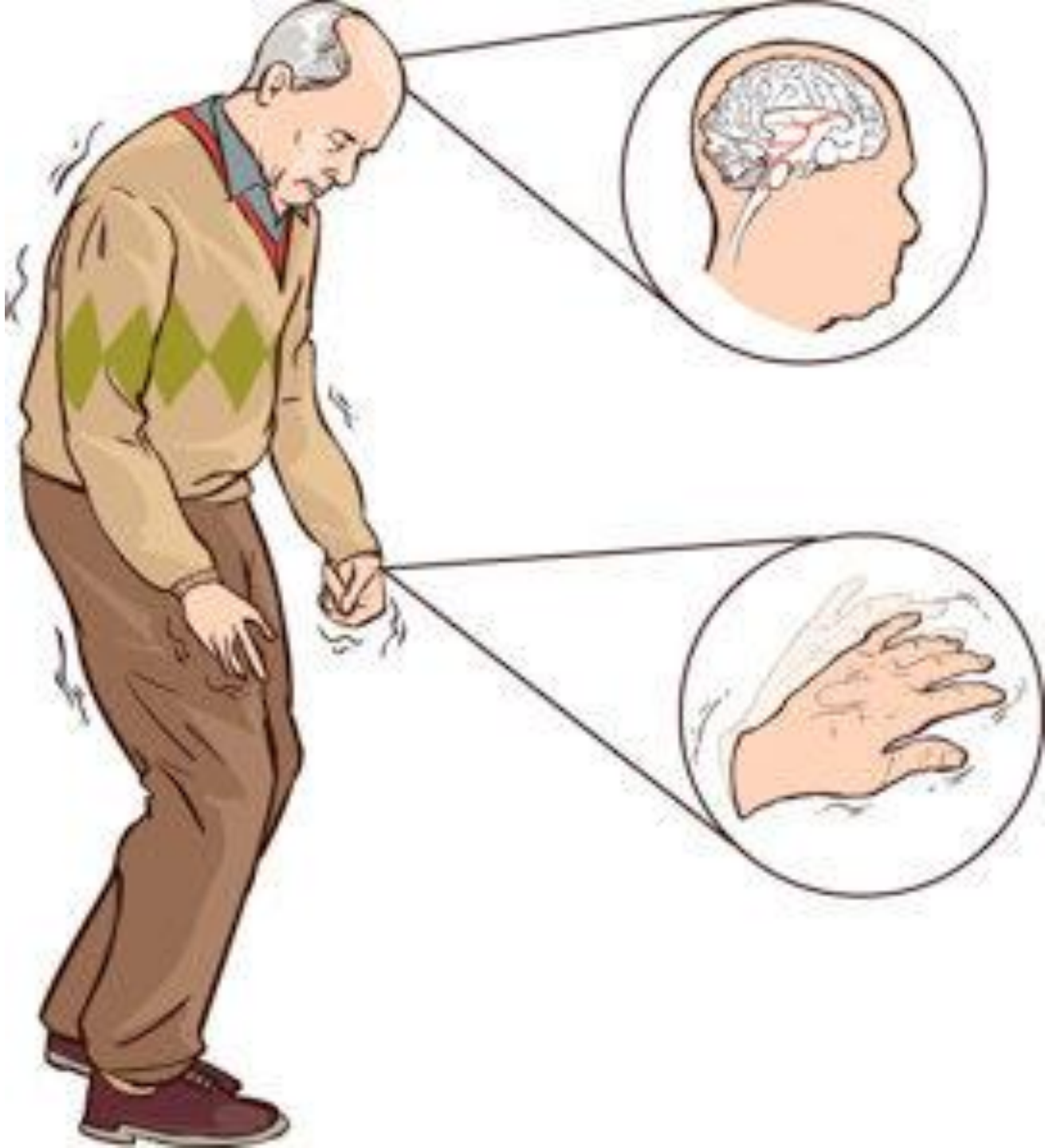
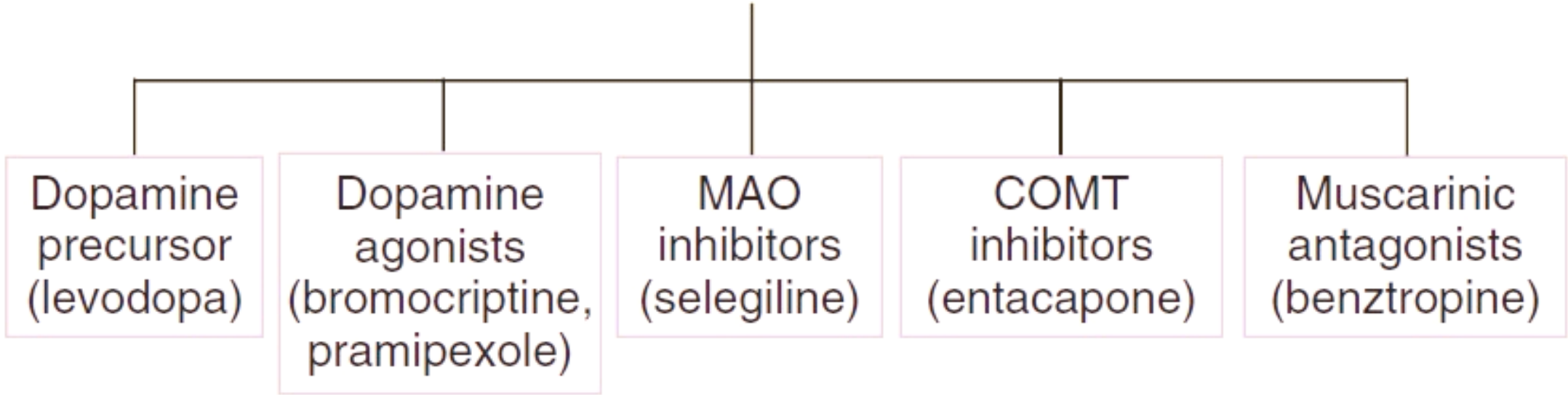
Drugs Used in Parkinsonism & Other Movement Disorders

Dr. Mohammad Jadaan

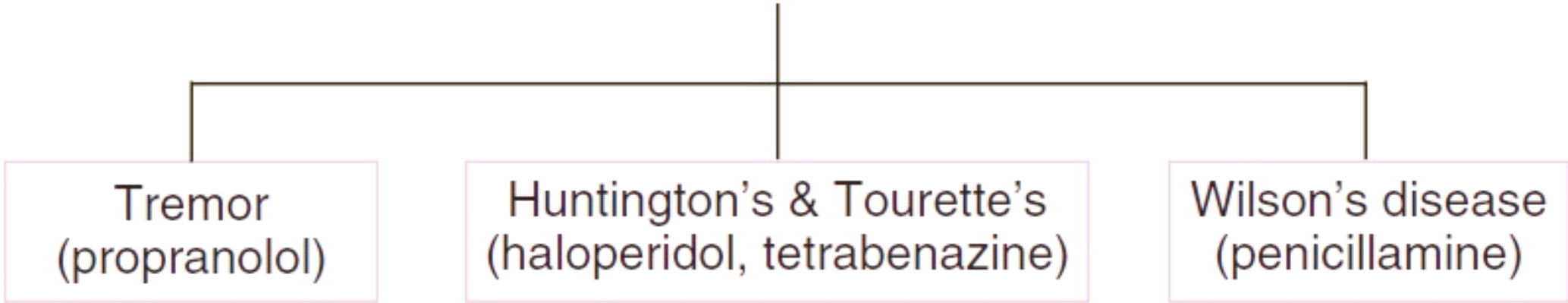


- Movement disorders constitute a number of heterogeneous neurologic conditions with very different therapies. They include parkinsonism, Huntington's disease, Wilson's disease, and Gilles de la Tourette's syndrome.
- Movement disorders, including athetosis, chorea, dyskinesia, dystonia, tics, and tremor, can be caused by a variety of general medical conditions, neurologic dysfunction, and drugs.

Drugs used in parkinsonism



Drugs for other movement disorders



Pathophysiology

Parkinsonism (paralysis agitans) is a common movement disorder that involves dysfunction in the basal ganglia and associated brain structures.

