Biological therapies in psychiatry

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Theory&MCQ

Contents

- Types of treatment in psychiatry
- Multiple Choice Questions

- Break included

Biological therapies in psychiatry

1. Pharmacological therapies (Psychotropics)
2. Electroconvulsive therapy (ECT)
3. Other:
   -Transcranial Magnetic Stimulation (rTMS)-MDD
   -Deep Brain Stimulation - MDD
   -Vagal Nerve Stimulation (VNS)- MDD
   -Sleep deprivation
   -Endocrine therapies -MDD
   -Psychosurgery (e.g., anterior cingulotomy)-OCD
   -Light therapy

Pharmacotherapy

1. Antipsychotics
   - FGA, SGA
2. Mood stabilizers MS
3. Antidepressants
   - TCA, SSRI, SNRI, NDRI, NaSSA, MAOI
4. Hypnotics/Anxiolytics

5. Anticholinergic (for side effects)

ECT

- It induces therapeutic **clonic seizure** lasting for about **30 sec**
- Mechanism of action isn't elucidated
  - neurogenesis in the hippocampus, particularly in the dentate gyrus
  - increased hippocampal volume
  - an increase in the seizure threshold
  - downregulation of postsynaptic β-adrenergic receptors

- A series of **15 sessions** (3 times a week)
- It is in urgent and severely disabling high-risk circumstances such as **psychotic, suicidal, or postpartum depressions, catatonia, drug resistant schizophrenia**
- Bifrontal or bitemporal electrodes
- High-intensity, bilateral stimulation produced the best response; low-intensity, unilateral stimulation, the weakest.

MCQ

A 53-year-old man is admitted to psychiatry after a serious suicide attempt. He remains nearly catatonic on the unit, **refusing to either eat or drink.** He also remains quite **suicidal**, and requires one-to-one observation at all times. Which of the following is the most appropriate treatment?

a. Tricyclic + SSRI in combination
b. SSRI at a higher than normal dose
c. SSRI + antipsychotic
d. Transcranial magnetic stimulation
e. ECT

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Bright-light therapy

- Patient is exposed to bright light in the range of 1,500 to **10,000 lux** or more, typically with a light box that sits on a table or desk.
- Patients sit in front of the box for approximately **1 to 2 hours before dawn each day**, although some patients may also benefit from exposure after dusk.
  For seasonal depression
- Every morning
- For a week
- Ultraviolet (UV) rays

are filtered out

- No SE

Deep Brain Stimulation (DBS)

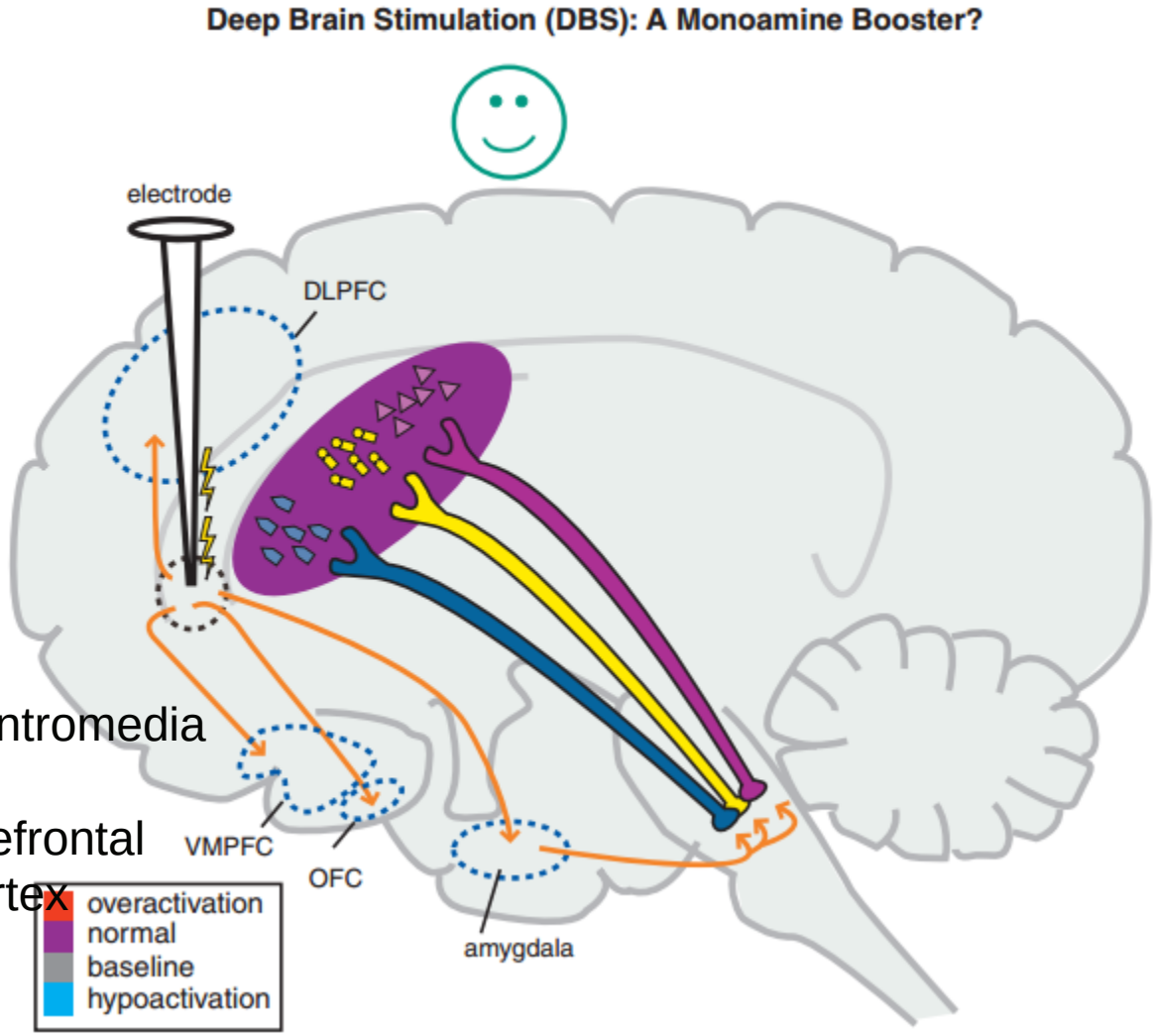

Figure 7-76. Deep brain stimulation. Deep brain stimulation involves a battery-powered pulse generator implanted in the chest wall. One or two leads are tunneled directly into the brain. The device then sends brief repeated pulses to the brain, which may have the result of boosting monoamine activity and thus alleviating depressive symptoms.

Ventromedial Prefrontal cortex

Electrical stimulation of **Ventromedial Prefrontal Cortex** results in activation of circuits that lead back to brainstem monoamine centres, to act as a **monoamine modulator** in patients.

Transcranial Magnetic Stimulation (rTMS)

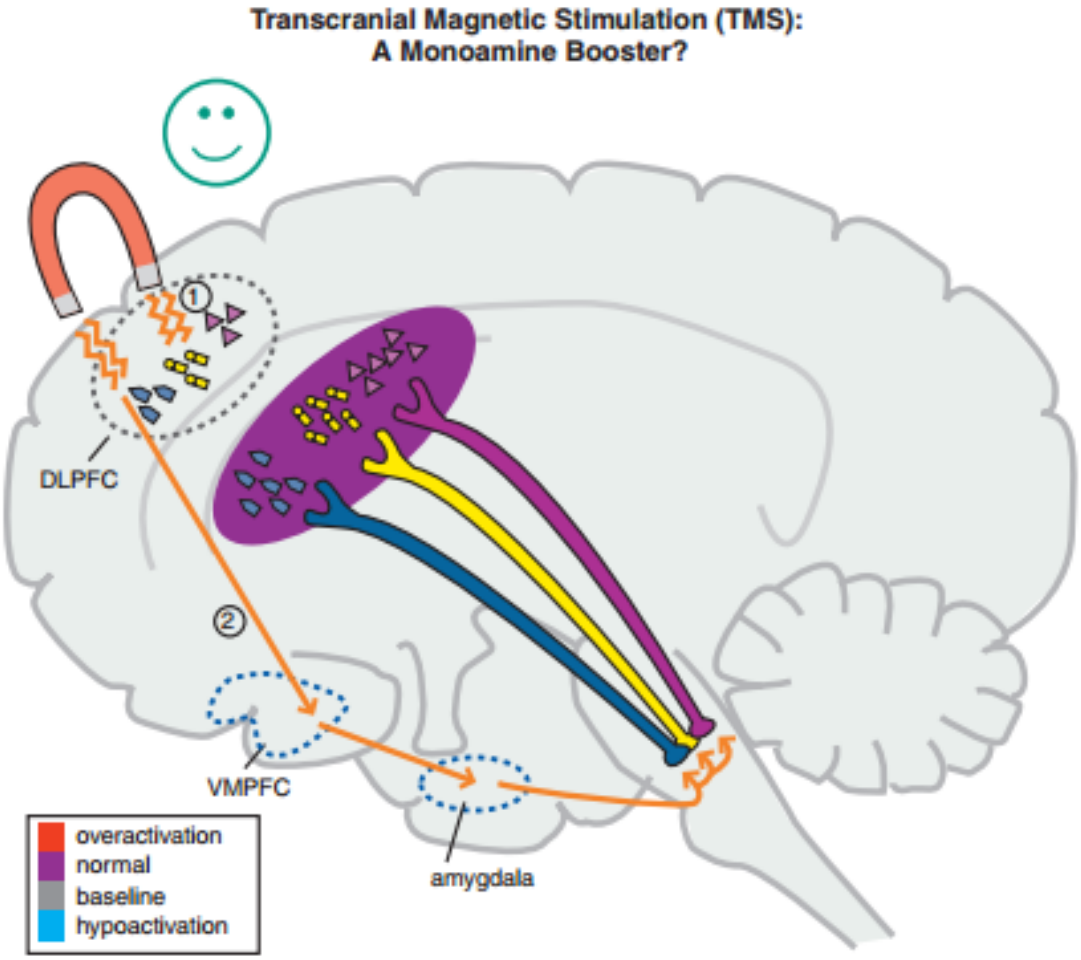

Figure 7-75. Transcranial magnetic stimulation. Transcranial magnetic stimulation is a treatment in which a rapidly alternating current passes through a small coil placed over the scalp. This generates a magnetic field that induces an electrical current in the underlying areas of the brain (dorsolateral prefrontal cortex, DLPFC). The affected neurons then signal other areas of the brain. Presumably, stimulation of brain regions in which there is monoamine deficiency would lead to a boost in monoamine activity and thus alleviation of depressive symptoms.

