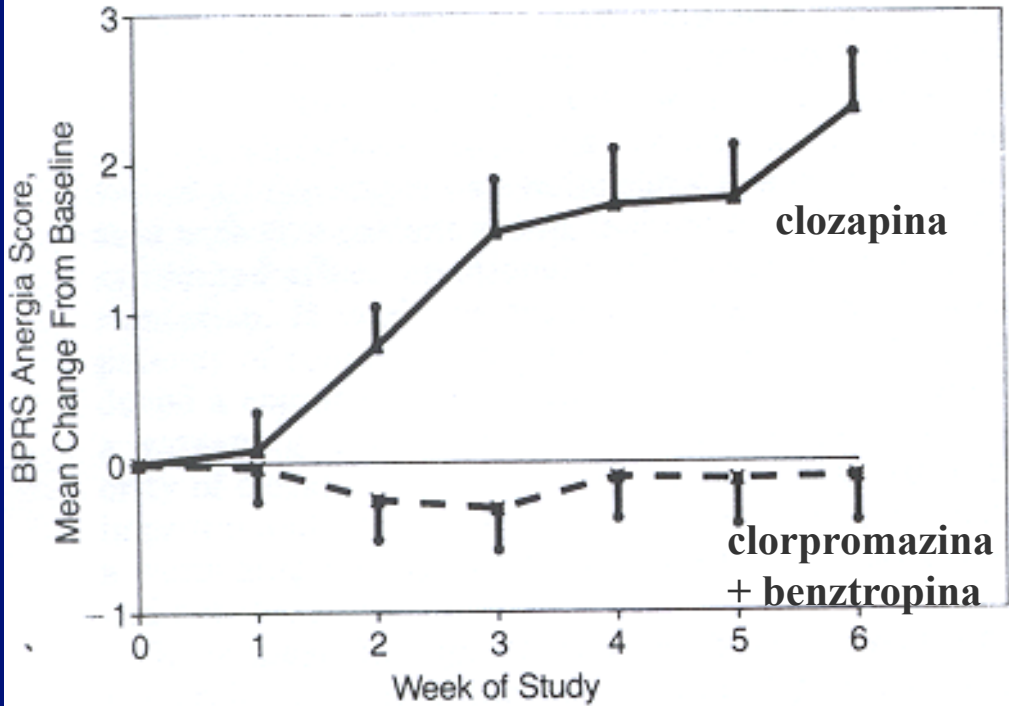


Fig 5.—Mean change from baseline in score on anergia item from Brief Psychiatric Rating Scale (BPRS) for patients treated with clozapine (solid line, n = 125) or chlorpromazine and benztropine mesylate (broken line, n = 139). For week 1, $P < .544$; week 2, $P = .002$; weeks 3 through 6, $P < .001$.

