FARMAKOTERAPI

OBAT ANTIPSIKOTIK

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INDIKASI

= to management of psychosis and/or agitation associated with:

- Schizophrenia and Schizoaffective Disorder
- Acute manic and mixed episodes of bipolar disorder
- Major depression with psychosis
- Delusional disorder
- Delirium
- Dementia
- Mental retardation
- Developmental disorders (e.g., Autism)
- Huntington's disease
- Tourette's syndrome
- Substance-induced psychoses (psychostimulants, phencyclidine, levodopa, steroids)

- Definition: Severe personality and thought disorder accopanied by marked emotional and behavioral impairments (severe defects in perception,ideation,mood,behavior)

Psychosis Symptoms

Positive Symptoms

- Delusion
- Hallucination
- Disorganized speech
- Disorganized behavior
- Agitation

Negative Symptoms

- Passivity
- Apathetic social withdrawal
- Stereotyped thinking
- Anhedonia
- Attentional impairment
- Emotional withdrawal

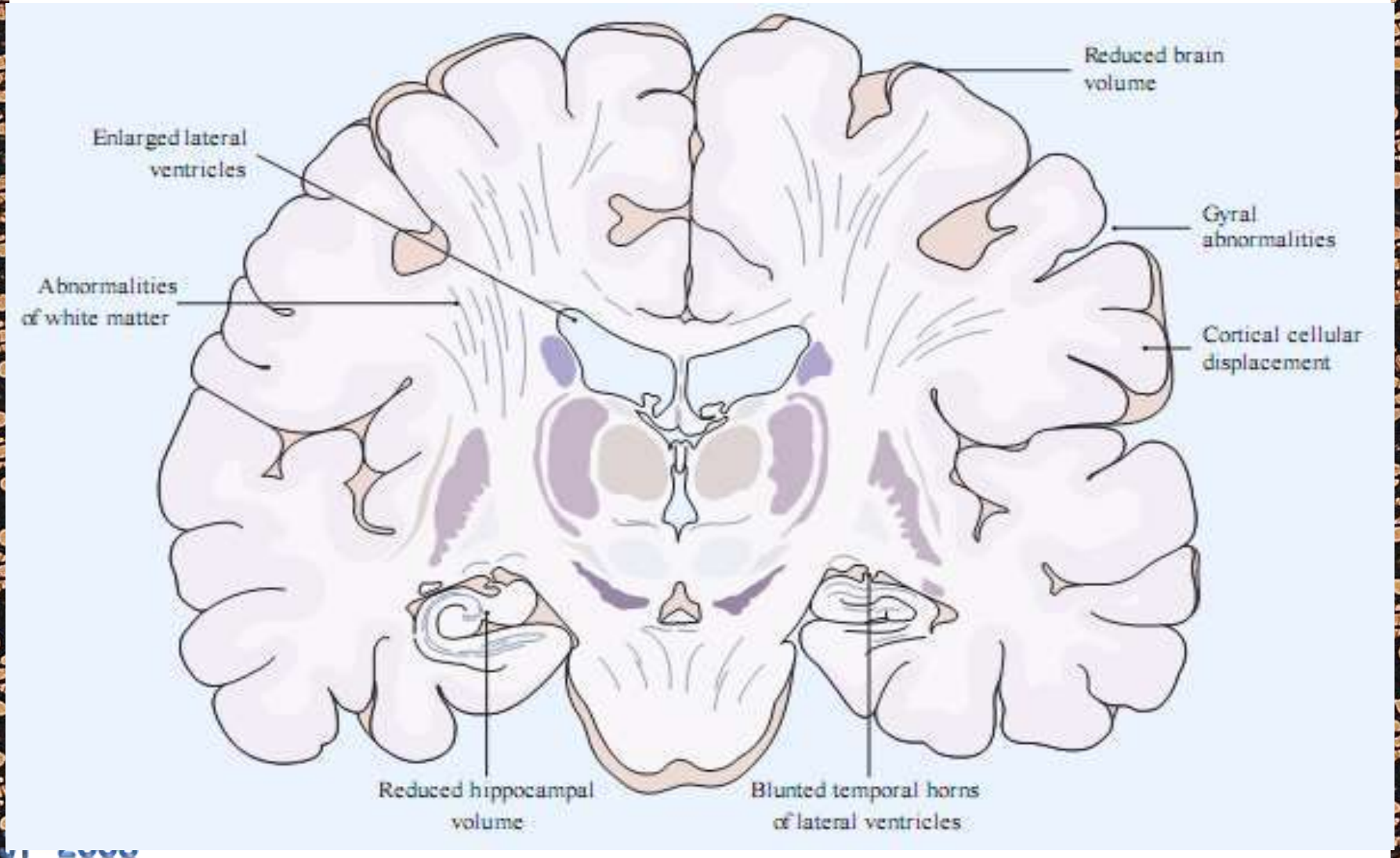
Cognitive Symptoms

- Impaired verbal fluency
- Problems with serial learning
- Problems with focusing attention
- Concentration

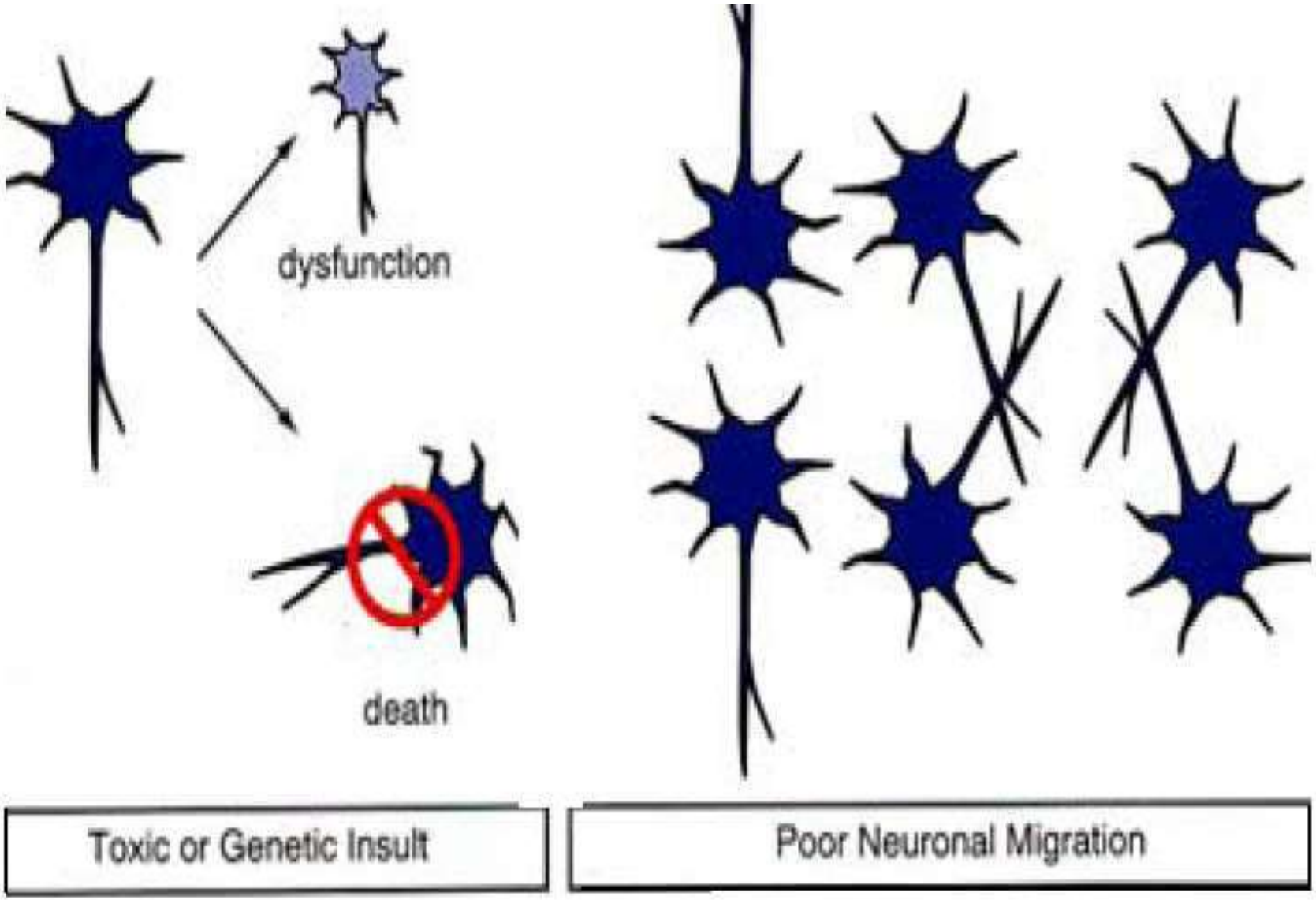
Table 13–2. SOME POSTULATED MECHANISMS FOR SCHIZOPHRENIA

Dopaminergic overactivity
? Increased dopamine receptors found at postmortem and demonstrated in vivo with PET scans
Improvement with dopamine-receptor blocking drugs
Other catecholamine abnormalities
? β-Phenethylamine increased in CSF
? Improvement with β-adrenoreceptor blocking drugs
Indolealkylamine abnormalities
Improvement with serotonin-receptor blocking drugs
Genetic factors
Concordance rate in 50% of identical twins
Concordance in 20% of first-degree relatives
Viral disease
Season of birth, increased during winter
? Viral particles in CSF, cells of brain
Autoimmune disorders
? Antibrain antibodies
Structural and metabolic abnormalities
Variable brain atrophy on CT and MRI scans
Variable decrease in brain metabolism on PET scans
Environment
Stress and emotional factors
Parental influences

