Anticonvulsant Drugs

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Partial seizures (Focal seizures)

- Occur in one part of the brain.
- Source of the seizure within the brain is localized.
- Consciousness preserved.

Types

1) Simple partial

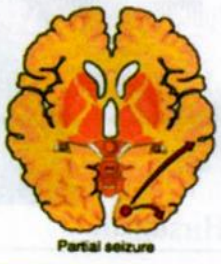
- No loss of consciousness.
- Clonic contraction of single or muscle group
- Sensory disturbance.

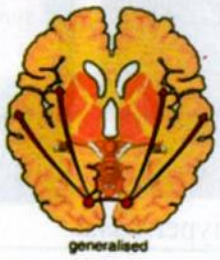
2) Complex partial

- Change in or loss of consciousness.
- Hallucination and mental distortion.
- Motor dysfunction e.g. chewing movement.

3) Partial with secondarily generalized

- Partial seizure that is followed by generalized attack due to spread of the discharge.





Generalized seizures

- Occur on both sides of the brain.
- Source of the seizure within the brain is distributed.
- Consciousness lost.

Types

1) Generalized Tonic-clonic (grand-mal)

- Sudden loss of consciousness.
- Followed by tonic (continuous contraction) then clonic (rapid contraction and relaxation) convulsion.
- The patient often sleeps then recovery.

2) Absence (petit mal) epilepsy

- Sudden loss of consciousness for short period
- Mild or no motor disturbances.

3) Myoclonic seizures

- Jerking of a single or muscle groups.
- Without loss of consciousness.

4) Atonic seizures

- Sudden loss of muscle tone, causing the person to fall to the ground.

5) Status epilepticus

- Sever sustained seizures, without period of recovery → Fatal.

FIRST-GENERATION AEDs

Phenobarbital
Primidone
Phenytoin
Ethosuximide
Carbamazepine
Valproic acid

SECOND-GENERATION AEDs

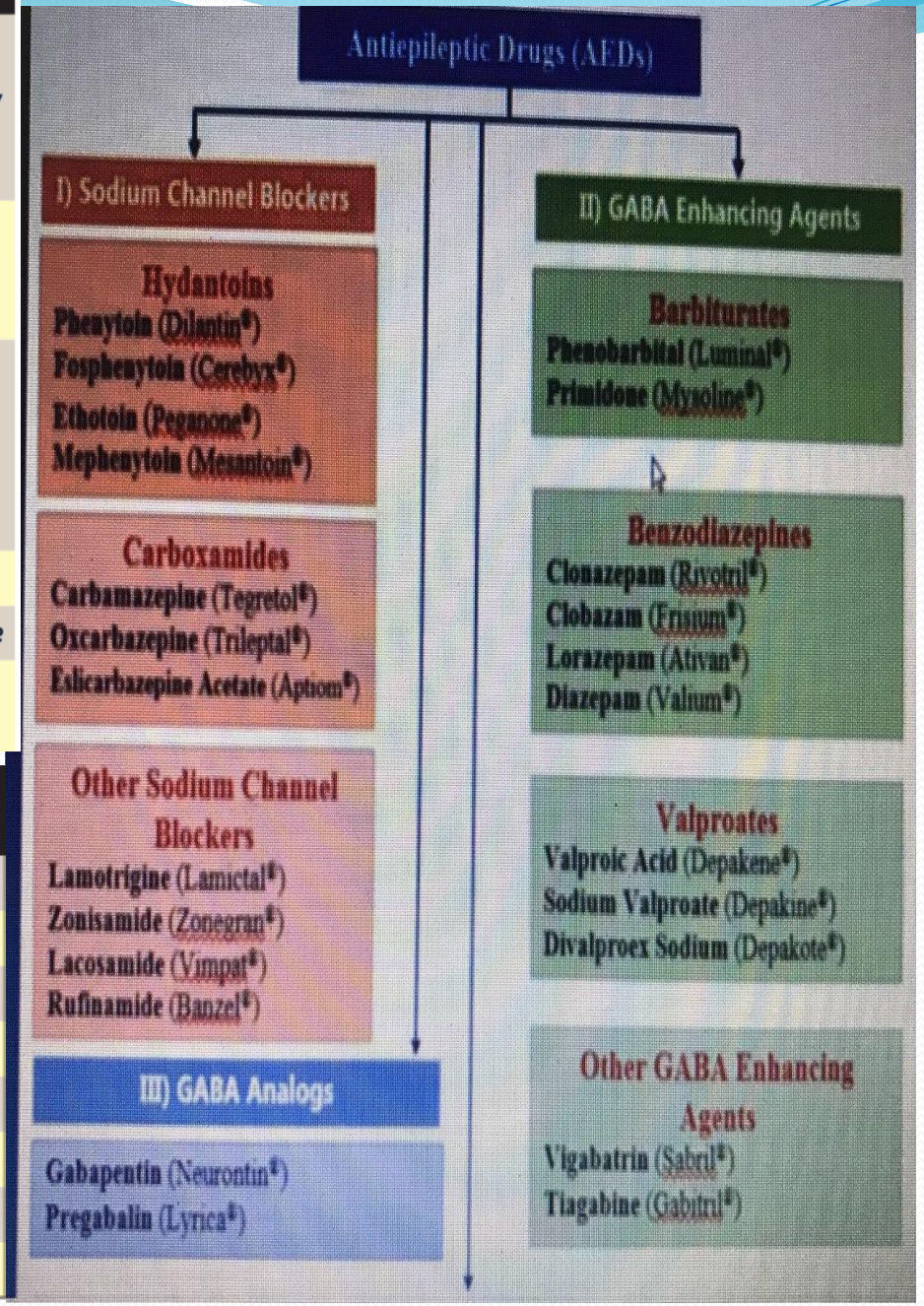
Felbamate
Gabapentin
Lamotrigine
Topiramate
Tiagabine
Levetiracetam
Oxcarbazepine
Zonisamide
Pregabalin

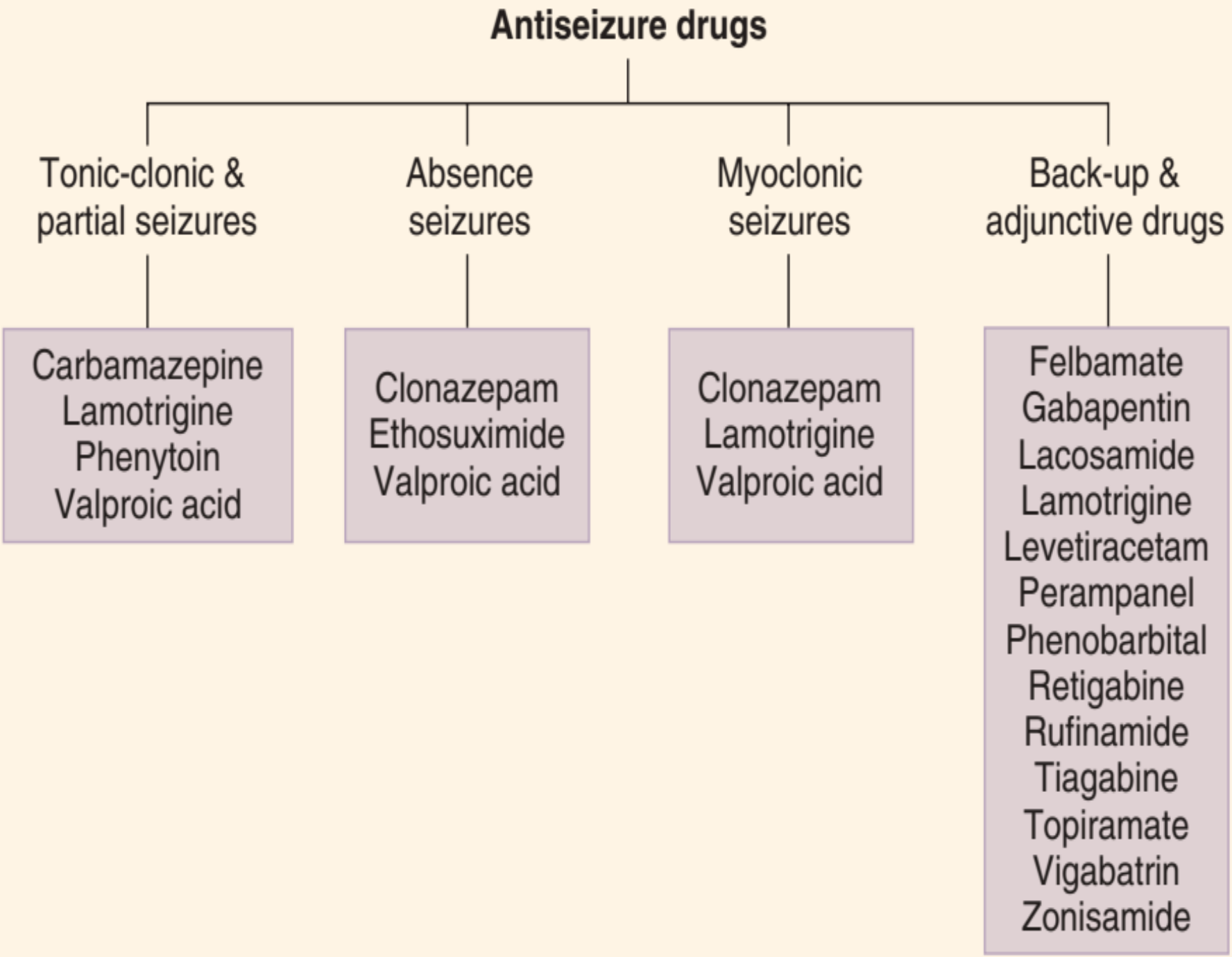
NEWEST DRUGS

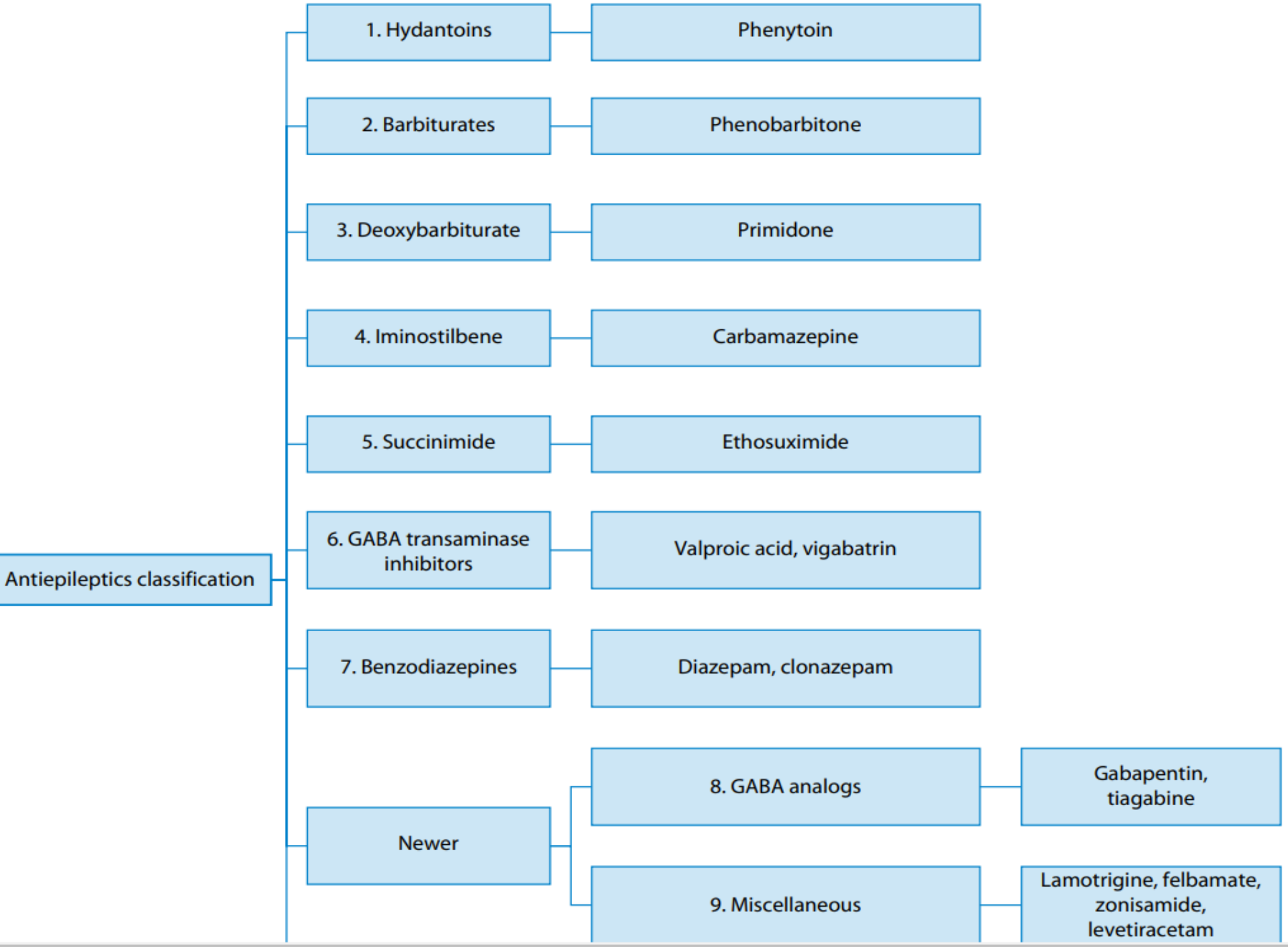
Rufinamide
Stiripentol
Lacosamide
Retigabine
Eslicarbazepine
Perampanel

