Antipsychotics

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Indications for use

- Schizophrenia (Acute, chronic, treatment resistant)
- Schizoaffective disorders
- Bipolar affective disorder (Monotherapy or adjunctive with mood stabilizers)- acute or maintenance to prevent recurrence
- Acute treatment of agitation (Schizophrenia and mania)
- Treatment resistant depression as adjunctive agents
- Severe childhood behavioural problems (Ex: Irritability associated with autism)

Pathophysiology of schizophrenia

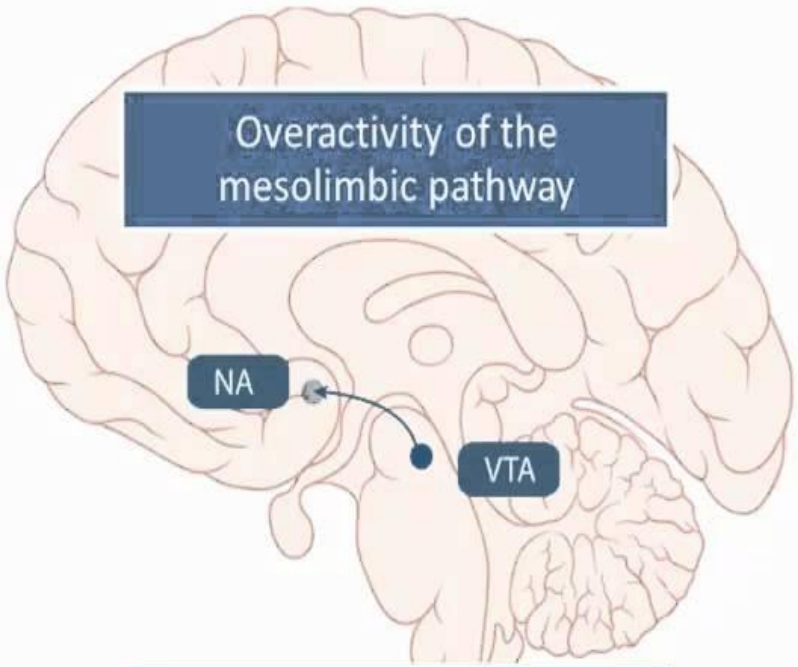
- **Positive symptoms**

↑ Dopamine in the mesolimbic pathway (From ventral tegmental area of midbrain to nucleus accumbens of basal ganglia)

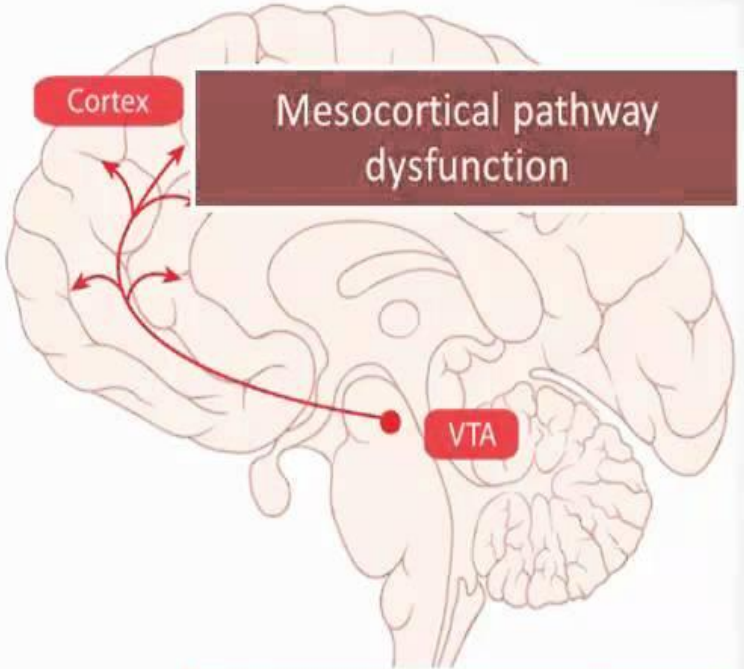
- **Negative symptoms**

↓ Dopamine in the mesocortical pathway (From ventral tegmental area of midbrain to prefrontal cortex)

Dopamine Pathways Relevant to Schizophrenia Symptoms



Positive symptoms



Negative and cognitive symptoms

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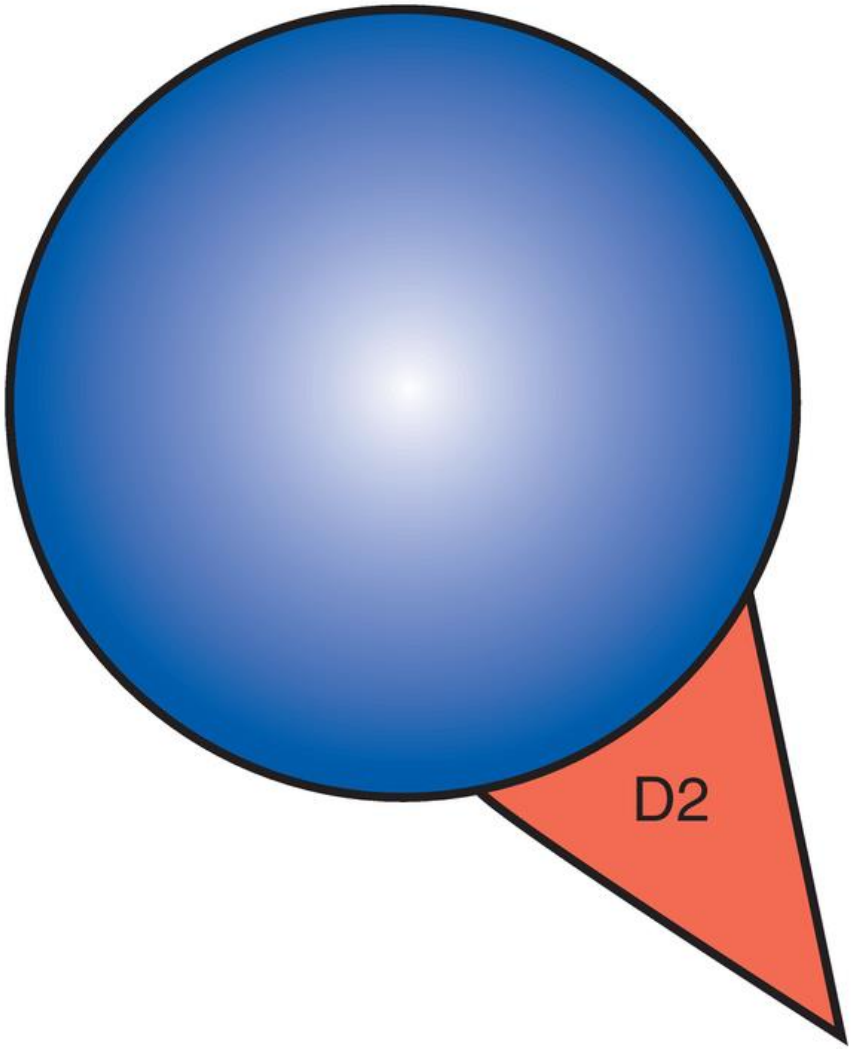
Typical antipsychotics

- **Phenothiazines**
  - Chlorpromazine
  - Thoridazine
  - Trifluoperazine
- **Thioxanthenes**
  - Flupenthixol
  - Thiothixene
- **Butyrophenones**
  - Haloperidol
- **Indole derivatives**
  - Oxypertine monolidone
- **Diphenyl butyl piperidine**
  - Pimozide
- **Benzamide**
  - Sulpride

What Makes an Antipsychotic Conventional?