The electrical current depolarizes the affected **cortical neurons**, thereby causing nerve impulse flow out of the underlying brain areas During the treatment the **patient is awake** and reclines comfortably in a chair. No SE. No anesthesia. An electrical impulse over the dorsolateral prefrontal cortex (DLPFC) is generated. **Daily stimulation** of this brain area for up to **an hour over several weeks** causes activation of various brain circuits that leads to an antidepressant effect.

MCQ

A patient reports that she has become depressed with the onset of winter every year for the past 6 years (**depression with seasonal pattern**). Which of the following treatments is most likely to be helpful?

a. Phototherapy
b. Biofeedback
c. Electroconvulsive therapy
d. Benzodiazepines
e. Steroid medication

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Pharmacotherapy

1. Antipsychotics
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5. Anticholinergics (for side effects)

„Disease-specific" treatments

- Alcohol use disorder: **acamprosate, disulfiram, naltrexone**
- Nicotine use disorder: **nicotine replacement patches, varenicline, bupropion**(NDRI)
- Opioid maintenance therapy: **methadone** (every day), levo-α-acetylmethadol (**LAAM**) (3 times a week)

- ADHD: **metylphenidate, dexamphetamine, atomoxetine**
- Narcolepsy: **stimulants – modafinil**

- Neurocognitive disordes: AChEI acetylcholinesterase inhibitors – **donepezil, rivastigmine, galantamine**, NMDA rec antagonist - **memantine**
- Tic disorder: **antipsychotics, clonidine**

For withdrawal

- Alcohol – **chlordiazepoxide**, benzodiazepines – **diazepam, vitamin B1**
- Opiates – **methadone, buprenorphine, clonidine**=> lofexidine (Lucemyra),
- BDZ- **BDZ reducing schedule**

Use of **naltrexone**: alcohol dependence, opioid dependence and overeating

- Obesity – (**naltrexone+bupropion**)

Treatment for symptoms

- Sleep disturbances: BZD, Z-drugs, trazodone, mirtazapine, mianserine, **melatonin receptors agonists** – melatonin, **ramelteon** (delayed sleep onset)
- Overeating and Vomiting (in **bulimia**): **fluoxentine**
- Insufficient eating in Anorexia nervosa: no specific pharmacological treatment
- Hypoactive sexual desire disorder (HSDD) - **bupropion**

Important side effects

Antipstchotics

- **Medication induced movement disorders**

(=Extrapyramidal side effects (EPS))

  - Parkinsonian syndrome (tremor, bradykinesia, rigidity)
  - Akathisia
  - Acute dystonias (*laryngeal dystonia, opisthotonus, oculogyric crisis*)
  - Tardive dyskinesias (*Rabbit syndrome; Pleurothotonus=Pisa syndrome*)
- **Neuroleptic malignant syndrome**
- **Clozapine induced neutropenia**

Antidepressants

- SSRI+other antidepressants + tramadol+triptans+St. John's wort+AMP
  - **Serotonin syndrome**
- TCA+anticholinergics(antiparkinson, atropine, pilocarpine eye drops) **Anticholinergic syndrome**
- MAOI
  - **Hypertensive crises** due to tyramine-rich foods („cheese reaction”)

Specific Symptoms

- Neuroleptic malignant syndrome

rigidity, elevated creatine phosphokinase (CPK), elevated WBC, tremor, fever, tachycardia, hypertension, altered mental status (AMS)

- Serotonin syndrome

flushing, diaphoresis, hyperthermia, *myoclonic jerks/clonus/ increased reflexes/ neuromuscular excitability/hyperreflexia /"electric jolt" limb movements;* tremor, hypertonicity, rhabdomyolysis, renal failure, (AMS),

- Anticholinergic syndrome

dry skin and mucous membranes, mydriasis with loss of accommodation, urinary retention, *fever*, flushing, (AMS)

The most serious side effects

- Neuroleptic malignant syndrome (DA) → **rigid, WBC, CPK**
- Anticholinergic syndrome (M) → **dry skin**
- Serotonin syndrome (5HT) → **clonus, diarrhoea**

Medications for specific **side effects** of antipsychotics

- **Clozapine-induced Hypersalivation**: amitryptyline (low dose), pirenzepine (M1 antagonist, for peptic ulcers)
- **Hypotension**: midodrine (α-agonist)
- **Tachycardia**: propranolol (β-blocker)
- **Neutropenia**: vitamin B6
- **Akathisia**: propranolol, (BDZ)
- **Acute dystonias:** anticholinergics – biperiden IM or PO, benztropine, trihexyphenidyl
- **Parkinsonian syndrome**: amantadine, anticholonergics
- **Hyperprolactinemia**: bromocriptine (rarely)

ATIPSYCHOTICS

Schizophrenia – dopamine theory

Dopamine agonists:

- Amphetamine (which releases dopamine) can produce a syndrome similar to the 'positive' features of schizophrenia
- Levodopa may aggravate the condition
- Apomorphine and bromocriptine (D2 agonists) produce behavioral abnormalities in animals

Dopamine antagonists:

- **D2 receptor antagonists are effective in controlling the positive features of the disorder**
- **Increased D2 receptor binding in the brains** of schizophrenic subjects.
- Evidence of **genetic variation in the D4 receptor** to which some anti-psychotic drugs have high affinity (clozapine displays a 10-fold higher affinity for D4 compared to D2 or D3 receptors).

Therapeutic Targets of antipsychotics

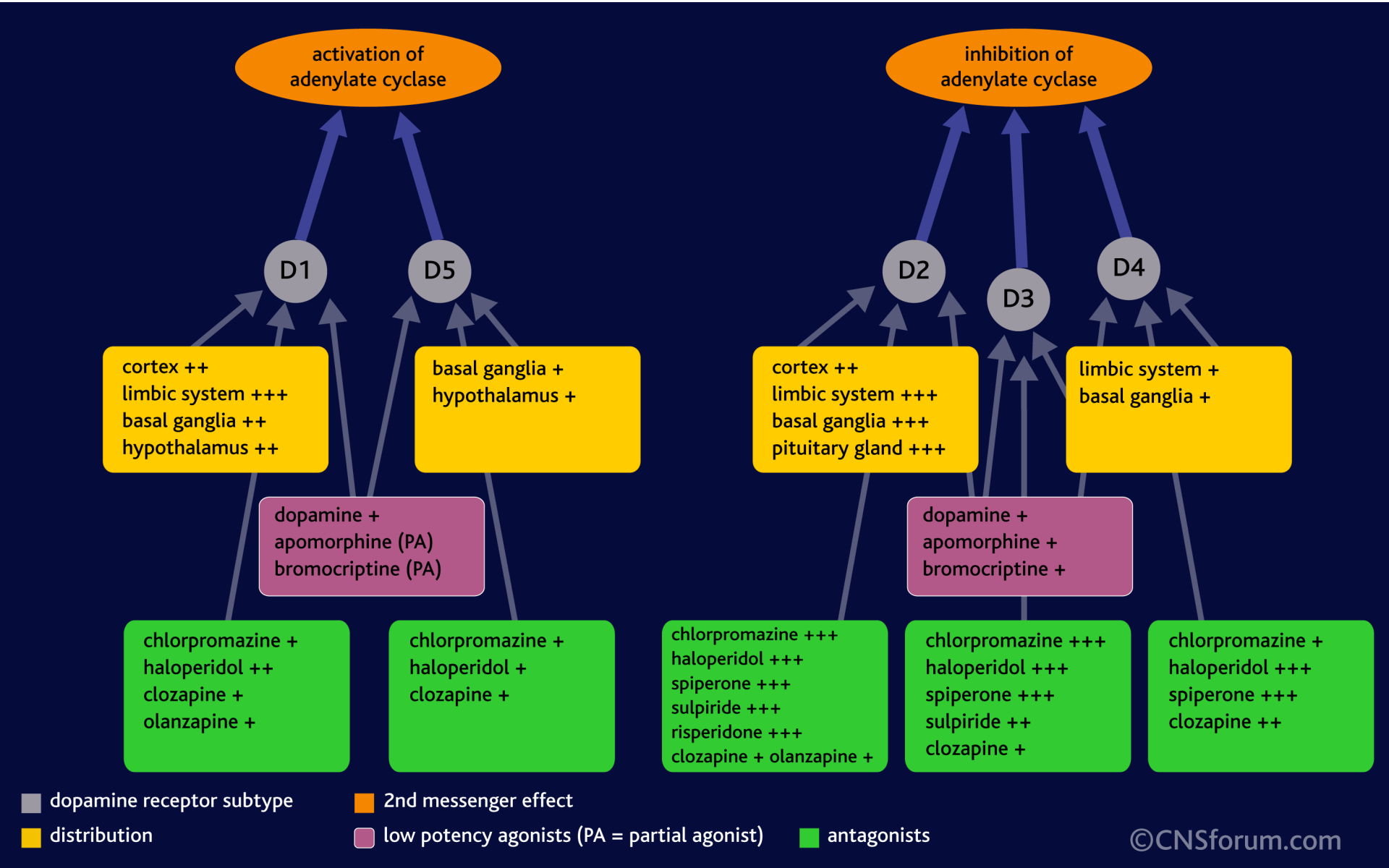
Dopamine: Antagonists at D2

Serotonin: Antagonists at 5-HT2A

Pharmacological Actions of Antipsychotics at CNS Receptors

- **Dopamine**: Antagonists at D2 or Partial Agonist at D2 (aripiprazole)
- **Serotonin**: Antagonists at 5-HT2A
- **Histamine**: Antagonists at H1
- **Cholinergic**: Antagonists at muscarinic M1-4
- **Noradrenergic**: Antagonists at α1