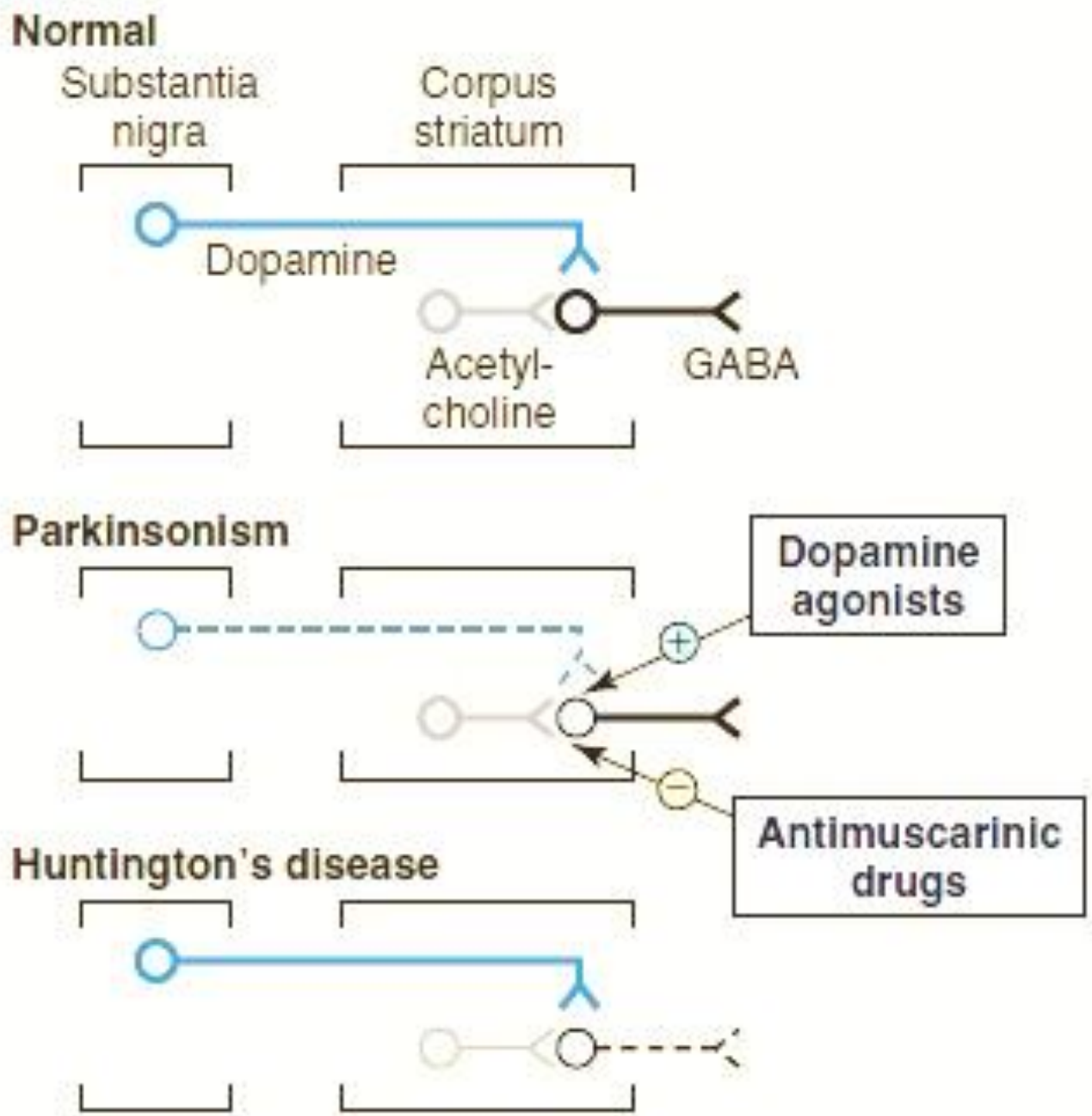
Signs include rigidity of skeletal muscles, akinesia (or bradykinesia), flat facies, and tremor at rest (mnemonic **RAFT**).

Naturally occurring parkinsonism

- The naturally occurring disease is of uncertain origin and occurs with increasing frequency during aging from the fifth or sixth decade of life onward.
- Pathologic characteristics include a decrease in the levels of striatal dopamine and the degeneration of dopaminergic neurons in the nigrostriatal tract that normally inhibit the activity of striatal GABAergic neurons.
- The reduction of normal dopaminergic neurotransmission leads to excessive excitatory actions of cholinergic neurons on striatal GABAergic neurons; thus, dopamine and acetylcholine activities are out of balance in parkinsonism.

Drug-induced parkinsonism

- Many drugs can cause parkinsonian symptoms; these effects are usually reversible. The most important drugs are the butyrophenone and phenothiazine **antipsychotic drugs,** which block brain dopamine receptors.
- At high doses, **reserpine** causes similar symptoms, presumably by depleting brain dopamine.
- **MPTP** (1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine), a by-product of the attempted synthesis of an illicit meperidine analog, causes irreversible parkinsonism through destruction of dopaminergic neurons in the nigrostriatal tract.


Normal
Substantia nigra
Corpus striatum
Dopamine
Acetyl-choline
GABA
Parkinsonism
Dopamine agonists
Antimuscarinic drugs
Huntington's disease

DRUG THERAPY OF PARKINSONISM

- Strategies of drug treatment of parkinsonism involve increasing dopamine activity in the brain, decreasing muscarinic cholinergic activity in the brain, or both.
- Although several dopamine receptor subtypes are present in the substantia nigra, the benefits of most antiparkinson drugs appear to depend on activation of the D2 receptor subtype.

A. Levodopa

- Because dopamine has low bioavailability and does not readily cross the blood-brain barrier, its precursor, L-dopa (levodopa), is used.
- This amino acid enters the brain via an L-amino acid transporter (LAT) and is converted to dopamine by the enzyme aromatic L-amino acid decarboxylase.
- Levodopa is usually given with **carbidopa,** a drug that does not cross the blood-brain barrier.

B. Dopamine Agonists

- **1. Bromocriptine**—Acts as a partial agonist at dopamine D2 receptors in the brain. The drug increases the functional activity of dopamine neurotransmitter pathways, including those involved in extrapyramidal functions.
- Bromocriptine has been used as an individual drug, in combinations with levodopa (and with anticholinergic drugs), and in patients who are refractory to or cannot tolerate levodopa.
- Common adverse effects include anorexia, nausea and vomiting, dyskinesias, and postural hypotension.

2. Pramipexole

- This drug has high affinity for the dopamine D3 receptor. It is effective as monotherapy in mild parkinsonism and can be used together with levodopa in more advanced disease.
- Pramipexole is administered orally 3 times daily and is excreted largely unchanged in the urine.
- The dose of pramipexole may need to be reduced in renal dysfunction.
- Adverse effects include anorexia, nausea and vomiting, postural hypotension, and dyskinesias.
- Mental disturbances are more common with pramipexole than with levodopa.
- In rare cases, an uncontrollable tendency to fall asleep may occur.
- Pramipexole may be neuroprotective because it is reported to act as a scavenger for hydrogen peroxide.

3. Ropinirole

- This drug has high affinity for the dopamine D2 receptor.
- It is effective as monotherapy and can be used with levodopa to smooth out response fluctuations.
- The standard form is given 3 times daily, but a prolonged release form can be taken once daily.
- Ropinirole is metabolized by hepatic CYP1A2, and other drugs metabolized by this isoform (eg, caffeine, warfarin) may reduce its clearance.
- Adverse effects and contraindications are similar to those of pramipexole.

4. Apomorphine

- A potent dopamine receptor agonist, apomorphine injected subcutaneously may provide rapid (within 10 min) but temporary relief (1–2 h) of "off-periods" of akinesia in patients on optimized dopaminergic therapy.
- Because of severe nausea, pretreatment for 3 days with antiemetics (eg, trimethobenzamide) is necessary.
- Other side effects of apomorphine include dyskinesias, hypotension, drowsiness, and sweating.