D2 Antagonist Actions



Mechanisms of action

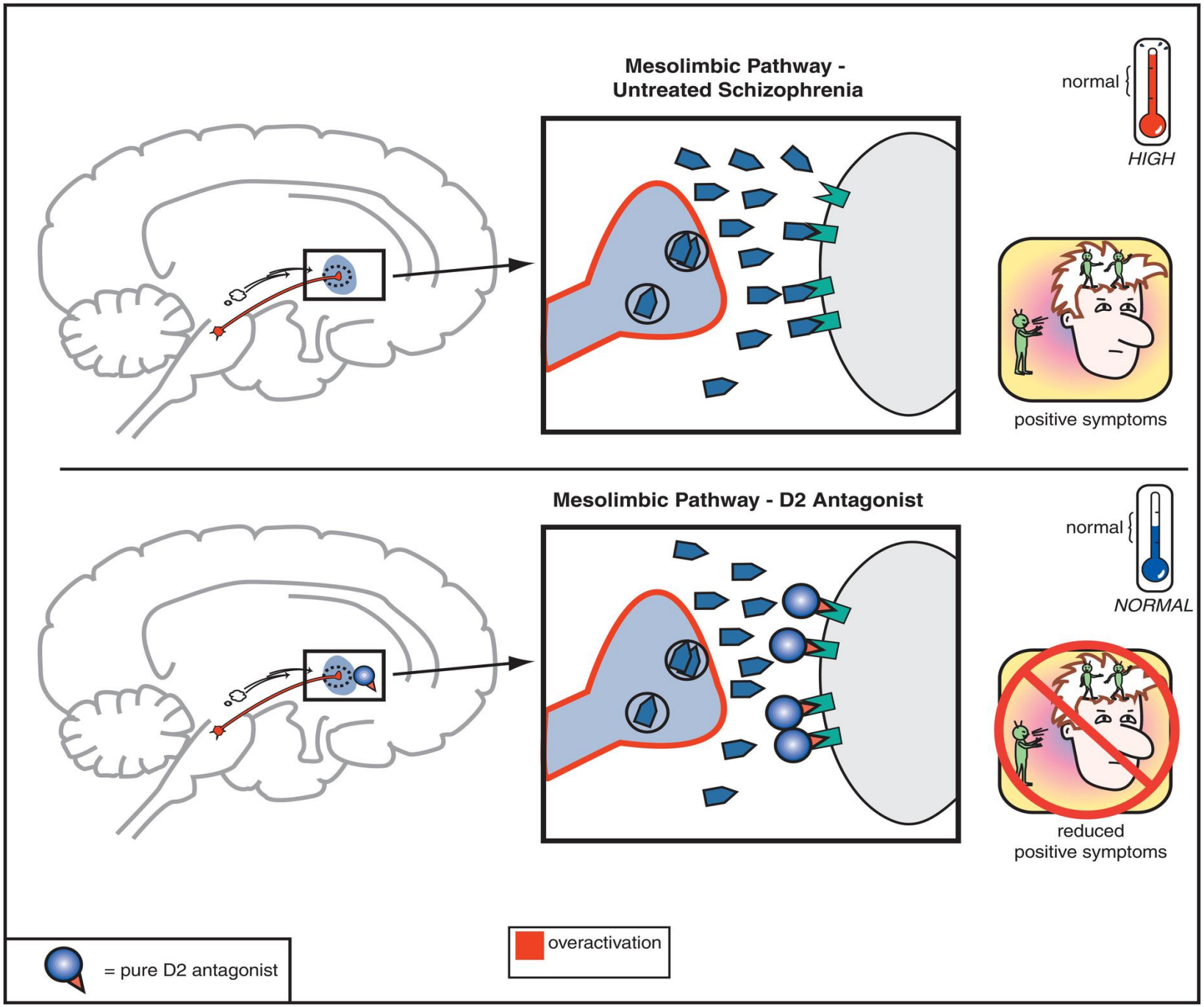
- Typical antipsychotics

-Inhibits D2 receptors

D2 receptor block in the mesolimbic pathway results in reduction of positive symptoms