D1 and D2 receptor family



Higher affinity = lower dose

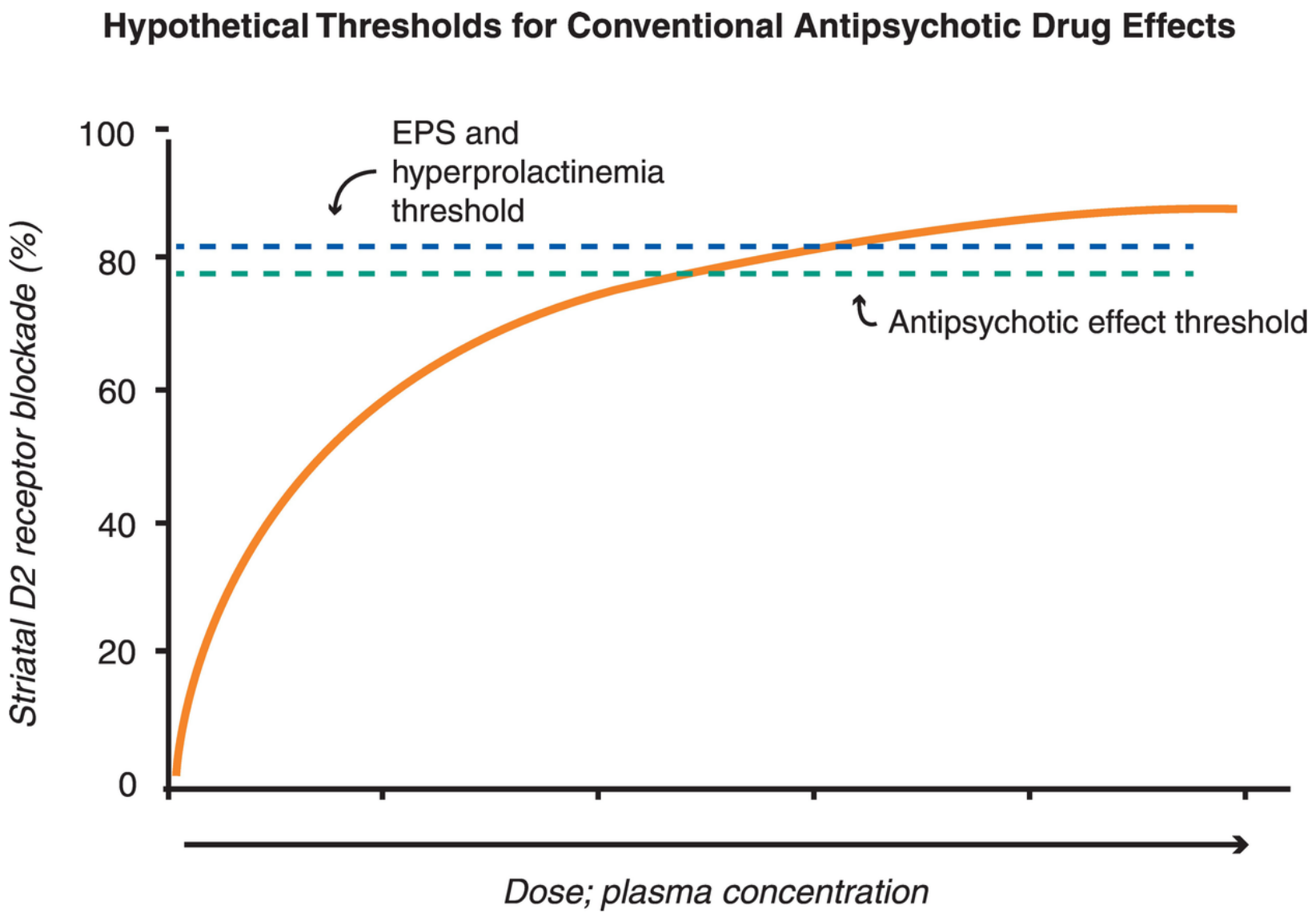
TABLE 1

NEUROLEPTIC AFFINITIES* FOR DOPAMINE RECEPTORS AND DOSE RELATIONSHIPS

Drug	Affinity†	Approximate daily dose (mg.)‡
Fluphenazine (Permitil, Prolixin)	83	2
Thiothixene (Navane)	71	4
Haloperidol (Haldol)	67	2
Trifluopromazine (Vesprin)	48	25
Trifluoperazine (Stelazine)	48	5
Prochlorperazine (Compazine)	21	15
Molindone (Lidone, Moban)	18	10
Chlorpromazine (Thorazine)	10	100
Thioridazine (Mellaril)	7	100
Clozapine¶	1.0	60
Promethazine	0.1	

*$10^{-7} \times 1/K_i$, where K_i = inhibitor constant in molarity.
†Data from references 20 and 21.
‡Data from references 22 and 23. These numbers are only an approximate guide. Daily dosage range for chlorpromazine is 50-400 mg. and 200-1,600 mg. for outpatients and inpatients, respectively.[24]

>80% striatal D2 blocked → EPS, ↑PRL



Typical/FGA/Traditional/Conventional Antipsychotics have antagonist actions that are greater for D2 than the 5-HT2A receptor

Phenothiazines

- **-chlorpromazine** (Chlorpromazine Mixture, ChlorpromazineMixture Forte, Largactil)
- -promazine
- -levomepromazine
- -trifluprom azine

- **-**fluphenazine (Anatensol, Modecate)
- -trifluoperazine (Stelazine)
- -perphenazine (Trilafon)
- -prochlorperazine

- -**thioridazine** (Aldazine) →retinitis pigmentosa
- -zuclopenthixol (Clopixol)
- -flupenthixol (Fluanxol)
- -pimozide (Orap)

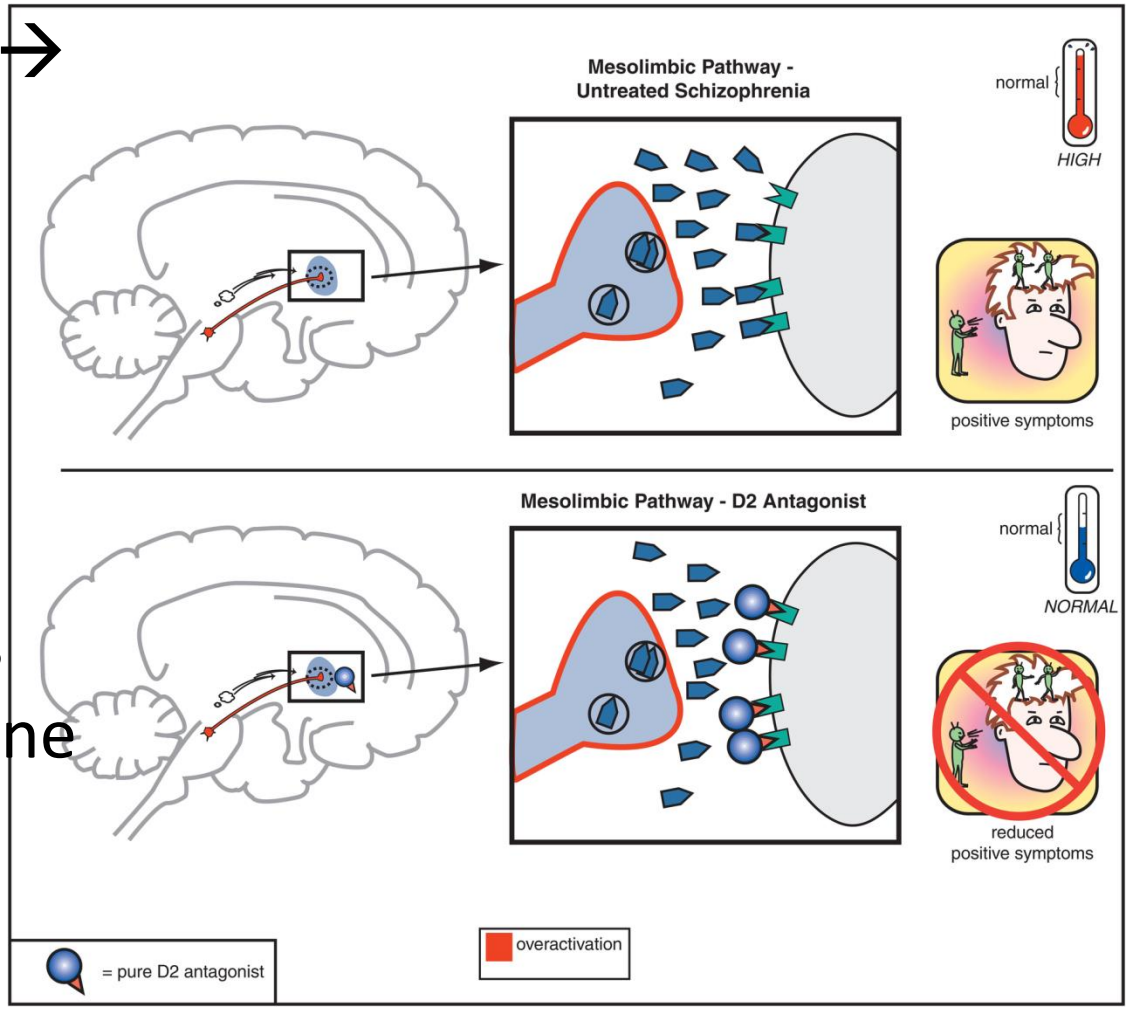
Butyrophenones

- **-**droperidol (Droleptan Injection)
- -**haloperidol** (Haldol, Serenace)