MECHANISM OF ACTION	ANTIEPILEPTIC DRUG
Sodium channel blockers:	
Fast-inactivated state	*Phenytoin, carbamazepine, lamotrigine, oxcarbazepine, eslicarbazepine*
Slow-inactivated state	*Lacosamide*
Calcium channel blockers:	
Low voltage–activated channel	*Ethosuximide*
High voltage–activated channel	*Gabapentin, pregabalin*
GABA-ergic drugs:	
Prolong chloride channel opening	*Barbiturates*
Increase frequency of chloride channel opening	*Benzodiazepines*
Inhibit GABA-transaminase	*Vigabatrin*
Block synaptic GABA reuptake	*Tiagabine*
Synaptic vesicle protein 2A modulation	*Levetiracetam*
Carbonic anhydrase inhibition	*Acetazolamide, topiramate, zonisamide*
Multiple pharmacological targets	*Sodium valproate, felbamate, topiramate, zonisamide, rufinamide*

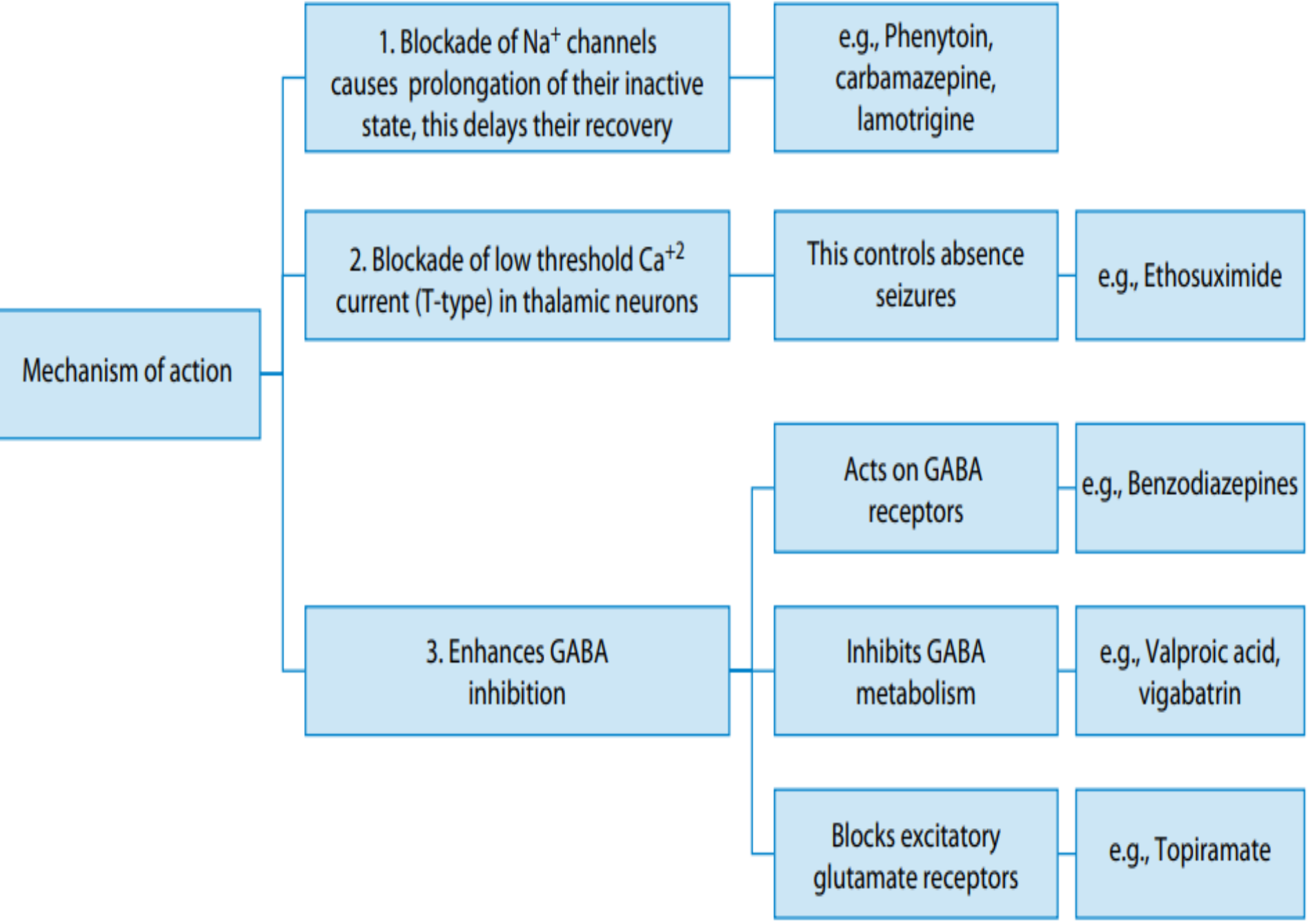
NARROW-SPECTRUM AEDs	BROAD-SPECTRUM AEDs
Phenytoin	*Valproic acid*
Phenobarbital	*Lamotrigine*
Carbamazepine	*Topiramate*
Oxcarbazepine	*Zonisamide*
Gabapentin	*Levetiracetam*
Pregabalin	*Clonazepam*
Vigabatrin	*Clobazam*
Tiagabine	*Felbamate*




Antiseizure drugs
Tonic-clonic & partial seizures
Absence seizures
Myoclonic seizures
Back-up & adjunctive drugs
Carbamazepine
Lamotrigine
Phenytoin
Valproic acid
Clonazepam
Ethosuximide
Valproic acid
Clonazepam
Lamotrigine
Valproic acid
Felbamate
Gabapentin
Lacosamide
Lamotrigine
Levetiracetam
Perampanel
Phenobarbital
Retigabine
Rufinamide
Tiagabine
Topiramate
Vigabatrin
Zonisamide


Antiepileptics classification
1. Hydantoins
Phenytoin
2. Barbiturates
Phenobarbitone
3. Deoxybarbiturate
Primidone
4. Iminostilbene
Carbamazepine
5. Succinimide
Ethosuximide
6. GABA transaminase inhibitors
Valproic acid, vigabatrin
7. Benzodiazepines
Diazepam, clonazepam
Newer
8. GABA analogs
Gabapentin, tiagabine
9. Miscellaneous
Lamotrigine, felbamate, zonisamide, levetiracetam

Antiepileptic Drug	Adverse Effects
Benzodiazepines	Sedation, tolerance, dependence
Carbamazepine	Diplopia, cognitive dysfunction, drowsiness, ataxia; rare occurrence of severe blood dyscrasias and Stevens-Johnson syndrome; induces hepatic drug metabolism; teratogenic potential
Ethosuximide	Gastrointestinal distress, lethargy, headache, behavioral changes
Felbamate	Aplastic anemia, hepatic failure
Gabapentin	Dizziness, sedation, ataxia, nystagmus; does not affect drug metabolism (pregabalin is similar)
Lamotrigine	Dizziness, ataxia, nausea, rash, rare Stevens-Johnson syndrome
Levetiracetam	Dizziness, sedation, weakness, irritability, hallucinations, and psychosis
Oxcarbazepine	Similar to carbamazepine, but hyponatremia is more common; unlike carbamazepine, does not induce drug metabolism
Perampanel	Dizziness, somnolence, headache; behavioral hostility, anger. Drug interactions with CYP inducers (carbamazepine, oxcarbazepine, phenytoin)
Phenobarbital	Sedation, cognitive dysfunction, tolerance, dependence, induction of hepatic drug metabolism; primidone is similar
Phenytoin	Nystagmus, diplopia, sedation, gingival hyperplasia, hirsutism, anemias, peripheral neuropathy, osteoporosis, induction of hepatic drug metabolism
Retigabine (ezogabine)	Dizziness, somnolence, confusion, dysarthria, pigment discoloration of retina and skin
Tiagabine	Abdominal pain, nausea, dizziness, tremor, asthenia; drug metabolism is not induced
Topiramate	Drowsiness, dizziness, ataxia, psychomotor slowing and memory impairment; paresthesias, weight loss, acute myopia
Valproic acid	Drowsiness, nausea, tremor, hair loss, weight gain, hepatotoxicity (infants), inhibition of hepatic drug metabolism
Vigabatrin	Sedation, dizziness, weight gain; visual field defects with long-term use, which may not be reversible
Zonisamide	Dizziness, confusion, agitation, diarrhea, weight loss, rash, Stevens-Johnson syndrome


Mechanism of action
1. Blockade of Na^+ channels causes prolongation of their inactive state, this delays their recovery
e.g., Phenytoin, carbamazepine, lamotrigine
2. Blockade of low threshold Ca^{+2} current (T-type) in thalamic neurons
This controls absence seizures
e.g., Ethosuximide
3. Enhances GABA inhibition
Acts on GABA receptors
e.g., Benzodiazepines
Inhibits GABA metabolism
e.g., Valproic acid, vigabatrin
Blocks excitatory glutamate receptors
e.g., Topiramate

Phenytoin and fosphenytoin

Phenytoin blocks voltage-gated sodium channels and slowing its rate of recovery. It is effective for treatment of focal and generalized tonic– clonic seizures and in the treatment of status epilepticus.

Phenytoin exhibits saturable enzyme metabolism resulting in nonlinear pharmacokinetic properties (small increases in the daily dose can produce large increases in plasma concentration, resulting in drug-induced toxicity.

Phenytoin can causing nystagmus and ataxia. Gingival hyperplasia may cause the gums to grow over the teeth. Long-term use may lead to development of peripheral neuropathies and osteoporosis.

Fosphenytoin is a prodrug that is rapidly converted to phenytoin in the blood within minutes. Fosphenytoin given (IM), phenytoin sodium should never be given IM, as it causes tissue damage and necrosis.

Carbamazepine

Carbamazepine blocks sodium channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus and preventing their spread.

Carbamazepine is effective for treatment of focal seizures and generalized tonic–clonic seizures, trigeminal neuralgia, and bipolar disorder.

Carbamazepine induces its own metabolism, resulting in lower total carbamazepine blood concentrations at higher doses. Carbamazepine is an inducer of the CYP1A2, CYP2C, and CYP3A. Hyponatremia may be noted in some patients, especially the elderly, and may necessitate a change in medication.

Oxcarbazepine

Oxcarbazepine is a prodrug that is rapidly reduced to the 10-monohydroxy (MHD) metabolite responsible for its anticonvulsant activity. MHD blocks sodium channels, preventing the spread of the abnormal discharge. It is also thought to modulate calcium channels. It is approved for use in adults and children with partial-onset seizures. Oxcarbazepine is a less potent inducer of CYP3A4 than carbamazepine. The adverse effect of hyponatremia limits its use in the elderly.

Eslicarbazepine

Eslicarbazepine acetate is a prodrug that is converted to the active metabolite eslicarbazepine (S- licarbazepine) by hydrolysis. It is a voltage-gated sodium channel blocker and is approved for partial-onset seizures in adults. The side effect profile includes dizziness, somnolence, diplopia, and headache.

Lamotrigine

Lamotrigine blocks sodium channels and high voltage-dependent calcium channels. Lamotrigine is effective in focal, generalized, absence seizures, and Lennox-Gastaut syndrome. It is also used to treat bipolar disorder. Lamotrigine dosages should be reduced when adding valproate to therapy. Slow titration is necessary with lamotrigine (particularly when adding lamotrigine to a regimen that includes valproate) due to risk of rash, which may progress to stevens- Johnson syndrome.

Lacosamide

Lacosamide affects voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing. Lacosamide binds to collapsin response mediator protein-2 (CRMP-2), a phosphoprotein involved in neuronal differentiation and control of axonal outgrowth. Lacosamide is approved for adjunctive treatment of focal seizures. The common adverse events include dizziness, headache, and fatigue.

Rufinamide

Rufinamide acts at sodium channels. It is approved for the adjunctive treatment of seizures associated with Lennox- Gastaut syndrome in children over age 4 years and in adults. Adverse effects include the potential for shortened QT intervals.

Zonisamide

Zonisamide is a sulfonamide derivative act by blockade of both voltage-gated sodium channels and T-type calcium currents. It has a limited amount of carbonic anhydrase activity. Zonisamide is approved for use in patients with focal epilepsy. Zonisamide may cause kidney stones. Oligohidrosis has been reported, and patients should be monitored for increased body temperature and decreased sweating.

Phenobarbital and primidone

The primary mechanism of action of phenobarbital is enhancement of the inhibitory effects of GABA-mediated neurons. Primidone is metabolized to phenobarbital (major) and phenylethylmalonamide, both with anticonvulsant activity. Phenobarbital is used primarily in the treatment of status epilepticus.

Benzodiazepines

Benzodiazepines bind to GABA inhibitory receptors to reduce firing rate. Most benzodiazepines are reserved for emergency or acute seizure treatment due to tolerance. Diazepam is also available for rectal administration to avoid or interrupt prolonged generalized tonic–clonic seizures or clusters when oral administration is not possible.