STRUCTURAL BRAIN ABNORMALITIES IN SCHIZOPHRENIA



Neurodevelopmental Abnormalities in Schizophrenia



Neurodevelopmental Abnormalities in Schizophrenia

Inadequate Synapse Selection

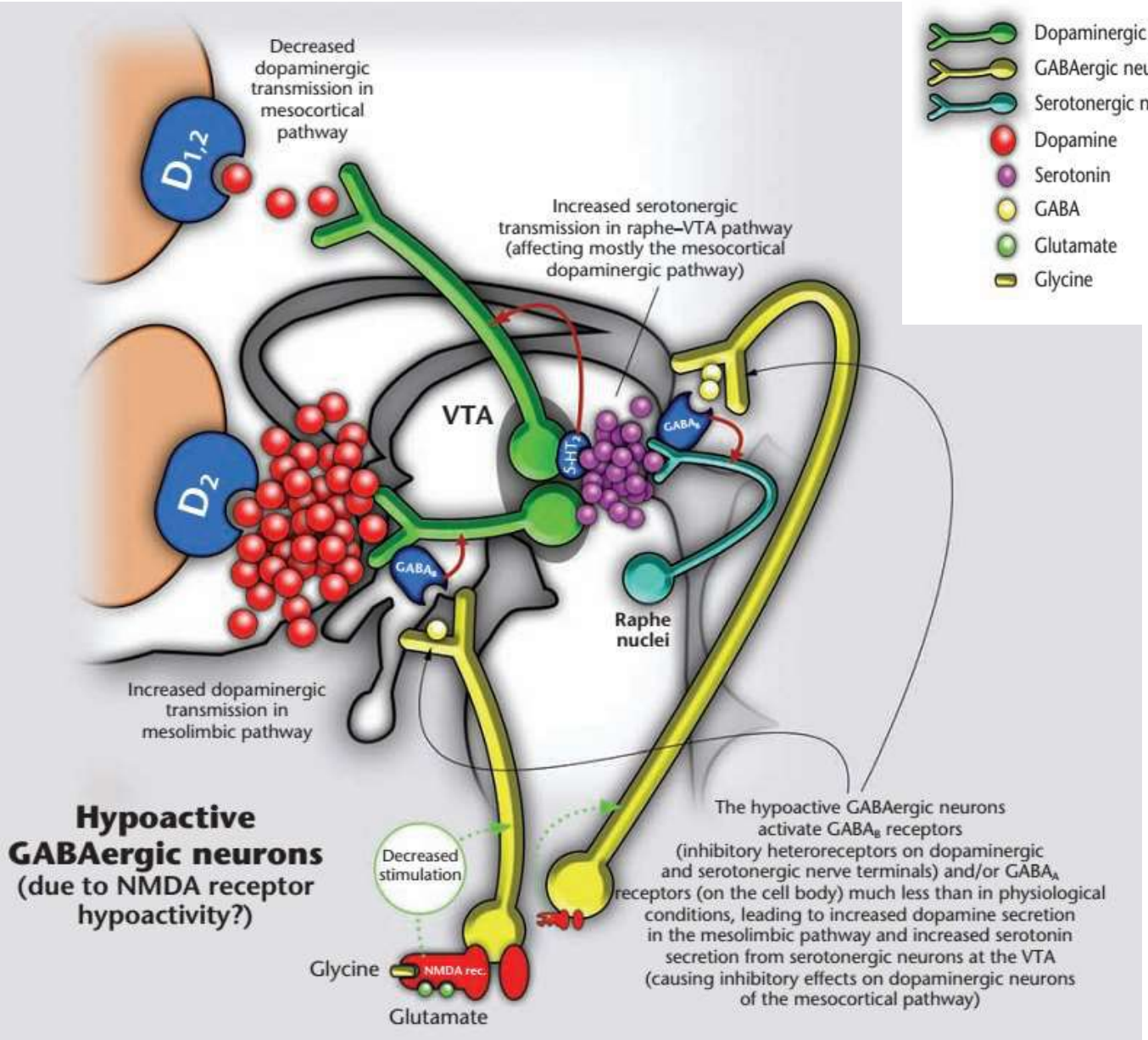
Poorly Innervated

Dopamine Hypothesis

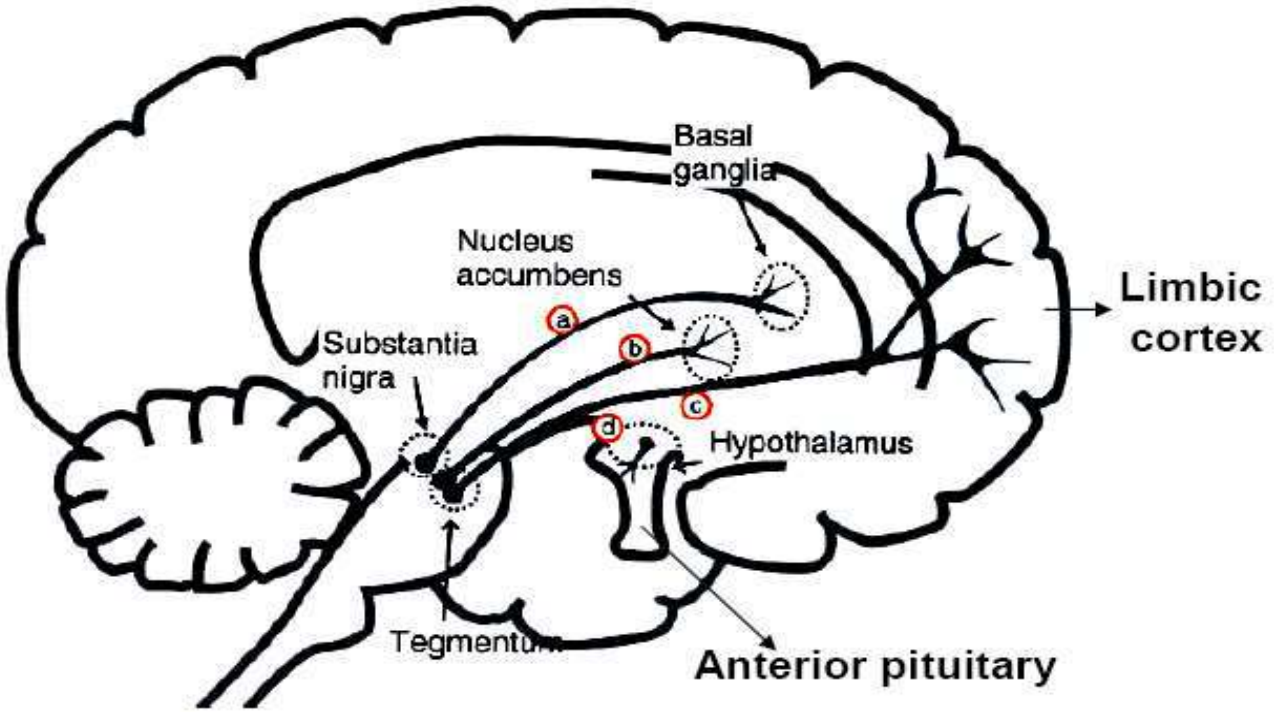
- ✓ Dopamine Depleters (mis, Reserpine) → Efek antipsychotic
  (mis → Psychotic symptom)
- ✓ Dopamine agonist (Dopaminemimetic) (Amphetamine, Cocaine, Apomorphine, Bromocriptine) → Menyebabkan atau memperhebat Psychotic symptom
- ✓ Dopamine antagonist → blokade Dopamine receptor → memperbaiki Psychotic Symptom
- ✓ Adanya korelasi antara afinitas thd D2 (bukan D1) terhadap efektifitas klinik dari efek Antipsychotic
- ✓ Obat yang mempunyai efek menghambat reseptor D2 (bukan D1) → Mempunyai efek Antipsychotic

→ Perubahan DA receptors/DA levels → schizophrenia

GABA Hypothesis



Dopamine Pathway



a = nigrostriatal pathway

b = mesolimbic pathway: *Increase in dopamine causes positive symptoms of schizophrenia*

c = mesocortical pathway: *Deficit in dopamine causes negative and cognitive symptoms of schizophrenia*

d = tuberoinfundibular pathway

Mesolimbic pathway **: VTA →limbic system =emotion, rewards, mood**

•Hyperactivity on this pathway is associated with positive symptoms of schizophrenia

Mesocortical pathway **: VTA →prefrontal cortex**
=motivation,planning,attention,social behaviour

•Deficit in dopamine in this pathway is associated with negative and cognitive symptom of schizophrenia **Blokade 5-HT-2 di mesocortical → Meningkatkan kadar DA**

Nigrostriatal pathway **: s.nigra → striatum = pengendalian motorik**

•Part of extrapyramidal system and controls motor movement

•Blockade of D2 receptors causes:
-- deficiency in dopamine in this pathway and thus movement disorder such as Parkinson's disease
-- hyperkinetic movement such as tardive dyskinesia

Tuberoinfundibular pathway **= Hypothalamus →Hypophyse : Kontrol sekresi Prolactine**

•Increased neuronal activity of this pathway inhibits prolactin release

•Blockade of D2 receptor increases prolactin release and causes:
-- galactorrhea
-- amenorrhea

ANTIPSYCHOTICS

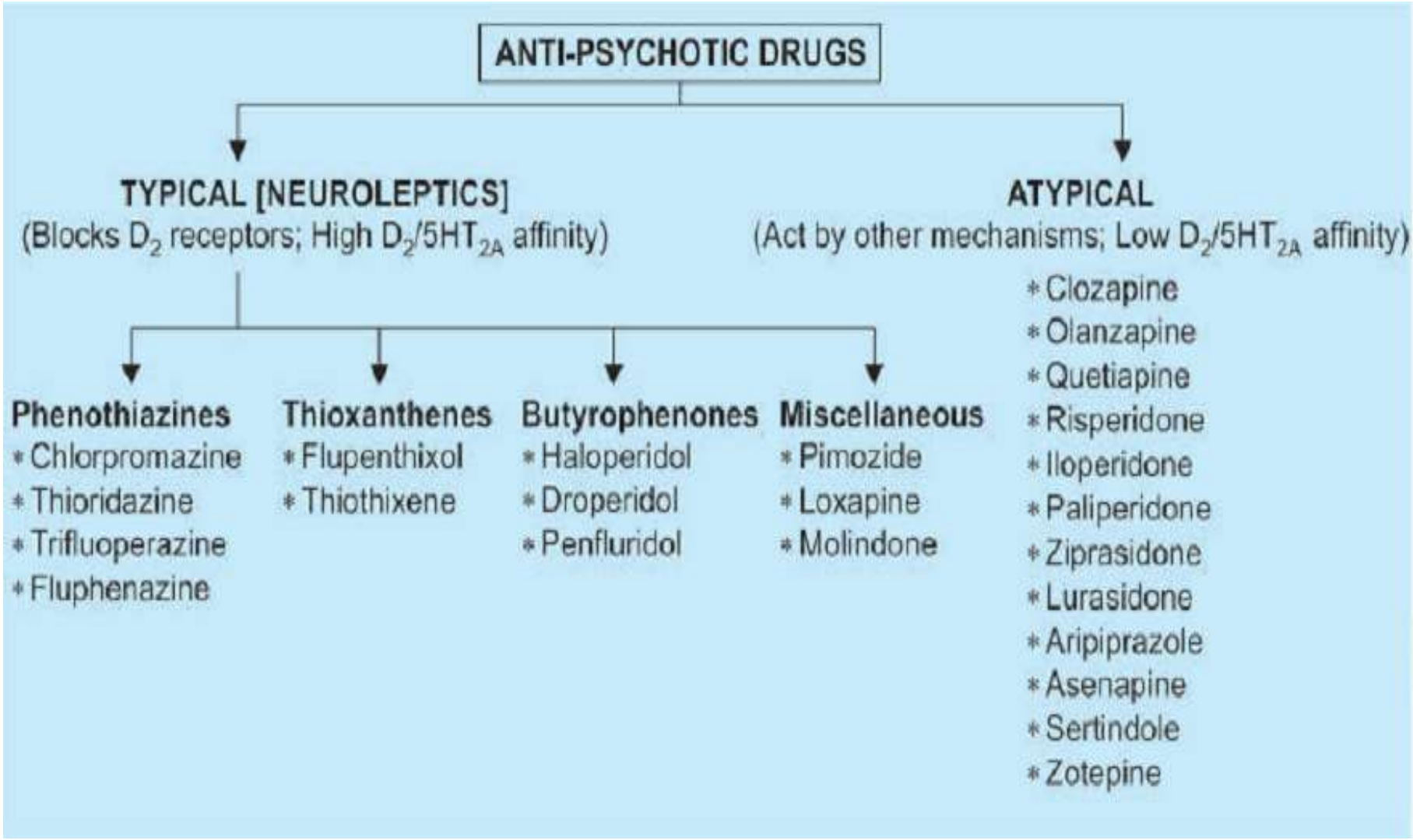
(neuroleptic= Major Tranquillizer)

First generation (Typical)

- Chlorpromazine
- Fluphenazine
- Haloperidol
- thioridazine
- Trifluoperazine
- Triflupromazine
- Thiothixene

Second generation (Atypical)

- Clozapine
- Risperidone
- Olanzapine
- Quetiapine
- Ziprasidone


ANTI-PSYCHOTIC DRUGS
TYPICAL [NEUROLEPTICS]
(Blocks D_2 receptors; High D_2/$5HT_{2A}$ affinity)
ATYPICAL
(Act by other mechanisms; Low D_2/$5HT_{2A}$ affinity)
Phenothiazines
* Chlorpromazine
* Thioridazine
* Trifluoperazine
* Fluphenazine
Thioxanthenes
* Flupenthixol
* Thiothixene
Butyrophenones
* Haloperidol
* Droperidol
* Penfluridol
Miscellaneous
* Pimozide
* Loxapine
* Molindone
* Clozapine
* Olanzapine
* Quetiapine
* Risperidone
* Iloperidone
* Paliperidone
* Ziprasidone
* Lurasidone
* Aripiprazole
* Asenapine
* Sertindole
* Zotepine

OBAT ANTIPSIKOTIK

❖ First Generation

Affinitas tinggi thd R/ D2

Affinitas thd R/ Adr, 5HT2, M, & H.

ES EPS (>>>) : parkinsonism, dystonia, akathisia

Resiko tardive dyskinesia (TD)>>

Serum prolaktin ↑

Ada 3 gol bds strukt : phenothiazines,butyrophenones (haloperidol), lain-lain (thiothixene, molindone, loxapine)

3 gol bds affinitas thd R/D2:

High(haloperidol), Mid (Loxapin), Low(CPZ)

❖ Second Generation

Spektrum Tx lebih luas

Affinitas thd R/ $5HT_{2a}$ > D2

Affinitas thd R/ Adr(α1& α2),DA,M, H

ES EPS (-/<<<)

Resiko TD <<<

Serum Prolaktin sedikit ↑

ANTIPSYCHOTIC

Gol	Struktur	Prototipe	Potensi	Mekanisme
	Phenothiazine :			
Typical	Aliphatic	Chlorpromazine	Low	D-2
	Piperidine	Thioridazine	Low	D-2
	Piperazine	Fluphenazine	High	D-2
	Butyrophenone	Haloperidol	High	D-2
Atypical		*Clozapine*	*D-4, 5HT-2*	
		Risperidone	*D-2, 5-HT-2*	
		Olanzapine	*D-2, D-4, 5-HT-2*	
		Quetiapine	*D-2, 5-HT-2*	

Table 13–8. DOSE EQUIVALENTS AND RANGES OF DAILY DOSES FOR VARIOUS ANTIPSYCHOTICS

DRUG	RELATIVE POTENCY	DOSE RANGE (MG/D)
Chlorpromazine	100	50–2000
Thioridazine	100	50–800
Mesoridazine	50	25–400
Clozapine	50	25–400
Perphenazine	10	8–64
Loxapine	10	15–160
Molindone	10	15–225
Trifluoperazine	5	4–60
Thiothixene	2–4	6–120
Fluphenazine	2–3	2–60
Haloperidol	2	2–100

First Generation Antipsychotics

- Blockade of D_2 receptors in mesolimbic pathway, resulting in reduced positive symptoms of schizophrenia

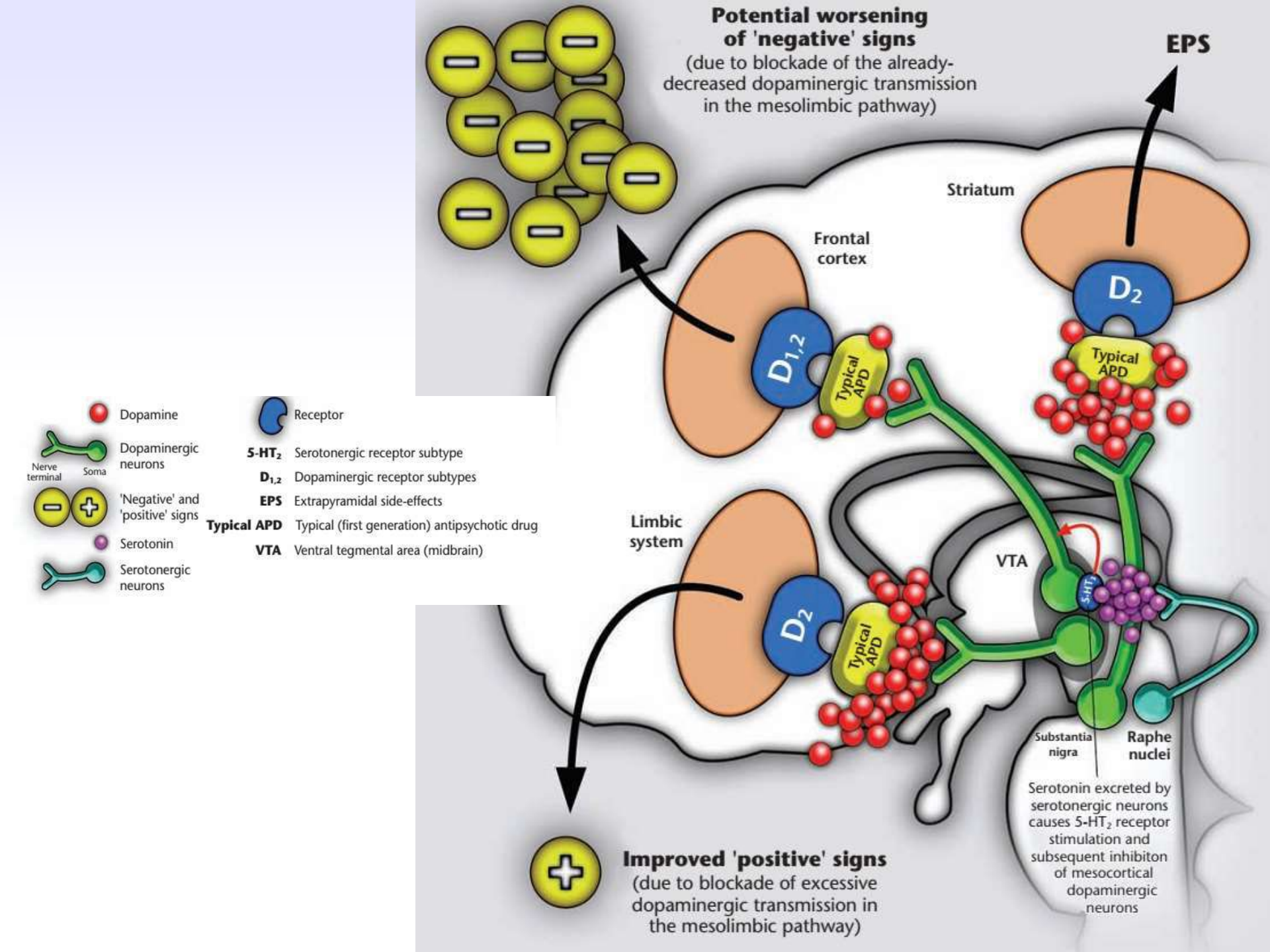
- Blockade of D_2 receptors in mesocortical pathway, which is already deficient in schizophrenia, causes cognitive symptoms or worsen negative symptoms