Antipsychotics

Untreated schizophrenia →
hyperactive dopamine pathway → positive symptoms

D2 antagonists →reduces hyperactivity in dopamine pathway → reduces positive symptoms



What are the indications for:

- Immediate release form – all drugs
  ****
- ODT Orally disintegrating tablet/ orally dissolving tablet – OLA
- SAI short acting injections: OLA, ARI, HALO, ZUC, ZIP
- XR extended release/ SR sustained-release - QUE
- LAI long acting injections – HALO, ZUC, OLA, RIS, ARI

FGA LAI

- **Decanoate** – oily injection – more painful>SGA
- Buttock/thigh but no deltoid muscle

FGA LAI	Formulation	Test dose for adults*	Usual dose range**	Usual dosing interval	Licensed injection site (IM)***
Flupentixol decanoate (Depixol®)	Oily injection (vegetable oil)	20mg	12.5–400mg weekly	Every 2–4 weeks	Outer buttock or lateral thigh
Fluphenazine decanoate (Modecate®)	Oily injection (sesame oil)	12.5mg	6.25–50mg weekly	Every 2–5 weeks	Gluteal
Haloperidol decanoate (Haldol®)	Oily injection (sesame oil)	25mg****	12.5–75mg weekly	Every 4 weeks	Gluteal
Zuclopenthixol decanoate (Clopixol®)	Oily injection (vegetable oil)	100mg	100–600mg weekly	Every 2–4 weeks	Outer buttock or lateral thigh

*After the test dose, wait 4–10 days before giving the next dose
**Doses stated are for adults, lower doses may be required for older adults
***See Figure 1
****Not stated by manufacturers

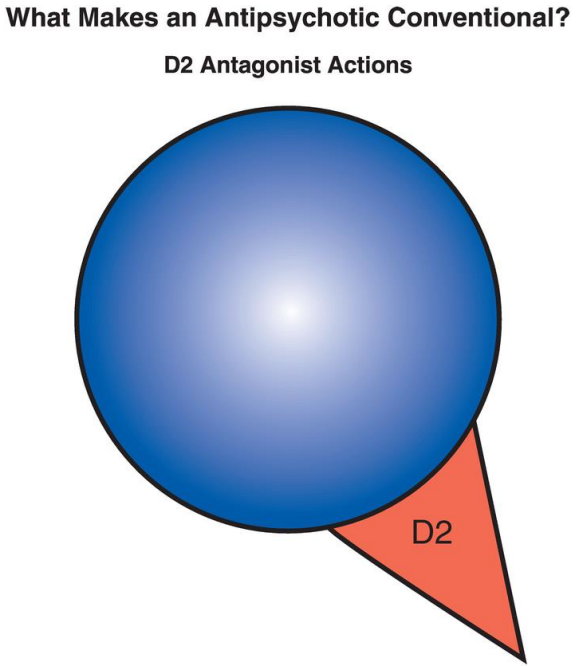
SGA LAI

SGA LAI	Initiation regimen	Dose and range frequency*	Licensed injection site (IM)**	Time to peak (days)[14]	Half-life (days)[14]	Time to steady state (weeks)[14]	Advantages	Disadvantages
Risperidone (Risperdal Consta®)	Tolerability and response to oral risperidone required. Initial dose based on oral risperidone dose. Requires oral supplementation for at least 3 weeks	25–50mg 2-weekly	Deltoid or gluteal	35	4	~8	Prefilled syringe	Requires refrigeration. 3-week time lag until drug released (requires oral supplementation at initiation) 2-weekly administration
Paliperidone palmitate (Xeplion®)	Tolerability and response to oral risperidone required. Two loading doses required: Day 1 and Day 8	25–150mg monthly	Loading doses: deltoid only Maintenance doses: deltoid or gluteal	13	29–45	~20	Prefilled syringe Flexibility in dosing to avoid missed doses Monthly Oral supplement-ation not required	Loading doses – deltoid route only (must be stable)
Olanzapine pamoate (ZypAdhera®)	Tolerability and response to oral olanzapine required. Initial dose based on equivalent oral olanzapine dose	150–300mg 2-weekly or 300–405mg 4-weekly	Gluteal only	2–3	30	~12	Can be given 4-weekly (unless max dose required) Oral supplement-ation not required	Requires reconstitution Post-injection syndrome 3 hours post-injection monitoring 2-weekly adminis-tration required for maximum dose (~20mg daily)
Aripiprazole (Abilify Maintena®)	Tolerability and response to oral aripiprazole required. Continue oral aripiprazole for 14 days after first injection	400mg monthly	Deltoid or gluteal	7	30–46	~20	Monthly Prefilled syringe (400mg dose only)	Requires oral supplementation at initiation Prefilled syringe not available for doses less than 400mg Doses less than 400mg require reconstitution

*Doses stated are for adults, lower doses may be required for older adults
**See Figure 1
NB Paliperidone palmitate 25mg LAI and aripiprazole 300mg prefilled syringe LAI are not available in the UK

FGA vs. SGA

- These days used less often
- EPS/Dyskinesias as SE
- Work mainly through D2 antagonism



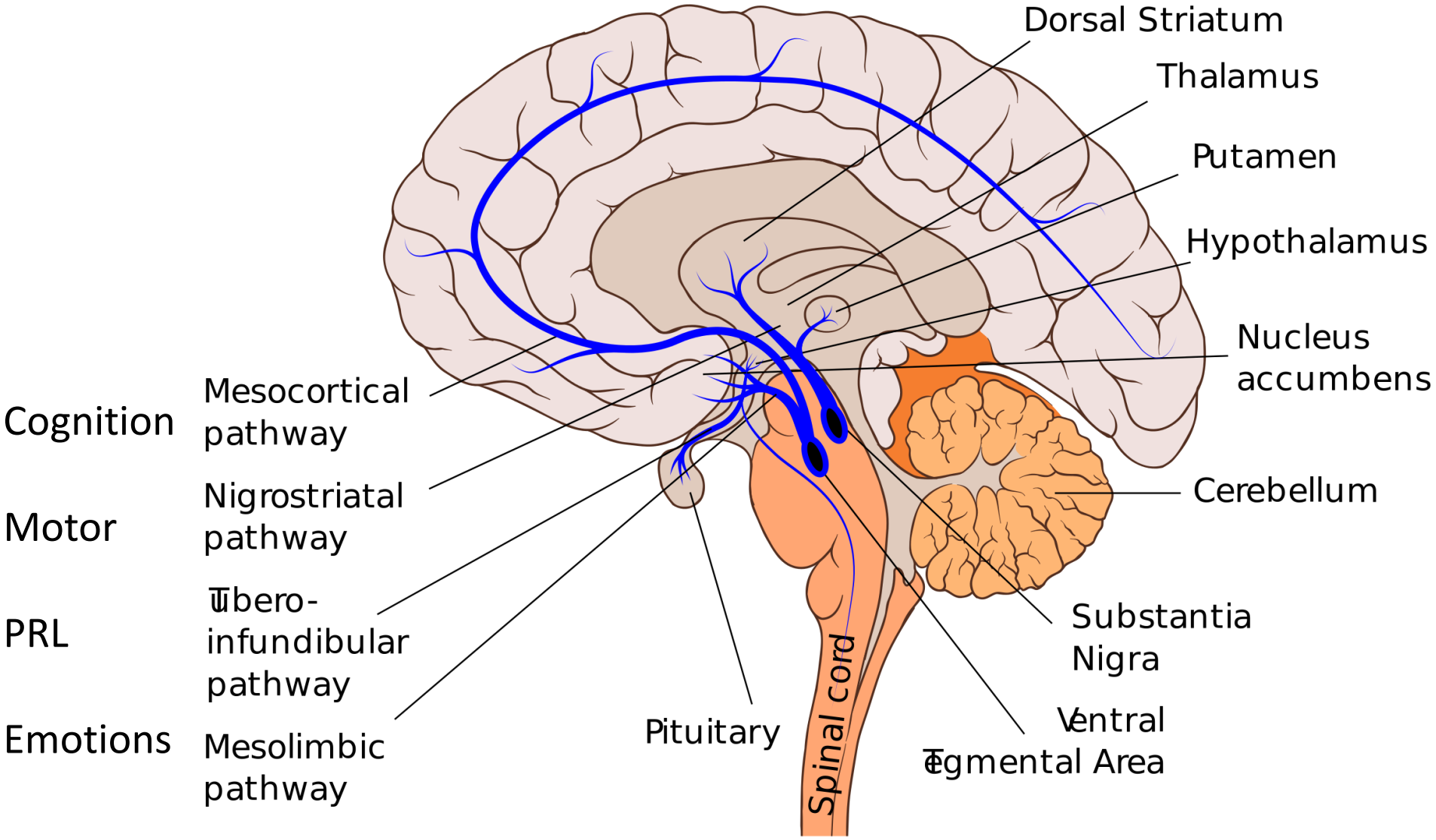
- First line treatment in newly diagnosed psychotic disorder
- Metabolic side-effects
- Works more through 5HT2 antagonism

How to choose antipsychotic?