Valproic acid and divalproex

Possible mechanisms of action include sodium channel blockade, blockade of GABA transaminase, and action at the T-type calcium channels. These varied mechanisms provide a broad spectrum of activity against seizures. It is effective for the treatment of focal and primary generalized epilepsies.

Divalproex sodium is a combination of sodium valproate and valproic acid that is converted to valproate when it reaches the gastrointestinal tract. It was developed to improve gastrointestinal tolerance of valproic acid. All of the available salt forms are equivalent in efficacy (valproic acid and sodium valproate). Valproate inhibits metabolism of the CYP2C9. Teratogenicity is also of great concern.

Tiagabine

Tiagabine blocks GABA uptake into presynaptic neurons permitting more GABA to be available for receptor binding, and therefore, it enhances inhibitory activity. Tiagabine is effective as adjunctive treatment in partial-onset seizures.

Vigabatrin

Vigabatrin acts as an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T). GABA-T is the enzyme responsible for metabolism of GABA. Vigabatrin is associated with visual field loss ranging from mild to severe in 30% or more of patients.

Gabapentin

Gabapentin is an analog of GABA. It is approved as adjunct therapy for focal seizures and treatment of postherpetic neuralgia. Gabapentin is well tolerated by the elderly population with partial seizures due to its relatively mild adverse effects. It may also be a good choice for the older patient because there are few drug interactions.

Pregabalin

Pregabalin binds to the α2-δ site, subunit of voltage-gated calcium channels in the CNS, inhibiting excitatory neurotransmitter release. It has proven effects on focal-onset seizures, diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia. Weight gain and peripheral edema have been reported.

Ethosuximide

Ethosuximide reduces propagation of abnormal electrical activity in the brain, most likely by inhibiting T-type calcium channels. It is only effective in treating absence seizures.

Ezogabine

Ezogabine is thought to open voltage-gated M-type potassium channels leading to stabilization of the resting membrane potential. Side effects are urinary retention, QT interval prolongation, blue skin discoloration, and retinal abnormalities.

Felbamate

Felbamate act by blocking of voltage-dependent sodium channels on the N-methyl-d-aspartate (NMDA) glutamate receptor, blocking of calcium channels, and potentiating GABA action. It is an inhibitor of drugs metabolized by CYP2C19 and induces drugs metabolized by CYP3A4. It is reserved for use in refractory epilepsies (particularly Lennox- Gastaut syndrome) because of the risk of aplastic anemia and hepatic failure.

Levetiracetam

Levetiracetam is approved for adjunct therapy of focal onset, myoclonic, and primary generalized tonic–clonic seizures in adults and children. The exact mechanism of anticonvulsant action is unknown. Levetiracetam can cause mood alterations that may require a dose reduction or a change of medication.

Topiramate

Topiramate blocks voltage-dependent sodium channels, reduces high-voltage calcium currents (L type), is a carbonic anhydrase inhibitor, and may act at glutamate (NMDA) sites. Topiramate is effective for use in partial and primary generalized epilepsy. It is also approved for prevention of migraine. Adverse effects include somnolence, weight loss, and paresthesias. Renal stones, glaucoma, oligohidrosis (decreased sweating), and hyperthermia have also been reported.

Perampanel

Perampanel is a selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid antagonist (AMPA is a compound that is mimics the effects of the neurotransmitter glutamate) resulting in reduced excitatory activity. Perampanel has a long half-life. It is approved for adjunctive treatment of partial-onset seizures in patients 12 years or older.

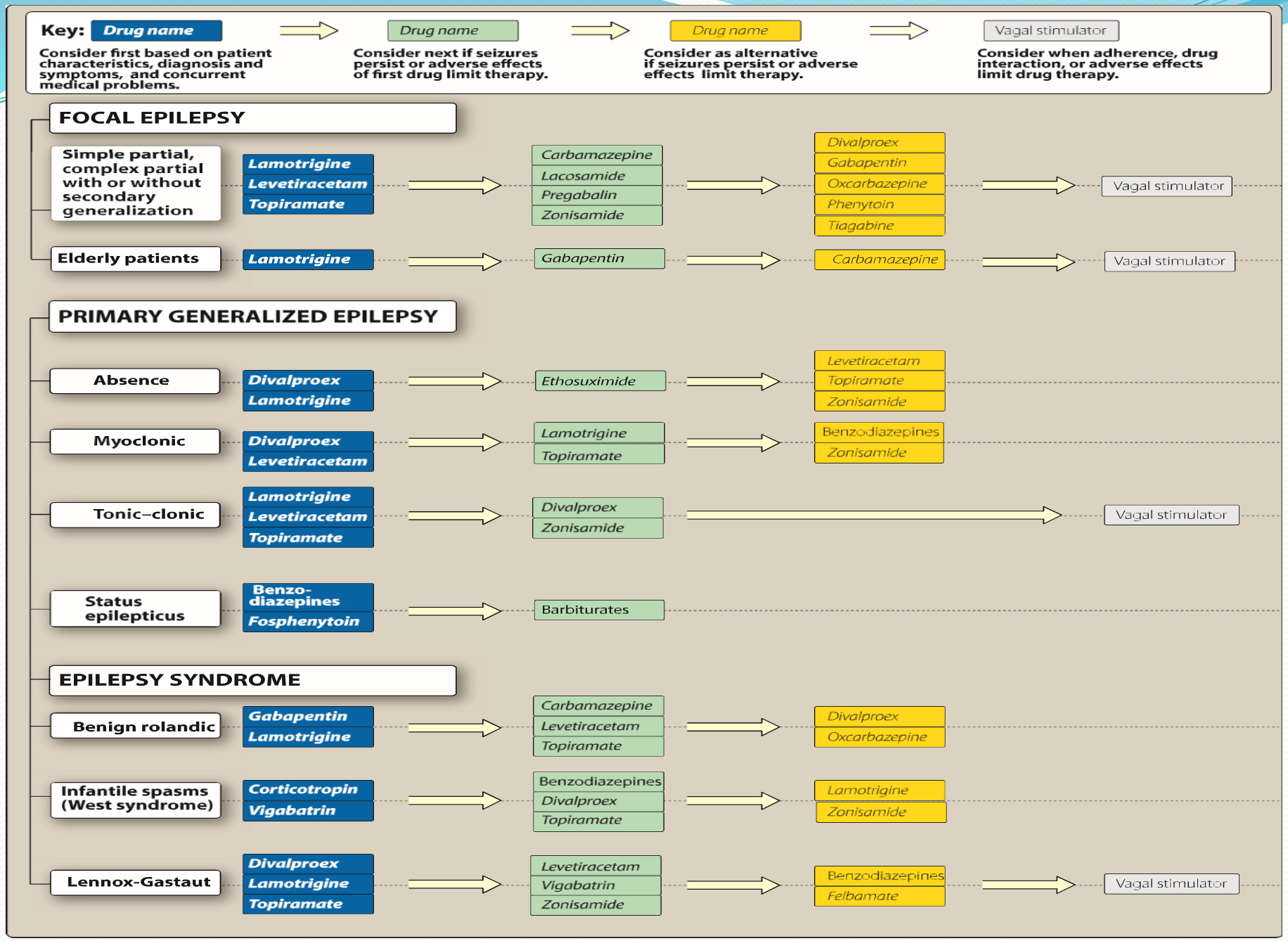
Stiripentol

Indicated for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate.

Stiripentol enhances GABAergic inhibition and prolongs the open duration of GABA-A receptor chloride channels by a barbiturate-like mechanism.

Acetazolamide

Carbonic anhydrase inhibitor used in the treatment of catamenial epilepsy.


Key: Drug name
Drug name
Drug name
Vagal stimulator
Consider first based on patient characteristics, diagnosis and symptoms, and concurrent medical problems.
Consider next if seizures persist or adverse effects of first drug limit therapy.
Consider as alternative if seizures persist or adverse effects limit therapy.
Consider when adherence, drug interaction, or adverse effects limit drug therapy.
FOCAL EPILEPSY
Simple partial, complex partial with or without secondary generalization
Lamotrigine
Levetiracetam
Topiramate
Carbamazepine
Lacosamide
Pregabalin
Zonisamide
Divalproex
Gabapentin
Oxcarbazepine
Phenytoin
Tiagabine
Vagal stimulator
Elderly patients
Lamotrigine
Gabapentin
Carbamazepine
Vagal stimulator
PRIMARY GENERALIZED EPILEPSY
Absence
Divalproex
Lamotrigine
Ethosuximide
Levetiracetam
Topiramate
Zonisamide
Myoclonic
Divalproex
Levetiracetam
Lamotrigine
Topiramate
Benzodiazepines
Zonisamide
Tonic–clonic
Lamotrigine
Levetiracetam
Topiramate
Divalproex
Zonisamide
Vagal stimulator
Status epilepticus
Benzo-diazepines
Fosphenytoin
Barbiturates
EPILEPSY SYNDROME
Benign rolandic
Gabapentin
Lamotrigine
Carbamazepine
Levetiracetam
Topiramate
Divalproex
Oxcarbazepine
Infantile spasms (West syndrome)
Corticotropin
Vigabatrin
Benzodiazepines
Divalproex
Topiramate
Lamotrigine
Zonisamide
Lennox-Gastaut
Divalproex
Lamotrigine
Topiramate
Levetiracetam
Vigabatrin
Zonisamide
Benzodiazepines
Felbamate
Vagal stimulator

Carbamazepine	**Blocks Na^+ channels**	Hyponatremia, drowsiness, fatigue, dizziness, and blurred vision. Drug use has also been associated with Stevens-Johnson syndrome. Blood dyscrasias: neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias.
Divalproex	**Multiple mechanisms of action**	Weight gain, easy bruising, nausea, tremor, hair loss, GI upset, liver damage, alopecia, and sedation. Hepatic failure, pancreatitis, and teratogenic effects have been observed. Broad spectrum of antiseizure activity.
Eslicarbazepine acetate	**Blocks Na^+ channels**	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
Ethosuximide	**Blocks Ca^{2+} channels**	Drowsiness, hyperactivity, nausea, sedation, GI upset, weight gain, lethargy, SLE, and rash. Blood dyscrasias can occur; periodic CBCs should be done. Abrupt discontinuance of drug may cause seizures.
Ezogabine	**Enhances K^+ channels**	Urinary retention, neuropsychiatric symptoms, dizziness, somnolence, QT prolongation, reports of blue skin discoloration, and retina changes.
Felbamate	**Multiple mechanisms of action**	Insomnia, dizziness, headache, ataxia, weight gain, and irritability. Aplastic anemia and hepatic failure. Broad spectrum of antiseizure activity. Requires patient to sign informed consent at dispensing.
Gabapentin	**Unknown**	Mild drowsiness, dizziness, ataxia, weight gain, and diarrhea. Few drug interactions. One hundred percent renal elimination.
Lacosamide	**Multiple mechanisms of action**	Dizziness, fatigue, and headache. Few drug interactions; Schedule V.
Lamotrigine	**Multiple mechanisms of action**	Nausea, drowsiness, dizziness, headache, and diplopia. Rash (Stevens-Johnson syndrome—potentially life threatening). Broad spectrum of antiseizure activity.
Levetiracetam	**Multiple mechanisms of action**	Sedation, dizziness, headache, anorexia, fatigue, infections, and behavioral symptoms. Few drug interactions. Broad spectrum of antiseizure activity.
Oxcarbazepine	**Blocks Na^+ channels**	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
Perampanel	**Blocks AMPA glutamate receptors**	Serious psychiatric and behavioral reactions, dizziness, somnolence, fatigue, gait disturbance, and falls, long half-life.
Phenytoin	**Blocks Na^+ channels**	Gingival hyperplasia, confusion, slurred speech, double vision, ataxia, sedation, dizziness, and hirsutism. Stevens-Johnson syndrome—potentially life threatening. Not recommended for chronic use. Primary treatment for status epilepticus (*fosphenytoin*).
Pregabalin	**Multiple mechanisms of action**	Weight gain, somnolence, dizziness, headache, diplopia, and ataxia. One hundred percent renal elimination.
Rufinamide	**Unknown**	Shortened QT interval. Multiple drug interactions.
Tiagabine	**Blocks GABA uptake**	Sedation, weight gain, fatigue, headache, tremor, dizziness, and anorexia. Multiple drug interactions.
Topiramate	**Multiple mechanisms of action**	Paresthesia, weight loss, nervousness, depression, anorexia, anxiety, tremor, cognitive complaints, headache, and oligohidrosis. Few drug interactions. Broad spectrum of antiseizure activity.
Vigabatrin	**Irreversible binding of GABA-T**	Vision loss, anemia, somnolence, fatigue, peripheral neuropathy, weight gain. Available only through SHARE pharmacies.
Zonisamide	**Multiple mechanisms of action**	Nausea, anorexia, ataxia, confusion, difficulty concentrating, sedation, paresthesia, and oligohidrosis. Broad spectrum of antiseizure activity.