C. Monoamine Oxidase Inhibitors

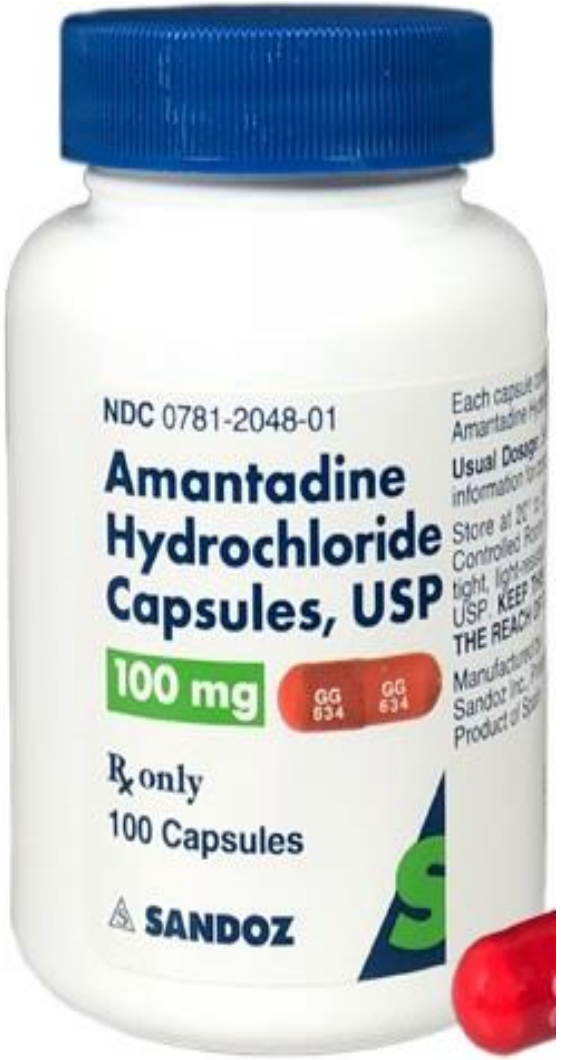
- Selegiline and rasagiline are selective inhibitors of monoamine oxidase type B, the form of the enzyme that metabolizes dopamine.
- Hepatic metabolism of selegiline results in the formation of desmethylselegiline (possibly neuroprotective) and amphetamine.
- Selegiline has minimal efficacy in parkinsonism if given alone but can be used adjunctively with levodopa.
- Rasagiline is more potent and has been used as monotherapy in early symptomatic parkinsonism as well as in combinations with levodopa.

D. Catechol-O-methyltransferase (COMT) Inhibitors

- Entacapone and tolcapone are inhibitors of COMT, the enzyme in both the CNS and peripheral tissues that converts levodopa to 3-O-methyldopa (3-OMD).
- Increased plasma levels of 3-OMD are associated with poor response to levodopa partly because the compound competes with levodopa for active transport into the CNS.
- The drugs are used individually as adjuncts to levodopa-carbidopa, decreasing fluctuations, improving response, and prolonging "on-time."
- Tolcapone is taken 3 times daily, entacapone 5 times daily.

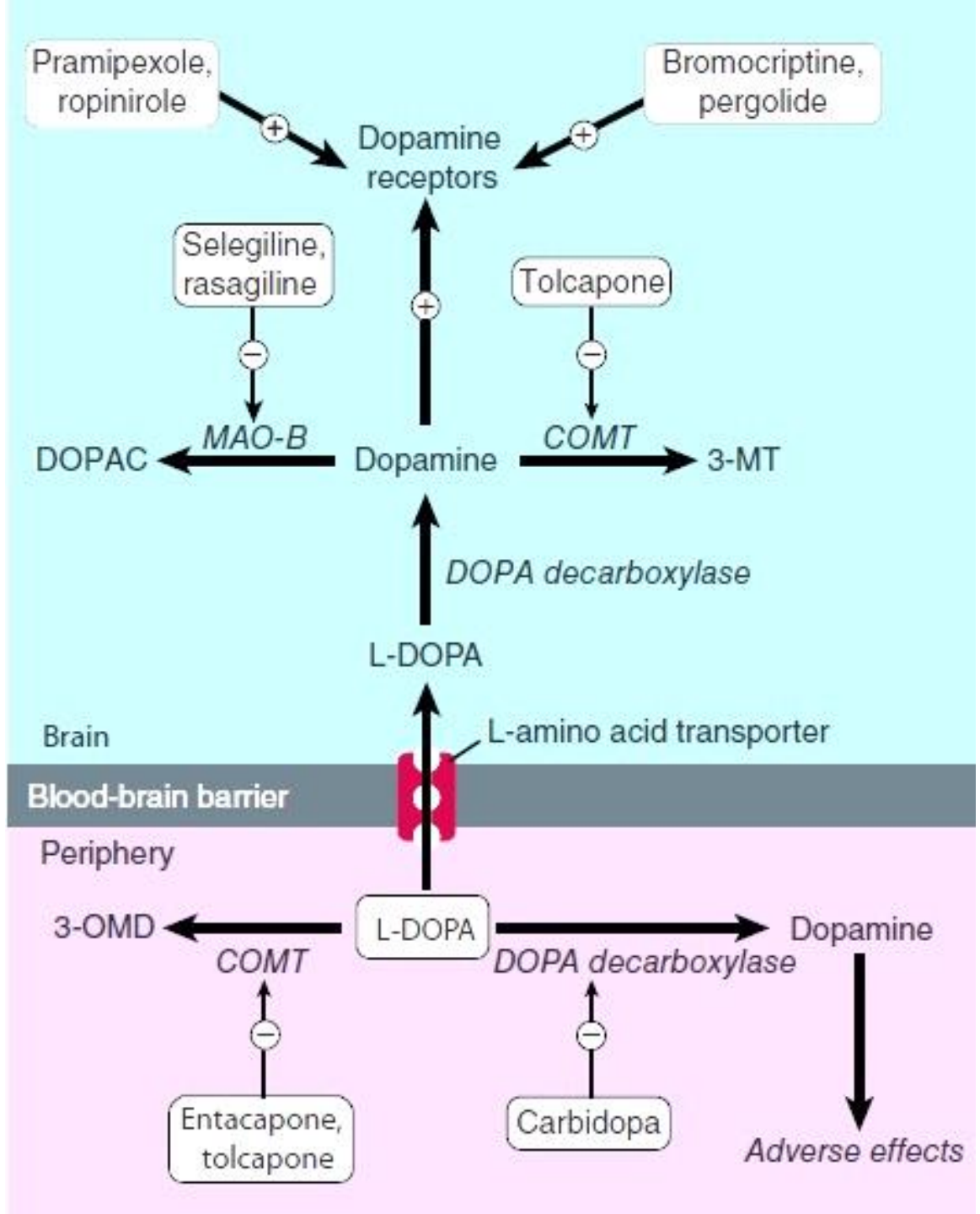
E. Amantadine

- Amantadine enhances dopaminergic neurotransmission by unknown mechanisms that may involve increasing synthesis or release of dopamine or inhibition of dopamine reuptake.
- The drug also has muscarinic blocking actions.
- Amantadine may improve bradykinesia, rigidity, and tremor but is usually effective for only a few weeks. Amantadine also has antiviral effects.



F. Acetylcholine-Blocking (Antimuscarinic) Drugs

- The drugs (eg, benztropine, biperiden, orphenadrine) decrease the excitatory actions of cholinergic neurons on cells in the striatum by blocking muscarinic receptors.
- These drugs may improve the tremor and rigidity of parkinsonism but have little effect on bradykinesia.
- They are used adjunctively in parkinsonism and also alleviate the reversible extrapyramidal symptoms caused by antipsychotic drugs.