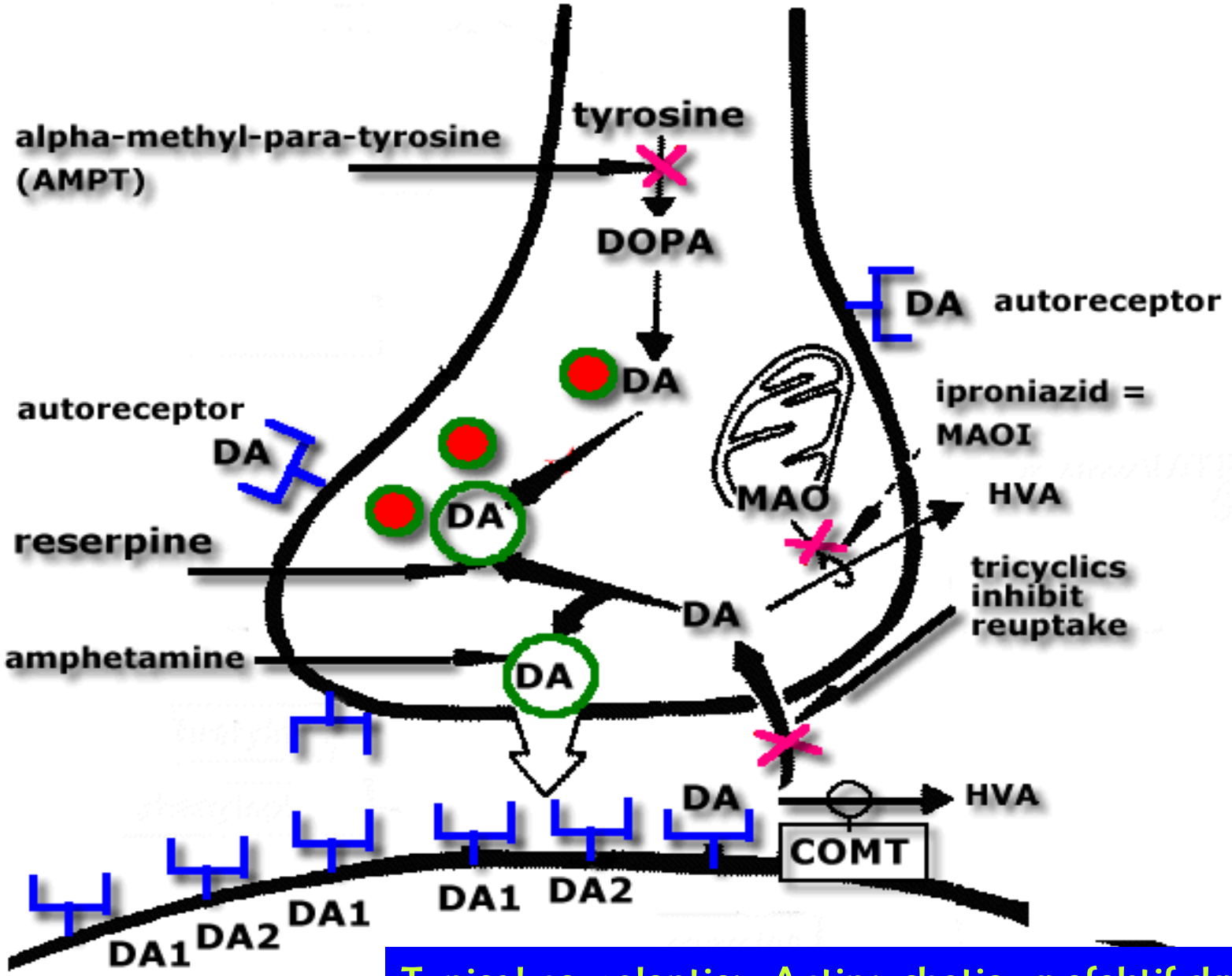
- Blockade of D_2 receptors in nigrostriatal pathway, produces EPS such as motor abnormalities (parkinsonism), tardive dyskinesia or hyperkinetic movement disorder

- Blockade of D_2 receptors in tuberoinfundibular pathway causes hyperprolactinemia

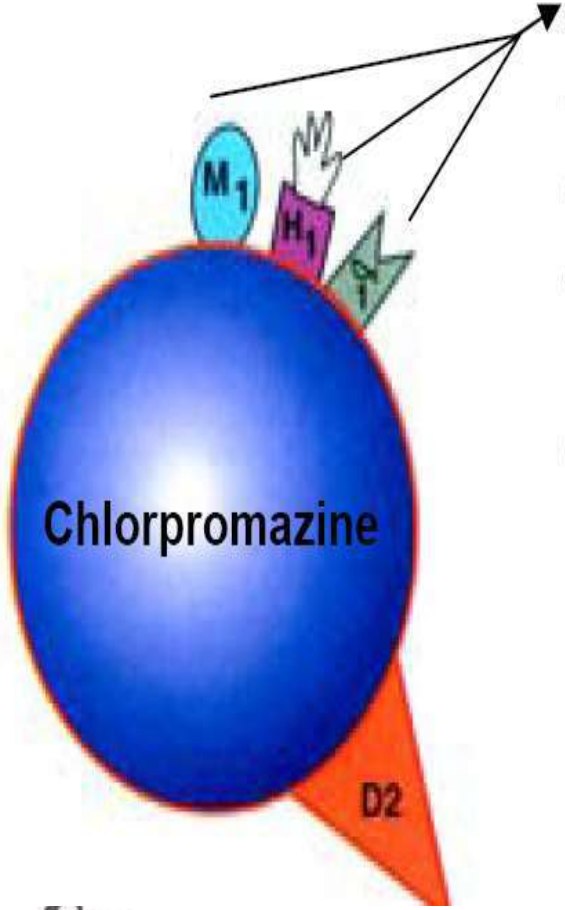
→ side effects:

JF 2008


Potential worsening of 'negative' signs
(due to blockade of the already-decreased dopaminergic transmission in the mesolimbic pathway)
EPS
Striatum
Frontal cortex
$D_{1,2}$
Typical APD
D_2
Typical APD
Limbic system
D_2
Typical APD
VTA
5-HT2
Substantia nigra
Raphe nuclei
Serotonin excreted by serotonergic neurons causes 5-HT_2 receptor stimulation and subsequent inhibiton of mesocortical dopaminergic neurons
Improved 'positive' signs
(due to blockade of excessive dopaminergic transmission in the mesolimbic pathway)
Dopamine
Dopaminergic neurons
Nerve terminal
Soma
'Negative' and 'positive' signs
Serotonin
Serotonergic neurons
Receptor
5-HT_2 Serotonergic receptor subtype
$D_{1,2}$ Dopaminergic receptor subtypes
EPS Extrapyramidal side-effects
Typical APD Typical (first generation) antipsychotic drug
VTA Ventral tegmental area (midbrain)

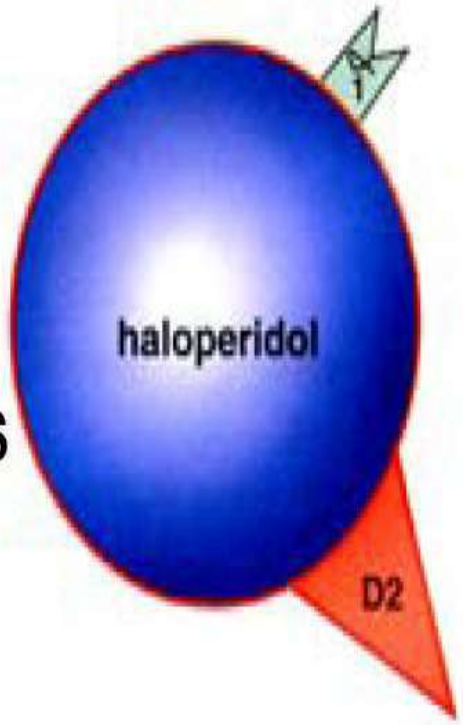


Typical neuroleptics : Antipsychotic yg efektif dgn memblokade reseptor dopamine-2 (DA2)



side effects:
dry mouth, blurred vision,
drowsiness, weight gain,
dizziness, low bp

cholinergic properties: EPS



Stahl, 2002

JF 2008

Side Effects Autonomic Typical Antipsikotik

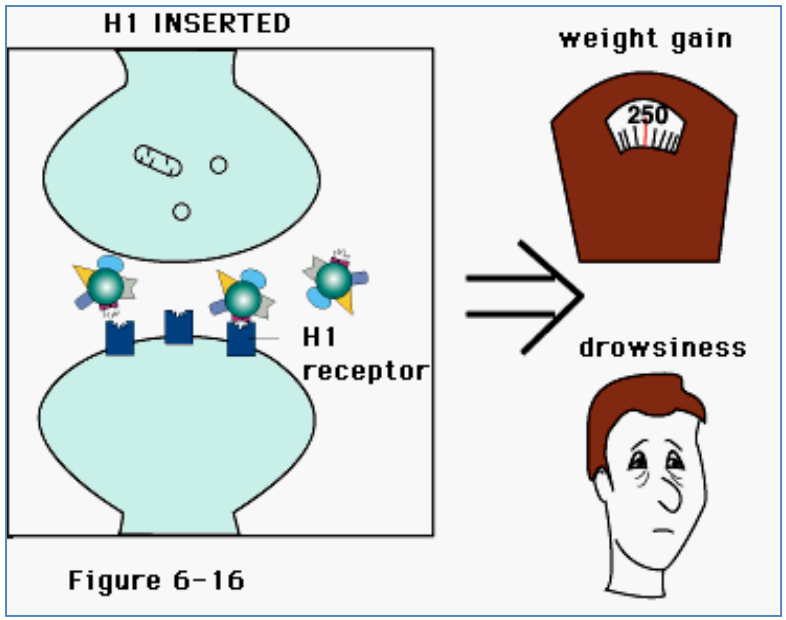


Figure 6-16

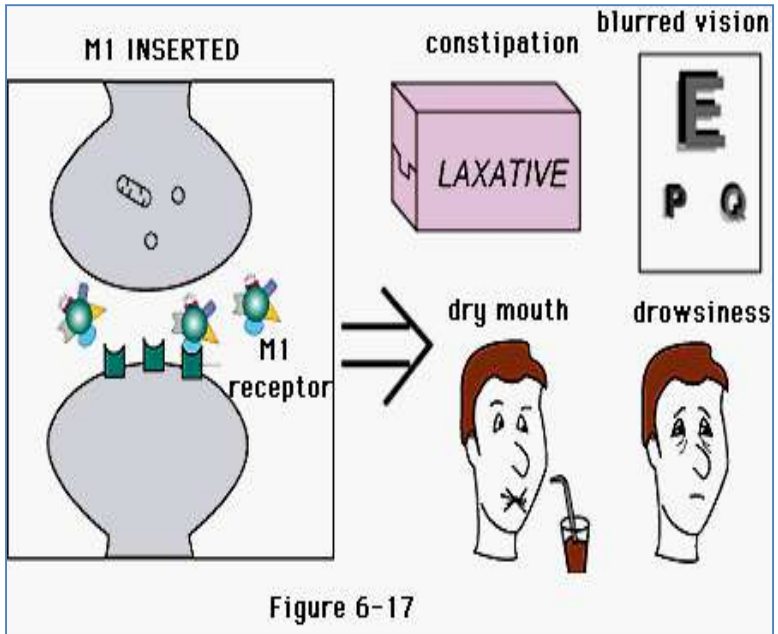


Figure 6-17

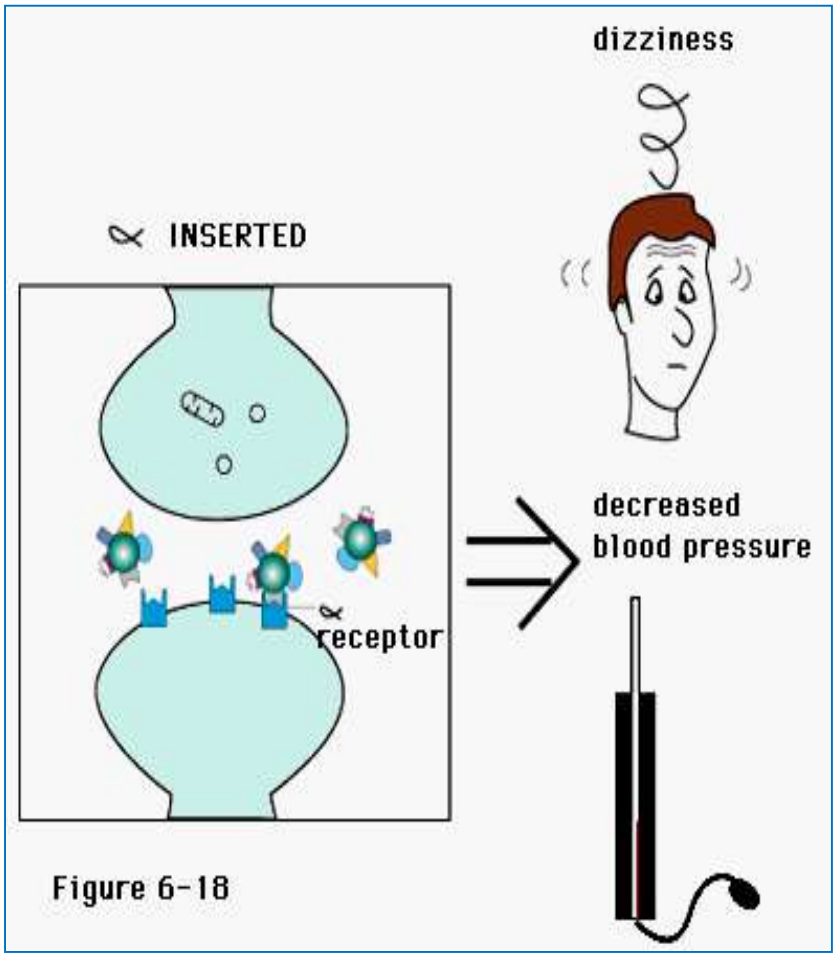


Figure 6-18

SIDE EFFECT OF TYPICAL ANTIPSYCHOTIC DRUGS

- Autonomik

  Blokade Alpha-1 : hipotensi postural, dizzines, refleks tachycardia, potensiasi efek antihipertensi

  Blokade Muscarinic: retensi urin,mulut kering,konstipasi,pandangan kabur,tachycardia,disfungsi memori,delirium

  Blokade H-1: sedasi, ngantuk,berat badan naik,potensiasi depresan SSP

- Endokrin

  Blokade D-2 di HP axis → sekresi Prolactin ↑ →gynecomastia, galactorrhea,amenorhhea,perubahan menstruasi,gangguan sexual