Antidepressants

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DRUG AND CLASSIFICATION	UPTAKE INHIBITORS	UPTAKE INHIBITION
	Norepinephrine	Serotonin
Tricyclic antidepressants:		
Tertiary amines		
Amitriptyline	++	+++
Imipramine	++	+++
Trimipramine	+	0
Doxepin	+	++
Clomipramine	+++	+++
Secondary amines		
Desipramine	+++	0
Nortriptyline	++	+++
Protriptyline	+++	0
Dibenzoxazepine		
Amoxapine	++	+
Selective serotonin reuptake inhibitors:		
Fluoxetine	0/+	+++
Paroxetine	0	+++
Sertraline	0	+++
Citalopram	0	+++
Escitalopram	0	+++
Fluvaxamine	0	+++
Other antidepressants:		
Trazodone	0	++
Maprotiline	+++	0
Buprapion	0/+	0/+
Venlafaxine	++	+++
Nefazodone	0	0/+
Mirtazapine	0	0
Duloxetine	+++	+++

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

Fluoxetine
Paroxetine
Citalopram
Escitalopram
Fluvoxamine
Sertraline

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

Duloxetine
Venlafaxine
Desvenlafaxine
Levomilnacipran

ATYPICAL ANTIDEPRESSANTS

Bupropion
Mirtazapine
Nefazodone
Trazodone
Vilazodone
Vortioxetine

TRICYCLIC ANTIDEPRESSANTS (TCAs)

Amitriptyline
Nortriptyline
Protriptyline
Doxepin
Amoxapine
Imipramine
Desipramine
Clomipramine
Trimipramine
Maprotiline

MONOAMINE OXIDASE INHIBITORS (MAOIs)

Isocarboxazid
Phenelzine
Selegiline
Tranylcypromine

Depression

➢ Definition :-

- Depression is a mood disorder or affective disorder.
- Not neurodegenerative disease.

➢ Types of depression :-

1- Major depression disorder (MDD) (Unipolar or Clinical depression)

- Sad for a long period of time (Unipolar).
- Hate him-self and hopelessness.
- Despair.
- Loss of appetite (weight loss) or overeating (weight gain).
- Insomnia or hypersomnia.
- Reduction in libido (Reduced sex drive).
- Fatigue (loss of energy).
- Thoughts of suicide (thoughts of death).

2- Bipolar depression (Manic depression or Mania)

- Mood swings from overly "high" (manic) to overly "low" (depressed) → (Bipolar).
- Extremely elevated mood (Mania).
- Abnormally elevated energy levels.

3- Dysthymia or Chronic Depression

- Symptoms are milder than that of major depression.
- The depression symptoms can linger for a long period of time, often two years or longer.

4- Seasonal Affective Disorder (SAD)

- Depressive symptoms in the winter or autumn in every year.
- Due to the lessening of natural sunlight lead to hormone level change.
- Light therapy is a common treatment for seasonal affective disorder.
- When the depression season ends, they get well and function normally again.

5- Atypical Depression (AD)

- Characterized by over-eating and over-sleeping (Hypersomnia).
- This type of depression is mild and can easily be cured compared to other types.
- Have a hard time maintaining romantic relationships and are especially afraid of rejection by others (is more common in women than in men).

6- Psychotic major Depression (PMD)	
- Severe form of major depression. - Characterized by hallucinations, hears voices and delusional. - If a person with untreated major depression, may suffer from a psychotic depression.	
7- Postpartum Depression	
- Usually begins in the first few months after childbirth. - Characterized by feelings of extreme sadness, fatigue, loneliness, hopelessness, fears about hurting the baby.	
8- Premenstrual Dysphoric Disorder	**9- Situational Depression**
- End shortly after menstruation begins	- Such as job loss and death of a loved one

➢ Causes of Major Depression :-

- The exact causes of depression are complex and unknown.
- Some cases have a number of causes are →
  - **Genetic factors:**
    - E.g. → BDNF gene.
  - **Medical conditions:**
    - E.g. → Heart disease, stroke, diabetes, cancer, hypothyroidism, Parkinson's disease, and Alzheimer's disease.
  - **Medications:**
    - E.g. → Antihypertensive agent (used for long periods).
  - **Substance abuse:**
    - Alcohol abuse.
  - **Situations and environmental factors.**
  - **Poor sleep may cause major depression.**
  - **Diet:**
    - Deficiencies in certain vitamins, such as folic acid, vit.B12, and omega-3 fatty acids may cause depression.

*The amine hypothesis of mood:

-Brain amines particularly NE and 5HT are neurotransmitter in pathway that function in the expression of mood.

-Functional decrease in activity of such amines result in depression while functional increase in activity result in mood elevation.

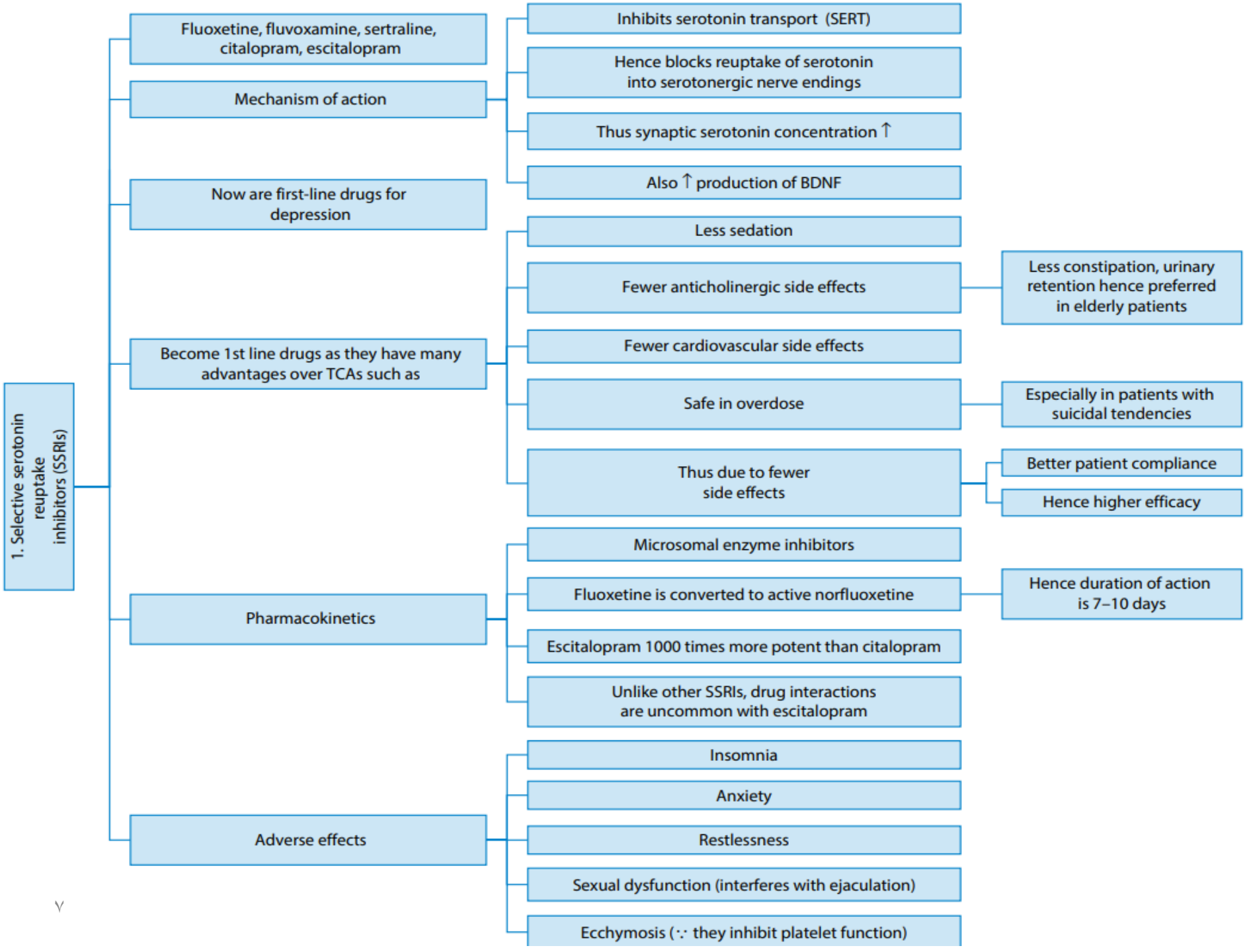
-Such hypothesis is based on studies showing that many antidepressants enhance the actions of CNS neurotransmitters NE and 5-HT

Antidepressant	ACh M	α_1	H_1	5-HT_2	NET	SERT
Amitriptyline	+++	+++	++	0/+	+	++
Amoxapine	+	++	+	+++	++	+
Bupropion	0	0	0	0	0/+	0
Citalopram, escitalopram	0	0	0		0	+++
Clomipramine	+	++	+	+	+	+++
Desipramine	+	+	+	0/+	+++	+
Doxepin	++	+++	+++	0/+	+	+
Fluoxetine	0	0	0	0/+	0	+++
Fluvoxamine	0	0	0	0	0	+++
Imipramine	++	+	+	0/+	+	++
Maprotiline	+	+	++	0/+	++	0
Mirtazapine	0	0	+++	+	+	0
Nefazodone	0	+	0	++	0/+	+
Nortriptyline	+	+	+	+	++	+
Paroxetine	+	0	0	0	+	+++
Protriptyline	+++	+	+	+	+++	+
Sertraline	0	0	0	0	0	+++
Trazodone	0	++	0/+	++	0	+
Trimipramine	++	++	+++	0/+	0	0
Venlafaxine	0	0	0	0	+	++
Vortioxetine[1]	ND	ND	ND	ND	+	+++

Antidepressant	Taken With	Consequence
Fluoxetine	Lithium, TCAs, warfarin	Increased blood levels of second drug
Fluvoxamine	Alprazolam, theophylline, TCAs, warfarin	Increased blood levels of second drug
MAO inhibitors	SSRIs, sympathomimetics, tyramine-containing foods	Hypertensive crisis, serotonin syndrome
Nefazodone	Alprazolam, triazolam, others (see text)	Increased blood levels of second drug
Paroxetine	Theophylline, TCAs, warfarin	Increased blood levels of second drug
Sertraline	TCAs, warfarin	Increased effects of second drug
TCAs	Ethanol, sedative hypnotics	Increased CNS depression

MAO, monoamine oxidase; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

A **serotonin syndrome**
was first described for an interaction between fluoxetine and an MAOI. This life-threatening syndrome includes severe muscle rigidity, myoclonus, hyperthermia, cardiovascular instability, and marked CNS stimulatory effects, including seizures. Drugs implicated include MAOIs, TCAs, dextromethorphan, meperidine, St. John's wort, and possibly illicit recreational drugs such as MDMA ("ecstasy"). Antiseizure drugs, muscle relaxants, and blockers of 5-HT receptors (eg, cyproheptadine) have been used in the management of the syndrome;


1. Selective serotonin reuptake inhibitors (SSRIs)
Fluoxetine, fluvoxamine, sertraline, citalopram, escitalopram
Mechanism of action
Inhibits serotonin transport (SERT)
Hence blocks reuptake of serotonin into serotonergic nerve endings
Thus synaptic serotonin concentration ↑
Also ↑ production of BDNF
Now are first-line drugs for depression
Become 1st line drugs as they have many advantages over TCAs such as
Less sedation
Fewer anticholinergic side effects
Less constipation, urinary retention hence preferred in elderly patients
Fewer cardiovascular side effects
Safe in overdose
Especially in patients with suicidal tendencies
Thus due to fewer side effects
Better patient compliance
Hence higher efficacy
Pharmacokinetics
Microsomal enzyme inhibitors
Fluoxetine is converted to active norfluoxetine
Hence duration of action is 7–10 days
Escitalopram 1000 times more potent than citalopram
Unlike other SSRIs, drug interactions are uncommon with escitalopram
Adverse effects
Insomnia
Anxiety
Restlessness
Sexual dysfunction (interferes with ejaculation)
Ecchymosis (∵ they inhibit platelet function)

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs):-

Actions

The SSRIs block the reuptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft.

SSRIs, typically take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more. A patient must be treated with an adequate dosage for at least 6 weeks before considering changing the treatment.

Therapeutic uses

The primary indication for SSRIs is depression. A number of other psychiatric disorders also respond favorably to SSRIs, including obsessive–compulsive disorder, panic disorder, generalized anxiety disorder, post-traumatic stress disorder, social anxiety disorder, premenstrual dysphoric disorder, and bulimia nervosa (only fluoxetine is approved for bulimia).

Fluoxetine has the longest half-life (50 hours), and the half-life of its active metabolite S- norfluoxetine is quite long, averaging 10 days. Fluoxetine and paroxetine are potent inhibitors of a CYP450 isoenzyme (CYP2D6).

Adverse effects

1. Sleep disturbances: Paroxetine and fluvoxamine are more sedating than activating. Conversely, patients who are fatigued or complaining of excessive somnolence may benefit from fluoxetine or sertraline.

2. Sexual dysfunction: Which may include loss of libido, delayed ejaculation, and anorgasmia.

3. Use in children and teenagers: Fluoxetine, sertraline, and fluvoxamine are approved for use in children to treat obsessive–compulsive disorder, and fluoxetine and escitalopram are approved to treat childhood depression.

4. Overdose and toxicity: Citalopram, which may cause QT prolongation. Seizures are a possibility because all antidepressants may lower the seizure threshold. SSRIs have the potential to cause serotonin syndrome, especially when used in the presence of an MAOI or other highly serotonergic drug.