Pramipexole, ropinirole
Bromocriptine, pergolide
Dopamine receptors
Selegiline, rasagiline
Tolcapone
MAO-B
COMT
DOPAC
Dopamine
3-MT
DOPA decarboxylase
L-DOPA
Brain
L-amino acid transporter
Blood-brain barrier
Periphery
3-OMD
L-DOPA
Dopamine
COMT
DOPA decarboxylase
Entacapone, tolcapone
Carbidopa
Adverse effects

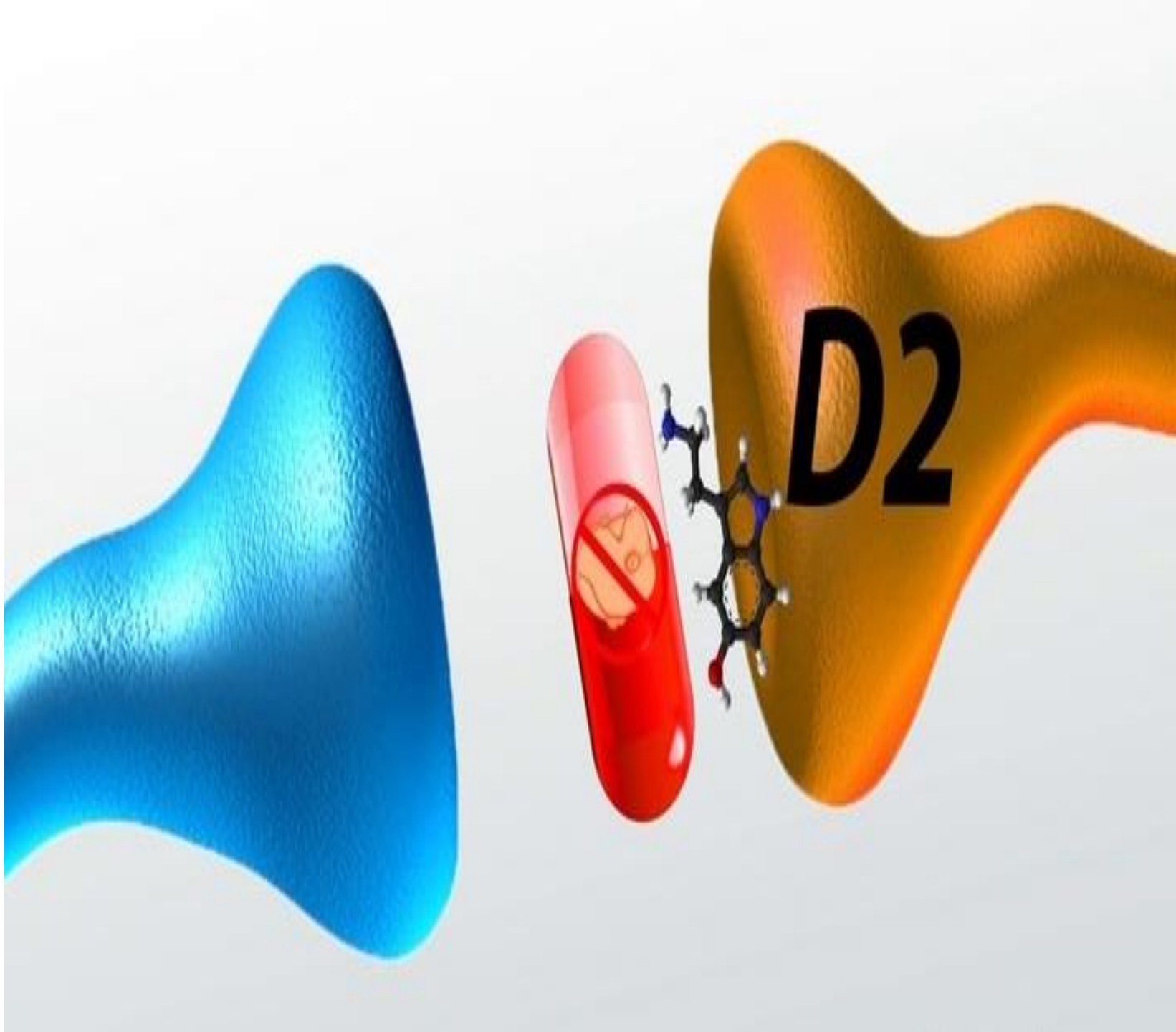
Antipsychotic Drugs

- The antipsychotic drugs (also called neuroleptics or major tranquilizers) are used primarily to treat schizophrenia, but they are also effective in other psychotic and manic states.
- Antipsychotic drugs are not curative and do not eliminate chronic thought disorders, but they often decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive environment.

Schizophrenia

- Schizophrenia is a type of chronic psychosis characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances.
- The onset of illness is often during late adolescence or early adulthood.
- It occurs in about 1% of the population and is a chronic and disabling disorder.
- Schizophrenia has a strong genetic component and probably reflects some fundamental biochemical abnormality, possibly a dysfunction of the mesolimbic or mesocortical dopaminergic neuronal pathways.

Antipsychotic

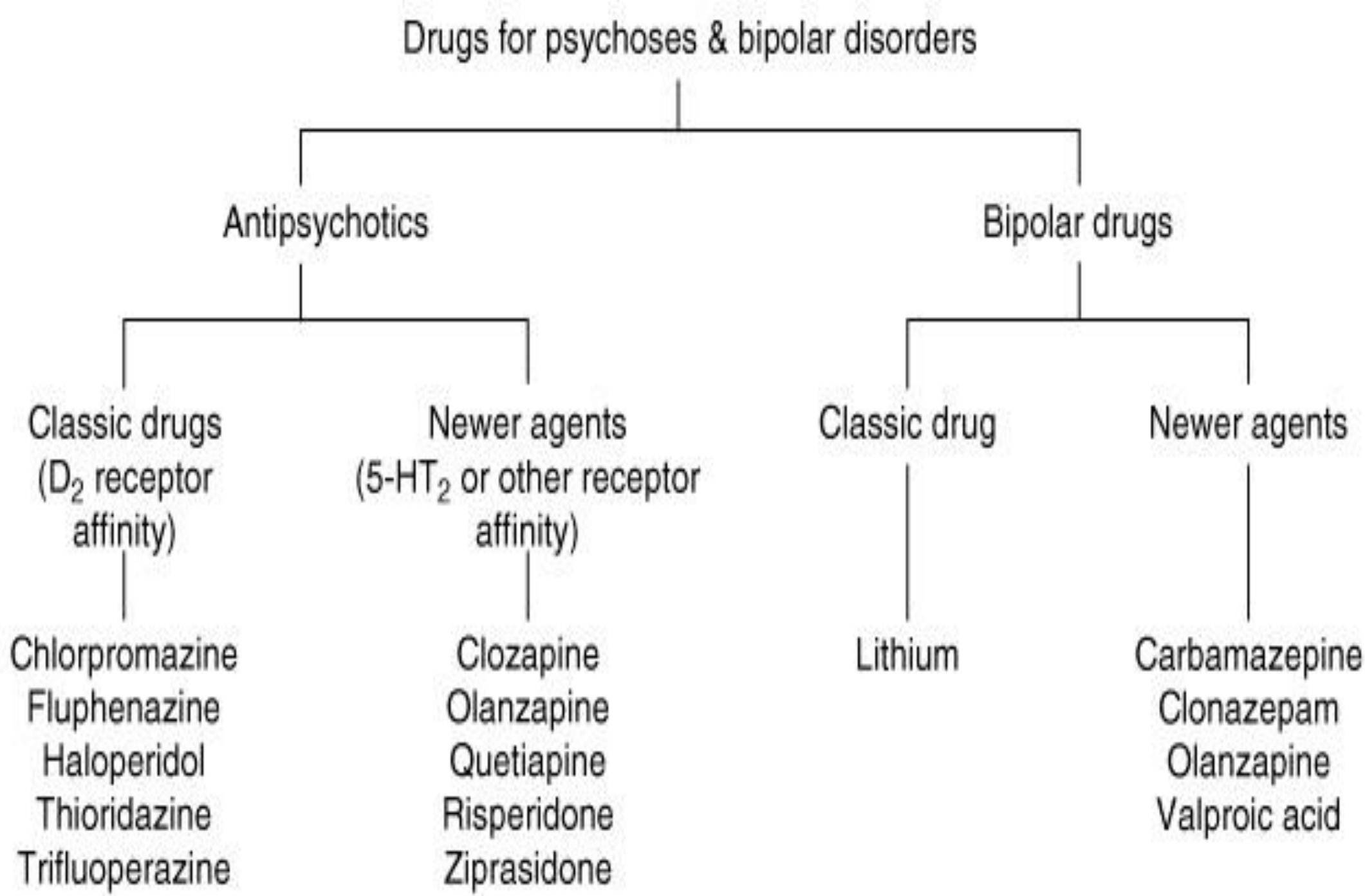


First-generation antipsychotics

- The first-generation antipsychotic drugs (also called conventional, typical, or traditional antipsychotics) are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of dopamine D2 receptors.