takes days or weeks to work

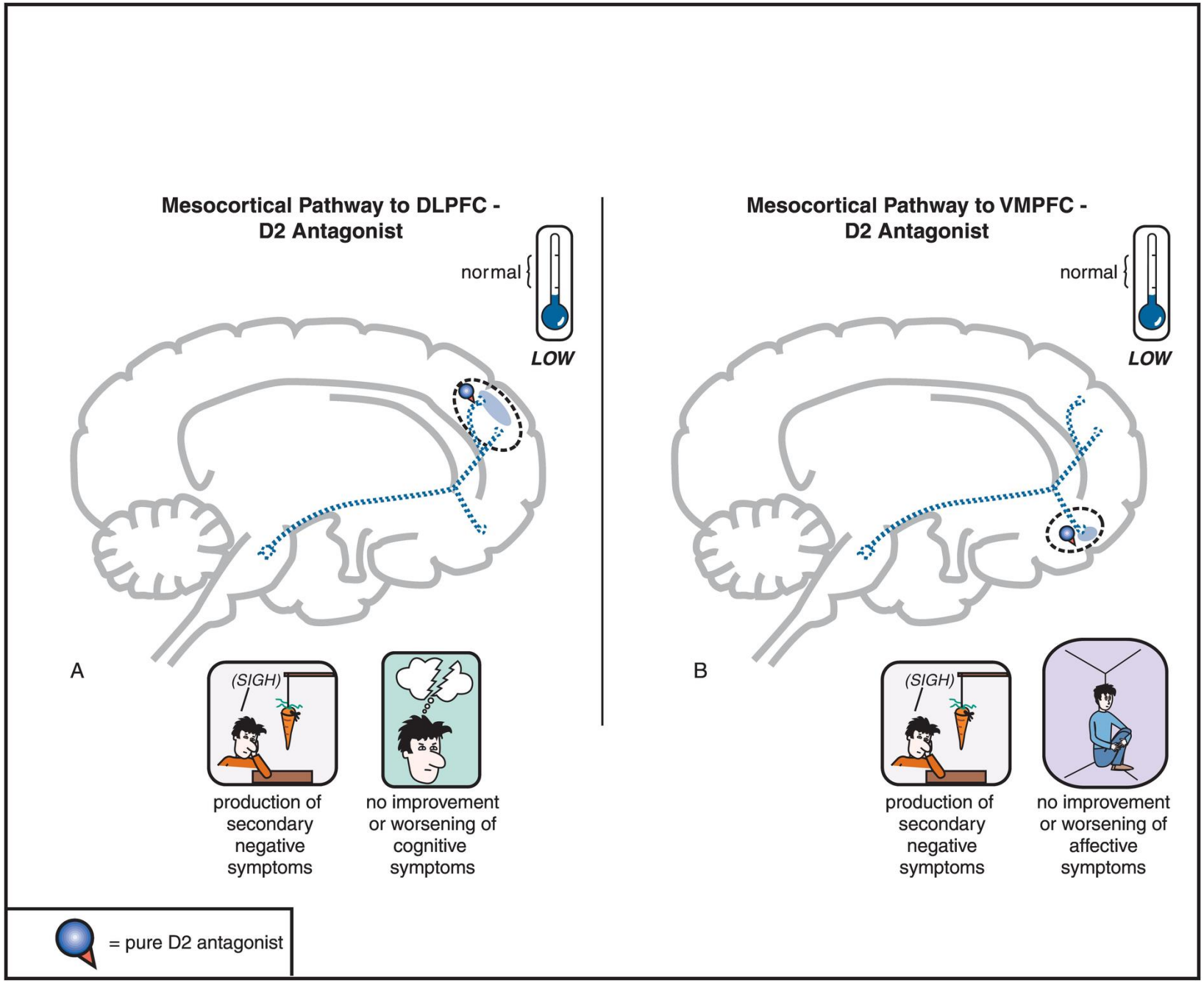
BUT.....


Mesolimbic Pathway -
Untreated Schizophrenia
normal
HIGH
positive symptoms
Mesolimbic Pathway - D2 Antagonist
normal
NORMAL
reduced
positive symptoms
= pure D2 antagonist
overactivation

Side effects

- D2 block in

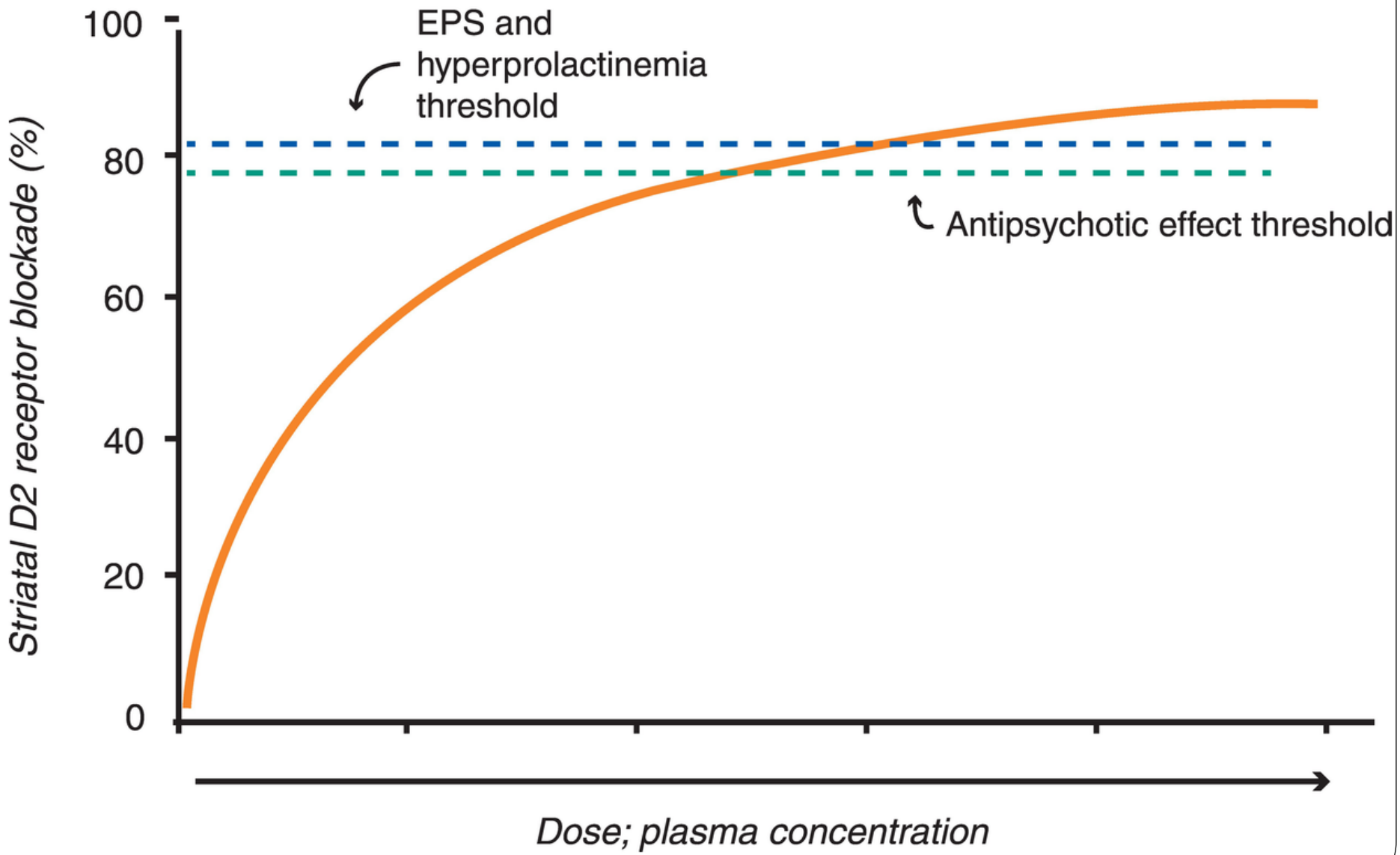
-meso cortical dopamine pathway results in further aggrevation of negative symptoms- **Neuroleptic induced deficient syndrome**