5. Discontinuation syndrome: Fluoxetine has the lowest risk of causing an SSRI discontinuation syndrome due to its longer half-life and active metabolite. Possible signs and symptoms of SSRI discontinuation syndrome include headache, malaise and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern. These effects may persist up to 2 months. SSRIs should be gradually withdrawn to minimize these effects.

*Drugs interaction with SSRIs:-

1-Serotonin syndrome.

2-CNS toxicity if given with dopaminergic drugs e.g. selegiline.

3- failure of anti-epileptic drugs (SSRIs lower convulsion threshold.

4-Enzyme inhibition by fluoxetine and paroxetine may cause:-

-exaggeration of antihypertensive effect of diltiazem and amlodipine metoprolol,

-augment effects of alcohol, tramadol and methadone

TRICYCLIC ANTIDEPRESSANTS

The TCAs include the tertiary amines imipramine (the prototype drug), amitriptyline, clomipramine, doxepin , and trimipramine, and the secondary amines desipramine and nortriptyline (the N-demethylated metabolites of imipramine and amitriptyline, respectively) and protriptyline. Maprotiline and amoxapine are related “tetracyclic” antidepressant agents and are commonly included in the general class of TCAs.

Mechanism of action

1. Inhibition of neurotransmitter reuptake: TCAs and amoxapine are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals. Maprotiline and desipramine are relatively selective inhibitors of norepinephrine reuptake.

2. Blocking of receptors: TCAs also block serotonergic, α-adrenergic, histaminic, and muscarinic receptors. Amoxapine also blocks 5-HT2 and dopamine D2 receptors.

Actions

The TCAs improve mood depression. The onset of the mood elevation is slow, requiring 2 weeks or longer.

Therapeutic uses

1-The TCAs are effective in treating moderate to severe depression.

2-Some patients with panic disorder also respond to TCAs.

3- Imipramine is used as an alternative to desmopressin or nonpharmacologic therapies (enuresis alarms) in the treatment of bedwetting in children.

4- The TCAs, particularly amitriptyline, have been used to help prevent migraine headache and treat chronic pain syndromes (for example, neuropathic pain) in a number of conditions for which the cause of pain is unclear.

5- Low doses of TCAs, especially doxepin, can be used to treat insomnia.

Adverse effects

Blockade of muscarinic receptors leads to blurred vision, xerostomia, urinary retention, sinus tachycardia, constipation, and aggravation of angle-closure glaucoma. These agents affect cardiac conduction similar to typical of class IA antiarrhythmics (quinidine) and may precipitate life-threatening arrhythmias in an overdose situation.

The TCAs also block α-adrenergic receptors, causing orthostatic hypotension, dizziness, and reflex tachycardia. Sedation is related to the ability of these drugs to block histamine H1 receptors. Weight gain is a common adverse effect of the TCAs. Sexual dysfunction occurs in a minority of patients, and the incidence is lower than that associated with the SSRIs.

All antidepressants, including TCAs, should be used with caution in patients with bipolar disorder, even during their depressed state, because antidepressants may cause a switch to manic behavior.

The TCAs have a narrow therapeutic index (for example, five- to six fold the maximal daily dose of imipramine can be lethal).

Depressed patients who are suicidal should be given only limited quantities of these drugs and be monitored closely.

*Drugs interaction with TCAs:-

1-Pronounced sedation with drugs which have sedative effects e.g. opioid analgesics, antihistamines, anxiolytics & alcohol

2-Prolongation of QT interval with

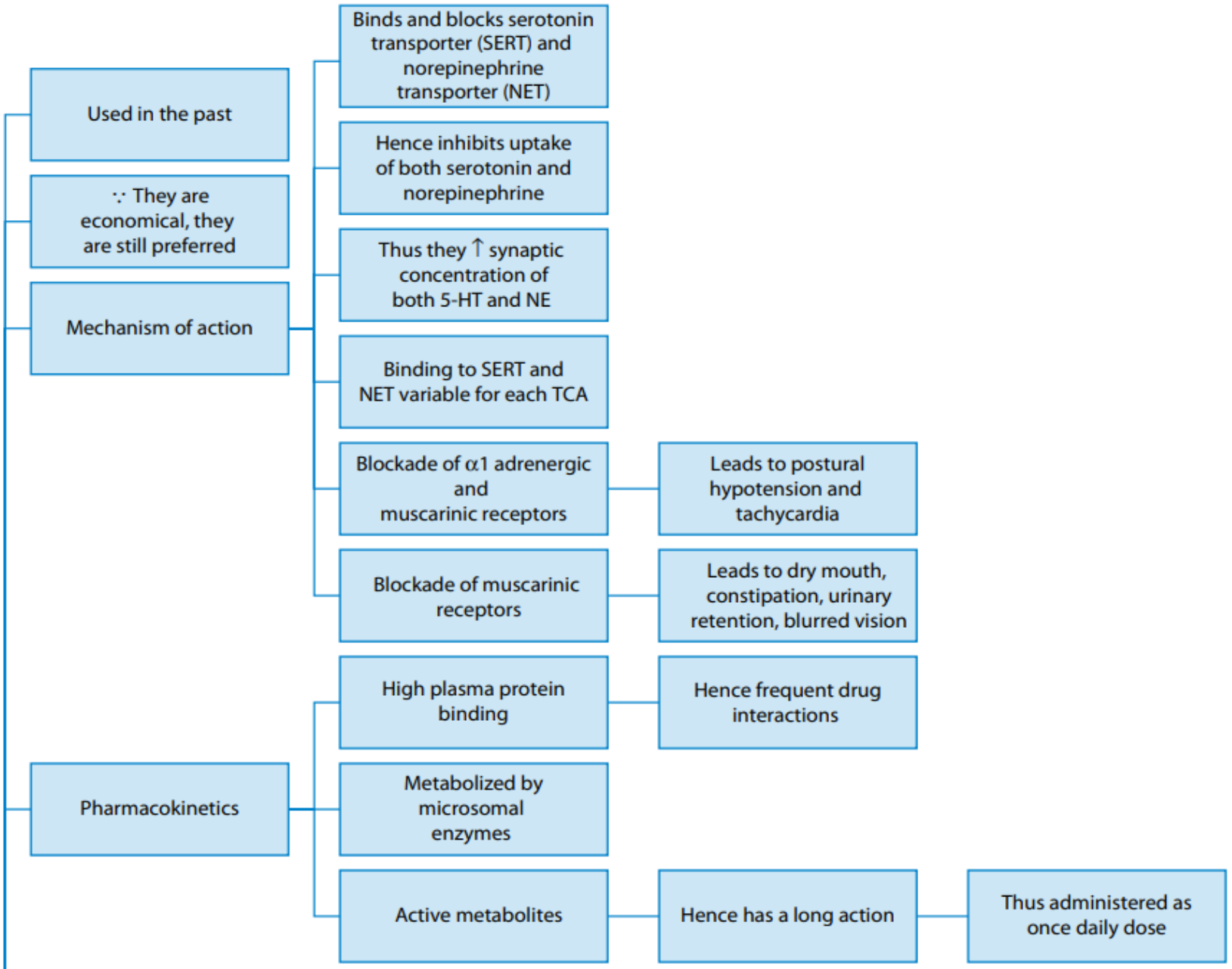
- cardiovascular drugs e.g. amiodarone, disopyramide, and procainamide

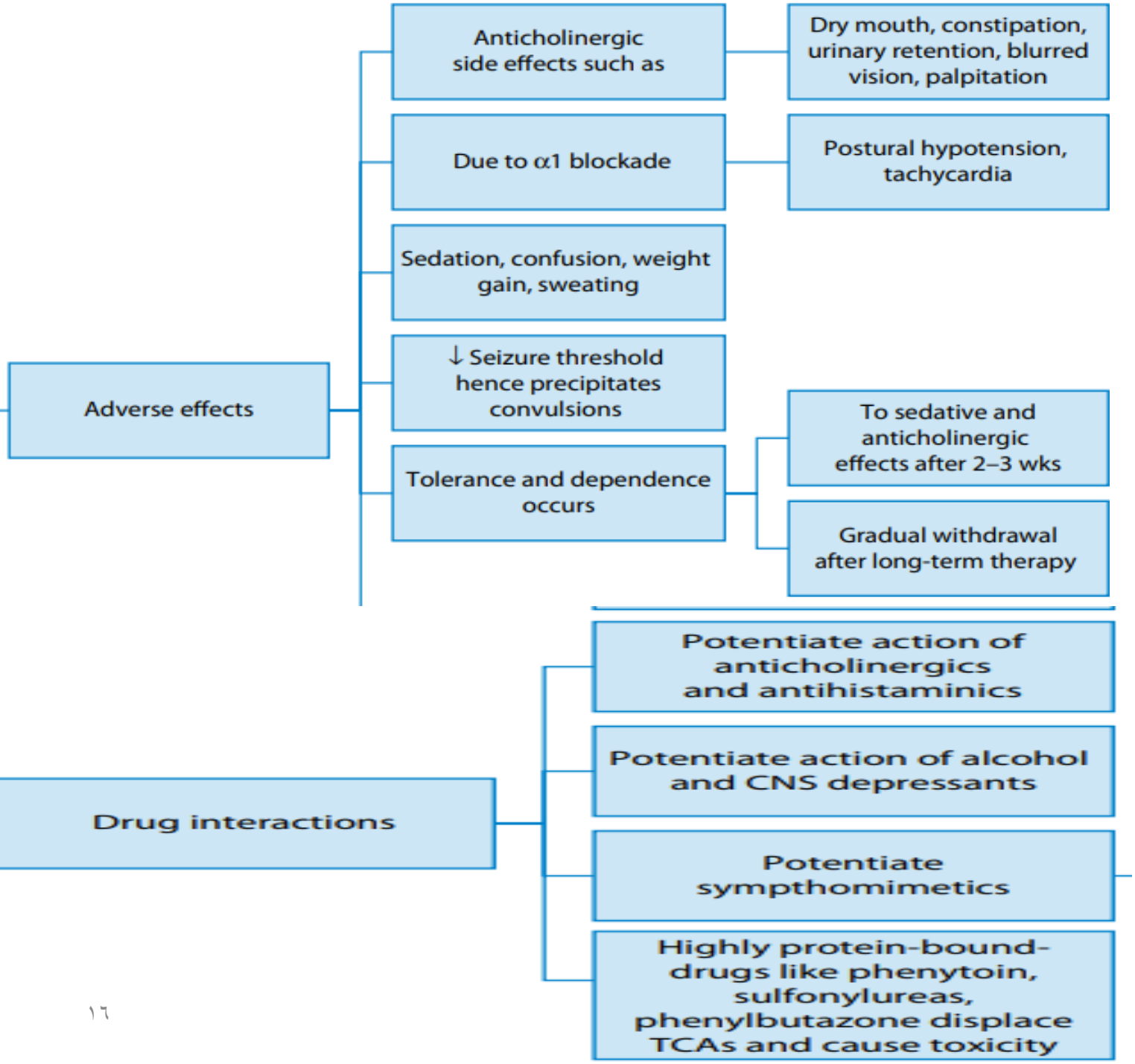
-antipsychotic drugs e.g. pimozide and thioridazine

3-Potentiate the effect of catecholamines and other direct acting sympathomimetics

4-CNS toxicity if given with dopaminergic drugs e.g. selegiline

TRICYCLIC ANTIDEPRESSANTS (TCAs)




Adverse effects
Anticholinergic side effects such as
Dry mouth, constipation, urinary retention, blurred vision, palpitation
Due to α1 blockade
Postural hypotension, tachycardia
Sedation, confusion, weight gain, sweating
↓ Seizure threshold hence precipitates convulsions
Tolerance and dependence occurs
To sedative and anticholinergic effects after 2–3 wks
Gradual withdrawal after long-term therapy
Drug interactions
Potentiate action of anticholinergics and antihistaminics
Potentiate action of alcohol and CNS depressants
Potentiate sympthomimetics
Highly protein-bound-drugs like phenytoin, sulfonylureas, phenylbutazone displace TCAs and cause toxicity

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS

Venlafaxine, desvenlafaxine, levomilnacipran, and duloxetine inhibit the reuptake of both serotonin and norepinephrine and, thus, are termed SNRIs.

A. Venlafaxine and desvenlafaxine

Venlafaxine is an inhibitor of serotonin reuptake and, at medium to higher doses, is an inhibitor of norepinephrine reuptake. Desvenlafaxine is the active, demethylated metabolite of venlafaxine. The most common side effects of venlafaxine are nausea, headache, sexual dysfunction, dizziness, insomnia, sedation, and constipation. At high doses, there may be an increase in blood pressure and heart rate.

B. Duloxetine

Duloxetine inhibits serotonin and norepinephrine reuptake at all doses. GI side effects are common with duloxetine, including nausea, dry mouth, and constipation. Insomnia, dizziness, somnolence, sweating, and sexual dysfunction are also seen. Duloxetine may increase blood pressure or heart rate.

C. Levomilnacipran

Levomilnacipran is an enantiomer of milnacipran.

ATYPICAL ANTIDEPRESSANTS

This group include bupropion, mirtazapine, nefazodone, trazodone, vilazodone, and vortioxetine.