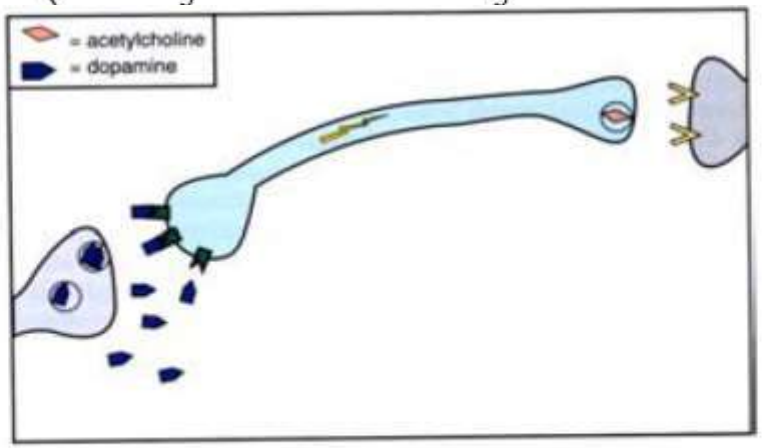
- Neurologi

  Blokade D-2 di basal ganglia → EPS (acute dystonia, parkinsonism, akathisia,tardive dyskinesia

Anticholinergic (M1) Drugs and EPS

(Acetylcholine may cause EPS)

1



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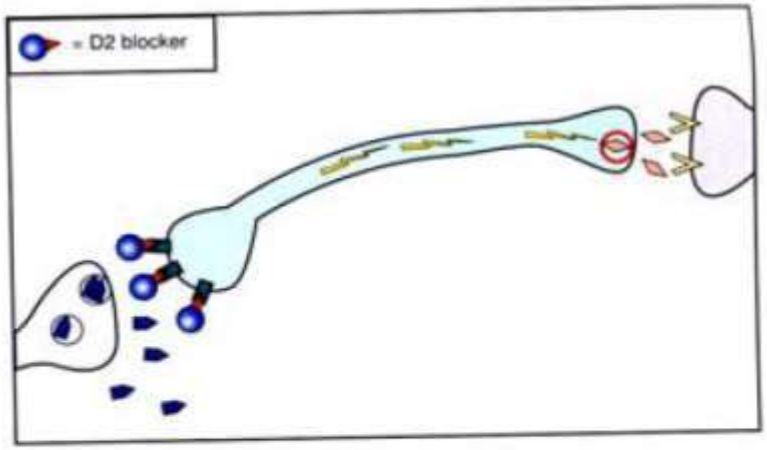

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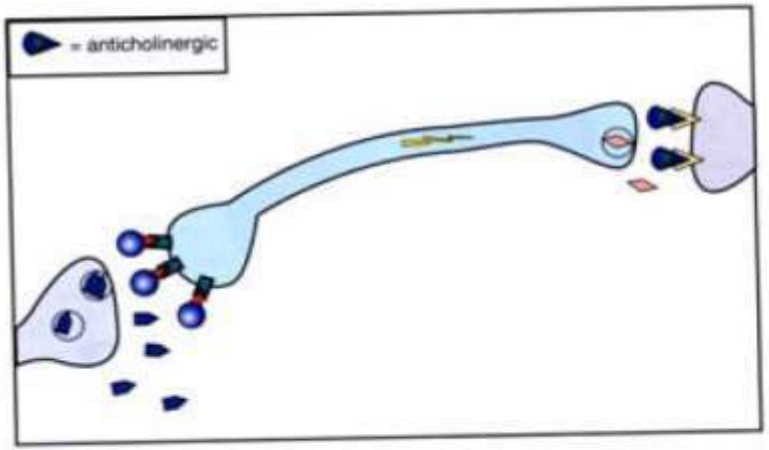
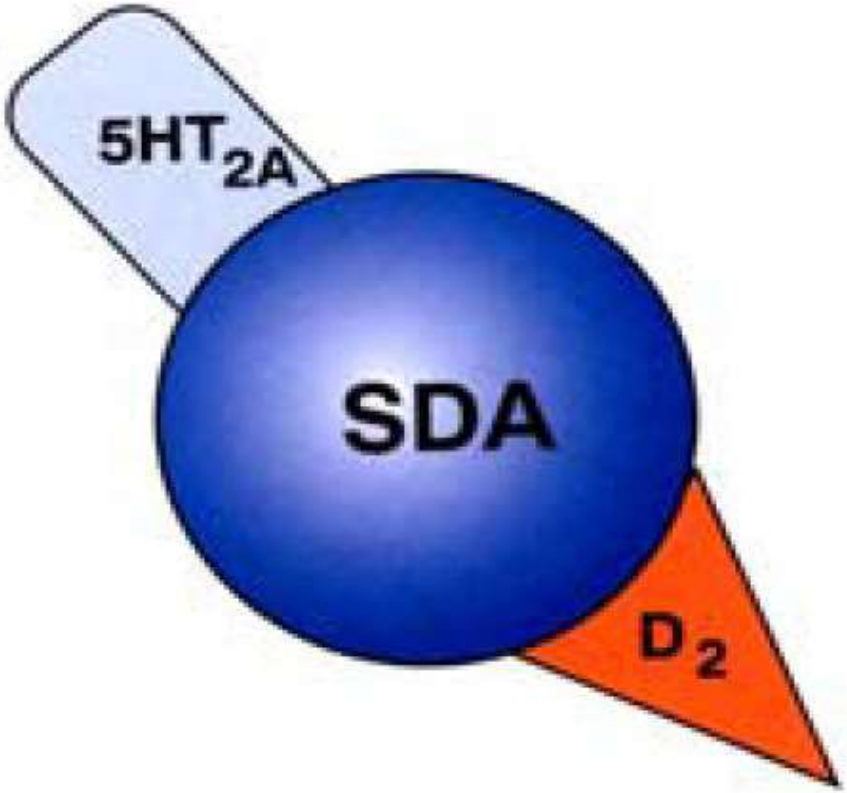


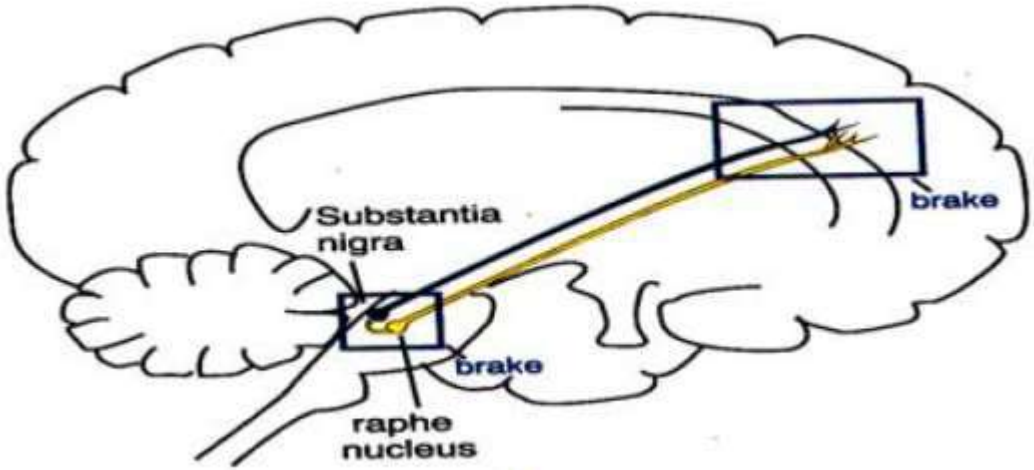
Dopamine and acetylchilone has reciprocal relationship
Stronger anticholinergic agents cause fewer EPS

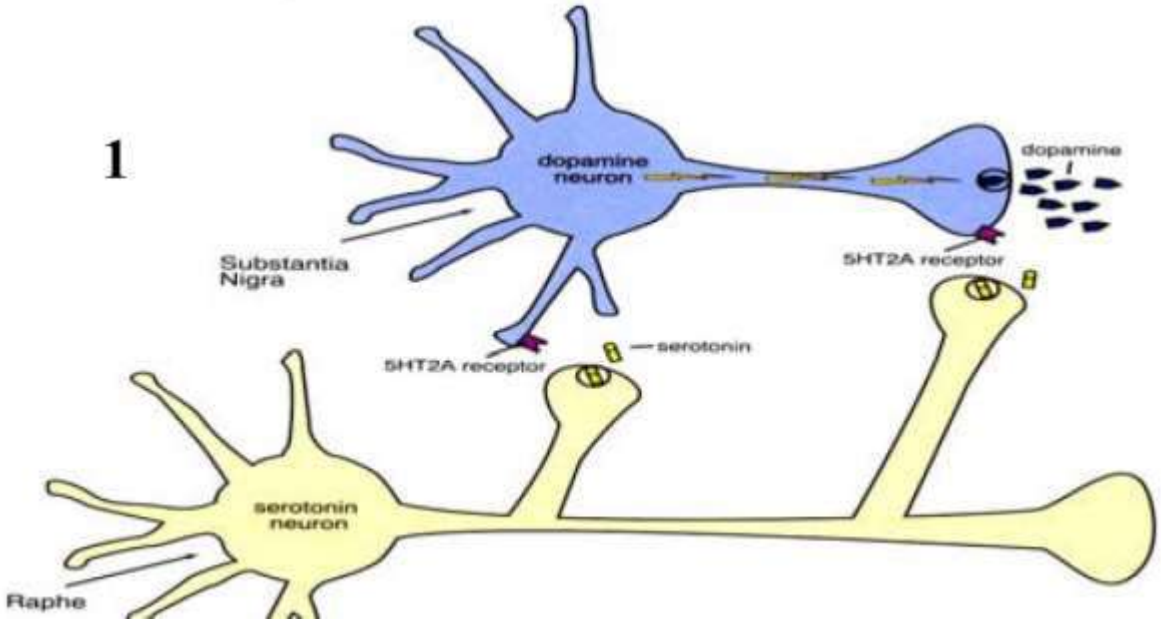
Second Generation Antipsychotics

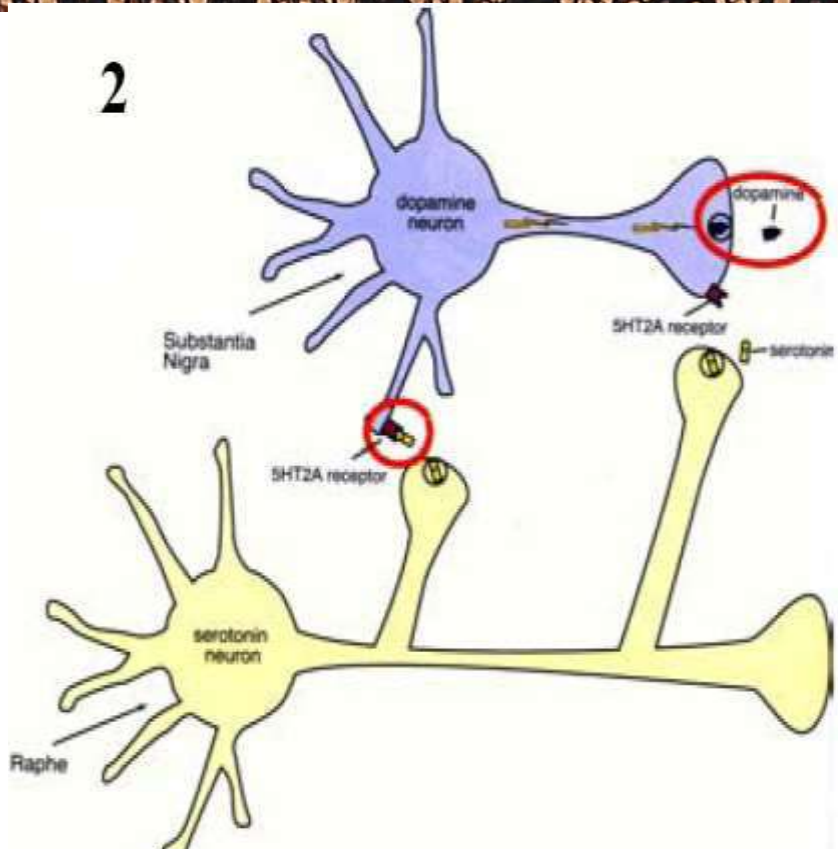


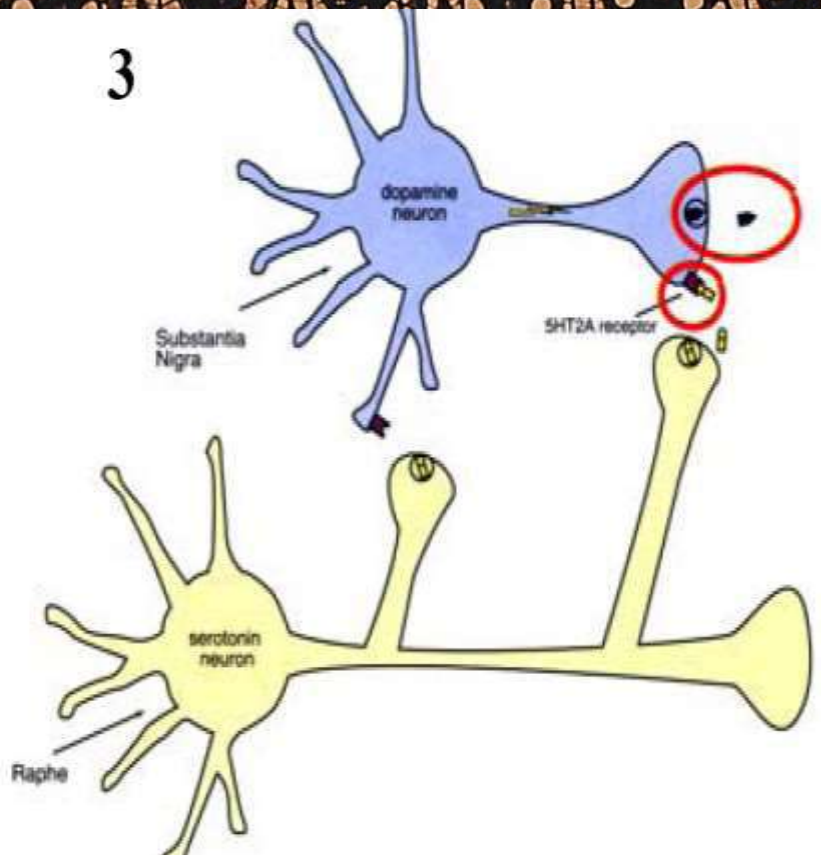
5HT$_{2A}$ and D$_2$ antagonists (SDAs)