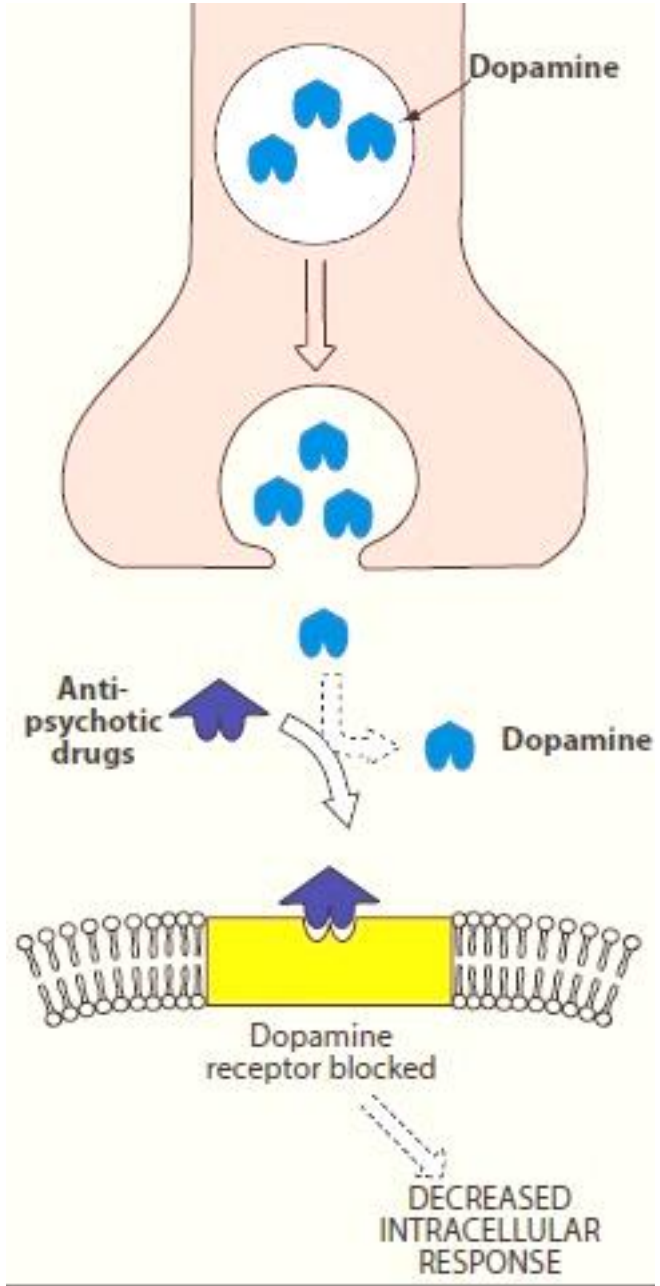
Second-generation antipsychotic drugs

- The second-generation antipsychotic drugs (also called "atypical" antipsychotics) have a lower incidence of EPS than the first-generation agents but are associated with a higher risk of metabolic side effects, such as diabetes, hypercholesterolemia, and weight gain.
- The second- generation drugs appear to owe their unique activity to blockade of both serotonin and dopamine and, perhaps, other receptors.


Drugs for psychoses & bipolar disorders
Antipsychotics
Bipolar drugs
Classic drugs (D_2 receptor affinity)
Newer agents (5-HT_2 or other receptor affinity)
Classic drug
Newer agents
Chlorpromazine
Fluphenazine
Haloperidol
Thioridazine
Trifluoperazine
Clozapine
Olanzapine
Quetiapine
Risperidone
Ziprasidone
Lithium
Carbamazepine
Clonazepam
Olanzapine
Valproic acid

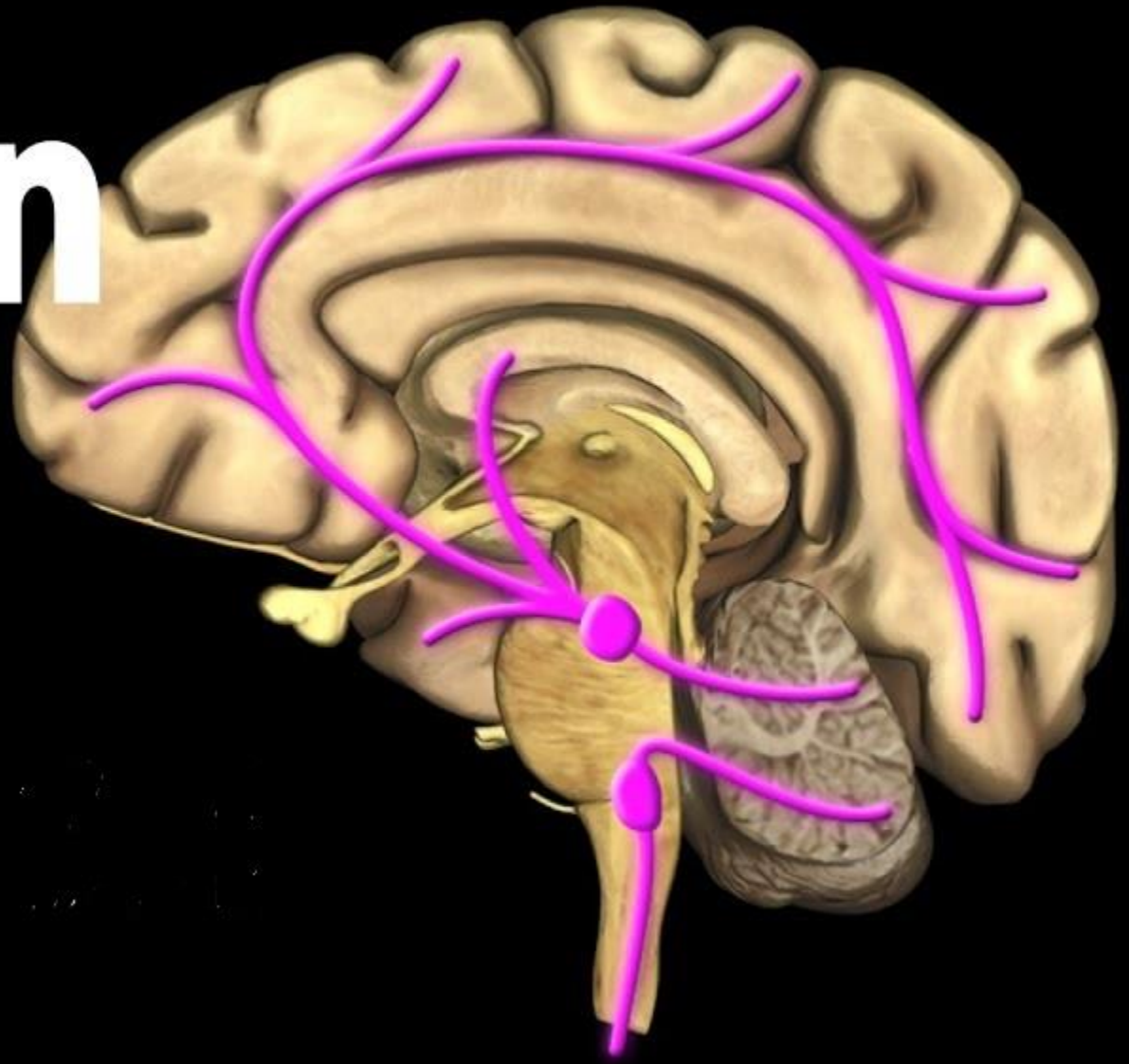
Mechanism of action

1. Dopamine antagonism: All of the first-generation and most of the second-generation antipsychotic drugs block D2 dopamine receptors in the brain and the periphery.



Serotonin

Receptor–blocking



- Most of the second generatio agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT), particularly 5-HT2A receptors.
- Clozapine has high affinity for D1, D4, 5-HT2, muscarinic, and α-adrenergic receptors, but it is also a weak dopamine D2 receptor antagonist.
- Risperidone blocks 5-HT2A receptors to a greater extent than it does D2 receptors, as does olanzapine.
- The second-generation antipsychotic aripiprazole is a partial agonist at D2 and 5-HT1A receptors, as well as an antagonist of 5-HT2A receptors.
- Quetiapine blocks D2 receptors more potently than 5-HT2A receptors but is relatively weak at blocking either receptor.

Antipsychotic effects:

- All antipsychotic drugs can reduce hallucinations and delusions associated with schizophrenia (known as“ positive” symptoms) by blocking D2 receptors in the mesolimbic system of the brain.
- The “ negative” symptoms, such as blunted affect, apathy, and impaired attention, as well as cognitive impairment, are not as responsive to therapy, particularly with the first-generation antipsychotics.
- Many second-generation agents, such as *clozapine*, can ameliorate the negative symptoms to some extent.