Clozapina é eficaz no tratamento de sintomas negativos

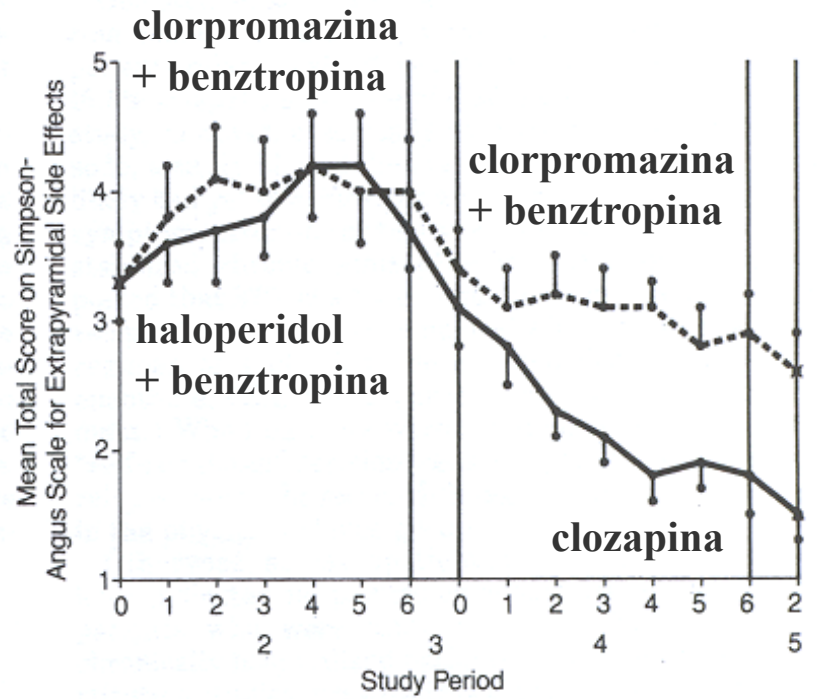
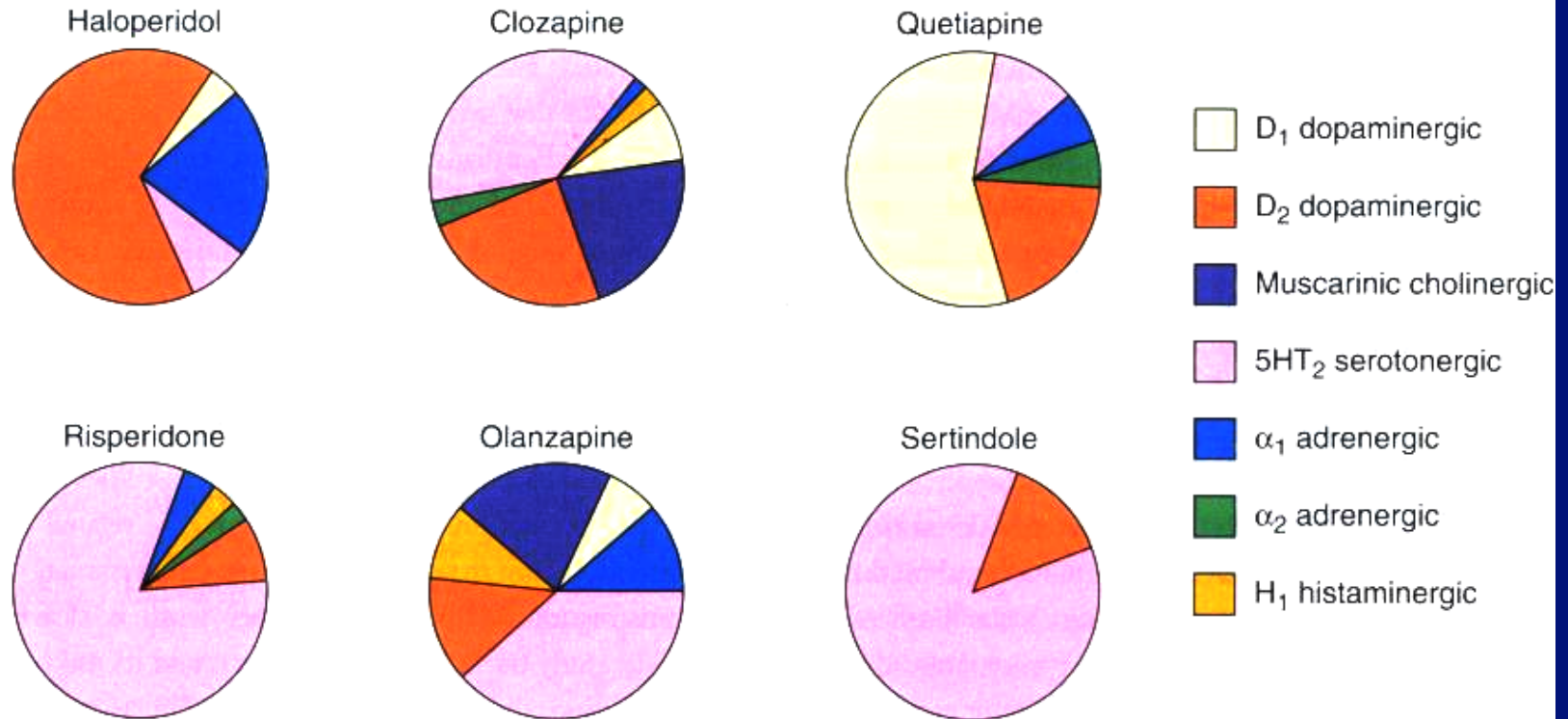


Fig 7.—Mean total scores (lower scores are better) on Simpson-Angus Scale for Extrapyramidal Side Effects, excluding salivation, for patients treated with clozapine (solid line, n = 116) or chlorpromazine and benztropine mesylate (broken line, n = 125) during period 2 (haloperidol and benztropine mesylate), period 3 (placebo washout phase); period 4 (double-blind phase), and period 5 (placebo washout phase).