- If obese → ARI
- If agitated/insomnia→ OLA
- If cardiac problems → avoid ZIP, SERT (QT prolongation)
- If negative symptoms → CLO, ARI
- If affective symptoms (e.g.psychotic depression) → QUE (SGA work as mood stabilizers)
- If hypotension/dizziness – avoid QUE
- If MS multiple sclerosis→ QUE
- If EPS → SGA/CLO

Dopamine Projection Pathways

- **Nigrostriatal**-Caudate/Putamenregulates **motor function**
- **Mesolimbic**-Nucleus Accumbens and Amygdala- regulates **emotions [**mesolimbic reward pathway]
- **Mesocortical**- Limbic Cortex regulates **attention/ cognition/motivation**
- **Tuberohypophysial** -Arcuate Nucleus-regulates **prolactin release**


Dorsal Striatum
Thalamus
Putamen
Hypothalamus
Nucleus accumbens
Cerebellum
Substantia Nigra
Ventral Tegmental Area
Spinal cord
Pituitary
Cognition
Mesocortical pathway
Motor
Nigrostriatal pathway
PRL
Tubero-infundibular pathway
Emotions
Mesolimbic pathway

Adverse Effects of Antipsychotics

Via receptors:

- **Dopamine**: Antagonists at D2
- **Serotonin**: Antagonists at 5-HT2A
- **Histamine**: Antagonists at H1
- **Cholinergic**: Antagonists at muscarinic M1
- **Noradrenergic**: Antagonists at α1

Which receptor blockade

-treats

-causes SE

Affinity → SE

Receptor Affinity of Typical and Atypical Neuroleptics

	D_2	D_4	5-HT_{2A}	H_1	M	Alpha$_1$
Typical agents (first generation neuroleptics)						
Chlorpromazine	+++	0	++	++	+++	+++
Thioridazine	+++	0	++	+	+++	+++
Fluphenazine	+++	0	+	0	0	+
Haloperidol	+++	0	+	0	0	+
Atypical agents (second generation neuroleptics)						
Clozapine	++	++	+++	+	+++	+++
Aripiprazole	+++	0	++	+	0	++
Quitiapine	+	+	++	+	+	++
Olanzapine	++	+	+++	++	+++	++
Risperidone	+++	+	+++	+	0	+++

Clozapine – ↓seizure threshold

Relative Adverse Effect Incidence of Antipsychotics

	Sedation	EPS	Anticholinergic	Orthostasis	Seizures	Prolactin Elevation	Weight Gain
Typical Low Potency							
Chlorpromazine	High	Moderate	Moderate	High	Moderate	Moderate	Low
Thioridazine	High	Low	High	High	Low	Very high	Moderate
Typical High Potency							
Trifluoperazine	Low	High	Low	Low	Moderate	Moderate	Low
Fluphenazine	Low	Very high	Low	Low	Low	Moderate	Low
Thiothixene	Low	High	Low	Low	Low	Moderate	Low
Haloperidol	Very low	Very high	Very low	Very low	Low	Moderate	Low
Loxapine	Moderate	High	Low	Moderate	Low	Moderate	Very low
Molindone	Very low	High	Low	Low	Low	Moderate	Very low
Atypicals							
Clozapine	High	Very low	High	High	High	0	High
Risperidone	Moderate	Very low*	Low	Moderate	Low	0 to moderate††	Low
Olanzapine	Moderate	Very low†	Moderate	Low	Low	Very low	Moderate
Quetiapine	Moderate	Very low	Low	Low	Low	0	Low
Ziprasidone	Low	Very low	Low	Low	Low	0	Very low
Aripiprazole	Low	Very low	Low	Low	Low	0	Very low

** Very low dosages (<8 mg/day); † With dosages <20 mg/day; †† Dose related. EPS: extrapyramidal symptoms.*

Anticholinergic actions of FGA/SGA

Muscarinic Receptor Types and Effects from Their Blockage		
Organ system	**Receptors**	**Effects and/or Adverse Effects from Blockage (Anticholinergic Effects)**
Salivary glands	M1, M3, M4	Dry mouth
Cardiac tissue	M2	Tachycardia, palpitations
Eye (ciliary muscle, iris)	M3, M5	Dry eyes, blurred vision, mydriasis
Gastrointestinal tract	M1, M2, M3	Slowing of transit time, constipation, effects on sphincter tone and gastric acid secretion
Central nervous system, brain (cortex and hippocampus)	M1, M2, M3, M4, M5	Effects on memory, cognition and psychomotor speed. Other: confusion, delirium, sedation, hallucinations, sleep disruption
Bladder (detrusor muscle)	M2, M3	Decreased contraction, urinary retention

M = Muscarinic (M) receptor. Source: Adapted from References 36-40.

Clozapine – hypersalivation = Sialorrhea (especially during night)

How to deal with it? → e.g. amitryptiline 10mg, pirenzepine (M1 selective antagonist)

Sexual dysfunction

- Hyperprolactinemia – lower testosterone, lower libido
- Alpha 1 antagonists – retrograde ejaculation

Sexual dysfunction -Retrograde ejaculation

e.g.RIS → α1 adrenergic receptor antagonist → relaxes bladder sphincter →semen is redirected to the urinary bladder during ejaculation → ”dry orgasm”

The medications that mostly cause it are antidepressant and **antipsychotic** medication, as well as NRIs such as atomoxetine; patients experiencing this phenomenon tend to quit the medications

Treatments for side effects - EPS

- **dystonias - anticholinergic agent:** benztropine, biperiden, diphenhydramine, and trihexyphenidyl.

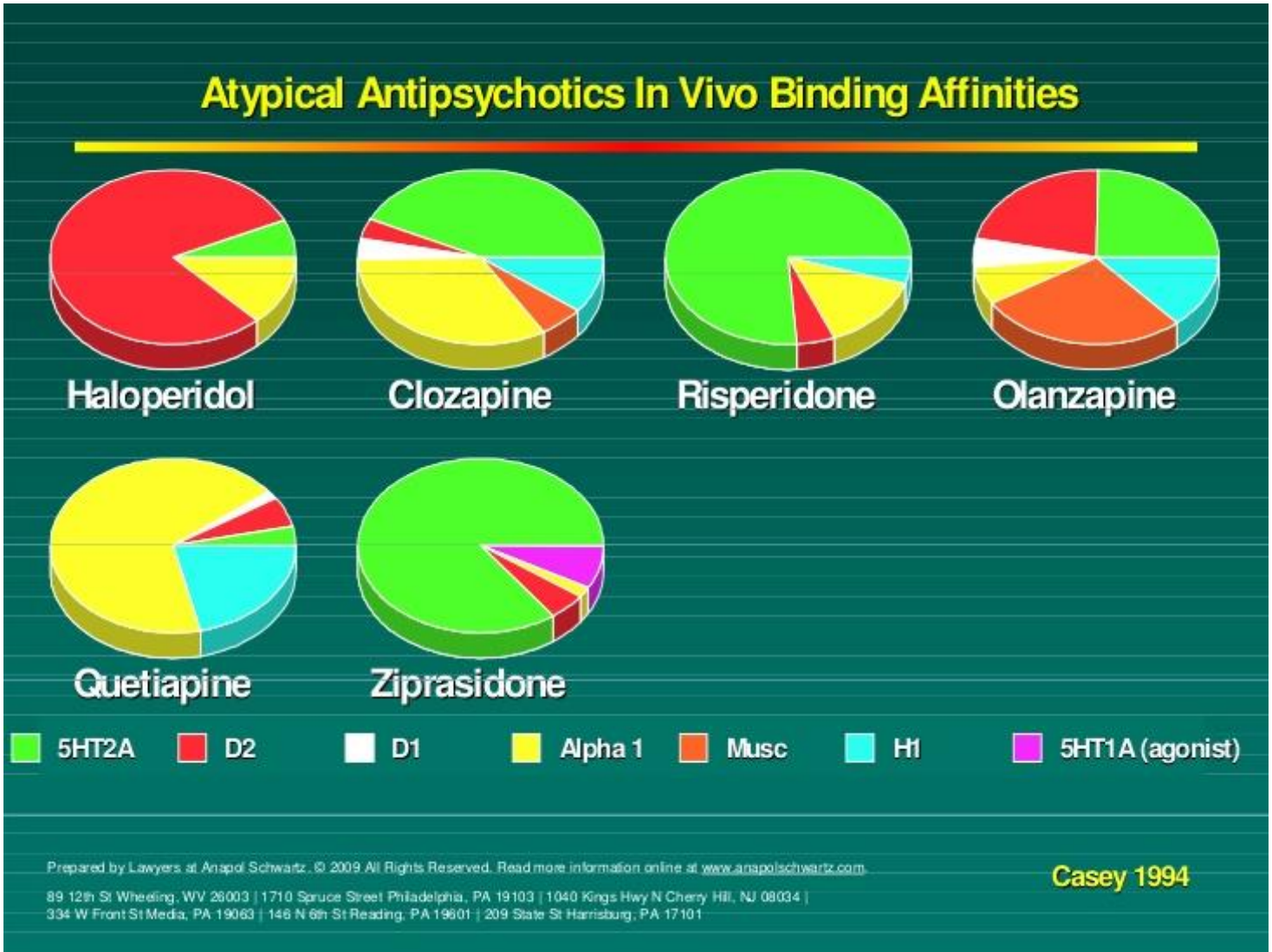
- **akathisias** - **propranolol and benzodiazepines**

- **parkinsonian** side effects - **amantadine and levodopa**

SGA/Atypical Antipsychotics Have Antagonist Actions that are Greater for 5-HT2A than D2

Risperidone RIS
Olanzapine OLA
Quetiapine QUE
Clozapine CLO
Ziprasidone ZIP
Aripiprazole ARI - Partial Agonist of the Dopamine D2 Receptor (mainly in prefrontal cortex – mesocortical pathway)

Predicting action and SE



Atypical antipsychotics

- **Claims**

– lower doses
– reduced side effects
– more effective (especially negative symptoms)
– better compliance