A. Bupropion

Bupropion is a weak dopamine and norepinephrine reuptake inhibitor that is used to alleviate the symptoms of depression. Bupropion is also useful for decreasing cravings and attenuating withdrawal symptoms of nicotine in patients trying to quit smoking.
Side effects may include dry mouth, sweating, nervousness, tremor, and a dose dependent increased risk for seizures. It has a very low incidence of sexual dysfunction.

B. Mirtazapine

Mirtazapine enhances serotonin and norepinephrine neurotransmission by serving as an antagonist at central presynaptic α2 receptors. Additionally, some of the antidepressant activity may be related to antagonism at 5-HT2 receptors. It is sedating because of its potent antihistaminic activity. Sedation, increased appetite, and weight gain frequently occur

C. Nefazodone and trazodone

These drugs are weak inhibitors of serotonin reuptake and are also antagonists at the postsynaptic 5-HT2a receptor. Both agents are highly sedating, probably because of their potent histamine

H1-blocking activity. Trazodone is commonly used off-label for the management of insomnia. These drugs cause gastrointestinal disturbances. Sexual effects are limited except that trazodone has been associated with priapism in men. Nefazodone has been associated with a rare risk for hepatotoxicity. Both agents also have mild-to-moderate α1 receptor antagonism, contributing to orthostasis and dizziness.

D. Vilazodone

Vilazodone is a serotonin reuptake inhibitor and a 5-HT1a receptor partial agonist. The adverse effect profile of vilazodone is similar to the SSRIs, including risk for discontinuation syndrome if abruptly stopped.

E. Vortioxetine

Vortioxetine utilizes a combination of serotonin reuptake inhibition, 5-HT1a agonism, and 5-HT3 and 5-HT7 antagonism as its suggested mechanisms of action to treat depression. The common adverse effects include nausea, constipation, and sexual dysfunction, which may be expected due to its serotonergic mechanism.

MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase (MAO) is a mitochondrial enzyme found in nerve and other tissues, such as the gut and liver. In the neuron, MAO functions as a "safety valve" to oxidatively deaminate and inactivate any excess neurotransmitters (for example, norepinephrine, dopamine, and serotonin) that may leak out of synaptic vesicles when the neuron is at rest. The MAOIs may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitters to escape degradation and, therefore, to accumulate within the presynaptic neuron and leak into the synaptic space. The four MAOIs currently available for the treatment of depression include phenelzine, tranylcypromine, isocarboxazid, and selegiline. [Note: Selegiline is also used for the treatment of Parkinson's disease. It is the only antidepressant available in a transdermal delivery system.]

Mechanism of action

Most MAOIs, such as phenelzine, form stable complexes with the enzyme, causing irreversible inactivation. This results in increased stores of norepinephrine, serotonin, and dopamine within the neuron and subsequent diffusion of excess neurotransmitter into the synaptic space. These drugs inhibit not only MAO in the brain but also MAO in the liver and gut that catalyzes oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods. The MAOIs, therefore, show a high incidence of drug–drug and drug–food interactions. Selegiline administered as the transdermal patch may produce less inhibition of gut and hepatic MAO at low doses because it avoids first-pass metabolism.

Actions

Although MAO is fully inhibited after several days of treatment, the antidepressant action of the MAOIs, like that of the SSRIs, SNRIs, and TCAs, is delayed several weeks. Selegiline and tranylcypromine have an amphetamine-like stimulant effect that may produce agitation or insomnia.

Therapeutic uses

MAOIs are considered last-line agents in many treatment settings.

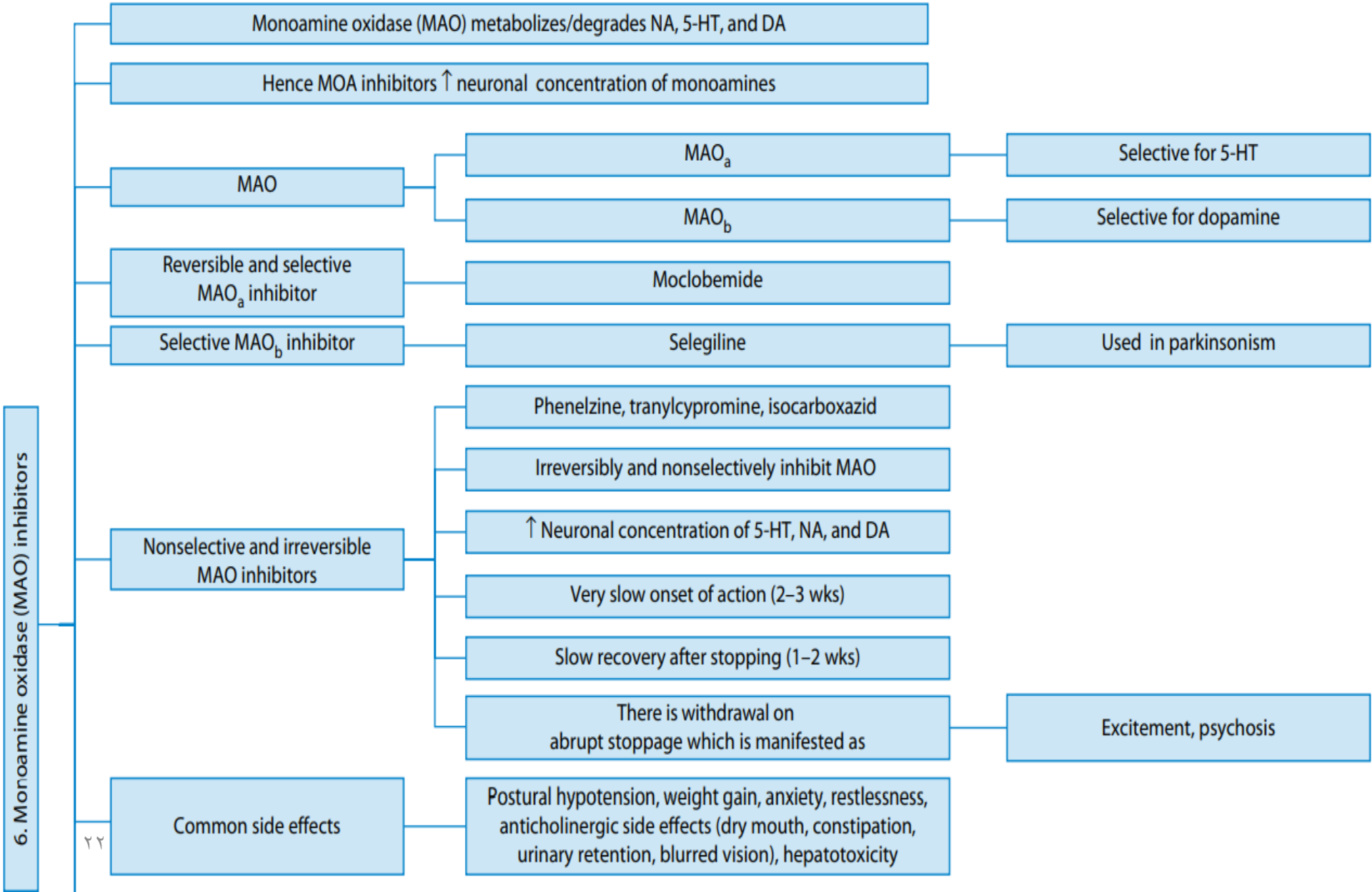
Adverse effects

Tyramine, which is contained in foods, such as aged cheeses and meats, liver, pickled or smoked fish, and red wines, is normally inactivated by MAO in the gut. Individuals receiving an MAOI are unable to degrade tyramine obtained from the diet. Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in a hypertensive crisis, with signs and symptoms such as occipital headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, and, possibly, stroke.

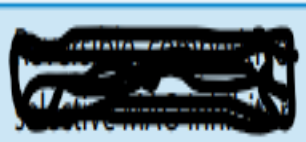
Other include drowsiness, orthostatic hypotension, blurred vision, dry mouth, and constipation.

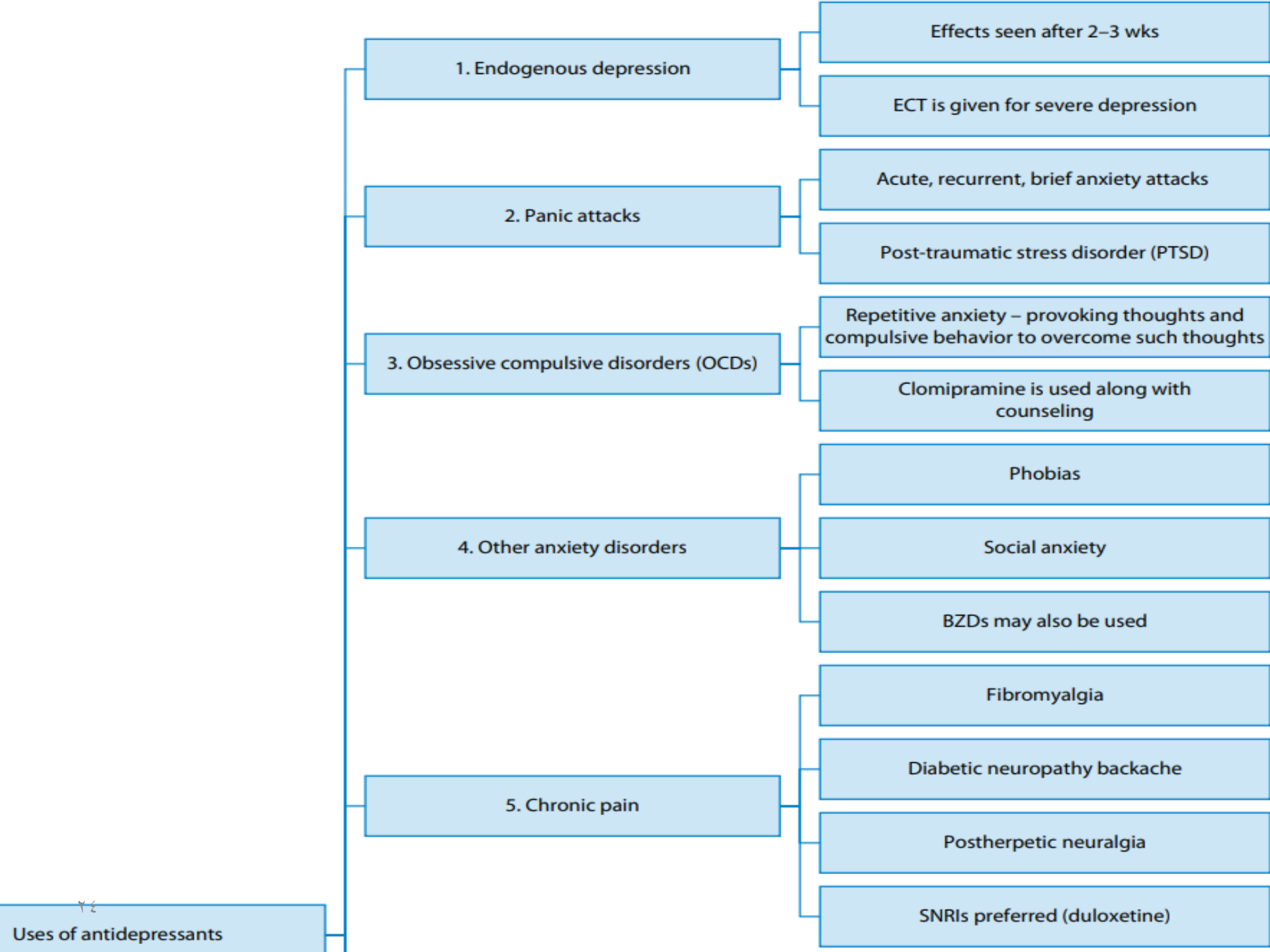
SSRIs should not be coadministered with MAOIs due to the risk of serotonin syndrome. Both SSRIs and MAOIs require a washout period of at least 2 weeks before the other type is administered, with the exception of fluoxetine, which should be discontinued at least 6 weeks before an MAOI is initiated.