Therapeutics

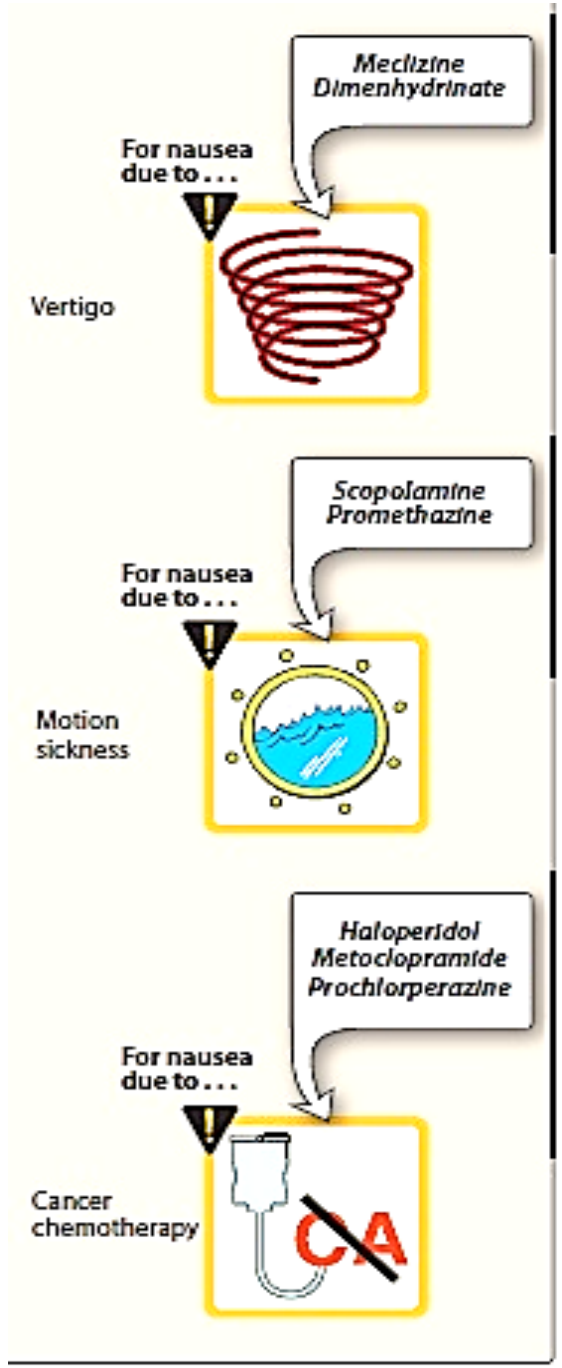
uses

1. Treatment of schizophrenia:

- The antipsychotics are considered the only efficacious pharmacological treatment for schizophrenia.
- The first-generation antipsychotics are most effective in treating positive symptoms of schizophrenia.
- The atypical antipsychotics with 5-HT2A receptor–blocking activity may be effective in many patients who are resistant to the traditional agents, especially in treating the negative symptoms of schizophrenia.

Prevention of nausea and vomiting:

- The older antipsychotics (most commonly, *prochlorperazine*) are useful in the treatment of drug-induced nausea.

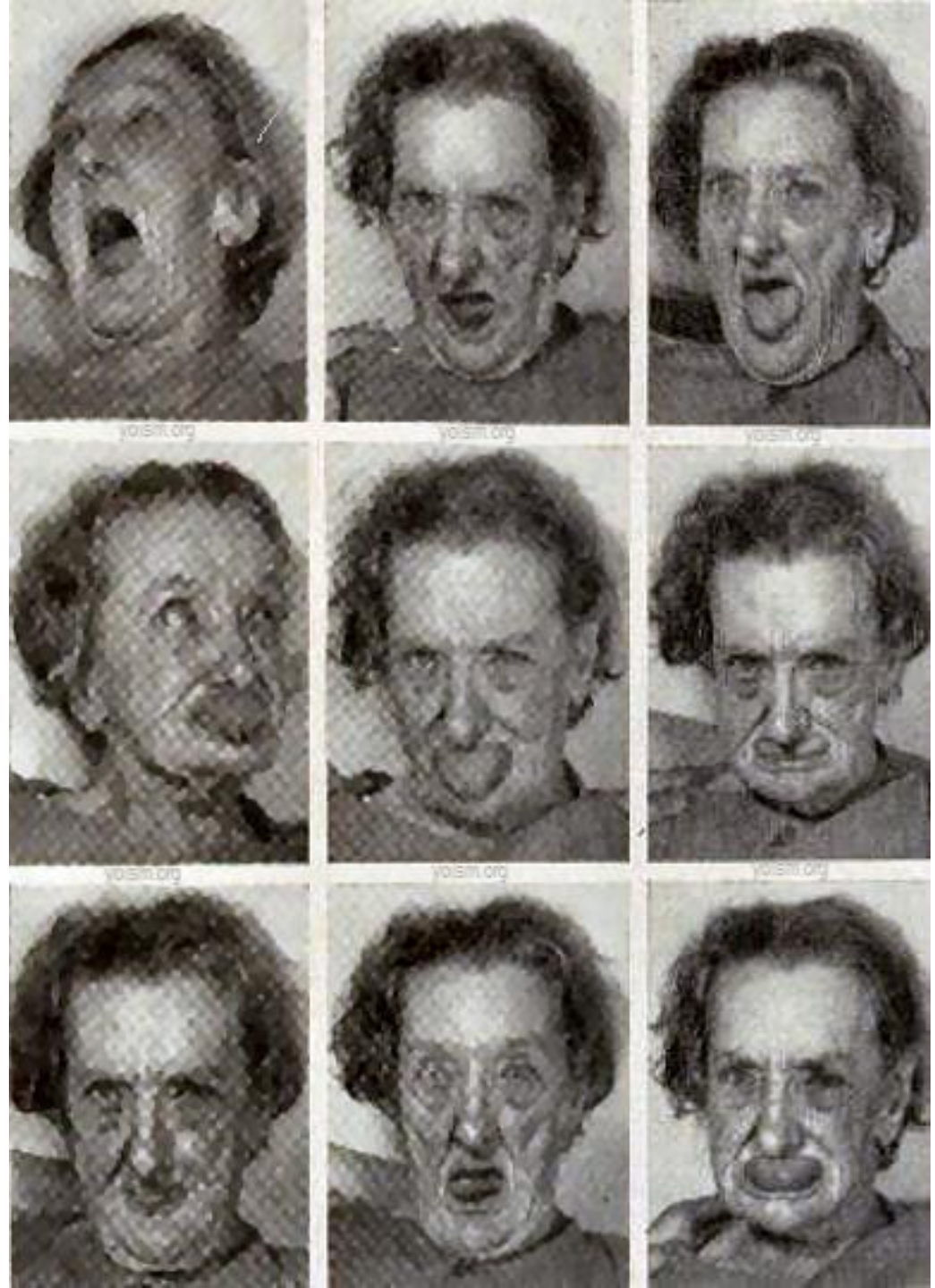


Extrapyramidal effects:

- Blocking dopamine receptors alters this balance, causing a relative excess of cholinergic influence, which results in extrapyramidal motor effects.
- The appearance of the movement disorders is generally time and dose dependent, with dystonias occurring within a few hours to days of treatment, followed by akathisias occurring within days to weeks.
- Parkinson like symptoms of bradykinesia, rigidity, and tremor usually occur within weeks to months of initiating treatment.

Tardive dyskinesia:

- Long-term treatment with antipsychotics can cause this motor disorder.
- Patients display involuntary movements, including bilateral and facial jaw movements and "fly-catching" motions of the tongue.
- A prolonged holiday from antipsychotics may cause the symptoms to diminish or disappear within a few months.
- However, in many individuals, tardive dyskinesia is irreversible and persists after discontinuation of therapy



BIPOLAR

Lows same as

MAJOR DEPRESSIVE DISORDER

(UNIPOLAR DEPRESSION)

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* Hopeless & Discouraged
* Lack energy & focus
* PHYSICAL SYMPTOMS
  - eating } too little or too much
  - Sleeping }

EXTREME LOWS

days to weeks

(HYPO) MANIC EPISODES

* Energetic
* overly happy / optimistic
* Euphoric
* High self-esteem

POSITIVE?