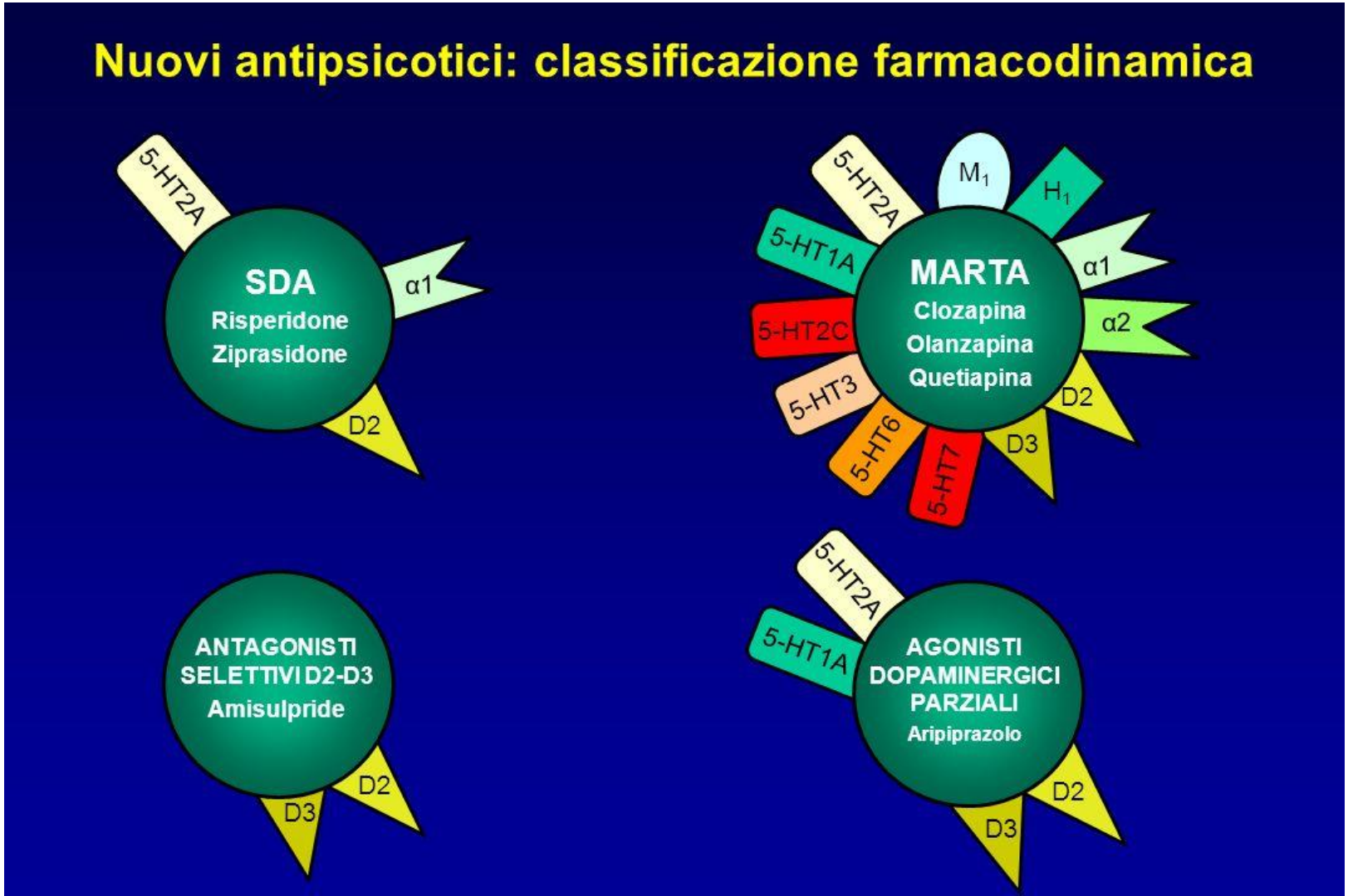
- **Evidence**

– trials have tended to show equivalent efficacy and better side effect profiles with newer drugs

- **Costs**

– Much higher with new drugs (10-40 times higher)

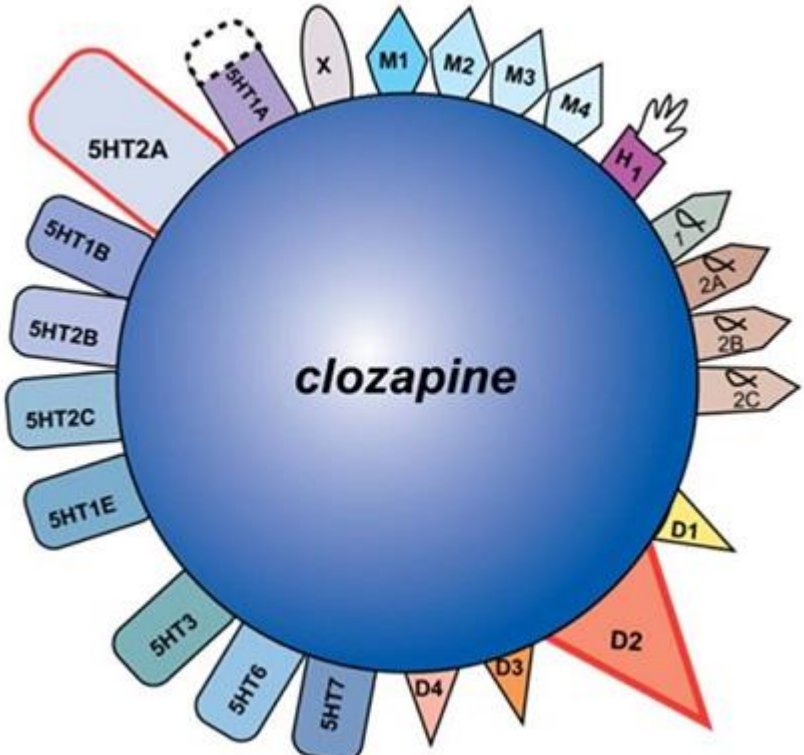
Clozapine- a multi-acting receptor targeted antipsychotic (MARTA)



SGA: CLOZAPINE

- Risk of **agranulocytosis**

- **Obligatory Tests:** Prior to starting treatment, obtain **CBC**, including white count and absolute neutrophil count.
- Repeat CBC **weekly** for the first 6 months of treatment, then **biweekly** for months 6-12 and **every 4 weeks** thereafter



Key phrases

Lack of compliance – LAI, long-acting, intramuscular forms (**decanoate**)

Clozapine – agranulocytosis– check WBC/differential count weekly(6months)→ every 2 wk→ monthly (chronic treatment)

Clozapine → drug resistant schizophrenia

Olanzapine →increase in body mass

SGA → metabolic syndrome

Hyperprolactinemia – symptomatic & asymptomatic

Metoclopramide→ acute dystonia

Concentration: lithium Li, valproate VAL, carbamazepine CBZ

Key words

- prolongation of the **QT interval – antipsychotics (mainly ziprasidone, sertindol)**
- Post injection syndrom – ola 3hrs observation

(when injected to vessel; NO predisposition)

- QUE – MS, improves remyelination (influences astrocytes)
- thioridazine – SE: irreversible pigmentation of the retina → abnormal night vision →blindness


Break Time

ANTIDEPRESSANTS

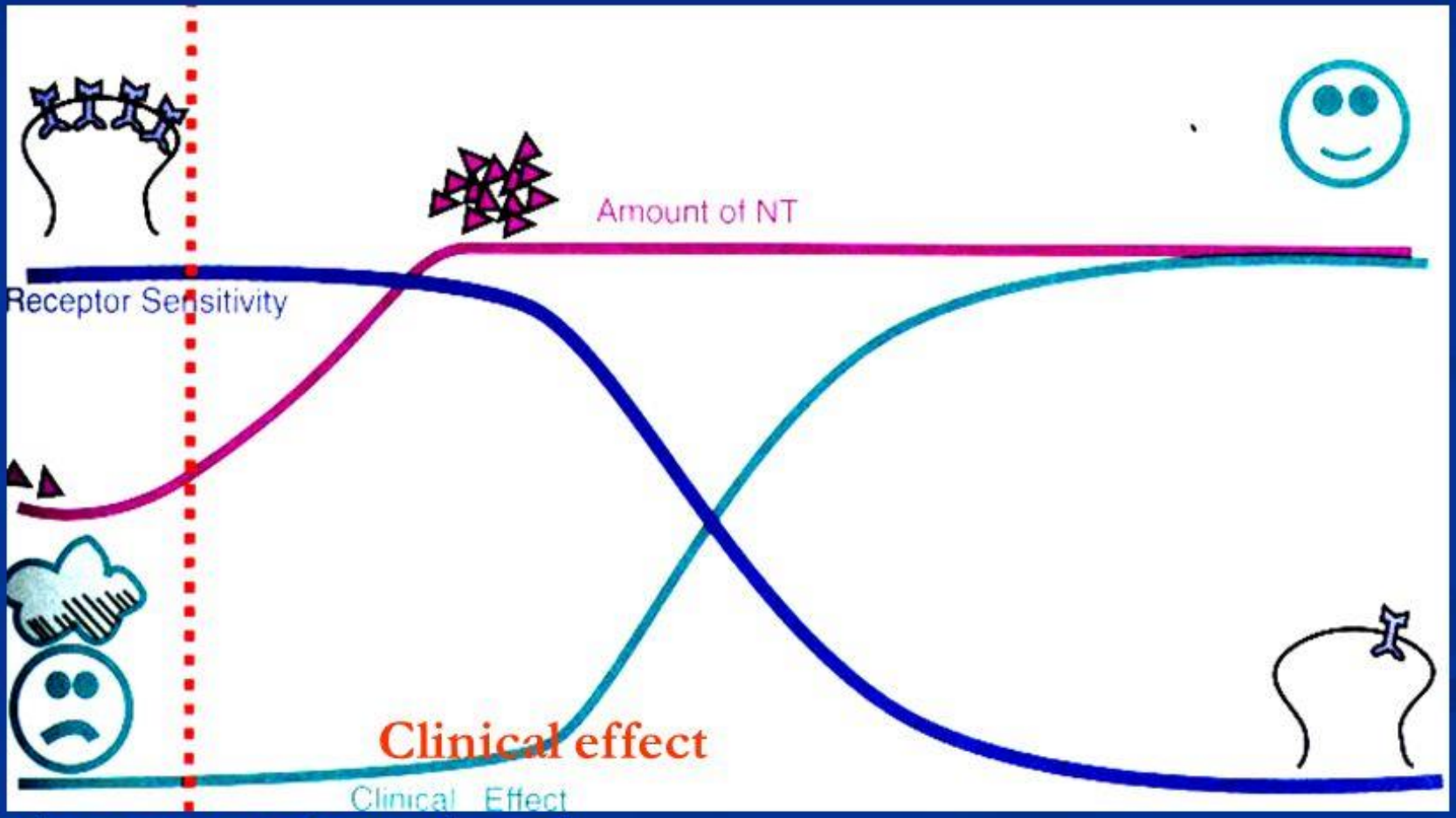
Classification of Antidepressants

1. Tricyclics & heterocyclics
2. **Selective Serotonin Reuptake Inhibitors (SSRIs)**
3. Mixed Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)
4. Norepinephrine-Selective Reuptake Inhibitors (NRIs)
5. Norepinephrine/Dopamine Reuptake Inhibitors (NDRIs)
6. Serotonin 2A Antagonist/Serotonin Reuptake Inhibitors (SARI)
7. Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)
8. Monoamine Oxidase Inhibitors (MAOIs)