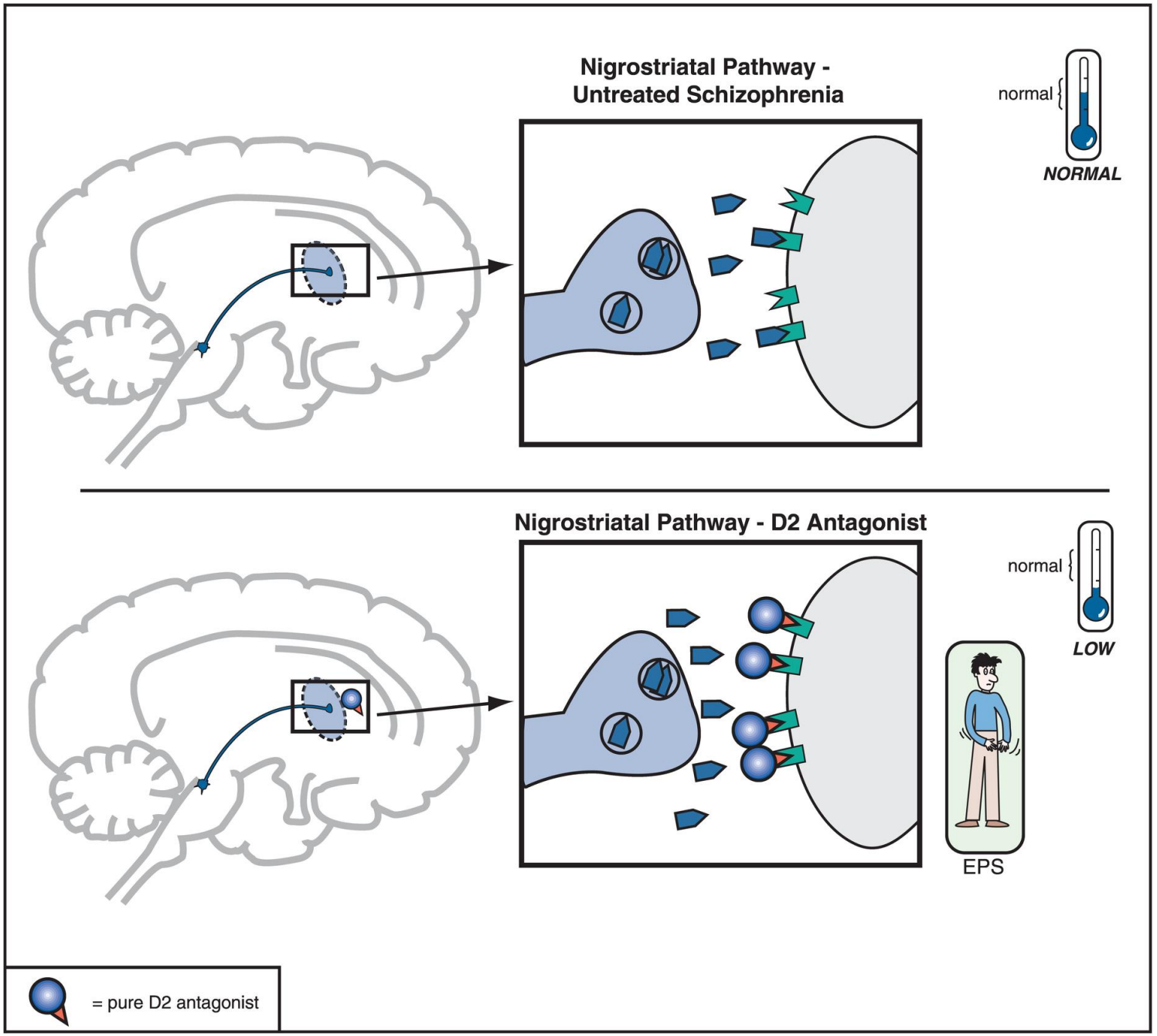

Mesocortical Pathway to DLPFC -
D2 Antagonist
normal
LOW
A
(SIGH)
production of secondary negative symptoms
no improvement or worsening of cognitive symptoms
Mesocortical Pathway to VMPFC -
D2 Antagonist
normal
LOW
B
(SIGH)
production of secondary negative symptoms
no improvement or worsening of affective symptoms
= pure D2 antagonist

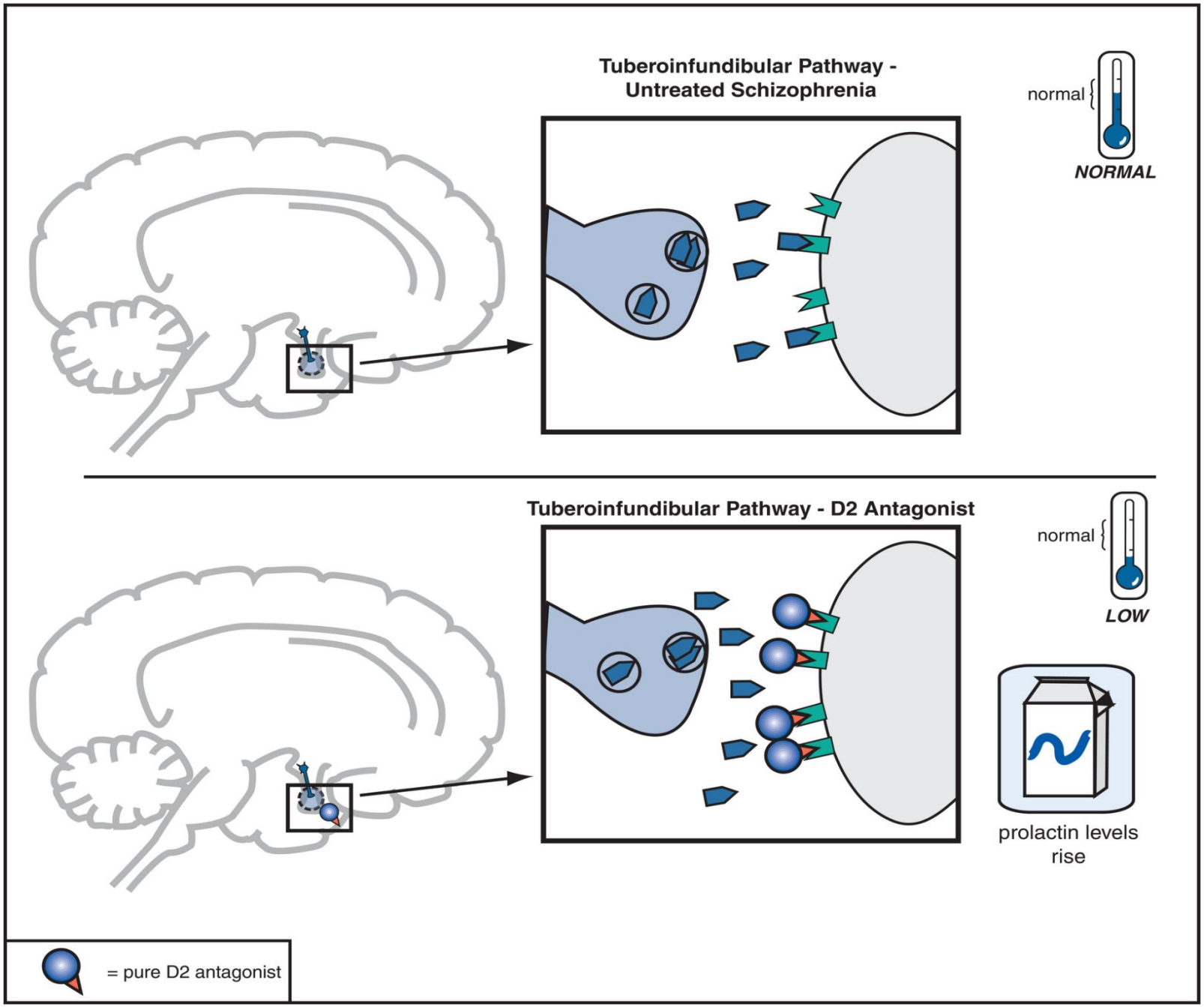
-nigrostriatal dopamine pathway results in extra pyramidal symptoms (↓DA / ↑ACh)
(dystonia, akathisia, pseudoparkinsonism)