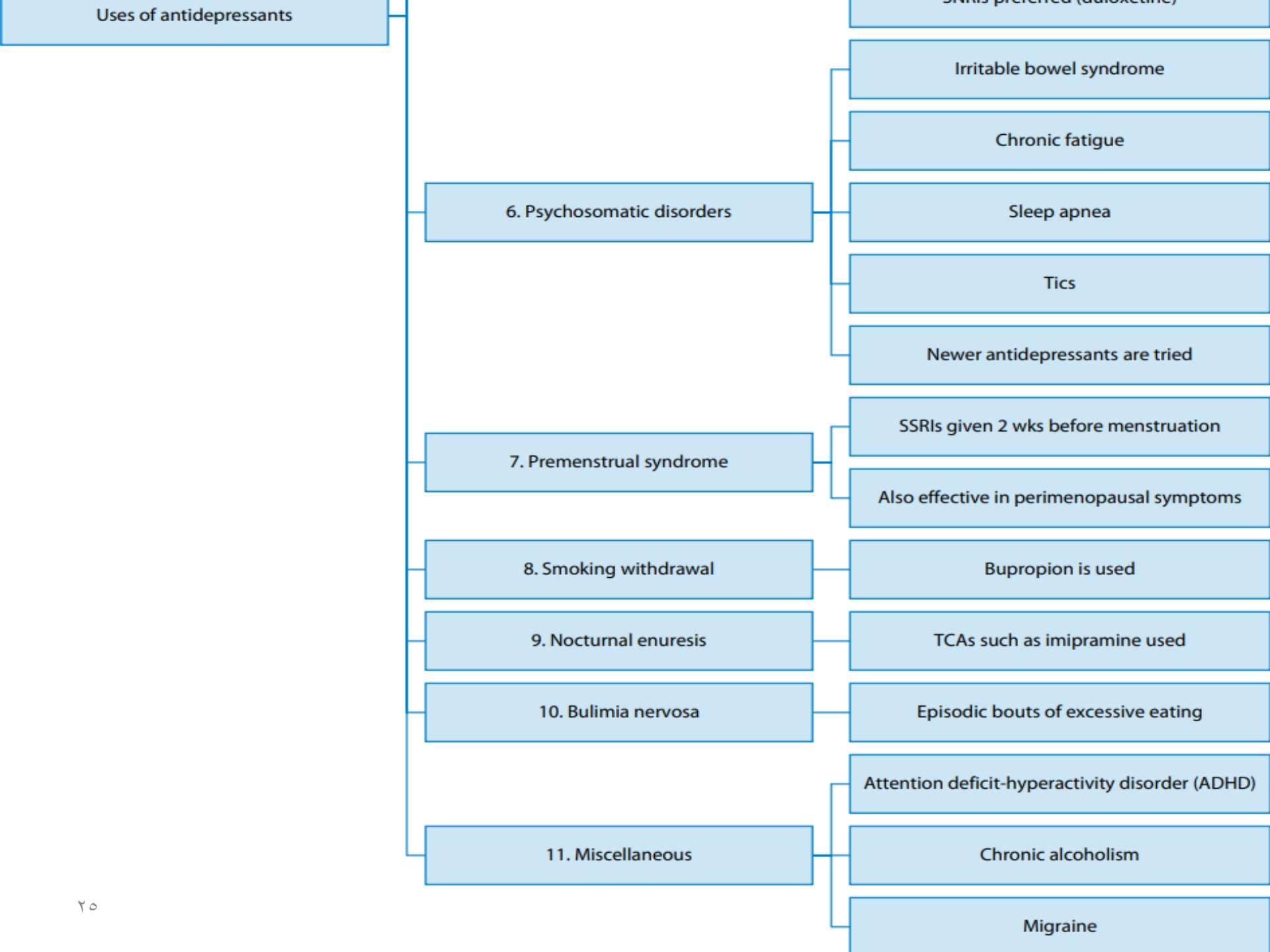
23.4 MONOAMINE OXIDASE (MAO) INHIBITORS

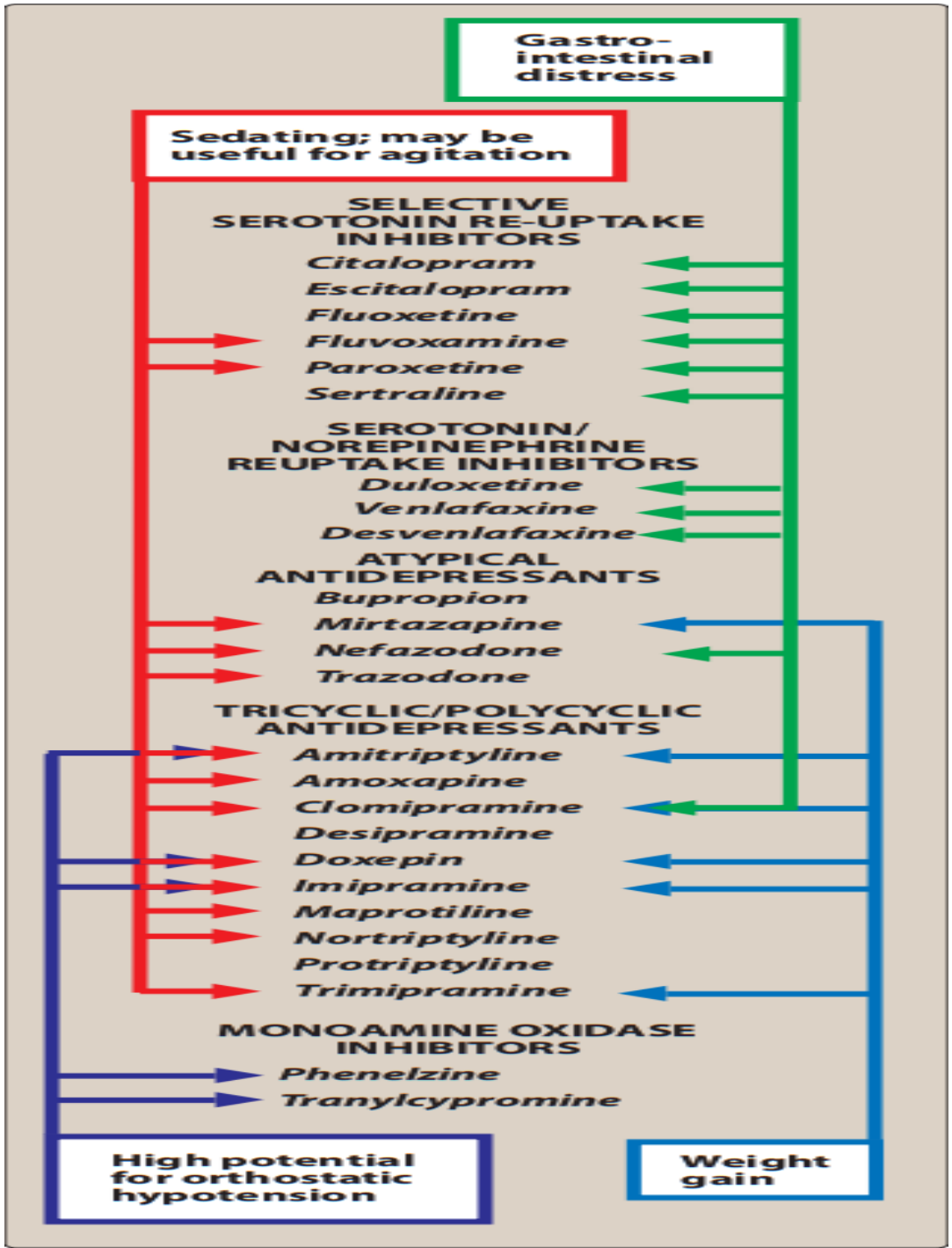


- Drug/food interactions
  - Cheese reaction
    - Patients concomitantly taking tyramine–rich food taking
      - Cheese, beer, wines, yeast, fish, buttermilk
    - Leads to severe hypertension
    - Normally tyramine is metabolized in GIT by MAO
      - Hence, MAO inhibitors ↑ concentration of tyramine
      - Tyramine displaces NA from nerve endings, causing hypertension
  - Serotonin syndrome
    - Due to concomitant SSRIs and MAOIs
    - Severe ↑ in synaptic serotonin concentration
      - ∵ There is both inhibition of reuptake and metabolism of serotonin
      - Leads to hyperthermia, muscle rigidity, tremor, restlessness, sweating, aggression, seizures, coma, which could be fatal
    - Can also occur with
      - Buspirone, sumatriptan (5-HT agonist)
      - Tryptophan (5-HT synthesis)
      - Amphetamines, cocaine (5-HT release)
    - ∴ Avoid such combinations

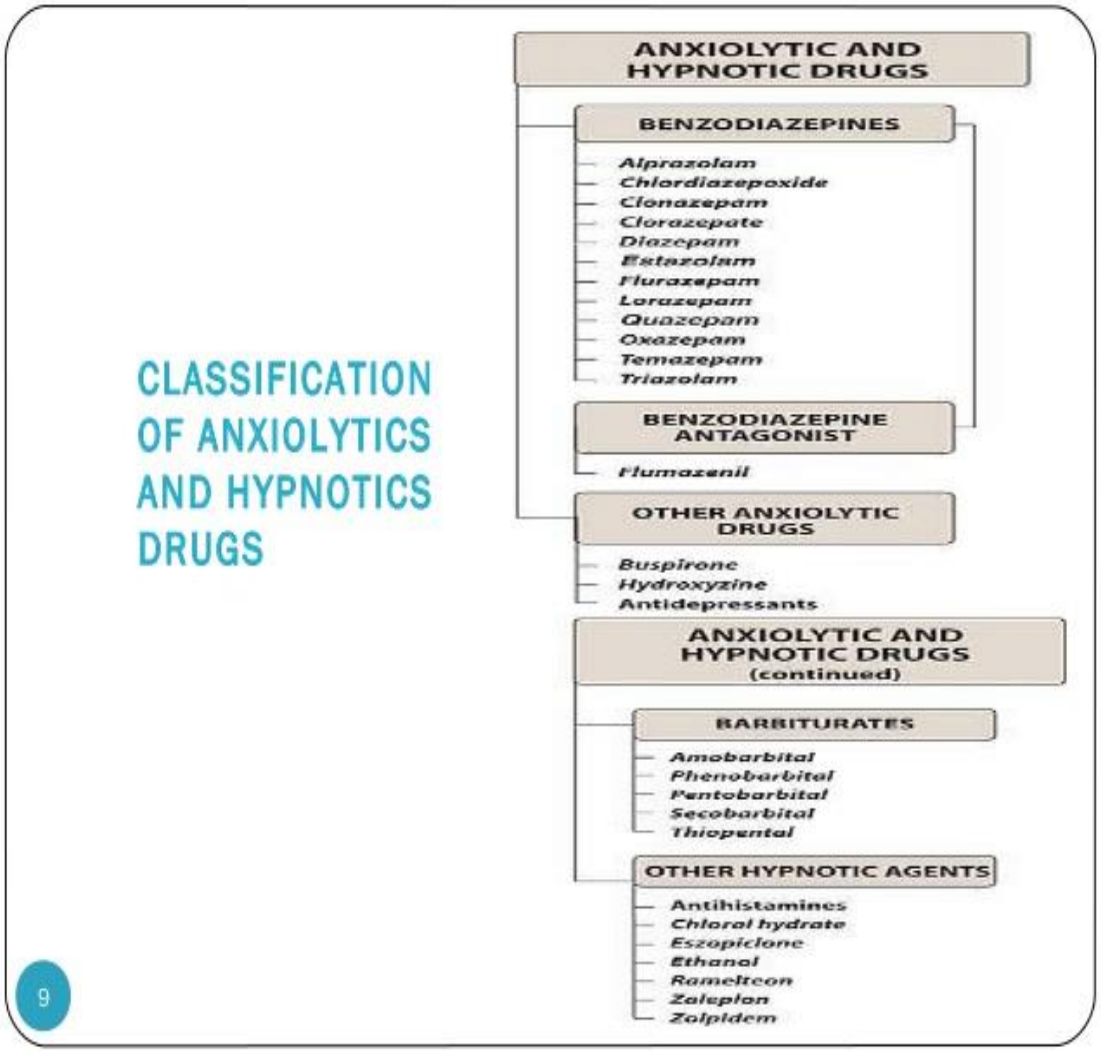



Uses of antidepressants
1. Endogenous depression
Effects seen after 2–3 wks
ECT is given for severe depression
2. Panic attacks
Acute, recurrent, brief anxiety attacks
Post-traumatic stress disorder (PTSD)
3. Obsessive compulsive disorders (OCDs)
Repetitive anxiety – provoking thoughts and compulsive behavior to overcome such thoughts
Clomipramine is used along with counseling
4. Other anxiety disorders
Phobias
Social anxiety
BZDs may also be used
5. Chronic pain
Fibromyalgia
Diabetic neuropathy backache
Postherpetic neuralgia
SNRIs preferred (duloxetine)


Uses of antidepressants
SNRIs preferred (duloxetine)
6. Psychosomatic disorders
Irritable bowel syndrome
Chronic fatigue
Sleep apnea
Tics
Newer antidepressants are tried
7. Premenstrual syndrome
SSRIs given 2 wks before menstruation
Also effective in perimenopausal symptoms
8. Smoking withdrawal
Bupropion is used
9. Nocturnal enuresis
TCAs such as imipramine used
10. Bulimia nervosa
Episodic bouts of excessive eating
11. Miscellaneous
Attention deficit-hyperactivity disorder (ADHD)
Chronic alcoholism
Migraine


Gastro-intestinal distress
Sedating; may be useful for agitation
SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS
Citalopram
Escitalopram
Fluoxetine
Fluvoxamine
Paroxetine
Sertraline
SEROTONIN/ NOREPINEPHRINE REUPTAKE INHIBITORS
Duloxetine
Venlafaxine
Desvenlafaxine
ATYPICAL ANTIDEPRESSANTS
Bupropion
Mirtazapine
Nefazodone
Trazodone
TRICYCLIC/POLYCYCLIC ANTIDEPRESSANTS
Amitriptyline
Amoxapine
Clomipramine
Desipramine
Doxepin
Imipramine
Maprotiline
Nortriptyline
Protriptyline
Trimipramine
MONOAMINE OXIDASE INHIBITORS
Phenelzine
Tranylcypromine
High potential for orthostatic hypotension
Weight gain