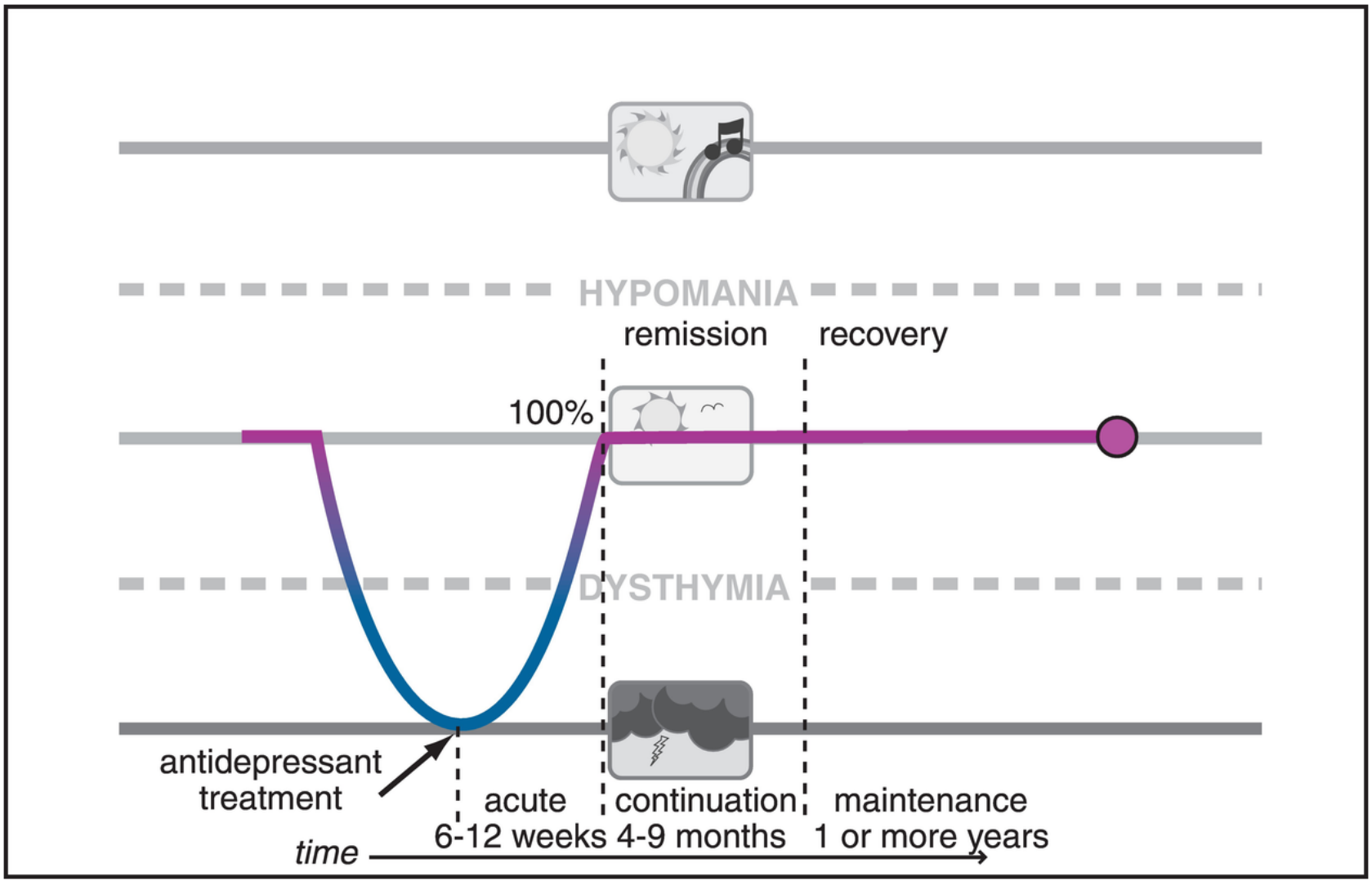
May act as:

- Reuptake inhibitor
- Receptors antagonists
- Enzyme inhibitor
- Transporter inhibitor

Postulated Neurotransmitter Receptor Hypothesis of Antidepressant Action



How fast they work?



Antidepressants: Indications

1. **Depression**
2. **Panic Disorder** (SSRIs, TCAs, MAOIs)
3. **GAD** (SSRIs, SNRIs (venlafaxine), TCAs)
4. **OCD** (SSRIs–in high doses, TCAs: Clomipramine)
5. **Enuresis/ sleepwetting** (IMI)
6. **Narcolepsy** (CLOMI/IMI appear to suppress REM sleep)
7. **Social phobia (**SSRIs, SNRIs, MAOIs)
8. **Eating disorder** (SSRIs (in high doses), e.g. fluoxetine for bulimia, TCAs)

Heterocyclics, including TCAs

All tricyclics block reuptake pumps for both 5HT and NE and they work as **negative** allosteric modulators of neurotransmitter **uptake process → more monoamines in the synapse**

Some have more potency for inhibition of **5HT** uptake pump **(e.g. clomipramine, imipramine, amitryptyline)**

Others have more potency for inhibition of **NE** uptake pump (**nortriptyline, desipramine)**

All tricyclics block **α1 adrenergic, histaminergic, and M1** cholinergic receptors (causes side effects, e.g., weight gain, drowsiness, blurred vision)

Tricyclics also **block Na+ channels**, thus may cause **cardiac arrythmia**

Heterocyclics, including TCAs

1. **Tricyclics - Secondary Amines**: (less anticholinergic)
   – Desipramine [Norpramin], Nortryptiline [Pamelor], protryptiline [Vivactil]

2. **Tricyclics - Tertiary Amines**:
   – IMI [Tofranil], Amitriptiline [Elavil], Doxepin [Sinequan], **Clomipramine to treat OCD** [Anafranil (SRI)]

3. **Tetracyclic: Amoxapine** [Asendin] (less anticholinergic; metabolite of FGA loxapine, risk of EPS/NMS)

! Narrow therapeutic to toxic range → Lethal in overdose
The treatment for TCA overdose is **IV sodium bicarbonate**

Heterocyclics, including TCAs: side effects

Anticholinergic:

- dry mouth
- blurred vision
- urinary retention
- constipation
- sedation
- tachycardia

Alpha-adrenergic blockade:

- orthostatic hypotension, dizziness
- reflex tachycardia
- prolongation of QT interval → obligatory test: ECG at the onset of treatment

Antihistamine-1 effect:

- weight gain
- sedation

Selective Serotonin Reuptake Inhibitors (SSRI)

Selective and more potent inhibitors of serotonin uptake than tricyclics -- no blockade of α1, histamine or M cholinergic receptors or Na+ pump. Similar efficacy to TCA, better safety.

fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram

Fluoxetine (active metabolite – norfluoxetine) longest t1/2: **9-11 days**, the others 20-24 hrs

Safe in pregnancy, approved for use in children and adolescents

SSRI: Side Effects

Usually safe & well tolerated → *first line treatment* in depression/anxiety

1.CNS:

- Nervousness, jitteriness → BDZ at the beginning of treatment
- Insomnia / sedation (Parox, Fluvo), fatigue
- Headaches, Tremors

2.GI (the most common side effects):

- Nausa / Vom 11-16%, Diarr (Sertr), Constip (Pax), anorexia (Proz), dry mouth

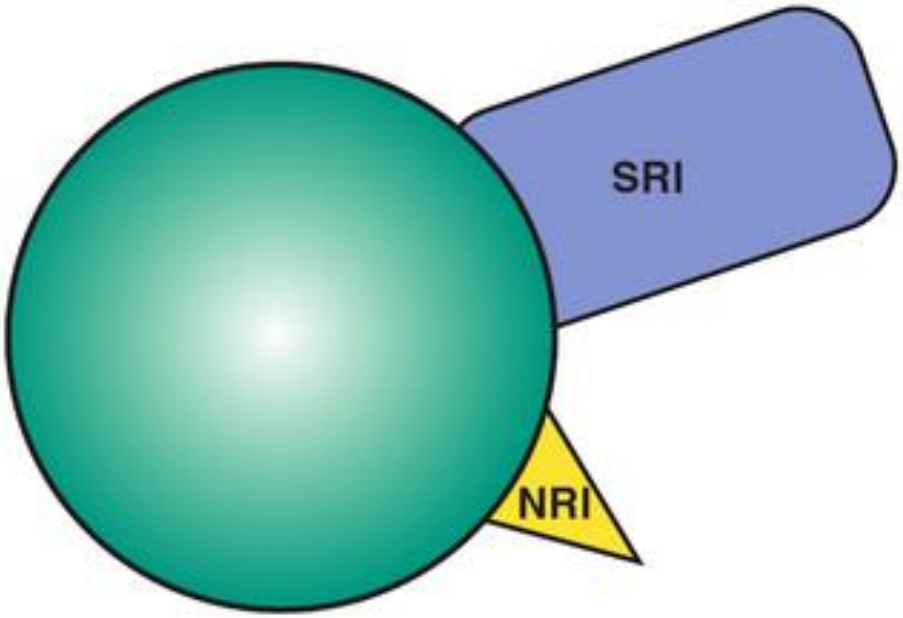
3.Sexual: 5-HT2 (25-50%)