-tuberoinfundibular dopamine pathway results in hyperprolactinaemia (amenorrhoea, sexual dysfunction, galactorrhoea, osteoporosis)

Hypothetical Thresholds for Conventional Antipsychotic Drug Effects



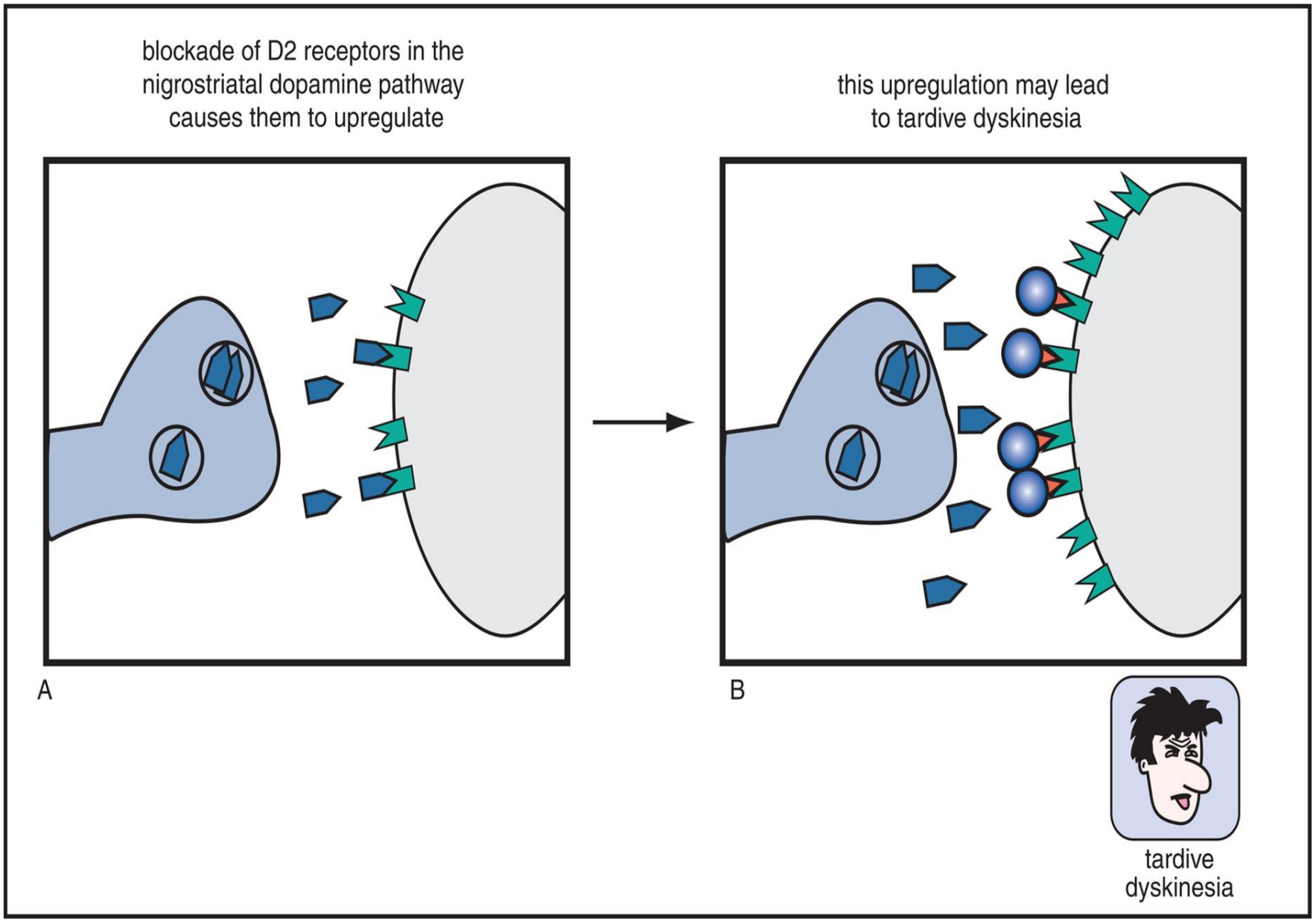

Nigrostriatal Pathway -
Untreated Schizophrenia
normal
NORMAL
Nigrostriatal Pathway - D2 Antagonist
normal
LOW
EPS
= pure D2 antagonist


Tuberoinfundibular Pathway -
Untreated Schizophrenia
normal
NORMAL
Tuberoinfundibular Pathway - D2 Antagonist
normal
LOW
prolactin levels
rise
= pure D2 antagonist

Tardive dyskinesia

- Long term blockade of D2 receptors in the nigrostriatal system result in upregulation of D2 receptors with increased affinity/sensitivity for dopamine.
- So at one point they will overcome the D2 block exerted by antipsychotics and will result in increased activity of DA at D2 receptors
- ↑ DA/ ↓ ACh
- Lip smacking, tongue protrusion, choreiform movements of hands-pill rolling, piano playing
- Rx: Stop anticholinergics, give cholinergics-Physostigmine, GABA facilitating drugs- Na Valproate, benzodiazepam;

tetra benzene, gingkobilabo,, Vit E, propranolol


blockade of D2 receptors in the nigrostriatal dopamine pathway causes them to upregulate
this upregulation may lead to tardive dyskinesia
A
B
tardive dyskinesia