Serotonin-Dopamine Interaction









- Key: 5HT interact with $5HT_{2A}$ receptors at postsynaptic level both at DA cell bodies and at axon terminals and inhibits the release of DA

or

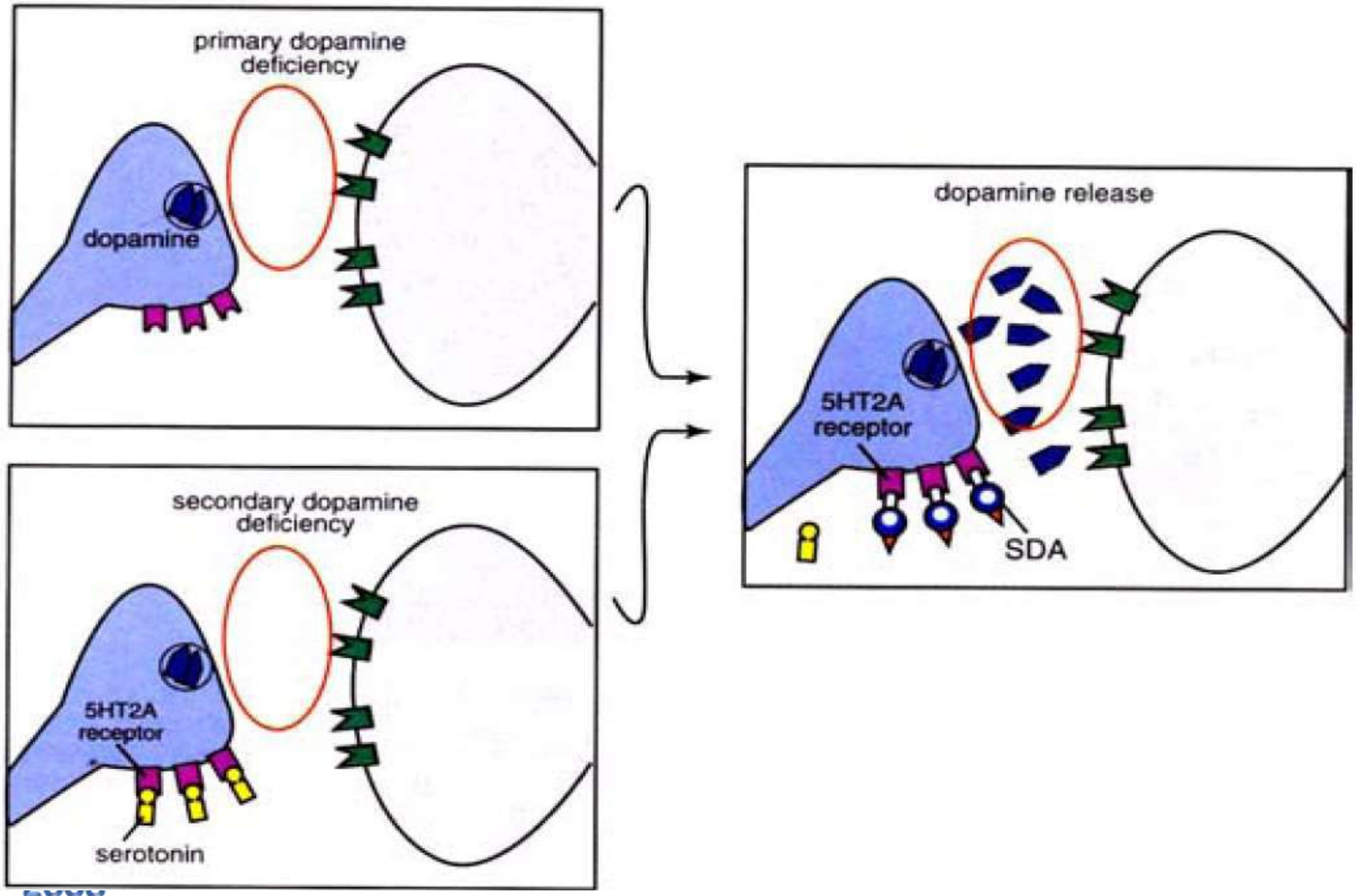
- $5HT_{2A}$ antagonists cause more release of DA

- The action of $5HT_{2A}$ and D_2 antagonism causes different effects in different dopamine pathways

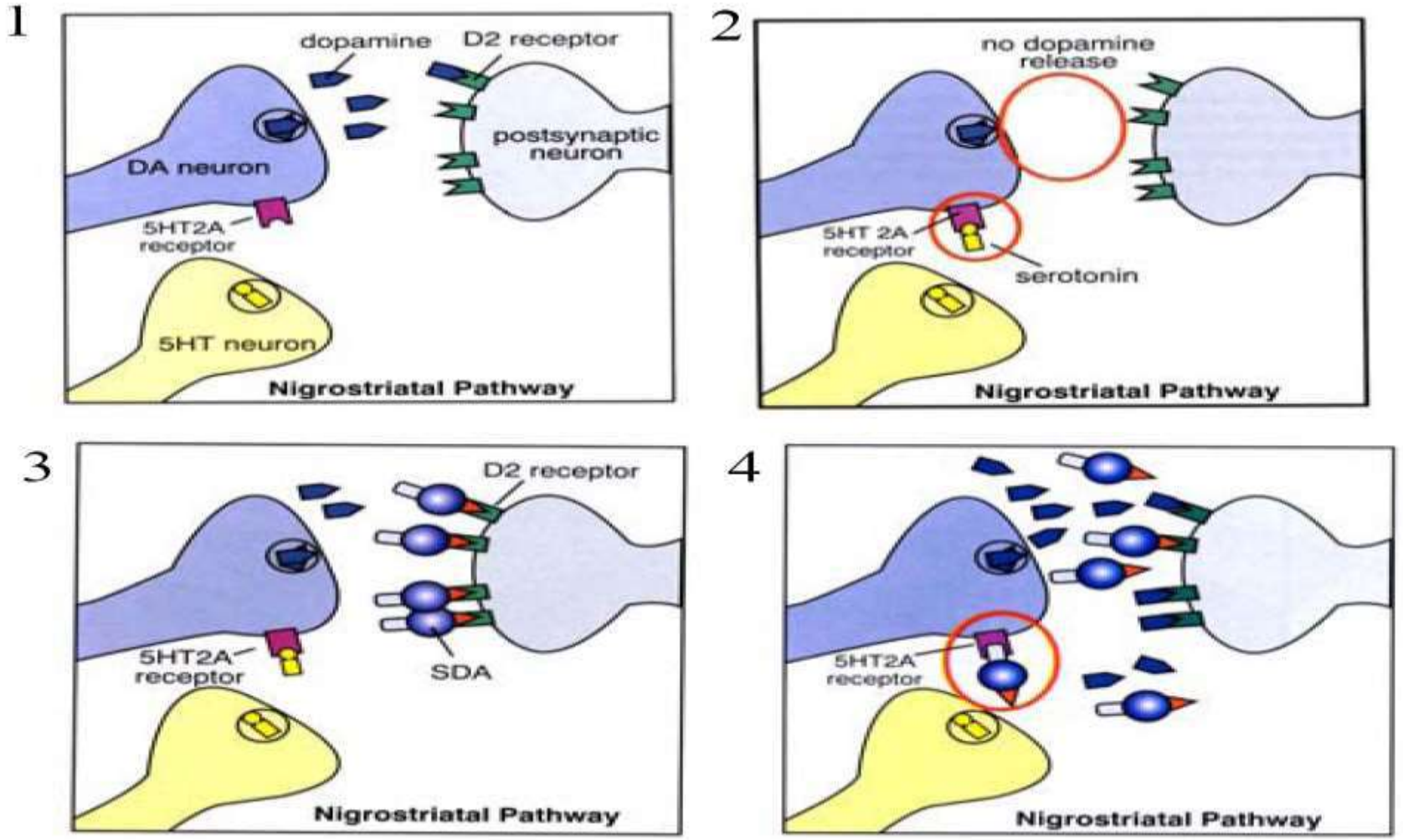
SECOND GENERATION ANTIPSYCHOTICS

- In mesolimbic pathway the action of D2 receptor blockade of antipsychotics are more robust than 5HT2A antagonism. This may help reducing positive symptoms
- In mesocortical pathway, dopamine deficiency causes negative and cognitive symptoms. In mesocortical pathway, there is more 5HT2A receptors than D2 receptors. Thus 5HT antagonistic property is more profound that D2 receptor blocking property. This may help improving negative symptoms

SECOND GENERATION ANTIPSYCHOTICS

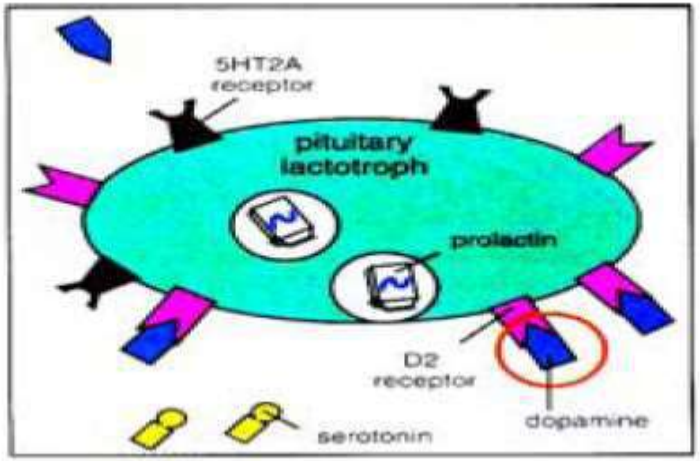


In nigrostriatal pathway: 5HT2A antagonists bind to 5HT2A receptors and block the release of 5HT and thus cause more DA to be released.This may reduce EPS



In tuberoinfundibular pathway: DA blocks the release of prolactin, whereas, 5HT2A causes release of prolactin. Antagonistic properties of antipsychotics cancel DA and 5HT2A action on prolactin release

1



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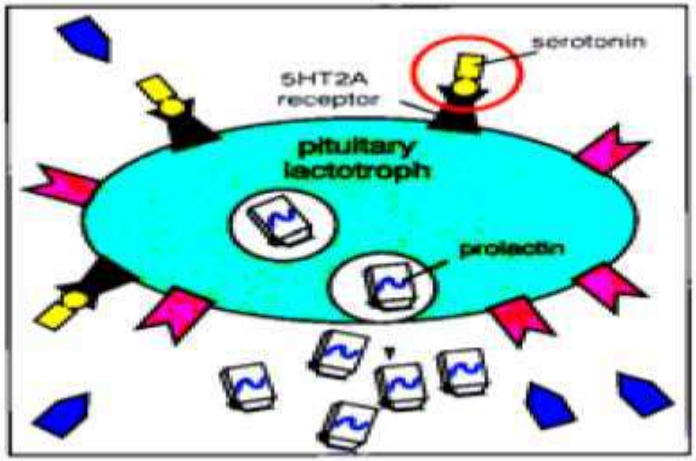

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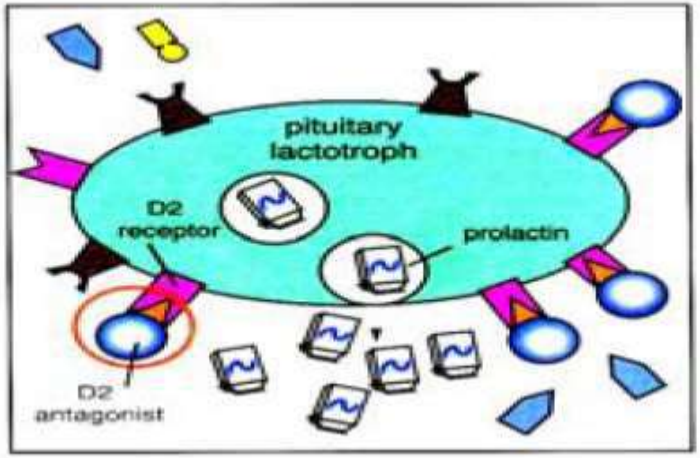

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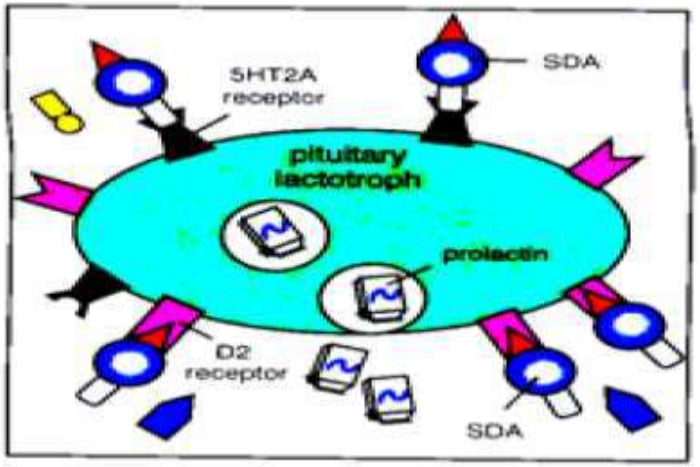
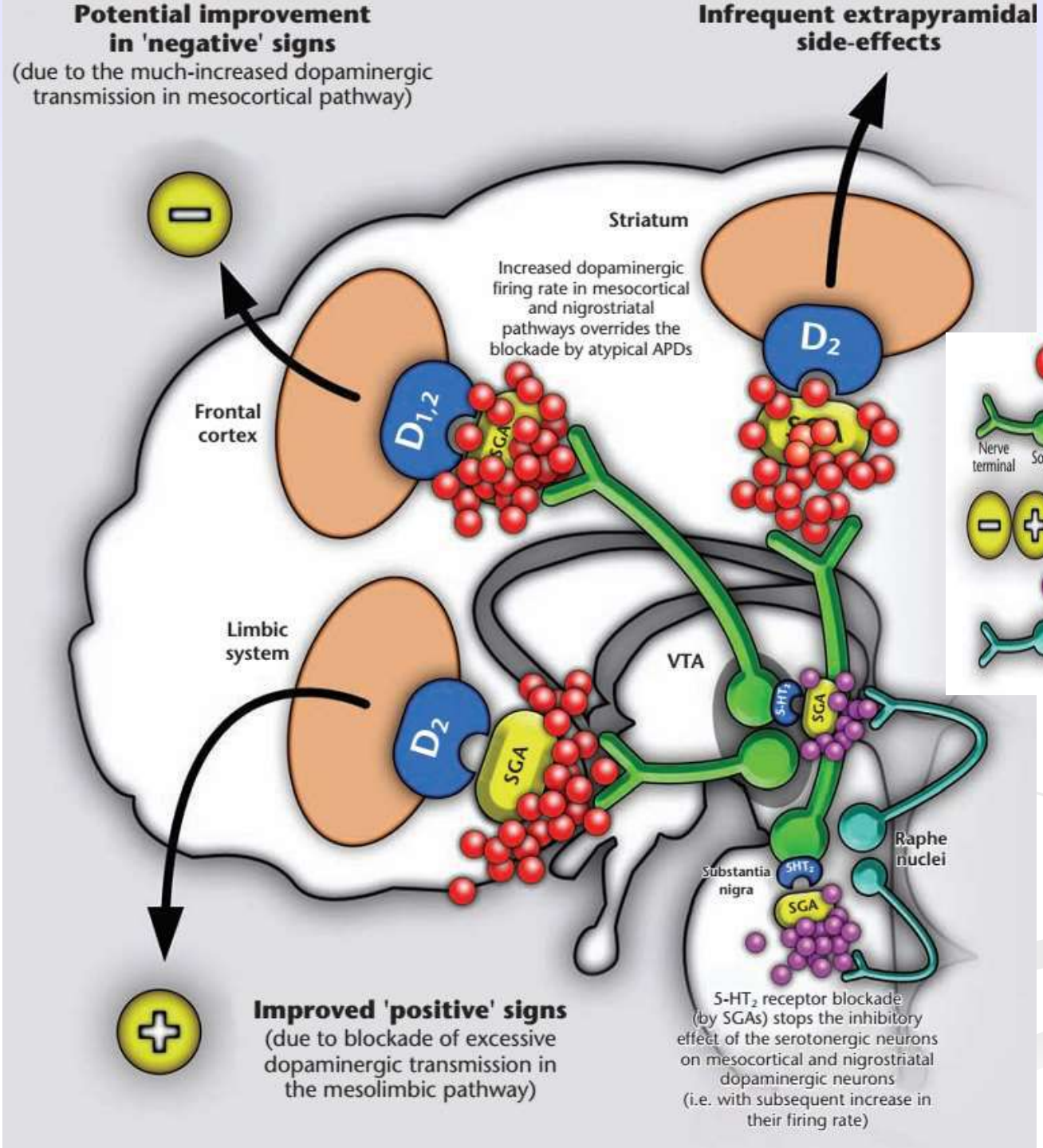