- delayed orgasm, ↓libido, ↓erection/lubrication

(lower dose, switch medication, add bupropion or sildenafil)

4.Induction of Mania

SNRI: Venlafaxine , Duloxetine



Mixed 5HT/NE Reuptake Inhibitors (SNRIs)

Other antidepressants

- **Venlafaxine** SNRI: **MDD, neuropathic pain, increases BP,**
- **Duloxetine** (Cymbalta) SNRI; MDD, GAD, **painful diabetic neuropathy**

- **Trazodone -** serotonin antagonist and reuptake inhibitor (SARI), to treat **insomnia** in depression, SE: **priapism**

- **Bupropion** (Norepinephrine-Dopamine Reuptake Inhibitor) Relative lack of **sexual** side effects as compared to the SSRI

- **Mirtazapine** (α2-Adrenergic Receptor Antagonist) – to treat MDD with **insomnia and weight loss**

- **MAOI: phenelzine,** isocarboxazide, selegiline (Parkinson's disease), tranylcypromine

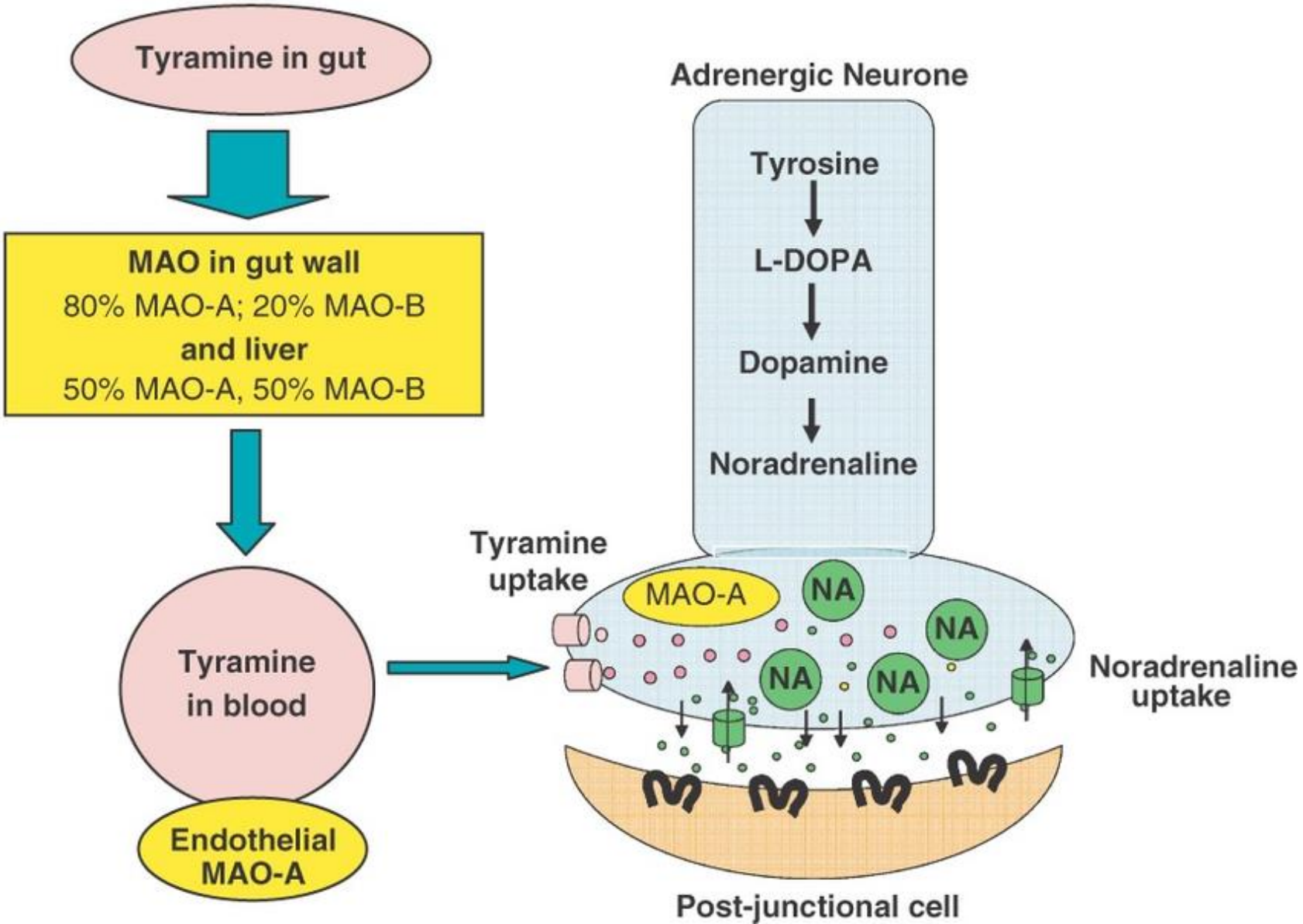
MAOI - Tyramine free diet

Avoid:

- cheese
- aged/fermented food
- wine
- liver

Hypertensive crisis: Risk when MAOIs are taken with tyramine-rich foods or sympathomimetics.

The ‘cheese reaction’



Serotonin syndrome

Caused by taking two or more medications, both of which ↑ serotonin leading to too much serotonin in the brain (e.g. SSRI + triptans used for migraine headaches).

1. fever, diaphoresis, flushing
2. tachycardia
3. hypertension
4. neuromuscular excitability (especially hyperreflexia and “electric jolt” limb movements)

Serotonin syndrome

- To avoid fatal serotonin syndrome no SSRI or SSNRI should be combined with a monoamine oxidase inhibitor (MAOI), and an **SSRI should be discontinued at least 2 wks before starting an MAOI (fluoxetine – 5-6 wks)**

„Distinguishing Characteristics”:
hyperreflexia = myoclonus = muscle spasms,
diarrhea,
shivering = hyperthermia.

- NMS- ridigity (severe muscle rigidity), elevated CPK, leukocytosis

Antidepressants and Eating disorders

- Bulimia nervosa: Most commonly prescribed – fluoxetine
- Drugs that **prolong the QT interval** (e.g., tricyclic antidepressants, some neuroleptics) may result in fatal arrhythmias in the context of intermittent **hypokalemia** induced by vomiting or laxative abuse.
- **Drugs excreted by the kidney**, such as **lithium**, should be avoided because of risk of toxicity due to recurrent **dehydration** and electrolyte disturbances.
- **Bupropion** is contraindicated because of the increased risk for **seizures (higher reported incidence**); patients should also be warned against its use for smoking cessation.

- Anorexia nervosa:
- Bupropion contraindicated. The incidence of weight loss greater than 5 pounds is approximately 28%, which may be undesirable in patients suffering from anorexia, malnutrition or excessive weight loss.

Key phrases

SSRIs – SE: GI disturbance and sexual dysfunction

Trazodone→ priapism

Duloxetine→ to treat urinary incontinence

Duloxetine → to treat painful diabetic neuropathy

Bupropione → SE: seizure, anorexia,

Bupropione → used for smoking cessation

MAOI ----- [2 wk break]----- switching to SSRI

MOOD STABILIZERS

Mood stabilizers

- Lithium Li
- Valproate Val
- Carbamazepine CBZ (trigeminal neuralgia)
- SGA: OLA, QUE, ARI

Anticonvulsants: **lamotrigine(bipolar depression)**, gabapentine (neuropathic pain), topiramate(impulse control), oxcarbazepine, pregabalin (GAD)

Lithium

- Inhibits adenylate cyclase enzyme
- **Side effects**:
  - **tremor**,
  - **polyuria/**diabetes insipidus = **increased thirst**
  - acne,
  - **hypothyroidism,**
  - cardiac dysrhythmias,
  - weight gain,
  - leukocytosis.

Lithium is **cleared through the kidneys** and must be used with caution in older patients and in those with renal insufficiency. Obligatory tests: WBC, serum electrolyte determination, **thyroid and renal function tests** (specific gravity, BUN, and creatinine), fasting blood glucose determination, pregnancy test, and an electrocardiogram (ECG) are recommended before treatment and yearly thereafter (every 6 mo for a TSH and creatinine).

Lithium levels **monitor every 3 mo**

Toxic levels of lithium cause altered mental status, tremors, **convulsions,** delirium, **coma,** and death

Valproic acid

- Opens chloride channels

- Valproic acid can be **teratogenic (neural tube defects in pregnancy**) and must not be used in women of childbearing age (check for serum hCG level; switch to another mood stabilizer).

- **Increases other drugs' plasma concentration**

Carbamazepine

- Inactivates sodium channels
- Currently first-line treatment for trigeminal neuralgia
- Potent inducer of P450 system→ **decreases other drugs' plasma concentration**
- Monitor CBZ level and CBC and electrolytes (risk of hyponatremia)

Other Mood stabilizers

- **Lamotrygine:**
  - **Antidepressant** action
  - **SE: rash,** dangerous SE: Stevens–Johnson syndrome/ toxic epidermal necrolysis
  - dose must be increased slowly to lower the incidence of allergic reactions

- **Gabapentine**:
  - no interactions
  - Painful diabetic neuropathy

- **Topiramate:** decreases apetite, impairs cognitive functions