Side effects

- **Anti histamine(H1) side effects**

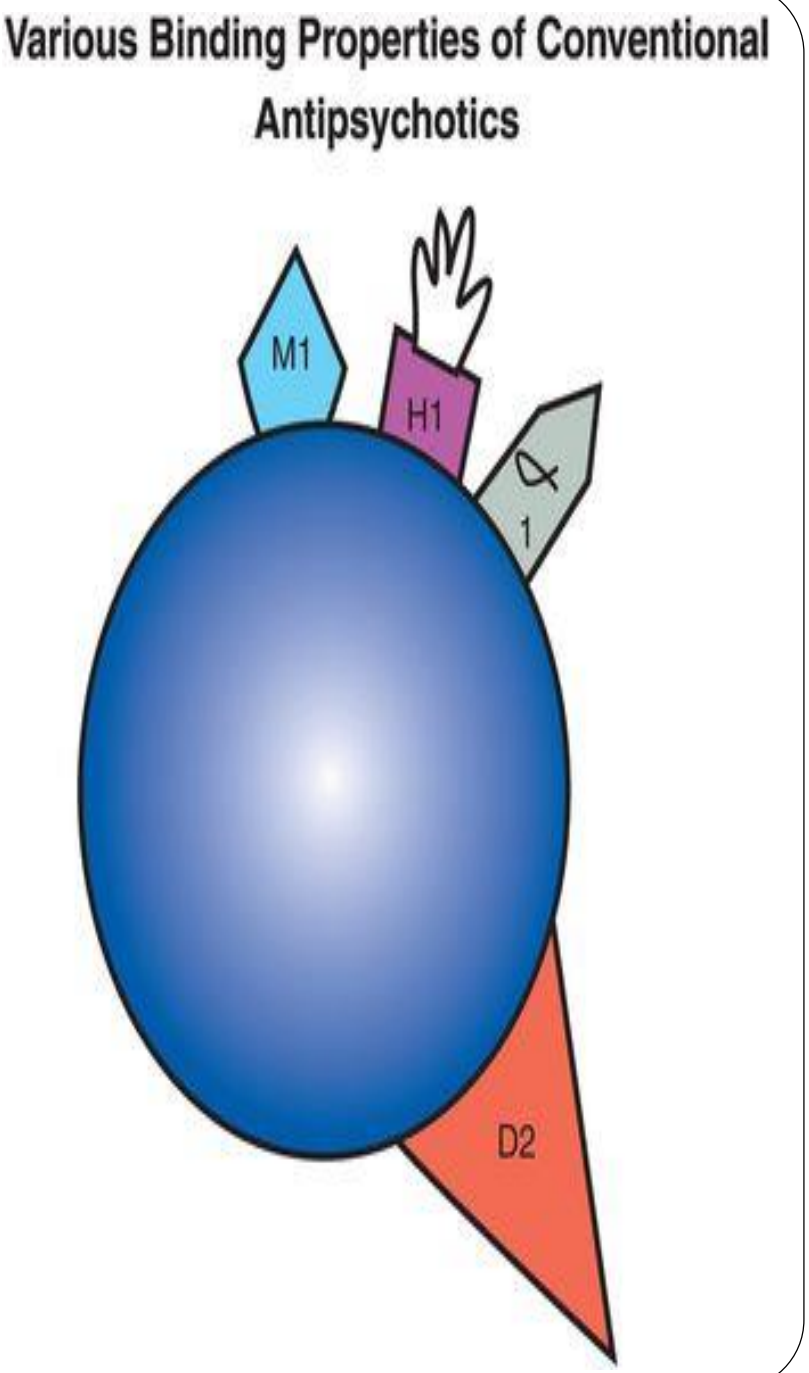
  -Sedation, Weight gain

- **Anti muscarinic(M1) side effects**

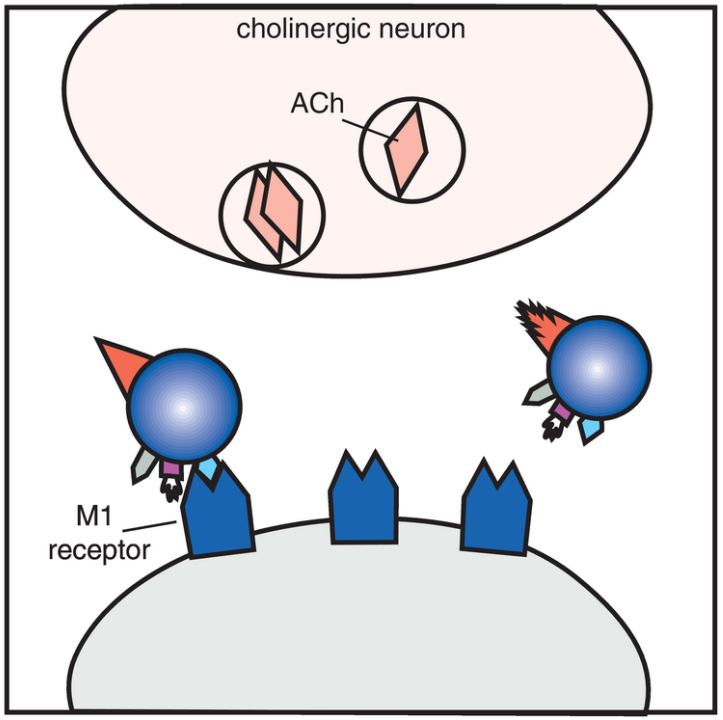
  -Dry mouth, blurring of vision, constipation, difficulty in micturition, drowsiness and cognitive impairment