Clozapina causa menor incidência de efeitos extrapiramidais

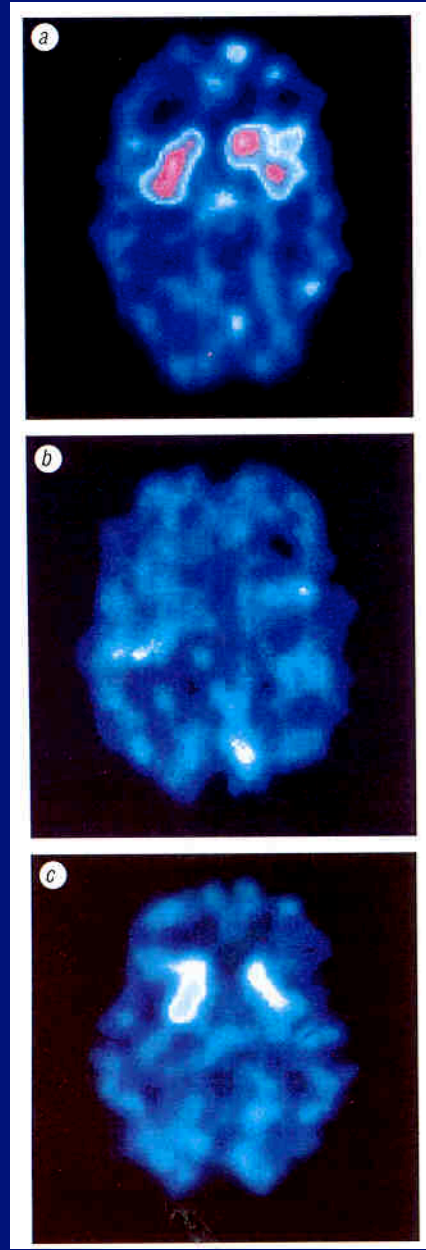
As bases da farmacologia atípica

(ou “desmontando a clozapina”)



16-8 Pie graphs comparing pharmacologic profiles of haloperidol, clozapine, and several second generation antipsychotic drugs. (From Casey DE. The relationship of pharmacology to side effects. *J Clin Psychiatry*. 1997;58(Suppl)10:55.)