EXTREME HIGHS

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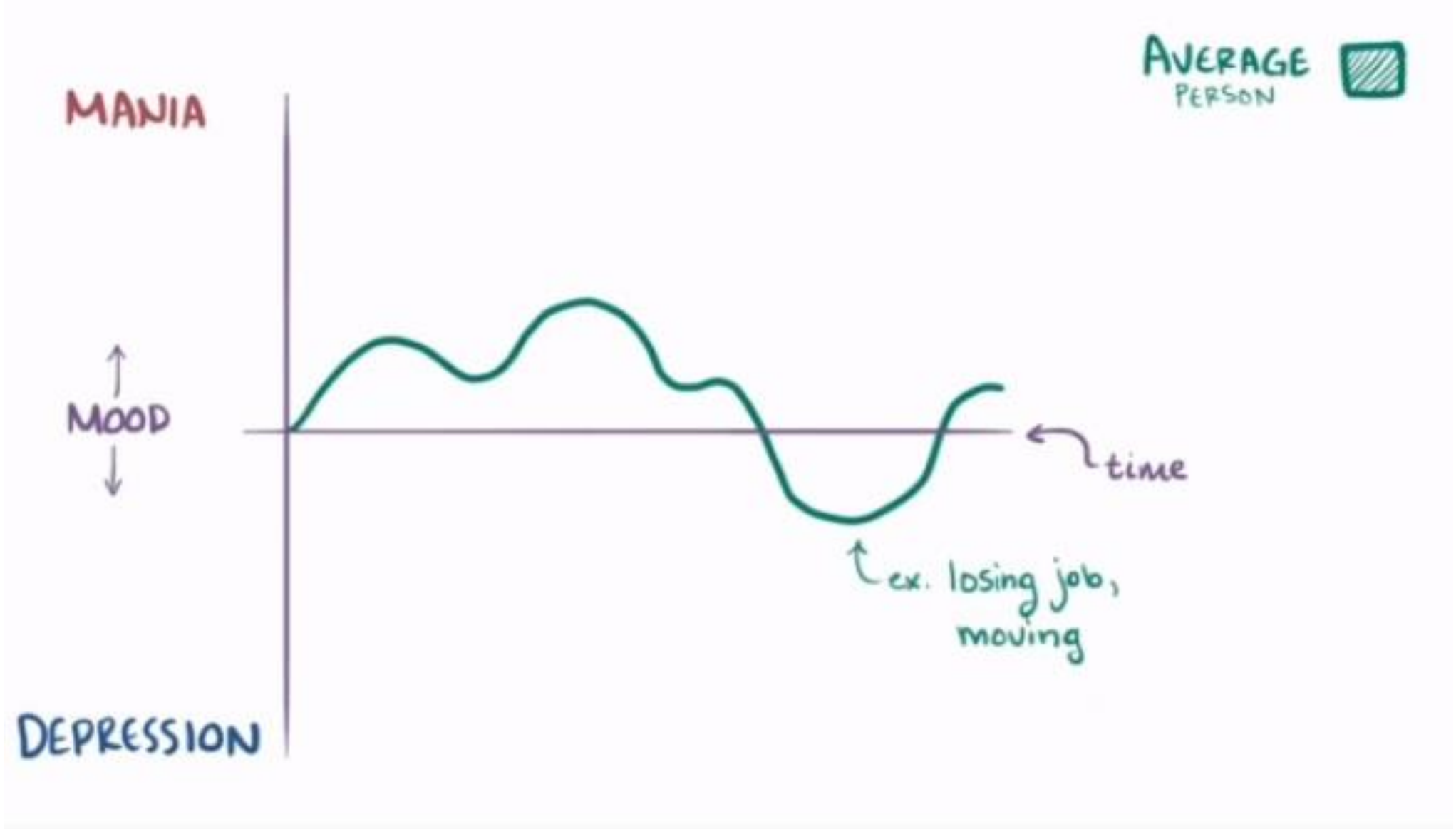
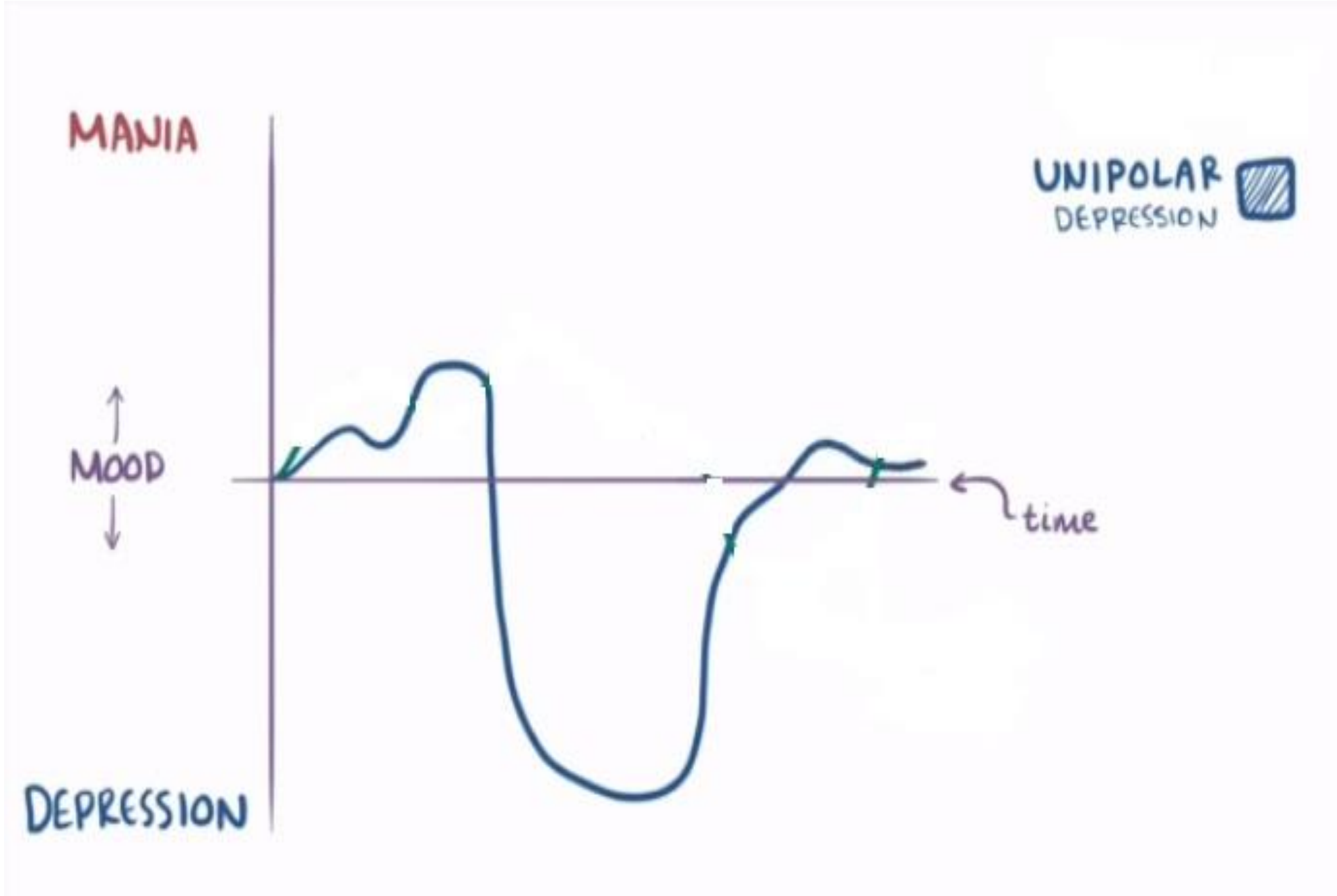
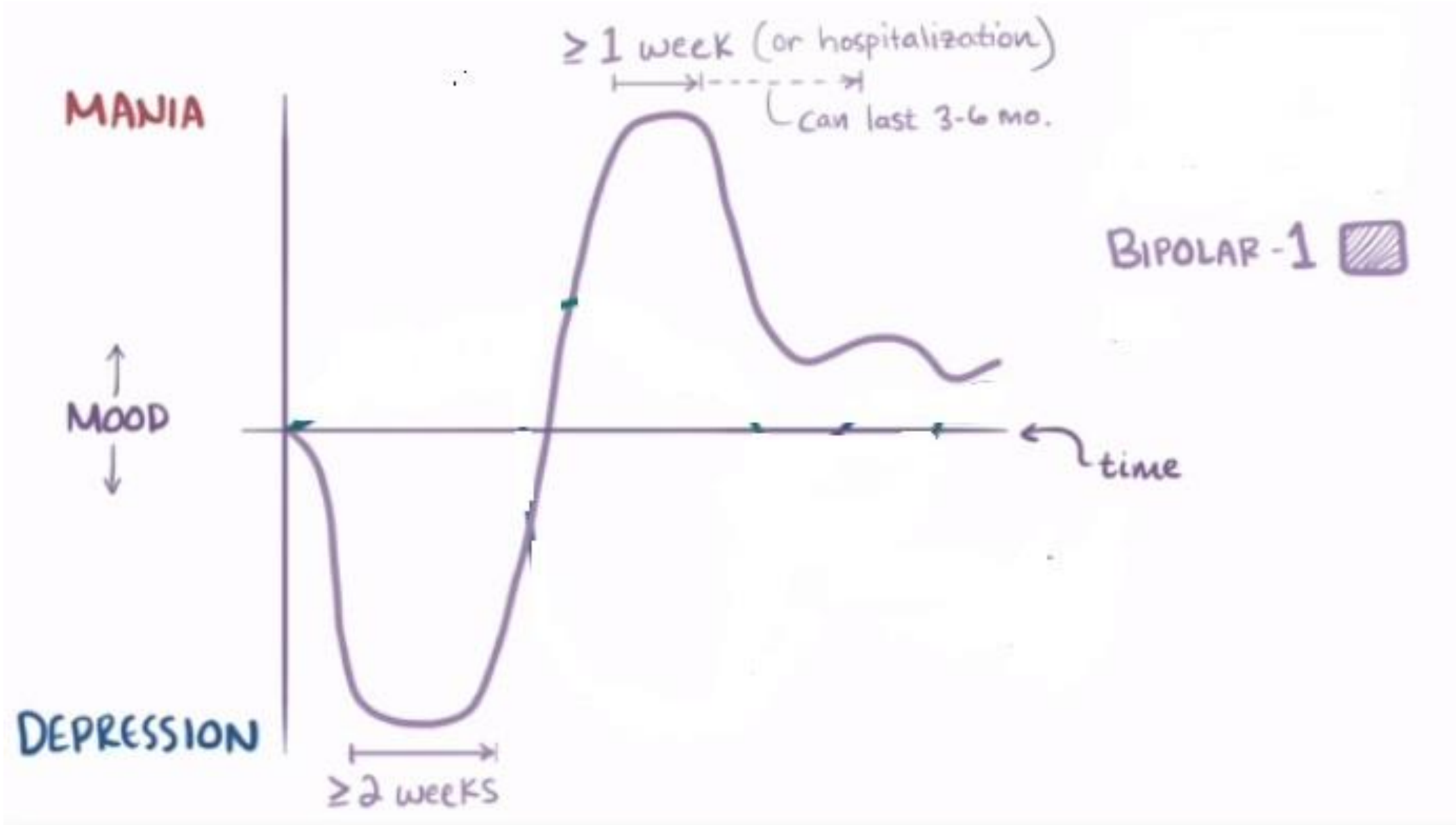
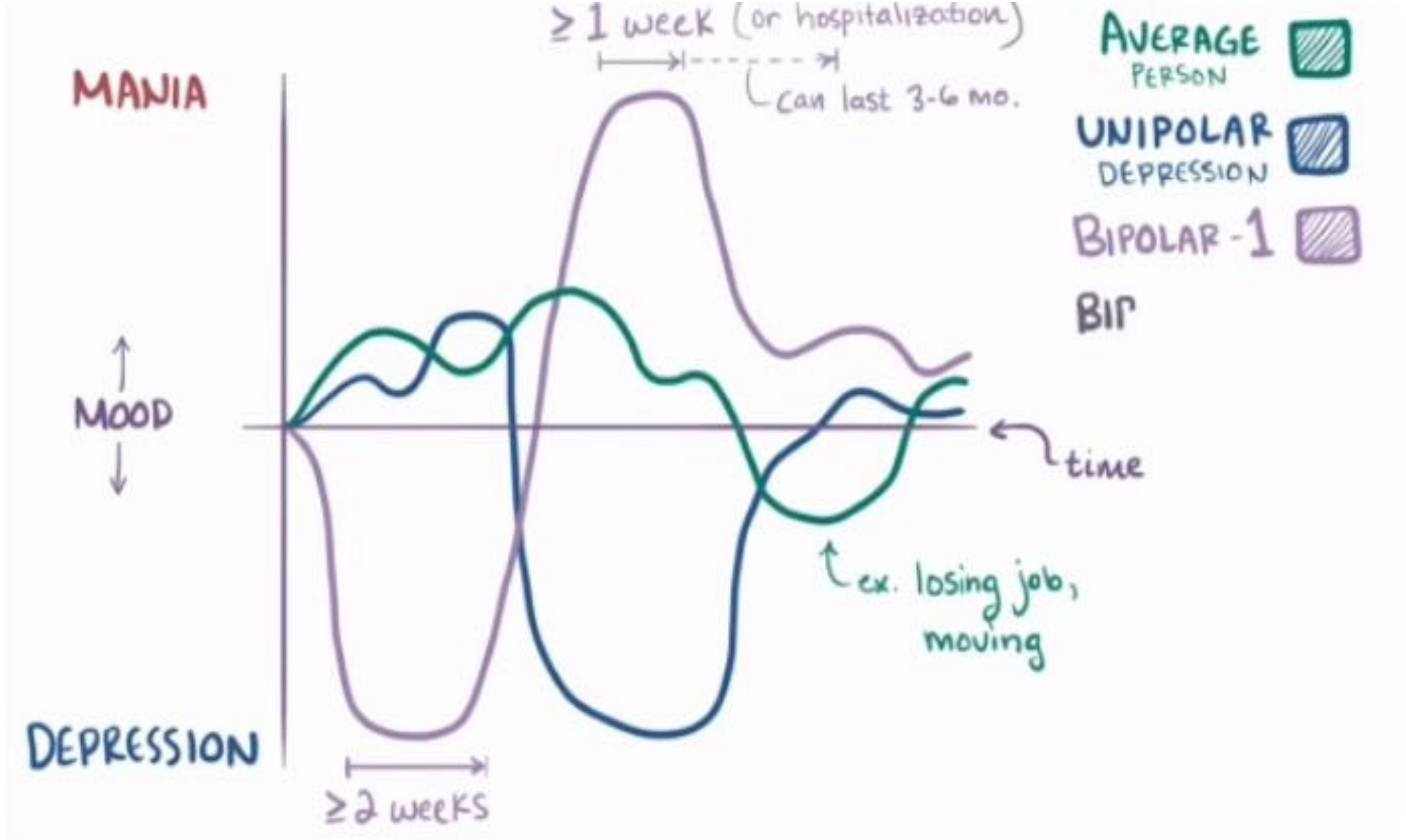

AVERAGE
PERSON
MANIA
MOOD
DEPRESSION
time
ex. losing job, moving


MANIA
UNIPOLAR
DEPRESSION
MOOD
time
DEPRESSION


≥ 1 week (or hospitalization)
can last 3-6 mo.
MANIA
BIPOLAR -1
MOOD
time
DEPRESSION
≥ 2 weeks


≥ 1 week (or hospitalization)
can last 3-6 mo.
MANIA
AVERAGE PERSON
UNIPOLAR DEPRESSION
BIPOLAR-1
BIP
MOOD
time
ex. losing job, moving
DEPRESSION
≥ 2 weeks

TRT

- Lithium carbonate continues to be used for the treatment of bipolar disorder (manic-depressive disease) although other drugs including valproic acid and carbamazepine are equally effective.
- Maintenance therapy with lithium decreases manic behavior and reduces both the frequency and the magnitude of mood swings.
- Antipsychotic agents and/or benzodiazepines are commonly required at the initiation of treatment because both lithium and valproic acid have a slow onset of action.
- Olanzapine and quetiapine are both approved as monotherapy for acute mania.