- **Alfa 1 block side effects**

  -Hypotension, dizziness and drowsiness



M1 Inserted


cholinergic neuron
ACh
M1
receptor


constipation
LAXATIVE


blurred
vision
E
P Q


dry mouth

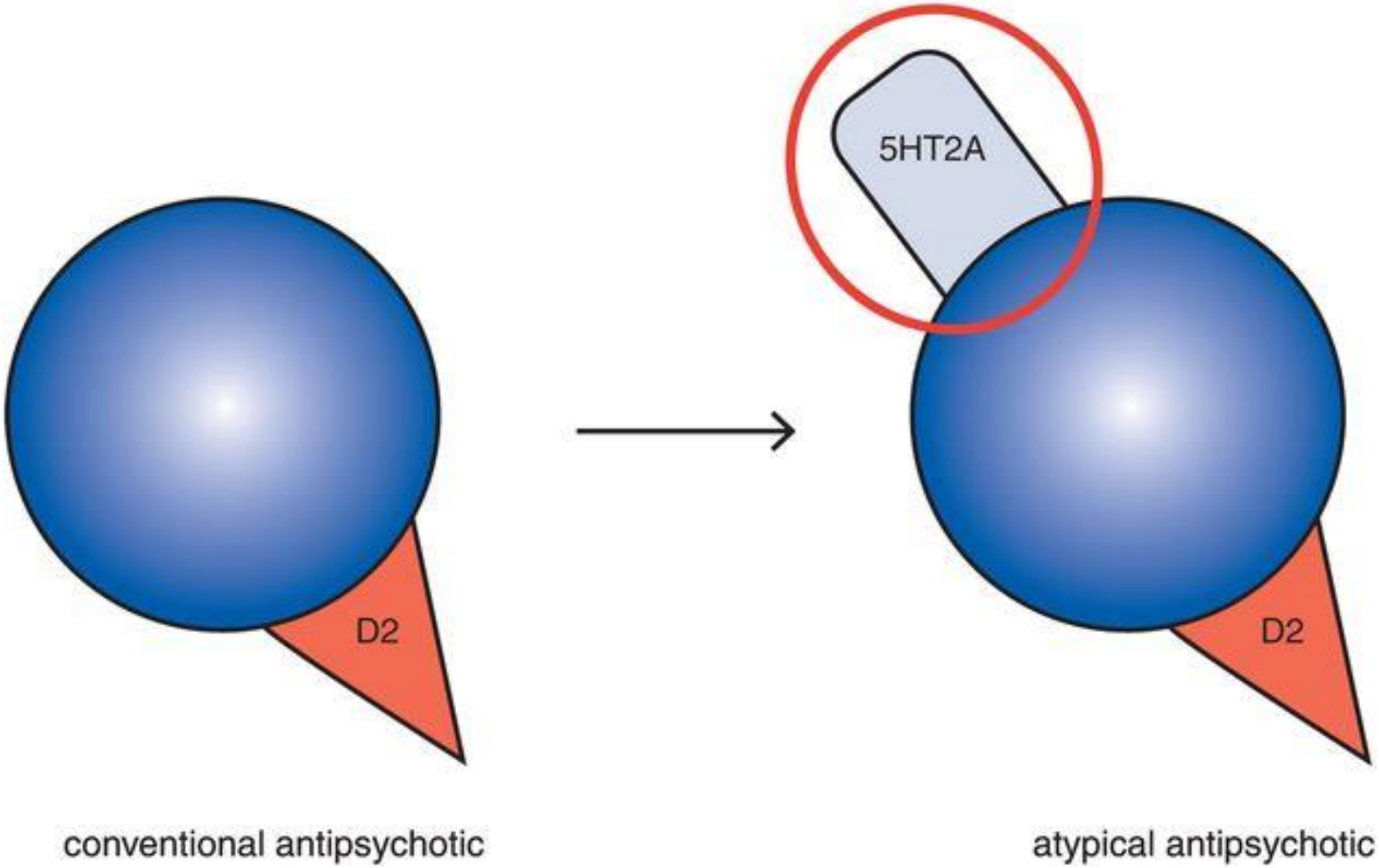

drowsiness

Atypical antipsychotics

- **Pines**
  - Clozapine
  - Olanzapine
  - Quetiapine
  - Asenapine
  - Zotepine
- **Dones**
  - Risperidone
  - Paliperidone
  - Ziprasidone
  - Iloperidone
  - Lurasidone
- **Pips**
  - Aripiprazole
  - Brexpiprazole
- **Rip**
  - Cariprazine

What Makes an Antipsychotic Atypical?

Adding 5HT2A Antagonist / Inverse Agonist Actions



Atypical antipsychotics

- Inhibits D2 receptors

-D2 receptor block in the mesolimbic pathway results in reduction of positive symptoms

- By means of inhibiting 5HT 2A receptors increases DA in other pathways

Thus results in "Less incidence of"

- Neuroleptic induced deficient syndrome

-Extra pyramidal side effects-Effective against negative symptoms

-Hyperprolactinaemia

- Effective against resistant patients
- H1,M1, Alfa 1 antagonism are present

Cardio metabolic action

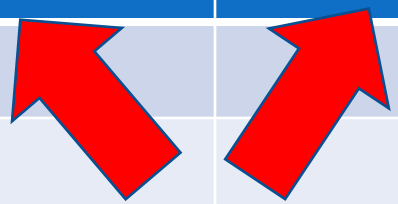
- Obesity, dyslipidemia, diabetes, cardiovascular disease & premature death

	High risk	Moderate risk	Low risk
Typical antipsychotics	Phenothiazine Chlorpromazine		Butyrophenone Haloperidol
Atypical antipsychotics	Clozapine Olanzapine	Risperidone Paliperidone Quetiapine	Ziprasidone Lurasidone Iloperidone(low for dyslipidemia) Aripiprazole Asennapine ?brexpiprazole ?cariprazine

Pines and dones can result in ↑ QT_c

Chlorpromazine & Haloperidol

Side effects	Chlorpromazine	Haloperidol
Sedation	++	+
Anticholinergic S/Es	++	+
Hypotension	++	+
Extra pyramidal S/Es	+	+++
Hyperprolactinaemia	+++	+
Sexual dysfunction	++	+
DM/Dyslipidaemia	++	+
	Side effects on eye	QT_c prolongation
	Antiemetic properties	Elevation of TSH
	T1/2 35 hours substantial hepatic first pass metabolism	Skin-Photosensitivity



Clozapine

- Weak D2 antagonism
- Effective in resistant schizophrenia
- Can reduce suicidal risk
- S/Es

-Agranulocytosis 0.8% (Neutropenia 3%)