**Receptores D2 no Estriado de
Esquizofrênicos – SPECT**



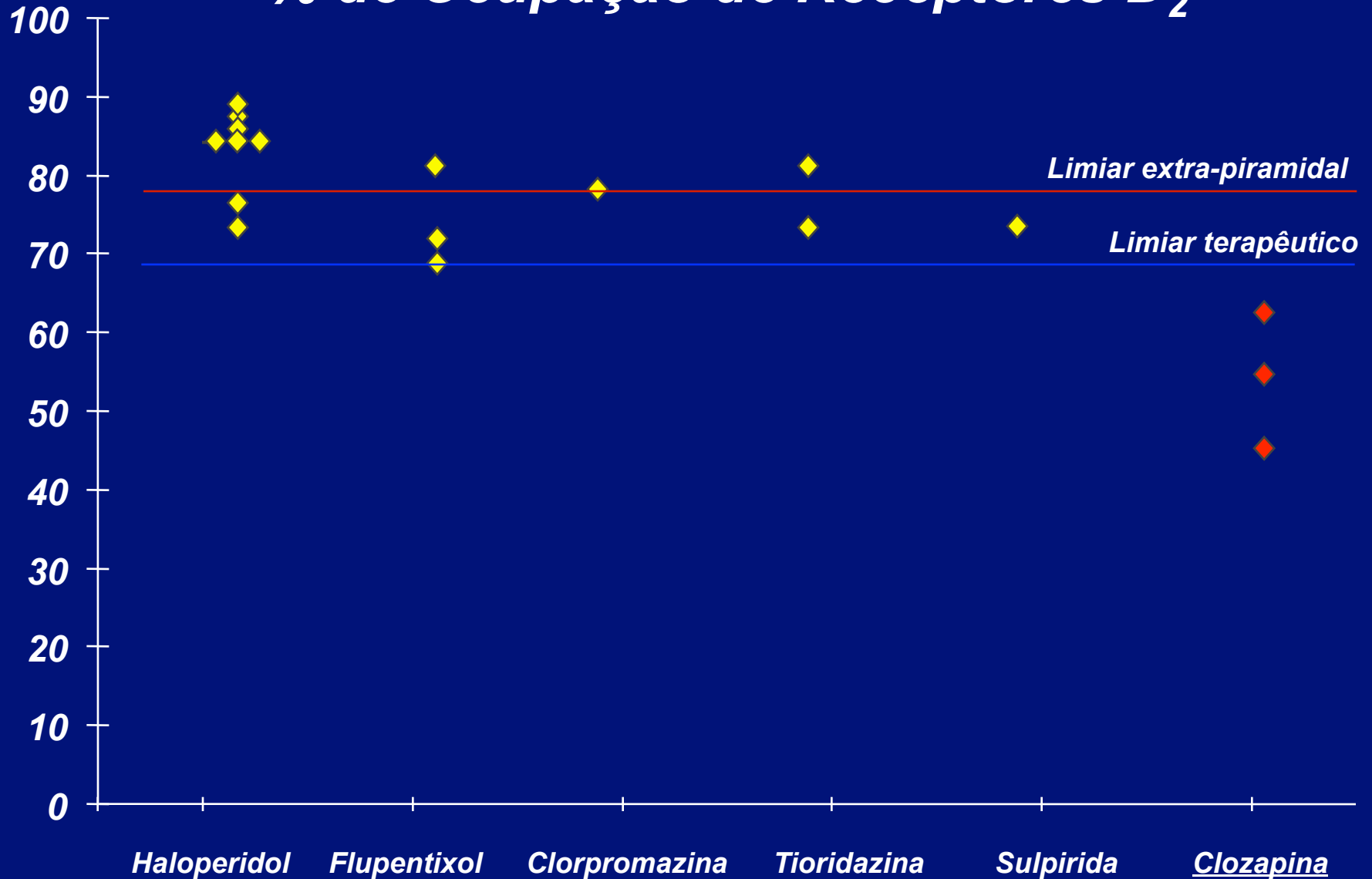
Sem tratamento

Haloperidol

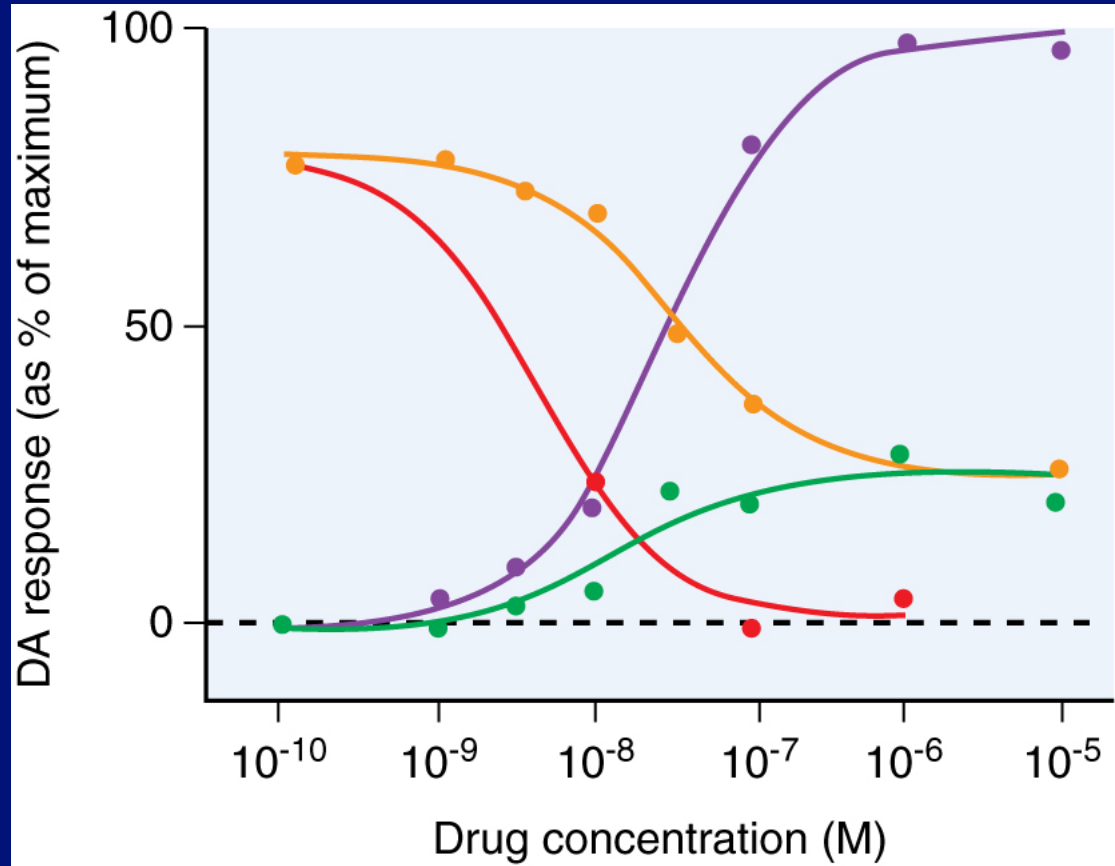
Clozapina

Tomografia por Emissão de Pósitrons

% de Ocupação de Receptores D₂

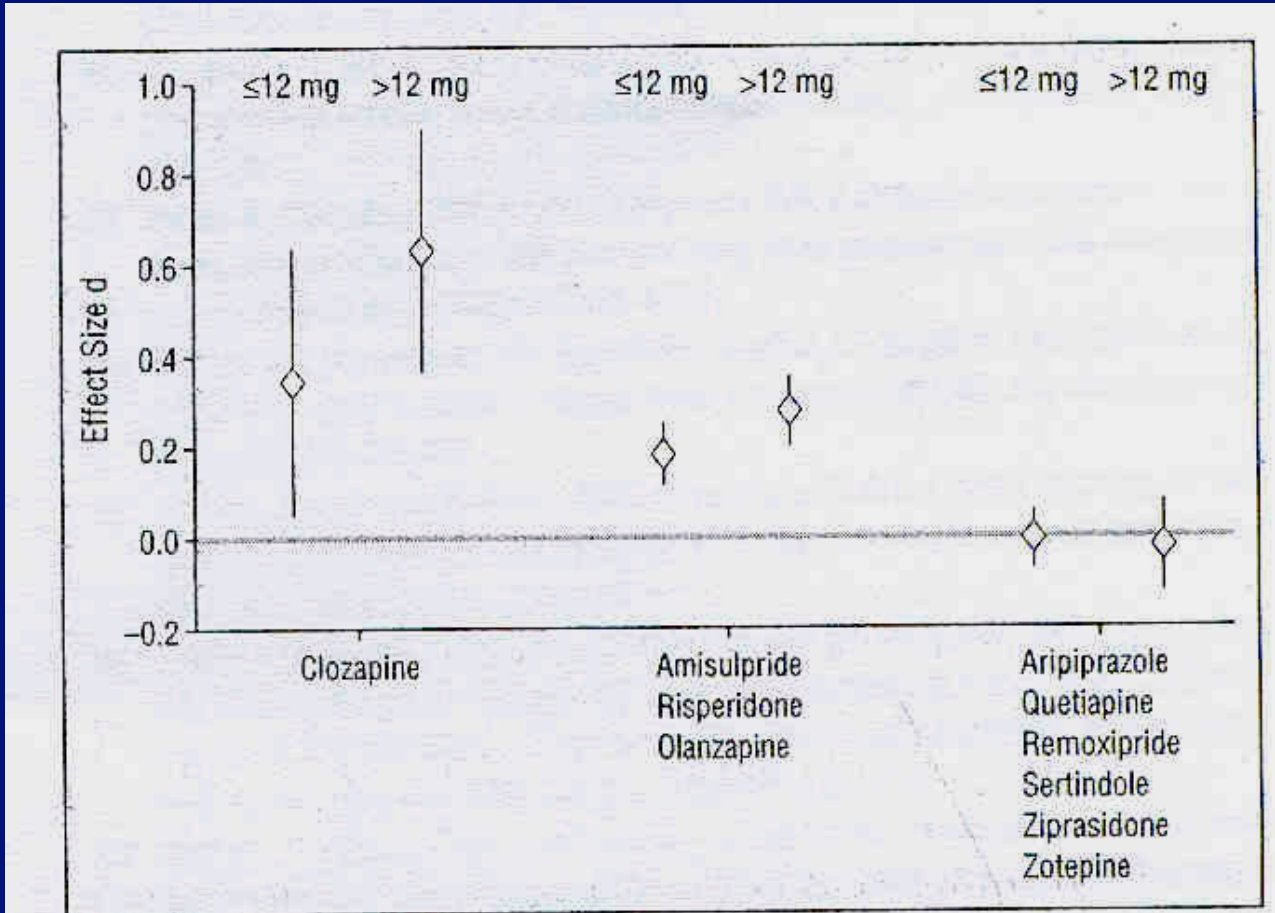


Aripiprazole:
agonista parcial
de receptores
D2



100 nM dopamine + aripiprazole	—	dopamine	—
100 nM dopamine + haloperidol	—	aripiprazole	—

Eficácia de novos antipsicóticos quando comparados com doses altas (>12 mg/d) ou baixas (<12 mg/d) de Haloperidol



Custos aproximados de alguns antipsicóticos (Reais-2011-13) tratamento mensal

Haloperidol	Genérico	5,30
	Haldol	12,10
Clozapina	Leponex	195,00
Quetiapina	Genérico	135,00
	Seroquel	189,00
Olanzapina	Genérico	182,00
	Zyprexa	362,00
Aripiprazole	Abilify	763,92