Potential improvement in 'negative' signs
(due to the much-increased dopaminergic transmission in mesocortical pathway)
Infrequent extrapyramidal side-effects
Striatum
Increased dopaminergic firing rate in mesocortical and nigrostriatal pathways overrides the blockade by atypical APDs
Frontal cortex
Limbic system
VTA
Raphe nuclei
Substantia nigra
Improved 'positive' signs
(due to blockade of excessive dopaminergic transmission in the mesolimbic pathway)
5-HT2 receptor blockade (by SGAs) stops the inhibitory effect of the serotonergic neurons on mesocortical and nigrostriatal dopaminergic neurons (i.e. with subsequent increase in their firing rate)
Dopamine
Receptor
Dopaminergic neurons
Nerve terminal
Soma
5-HT2 Serotonergic receptor subtype
D1,2 Dopaminergic receptor subtypes
'Negative' and 'positive' signs
SGA Second-generation ('atypical') antipsychotic drug
Serotonin
VTA Ventral tegmental area (midbrain)
Serotonergic neurons

Atypical antipsychotics

→Menekan simptom positive dan negative

→Lebih efektif dari typical antipsychotics,

→Memperbaiki fungsi cognitive
(bila dibandingkan thd typical antipsychotic).

Antipsychotic	Receptor Binding					
	D_1	D_2	$5\text{-}HT_2$	$Alpha_1$	Chol	Hist
Clozapine	++	+	+++	+++	+++	++
Olanzepine	++	++	+++	++	+++	++
Quetiapine	(+)	+	+	++	-	++
Risperidone	-	+++	+++	+++	-	-
Sertindole	-	+	+++	++	-	-
Ziprasidone	+	+++	+++	++	-	-

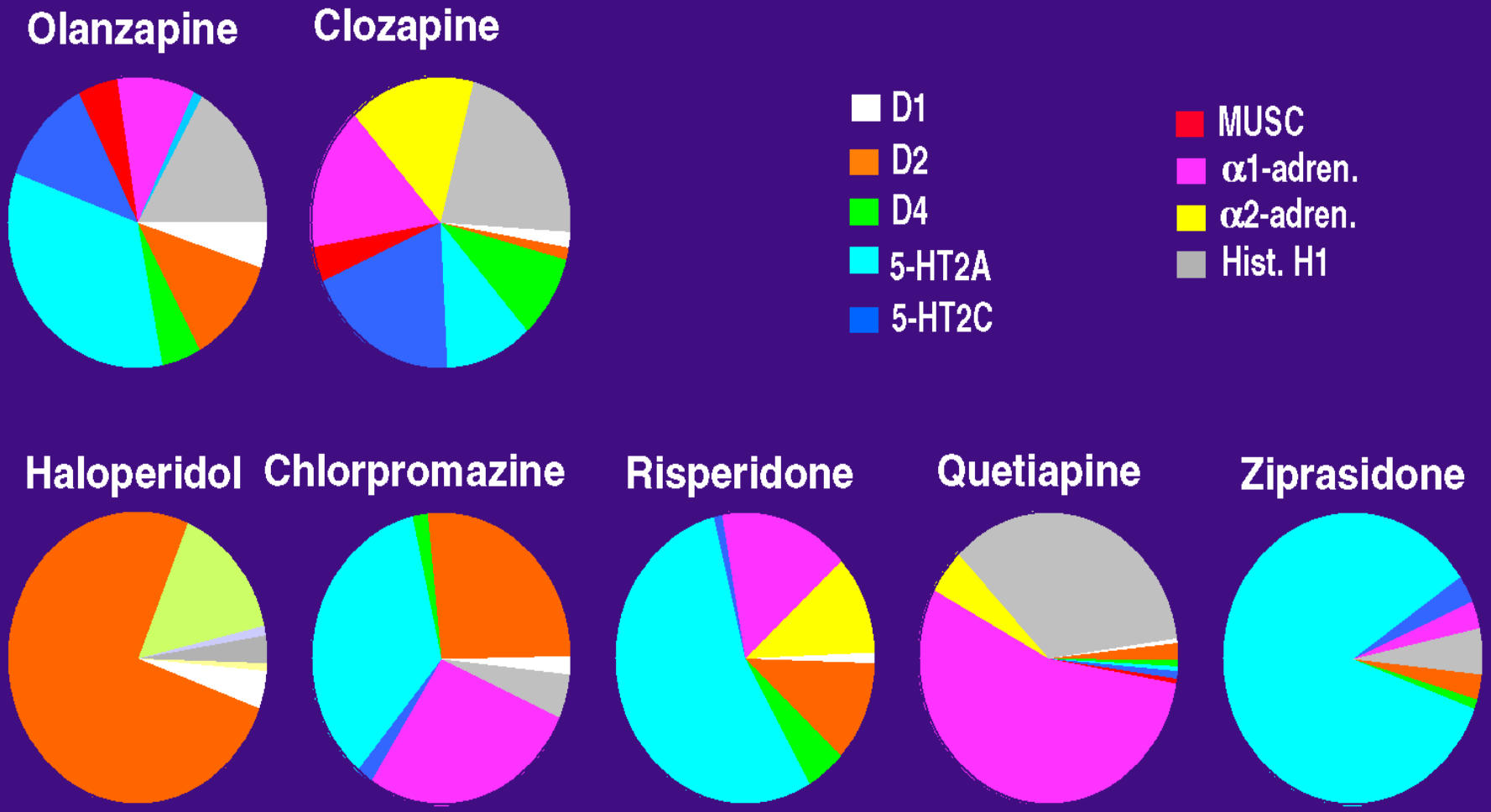
BLOKADE RESEPTOR DARI OBAT OBAT ANTIPSIKOSIS

Table 29–1. Relative receptor blocking actions of neuroleptic drugs.[1]

Drug	D_2 Block	D_4 Block	$Alpha_1$ Block	$5\text{-}HT_2$ Block	M Block	H_1 Block
Most phenothiazines and thioxanthenes	++	–	++	+	+	+
Thioridazine	++	–	++	+	+++	+
Haloperidol	+++	–	+	–	–	–
Clozapine	–	++	++	++	++	+
Molindone	++	–	+	–	+	+
Olanzapine	+	–	+	++	+	+
Quetiapine	+	–	+	++	+	+
Risperidone	++	–	+	++	+	+
Sertindole	++	–	+	+++	–	–

[1] **Key:** +, blockade; –, no effect. The number of plus signs indicates the intensity of receptor blockade.

Broad Spectrum Receptor Binding Profile of Olanzapine and Clozapine as Compared to Other Antipsychotic Drugs



Data from: Bymaster FP, et al. Unpublished observations. 1996.
Schotte A, et al. *Psychopharmacology (Berl.).* 1996;124(1-2):57-73.

SIDE EFFECT OF ATYPICAL ANTIPSYCHOTIC DRUGS

- Efek Anti-adrenergic, anti-cholinergic, anti-histamine mirip dgn typical antipsychotic

  Kecuali Risperidone dan Quetiapine bukan anti-cholinergic. Olanzapine merupakan anti-histamine kuat (165xDiphenhydramine)

- Gangguan EPS pada umumnya lebih jarang

  Tdk ada laporan ttg dystonia dan akathisia

  Olanzapine dan Clozapine menurunkan insiden tardive dyskinesia pada pemakaian Typical AP

  Kecuali Risperidone : insiden EPS meningkat dengan kenaikan dosis (pada dosis besar). Pada dosis kecil, insiden EPS sangat rendah

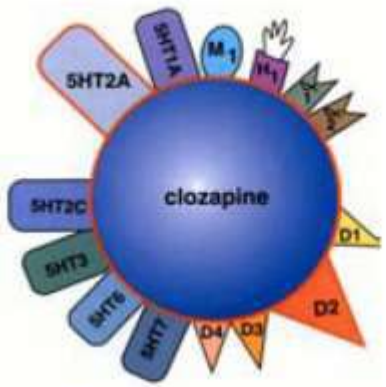
- Efek neuroendocrine:

  Clozapine, Olanzapine, Quetiapine tdk meningkatkan sekresi prolactin

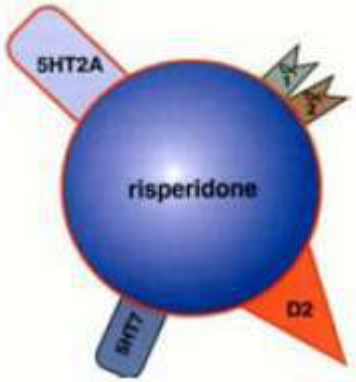
  Risperidone mungkin menyebabkan sekresi prolactin

- Clozapine menyebabkan granulocytopenia dan agranulocytosis

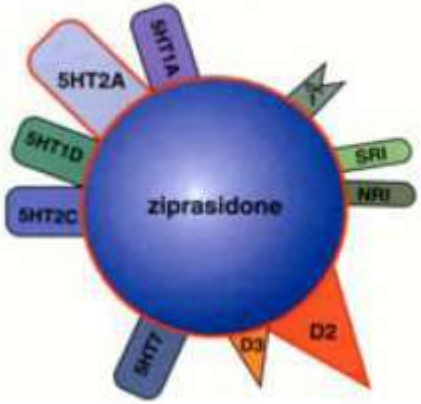
Other Actions of Second Generation Antipsychotics



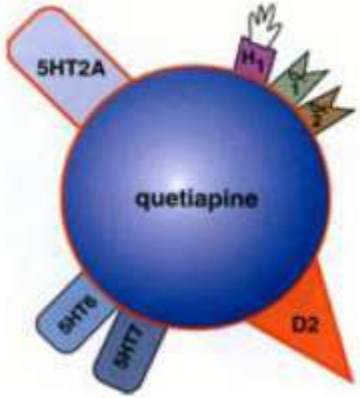
Clozapine:
- Very few EPS
- No prolactin release
- Causes agranulocytosis
- Weight gain
- Seizures
- Sedative



Risperidone:
- EPS at high dose
- Low TD
- Less weight gain



Ziprasidone:
- Very few EPS
- No prolactin release
- No weight gain
- SRI and NRI, thus act as AD and anxiolytic



Quetiapine:
- No EPS
- No prolactin release
- Weight gain

Olanzapine:
- No prolactin release
- Nonsedative
- Weight gain
- Low level of TD

Stahl, 2002

TABLE 1-3. Clinical Profile of Second-Generation Antipsychotic Drug Efficacy

DRUG	CLOZAPINE	RISPERIDONE	OLANZAPINE	QUETIAPINE	ZIPRASIDONE	SERTINDOLE	AMISULPRIDE	ARIPIPRAZOLE	ILOPERI
Clinical effect									
Psychotic symptoms	+++	+++	+++	++	++	+++	+++	+++	+++
Negative symptoms	+	+	+	+	+	++	++	++	++
Cognitive symptoms	++	++	++	+	?	?	?	++	?
Mood symptoms	+++	++	+++	+++	++	++	++	++	?
Refractory symptoms	+++	++	++	++	?	?	++	?	?

+ to +++, weakly to strongly active; ?, questionable to unknown activity.

Source: Adapted from Dawkins K, Lieberman JA, Lebowitz BD, et al. (1999) Antipsychotics: Past and future. National Institute of M
Health Division of Services and Intervention Research Workshop (July 14, 1998). *Schizophr Bull* 25, 395–404, with permission from O
University Press.

DRUG	CONVENTIONAL AGENTS	CLOZAPINE	RISPERIDONE	OLANZAPINE	QUETIAPINE	ZIPRASIDONE	SERTINDOLE	AMISULPRIDE	ARIPIPRAZOLE	ILOPERIDO
Side effect										
EPS[a]	+++	0	++	+	0	+	0	++	+	+
TD	+++	0	++	+	0	+	0 to +	+	+	+
NMS	++	+	+	+	?	+	+	+	?	?
Prolactin elevation	+++	0	+++	0 to +	0	0 to +	0 to +	++	0	0 to +
Weight gain	+ to ++	+++	+	+++	+	0	+	+	0	?
Prolonged QT[a]	+ to +++	0	+	0	+	++	+++	+	0	0
Hypotension[a]	+ to ++	+++	+	++	++	+	+	0	+	+
Sinus tachycardia[a]	+ to +++	+++	+	++	++	+	+	0	0	+
Anticholinergic effects[a]	+ to +++	+++	0	++	+	0	0	0	0	0
Hepatic transaminitis	+ to ++	++	+	++	+	+	+	+	0	+
Agranulo-cytosis	0 to +	++	0	0	0	0	0	0	0	0
Sedation	+ to +++	+++	+	++	+++	+	+	+	+	+
Seizures[a]	0 to +	+++	0	0 to +	0 to +	0 to +	0 to +	0 to +	0 to +	0 to +

EPS, extrapyramidal side effects; TD, tardive dyskinesia; NMS, neuroleptic malignant syndrome.
+ to +++, active to strongly active; 0, minimal to none; ?, questionable to unknown activity.
[a] Dose dependent.

Adapted and modified with permission from Dawkins K, Lieberman JA, Lebowitz BD, et al. (1999) Antipsychotics: Past and future. National Institute of Men Health Division of Services and Intervention Research Workshop (July 14, 1998). *Schizophr Bull* 25, 395–404; Burns MJ (2001) The pharmacology and toxicolo of atypical antipsychotic agents. *J Clin Toxicol* 39, 1–14.