-Seizures

-Myocarditis

Olanzapine

- Used as first line treatment
- More potent than clozapine
- S/Es

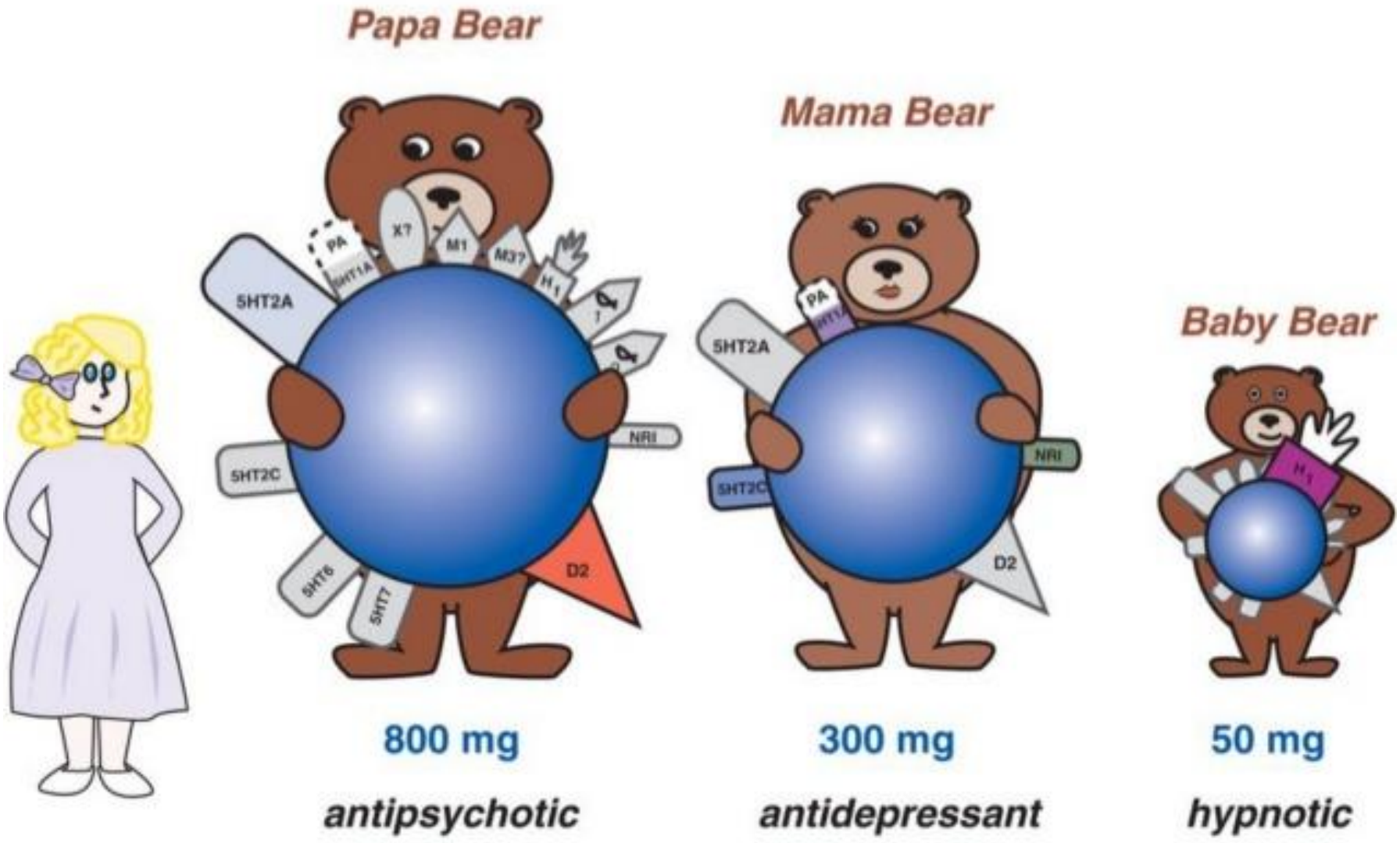
-Weight gain

-Seizure risk

-EPSEs and hyperprolactinaemia are seen more than in clozapine and quetiapine

Quetiapine

- Can function as a serotonin and norepinephrine reuptake inhibitior
- Metabolic effects less
- EPSEs and Hyperprolactinemia are less


Papa Bear
Mama Bear
Baby Bear
PA
X7
M1
M37
H1
5HT2A
NRI
5HT2C
5HT6
5HT7
D2
800 mg
antipsychotic
300 mg
antidepressant
50 mg
hypnotic

Risperidone

- EPSEs
- Hyperprolactinaemia

Aripiprazole

- Pips and rip are

D2 partial agonists >5HT1A partial agonists >5HT2A antagonists

- Aripiprazole S/Es

-No weight gain

-No sexual effects

-Very low parkinsonism, hyperprolactinaemia

-Very low H1,M1, Alfa 1 antagonism

Injectable preparations

- 40% of schizophrenics do not take regular medications
- Can be given at 3-4 week intervals
- Ex:

✓ Haloperidol

✓ Fluphenazine

✓ Flupentixol

✓ Clopixol

✓ Risperidone

✓ Paliperidone

✓ Olanzapine

Neuroleptic malignant syndrome

Young/M/Naive/High dose/IM/

Typical antipsychotic-Haloperidol, Chlorpromazine, Flupenthixol

Aypical antipsychotics- Clozapine, Olanzapine, Risperidone, Quetiapine

Antidepressants-clomipramine, venlafaxine

Withdrawal of antiparkinson drugs- amantadine, L-dopa, anti cholinergics

Metaclopromide, OCP, Methylphenidate, $FeSO_4$, Lithium, Carbamazepine

Dehydration, Organic brain disorders, Alcoholism

D_2 receptor blockade
Reduced Dopamine availability

Neuroleptic malignant Xn (0.5% prevalence)

Neuroleptic malignant syndrome Symptoms and signs

- Fever>38°C (Hypothalamus-thermoregulation)
- Rigidity (Striatum/Low Ca^{2+} mobility in muscles)
- Autonomic instability- (High PR/Labile BP/Sweating) (High sympathetic activity)
- Fluctuations in the level of consciousness

Neuroleptic malignant syndrome Differential diagnosis

- Serotonin Syndrome
- Malignant hyperthermia
- Catatonia
- Parkinsonism
- Delirium
- Encephalitis

Neuroleptic malignant syndrome Investigations

- FBC- Neutrophil leukocytosis with left shift blood picture
- SGPT/OT – to decide on treatment
- CPK - >1000 (serial)
- RFT- Rhabdomyolysis can result in renal failure

Neuroleptic malignant syndrome Management

General Measures	Specific Measures
Fever – Antipyretics cooling	Antidote/Dopamine agonist Bromocriptine 2.5mg tds 0ral 2-3days (max 45mg/day)
Rehydration – Normal saline	To reduce muscle rigidity- Calcium channel blockers-Dantrolene Benzodiazepam (IM Lorazepam)
Renal Failure – Maintain IP/output chart **Do RFT** **Look for AKI due to rhabdomyolysis**	To reduce autonomic instability- β blockers
	Monitoring (BP/PR/RR/Temp)
	NM Xn + psychotic symptoms (ECT)

Neuroleptic malignant syndrome Prognosis

- Mortality 5 – 20%
- Cardiac arrhythmia- CV collapse
- Respiratory failure (aspiration pneumonia due to rigidity causing dysphagia, rigidity causing dyspnoea)
- Rhabdomyolysis – Myoglobinuria & renal failure
- DIC

Neuroleptic malignant syndrome 2ry prevention

- 2/52 after symptom settlement resume anti-psychotic (Not the one which provoked NM Xn , usually an atypical in a low dose/low potent ± prophylaxis – bromocriptine)
- Documentation
- Begin with lower dose, increase slowly while monitor PR/BP/Temperature/(CPK – monitoring is controversial)


Thank you