Antipsikotik atipikal dan sindroma metabolik

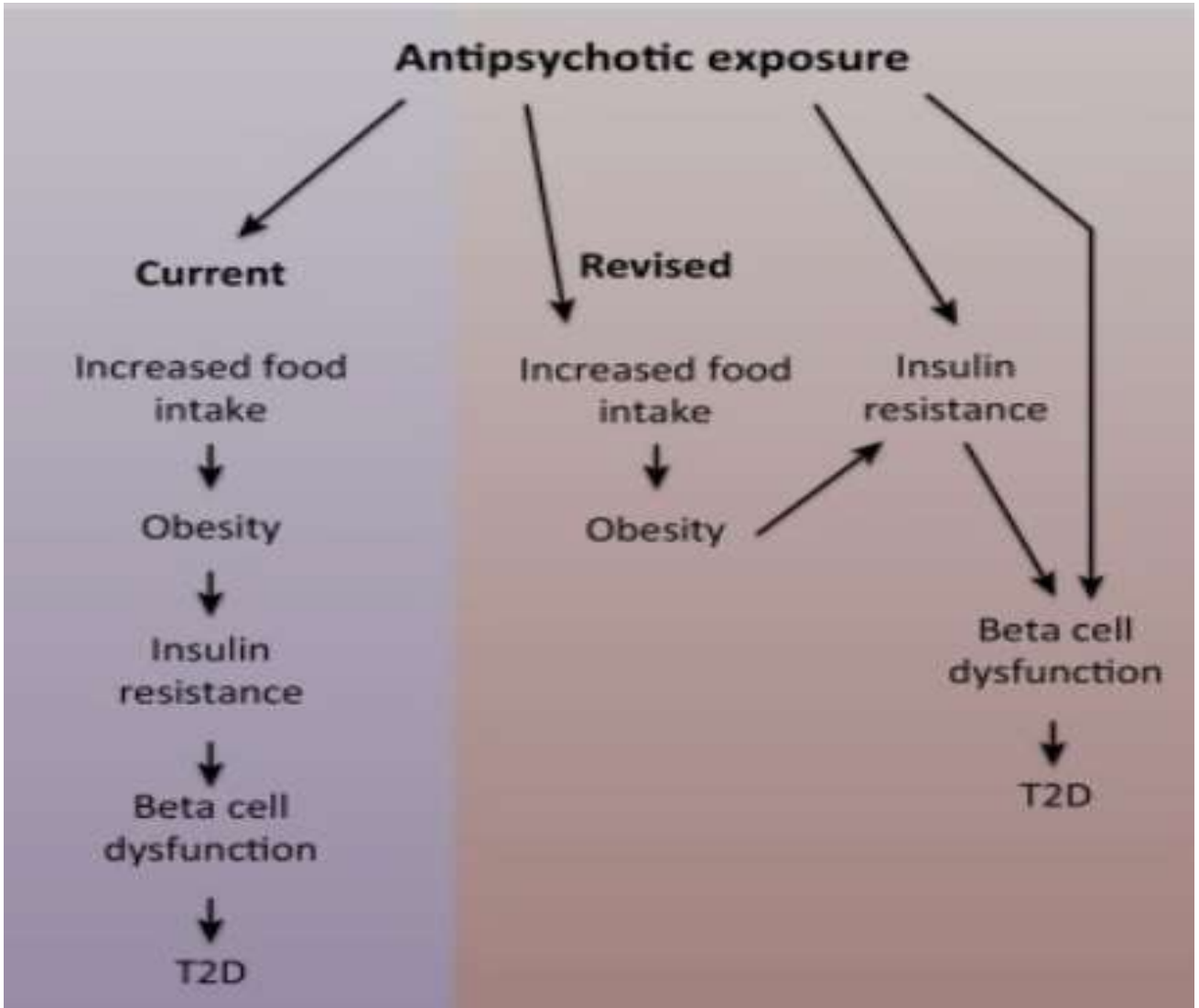


Table 2 – Approximate relative likelihood of metabolic disturbances with atypical antipsychotic medications (see text for discussion).

Medication	Weight gain	Glucose metabolism abnormalities	Dyslipidemia	Metabolic syndrome
Amisulpride	Low	Low	Low	–
Aripiprazole	Low	Low	Low	Low
Clozapine	High	High	High	High
Melperone	–	–	–	–
Olanzapine	High	High	High	High
Paliperidone	–	–	–	–
Risperidone	Medium	Medium to low	Low	–
Sulpiride	–	–	–	–
Quetiapine	Medium	Medium to low	High	–
Sertindole	Low	–	–	–
Ziprasidone	Low	Low	Low	Low
Zotepine	Medium	–	–	–

Table 2. Adverse Metabolic Changes Occurring With Atypical Antipsychotics[39]

Medication	Weight Gain	Elevated Glucose Levels	Elevated Lipid Levels
Clozapine	+++	+++	+++
Olanzapine	+++	+++	+++
Quetiapine	++	++	++
Risperidone	++	++	++
Aripiprazole	0	0	0
Ziprasidone	0	0	0

0, no risk or rarely causes adverse effects at therapeutic doses; +, mild or occasionally causes adverse effects at therapeutic doses; ++, sometimes causes adverse effects at therapeutic doses; +++, frequently causes adverse effects at therapeutic doses.

Evidence-Based Perspective on Metabolic Syndrome and Use of Antipsychotics

April 17, 2010
Meera Narasimhan, MD, Jeffrey D. Raynor, MD
Drug Benefit Trends, Drug Benefit Trends Vol 22 No 3, Volume 22, Issue 3

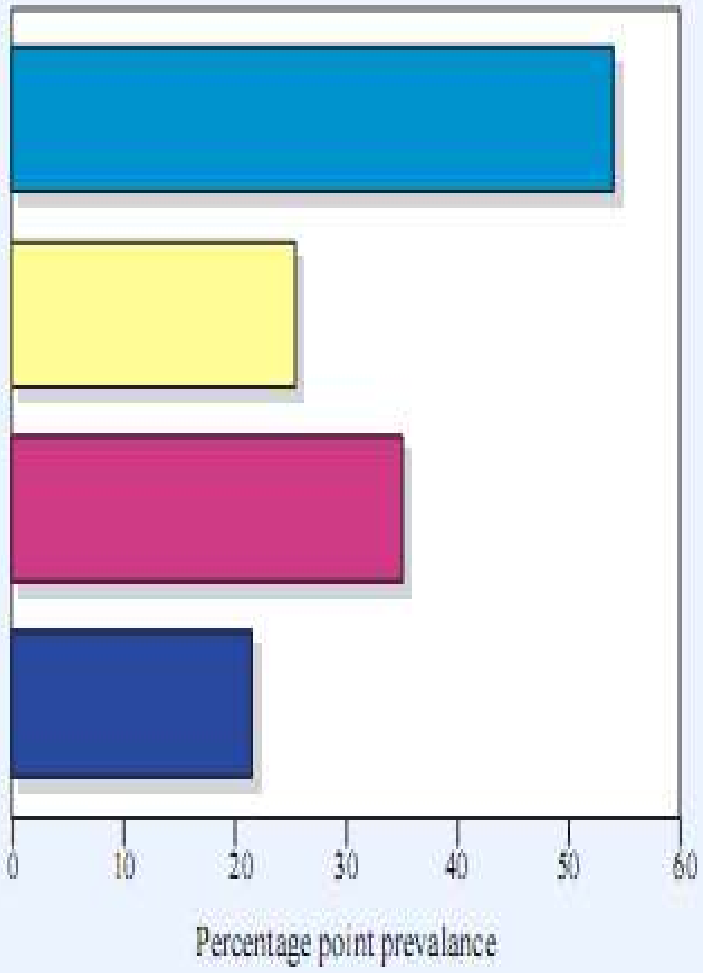
Drug	Chemical Classification	Equivalent Oral Dose (mg)	Side Effects		
			Sedation	Autonomic[a]	Extrapyramidal Reactions[b]
Haloperidol	Butyrophenone	2	+	+	+++
Pimozide[c]	Diphenylbutylpiperidine	2	+	+	+++
Risperidone	Benzisoxazole	4	++	++	++
Thiothixene	Thioxanthene	5	++	++	++
Olanzapine	Thienobenzodiazepine	5	+	++	+
Clozapine	Dibenzodiazepine	75	+++	+++	+/-
Chlorpromazine	Phenothiazine (Aliphatic)	100	+++	+++	++
Thioridazine	Phenothiazine (Piperidine)	100	+++	+++	+

[a] α_1-Antiadrenergic and anticholinergic effects.
[b] Excluding tardive dyskinesia, which appears to be produced to the same degree and frequency by all agents except clozapine.
[c] Pimozide is used principally in the treatment of Tourette's syndrome.

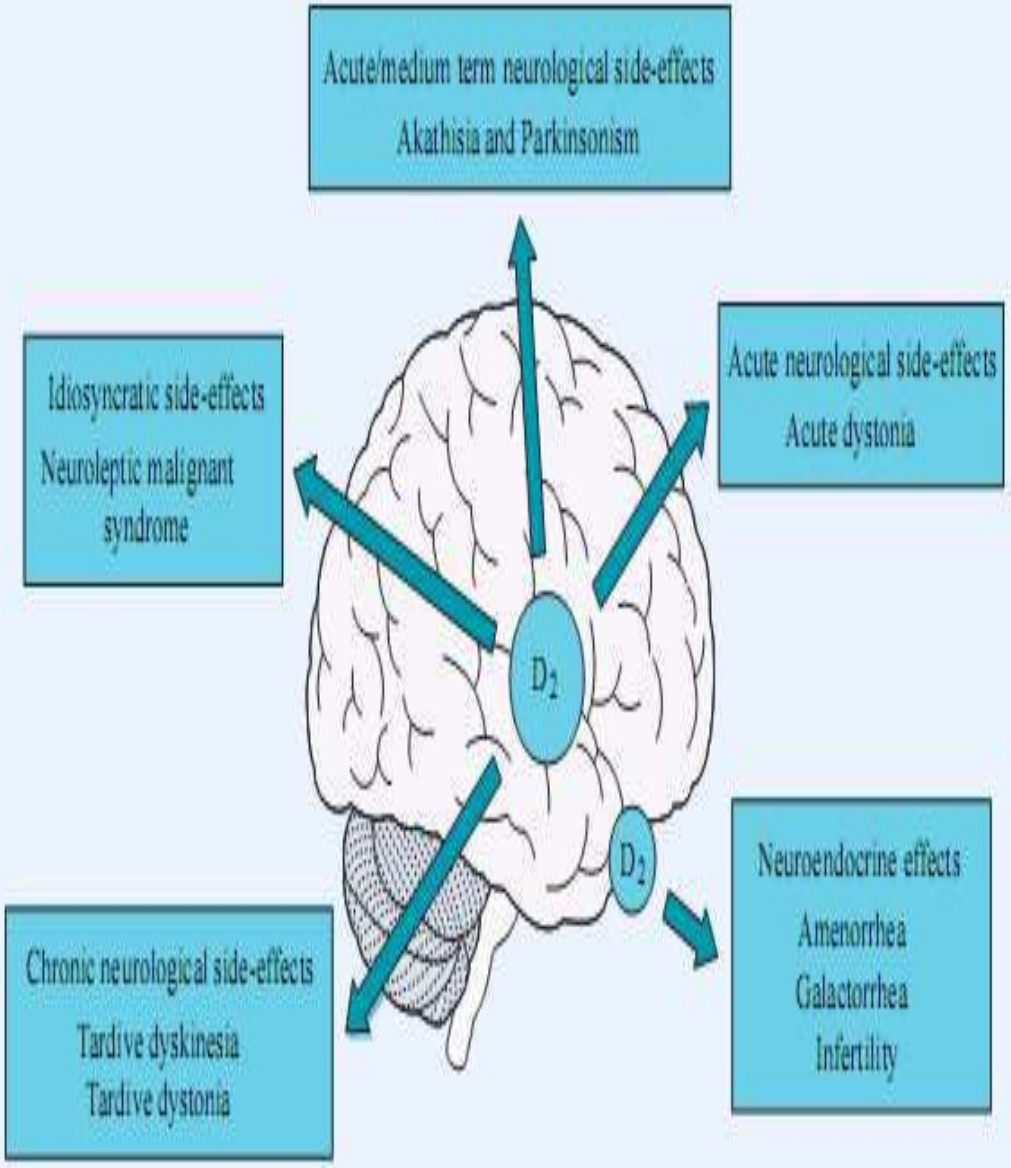
Significant Adverse Effects of Antipsychotic Drugs

Type	Manifestations	Mechanism
Sedation	Drowsiness, lethargy	α_1-adrenoceptor block, H_1 histamine receptor block
Extrapyramidal reactions	Dystonias, akathisia, parkinsonism	D_2-receptor block
	Tardive dyskinesia	D_2-receptor up-regulation (?)
	Neuroleptic malignant syndrome	Extrapyramidal sensitivity
Autonomic signs	Dry mouth, blurred vision, urinary retention, constipation	Muscarinic cholinoreceptor block
	Orthostatic hypotension, impotence	α_1-Adrenoceptor block
Endocrine signs	Amenorrhea, galactorrhea, infertility, impotence	D_2-receptor block resulting in hyperprolactinemia

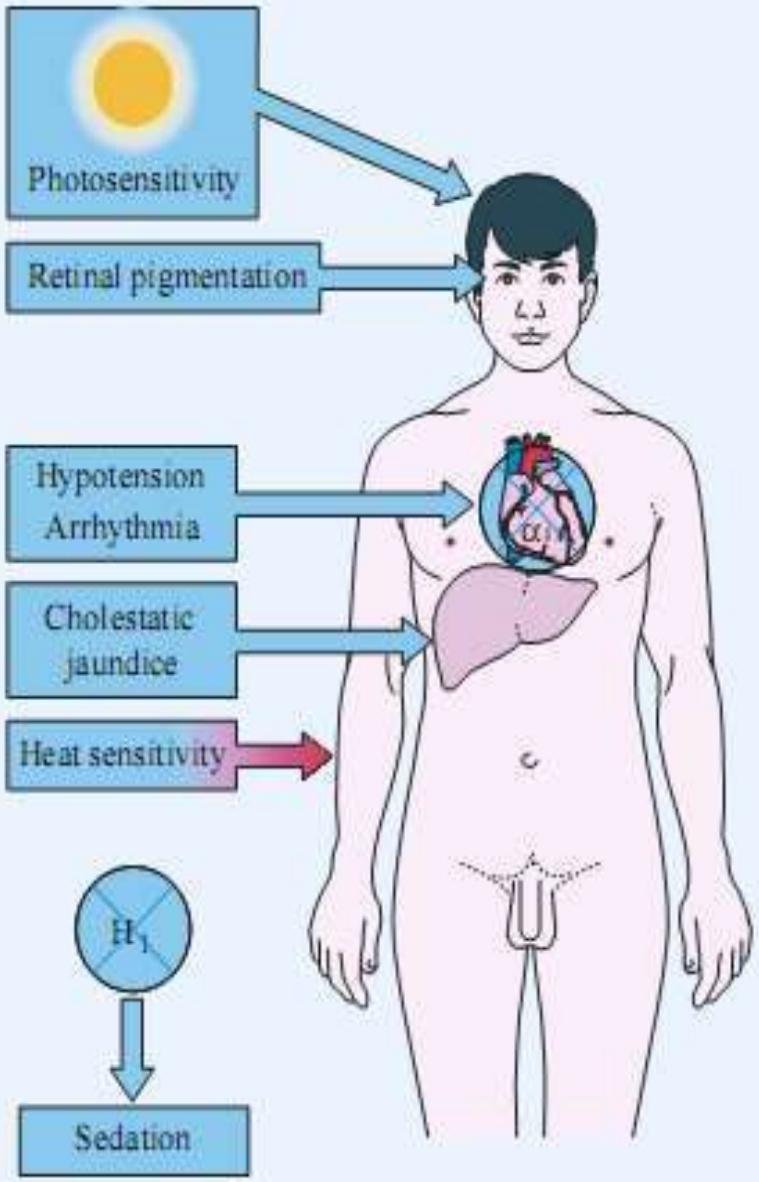
SIDE-EFFECTS OF CONVENTIONAL ANTIPSYCHOTICS



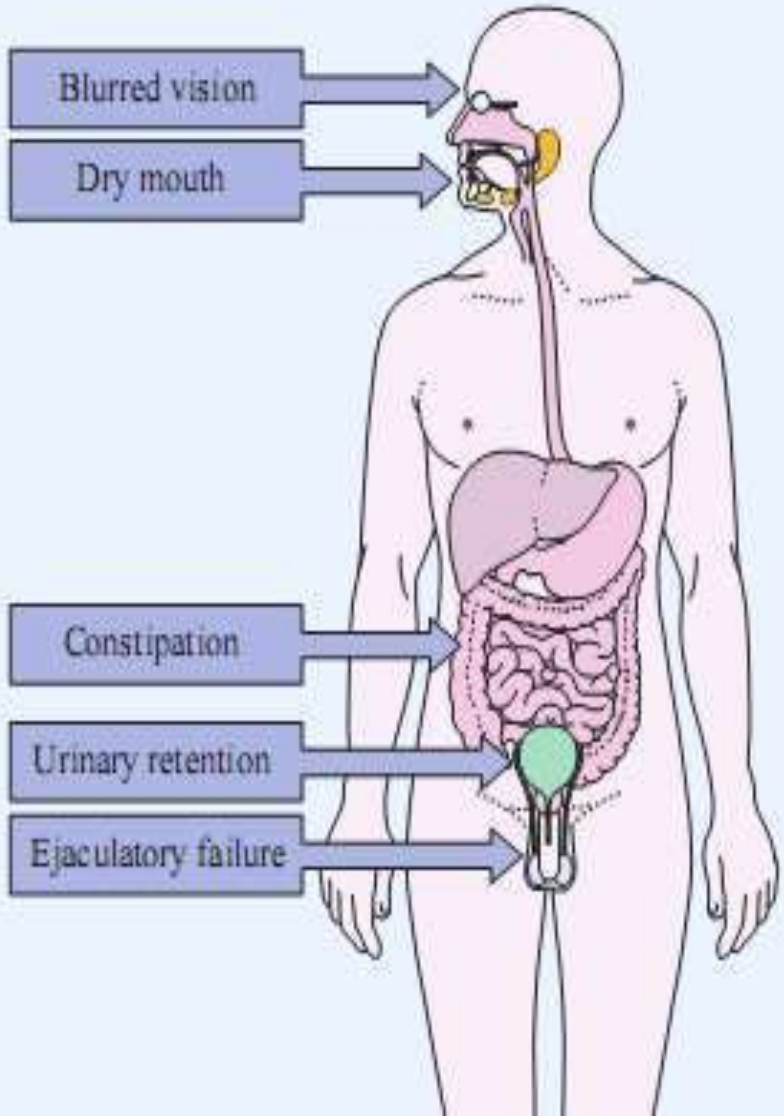
Antidopaminergic side-effects due to D_2 receptor blockade



Idiosyncratic side-effects due to histaminergic (H1) and adrenergic (α1) receptor blockade



Anticholinergic side-effects due to muscarinic acetyl choline receptor blockade



Problem with use of the antipsychotic drugs

Parkinsonism, akinesia, tremor, regidity, etc

Treatment: reduce dose or change drugs (e.g., atypical or clozapine if severe); anticholinergic antiparkinson drugs or amantadine.

Mechanism: Antipsychotic drug antagonism of dopamine D_2 receptors in nigrostriatal system

Acute dystonia:

Spasms involving head, neck, trunk and extremities.

Treatment: benztropine or diphenhydramine. Diazepam may be helpful.

Mechanism: Dopamine receptor blockade by antipsychotic drugs

Akathisia:

State of extreme motor restlessness and drive to move.

Treatment: reduce dose; switch to low potency or atypical; propranolol; benzodiazepines; amantadine; sometimes resistant to anticholinergic antiparkinson agents.

Mechanism: uncertain

Tardive dyskinesia (TD):

Stereotyped, repetitive, involuntary movements of the mouth, lips, and tongue and choreiform movements of the limbs and body.

Treatment: gradual reduction of dose; avoid anticholinergic drugs; switch to clozapine; switch to atypical; benzodiazepines may be used with limited success; calcium channel blockers (nifedipine, verapamil, diltiazem) have produced improvement in some patients.

Mechanism: development of supersensitivity of dopamine receptors as consequence of long term blockade.

Perioral tremor:

"Rabbit Syndrome"; late appearing

Treatment: Responds to anticholinergic antiparkinson drugs or reduction in dose of antipsychotic agent**.**

Mechanism: Uncertain; dopamine receptor blockade.

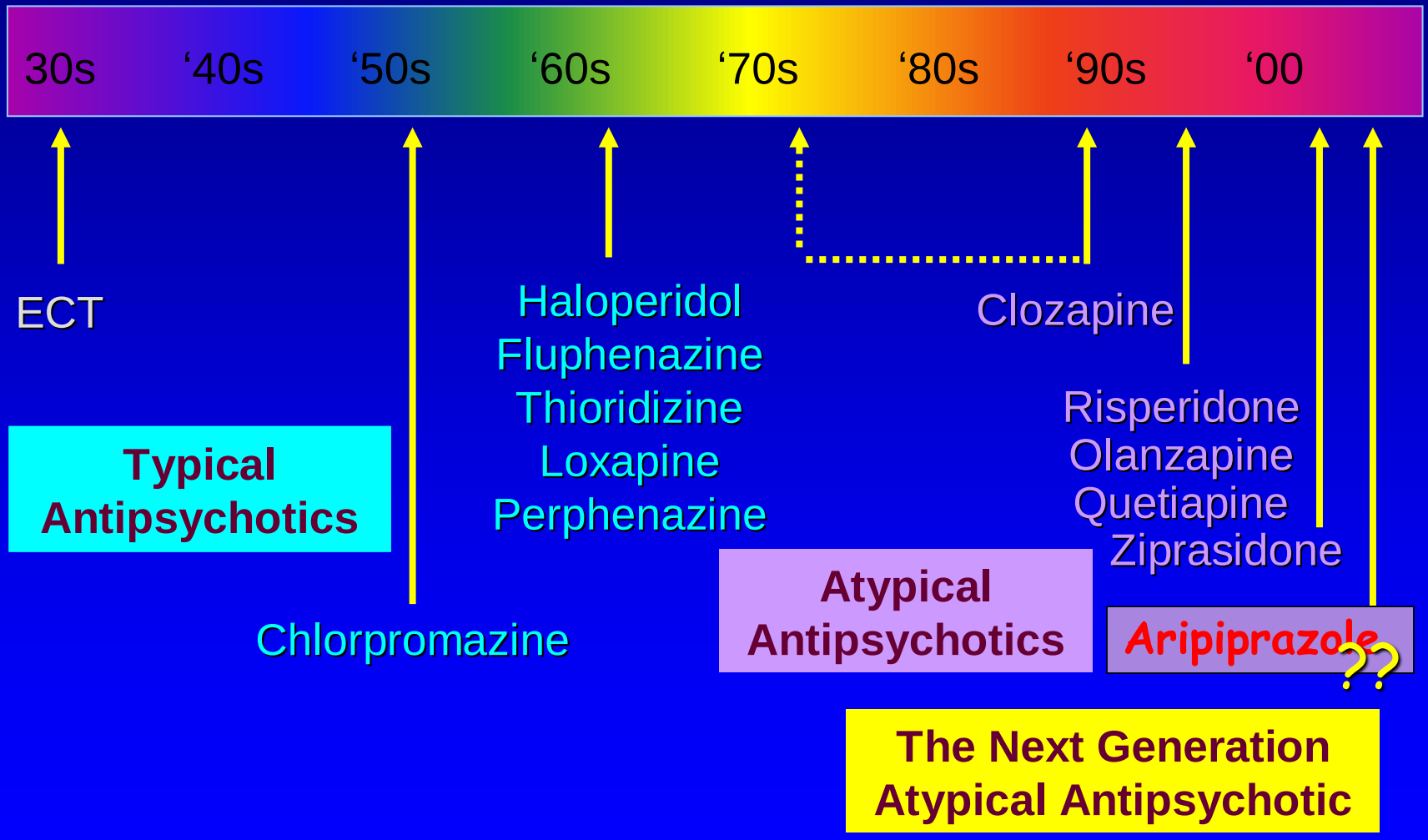
NEUROLEPTIC MALIGNANT SYNDROME

- Dapat terjadi akibat penggunaan typical/atypical antipsychotic drug
- **Tanda tanda/simtom:**
  - rigidity
  - Instabilitas autonomic
  - fever
  - rhabdomyolysis (CPK naik; myoglobinuria/emia)
  - Perubahan mental status
- **Pengobatan:**
  - Stop pengobatan antipsychotic
  - Transfer menuju ICU
  - Aggressive hydration
  - Dantrolene
  - Bromocryptine

Schizophrenia Pathophysiology And Pharmacologic Profile of Antipsychotic Drugs (APDs)

Schizophrenia Pathophysiology		Pharmacologic Profile of APDs
Past	Aktifitas dopaminergic berlebihan	Dopamine D2-receptor antagonists
Present	Adanya peran dari serotonin (5-HT)	Kombinasi 5-HT2 / D2 antagonists
Future	Imbalance in cortical communication and cortical-midbrain integration, involving multiple neurotransmitters	More selective antagonist Mixed agonist/antagonists Neuropeptide analogs

Perkembangan dlm Pengobatan Psychotic Disorders



Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics and Interactions	Toxicities
Phenothiazines					
Chlorpromazine Fluphenazine Thioridazine	Block of D_2 receptors >> 5-HT_2 receptors	Block α, M, and H_1 receptors • sedation, decreased seizure threshold	Schizophrenia • bipolar disorder (manic phase), antiemesis, preop sedation	Oral and parenteral forms, hepatic metabolism, long half-life	Extensions of α- and M receptor-blocking actions • extrapyramidal dysfunction, tardive dyskinesias, hyperprolactinemia
Thioxanthene					
Thiothixene					
Butyrophenone					
Haloperidol	Block of D_2 receptors >> 5-HT_2 receptors	Some α block • less M block and sedation than phenothiazines	Schizophrenia; bipolar disorder (manic phase), Huntington's chorea, Tourette's syndrome	Oral and parenteral forms • hepatic metabolism	Extrapyramidal dysfunction (major)
Atypicals					
Aripiprazole Clozapine Olanzapine Quetiapine Risperidone Ziprasidone	Block of 5-HT_2 receptors >> D_2 receptors	Some α block (clozapine, risperidone, ziprasidone) and M block (clozapine, olanzapine), variable H_1 block	Schizophrenia (positive and negative symptoms) • bipolar disorder (olanzapine, risperidone), major depression (aripiprazole), agitation in Alzheimer's and Parkinson's	Oral and parenteral forms • hepatic metabolism	Agranulocytosis (clozapine) • diabetes and weight gain (clozapine, olanzapine), hyperprolactinemia (risperidone) • QT prolongation (ziprasidone)

DRUGS ASSOCIATED WITH SCHIZOPHRENIC-LIKE REACTIONS

Social: phencyclidine, LSD, and others; sympathomimetics (amphetamines, phenmetrazine, diethylpropion, Khat); cannabis

Dopaminomimetic: levodopa, bromocriptine, baclofen, ketamine, bupropion

Anti-inflammatory: indomethacin, sulindac

Corticosteroid: many; rare

Cardiac: procainamide, lignocaine (lidocaine), tocainide, propranolol (also withdrawal); withdrawal—clonidine

Anticonvulsant: phenytoin, primidone, carbamazepine

Miscellaneous: fenfluramine, methysergide, disulfiram, procainamide, carbimazole, isoniazid, anabolic steroids

OBAT YG MENYEBABKAN GANGGUAN PSIKOMOTOR

Psychotherapeutic: antipsychotics, e.g., phenothiazine, butyrophenones; antidepressives, e.g., tricyclics, MAO inhibitors, second-generation drugs; mood stabilizers, e.g., lithium, carbamazepine; antianxiety agents, e.g., benzodiazepines; hypnosedatives, e.g., barbiturates, nonbarbiturates

Antihistamine, anti–motion sickness: most common antihistamines are sedating; astemizole and terfenadine may be exceptions

Narcotic-analgesic: morphine, codeine, pentazocine, dextropropoxyphene

"Social": alcohol, marijuana, hallucinogens, cocaine, amphetamines

Miscellaneous: methyldopa, clonidine, indomethacin, any drug that primarily produces other psychiatric syndromes

OBAT YG MENYEBABKAN DELIRIUM

Anticholinergic: atropine family, e.g., atropine, hyoscine (scopolamine); antihistamines, e.g., diphenhydramine, dimenhydrinate; mydriatics, e.g., cyclopentolate

Antidepressant: tricyclics, e.g., imipramine, amitriptyline

Antiparkinsonian: conventional, e.g., trihexiphenidyl, benztropine; newer, e.g., levodopa, amantadine, bromocriptine

Gastrointestinal: cimetidine, ranitidine, famotidine (especially in elderly); metoclopramide

Social: withdrawal from alcohol, sedative-hypnotic; use of hallucinogens, cannabis, nitrous oxide

Narcotic: dextropropoxyphene, pentazocine

Cardiac: antiarrhythmics, e.g., disopyramide, lignocaine (lidocaine), procainamide; positive inotropics, e.g., digitalis preparations; antihypertensives, e.g., clonidine, propranolol; others, e.g., theophylline, captopril, calcium-channel blockers

Anti-infective: penicillins, cephalosporins

TERIMAKASIH