Anxiolytics & Hypnotics
Rabei Abdullah Salih



BENZODIAZEPINES

Long-acting
Chlordiazepoxide
Diazepam
Flurazepam

Intermediate-acting
Alprazolam
Clonazepam
Clorazepate
Estazolam
Lorazepam
Oxazepam
Quazepam
Temazepam

Short-acting
Triazolam
Midazolam

BENZODIAZEPINE ANTAGONIST

Flumazenil

NONBENZODIAZEPINE HYPNOTICS

Zaleplon
Zolpidem
Eszopiclone

MELATONIN AGONISTS

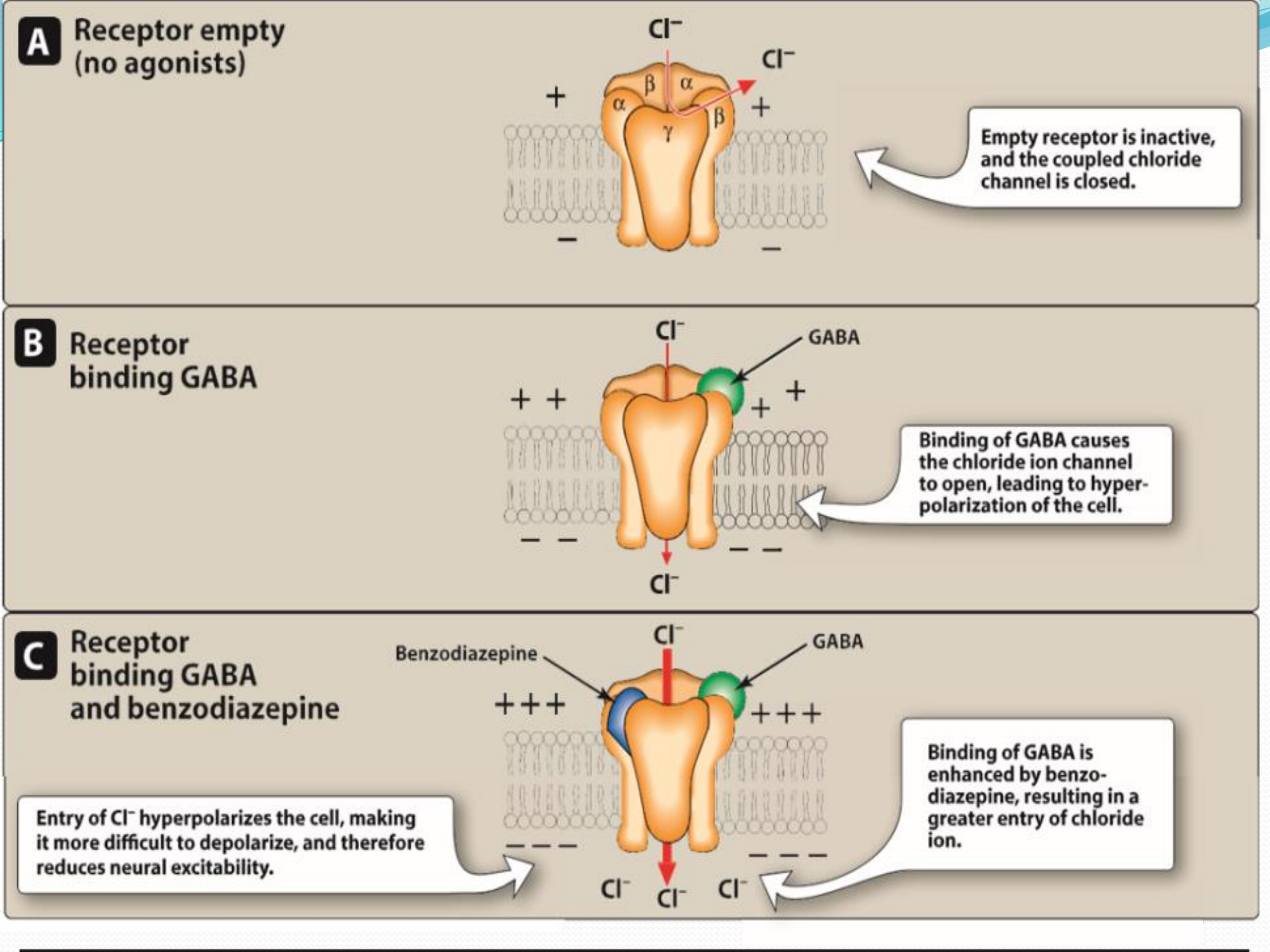
Ramelteon
Tasimelteon

OTHER ANXIOLYTIC DRUGS

Antidepressants
Buspirone
Meprobamate

BARBITURATES

Amobarbital
Pentobarbital
Phenobarbital
Secobarbital


A
Receptor empty (no agonists)
Cl⁻
Cl⁻
β
α
α
β
γ
+
+
−
−
Empty receptor is inactive, and the coupled chloride channel is closed.
B
Receptor binding GABA
Cl⁻
GABA
+ +
+
+
− −
− −
Cl⁻
Binding of GABA causes the chloride ion channel to open, leading to hyper-polarization of the cell.
C
Receptor binding GABA and benzodiazepine
Cl⁻
Benzodiazepine
GABA
+++
+++
− − −
− − −
Cl⁻
Cl⁻
Cl⁻
Entry of Cl⁻ hyperpolarizes the cell, making it more difficult to depolarize, and therefore reduces neural excitability.
Binding of GABA is enhanced by benzo-diazepine, resulting in a greater entry of chloride ion.

Tolerance

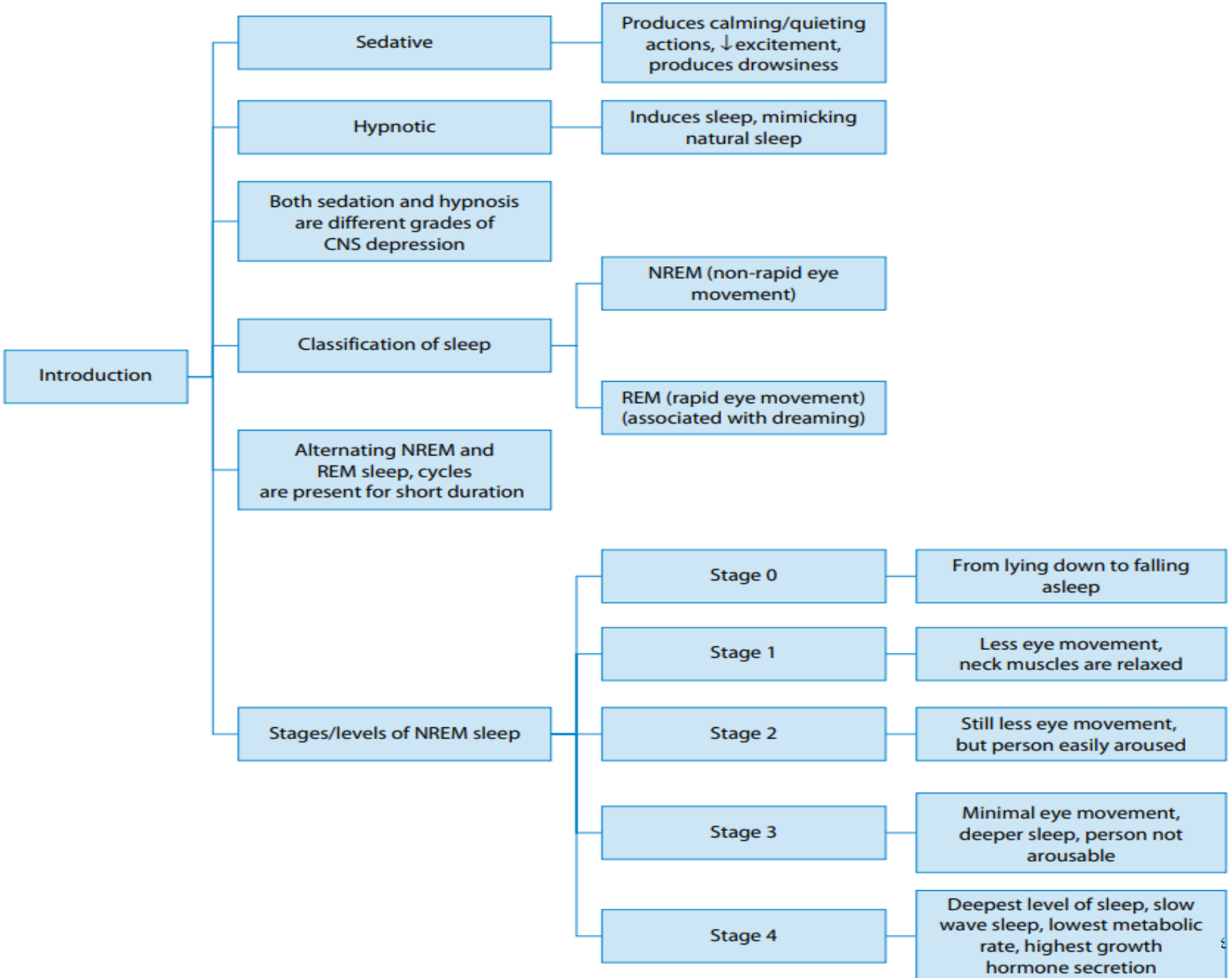
Drug tolerance occurs when someone abuses a substance over a long period. When someone continuously abuses a substance, their body becomes used to it, meaning the drug will stop having as much of an effect. When someone develops a tolerance to an addictive substance, they will begin taking a higher dose to get the same effects as before. Taking high doses of a substance may lead to many negative consequences.

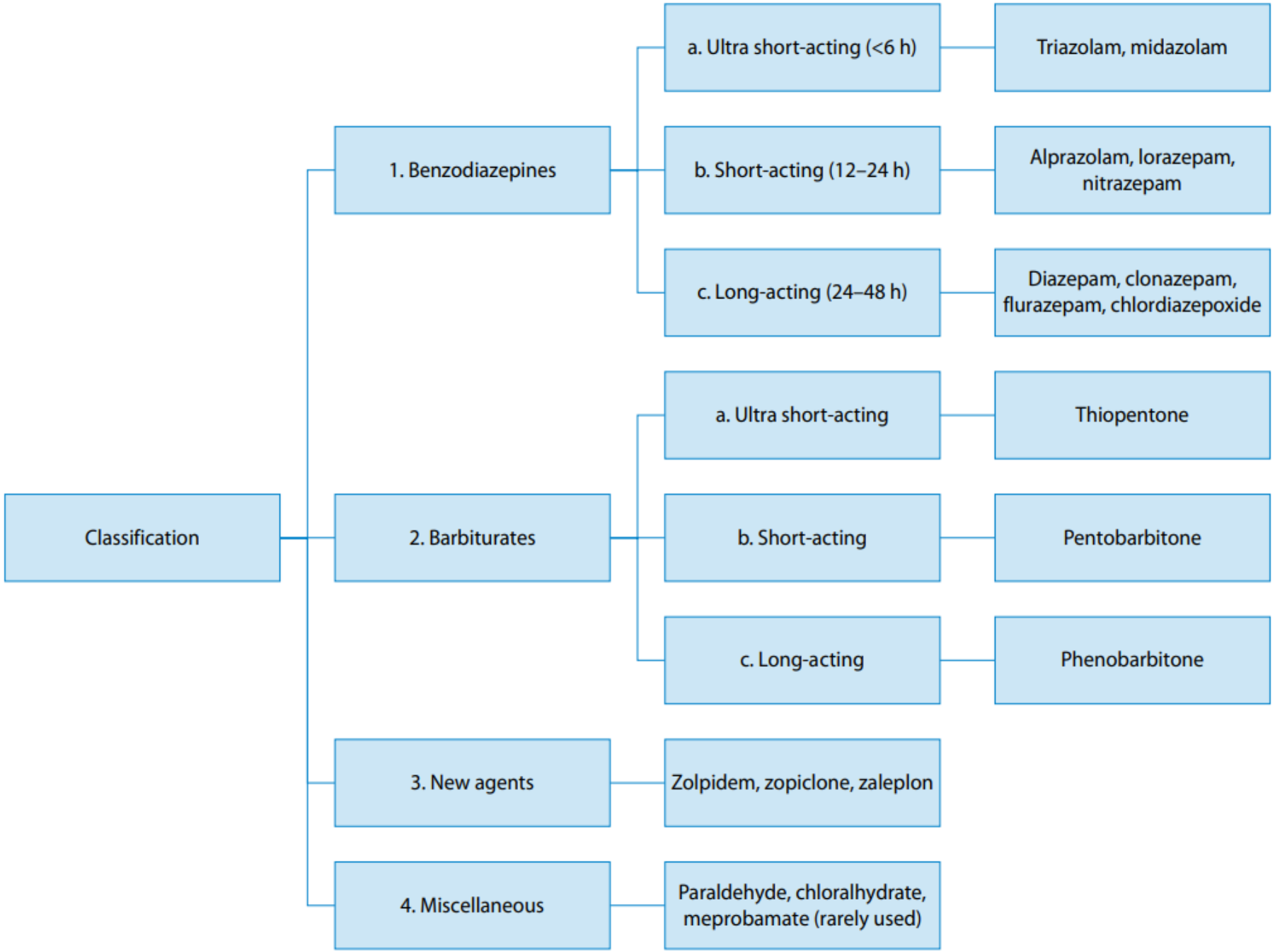
Dependence

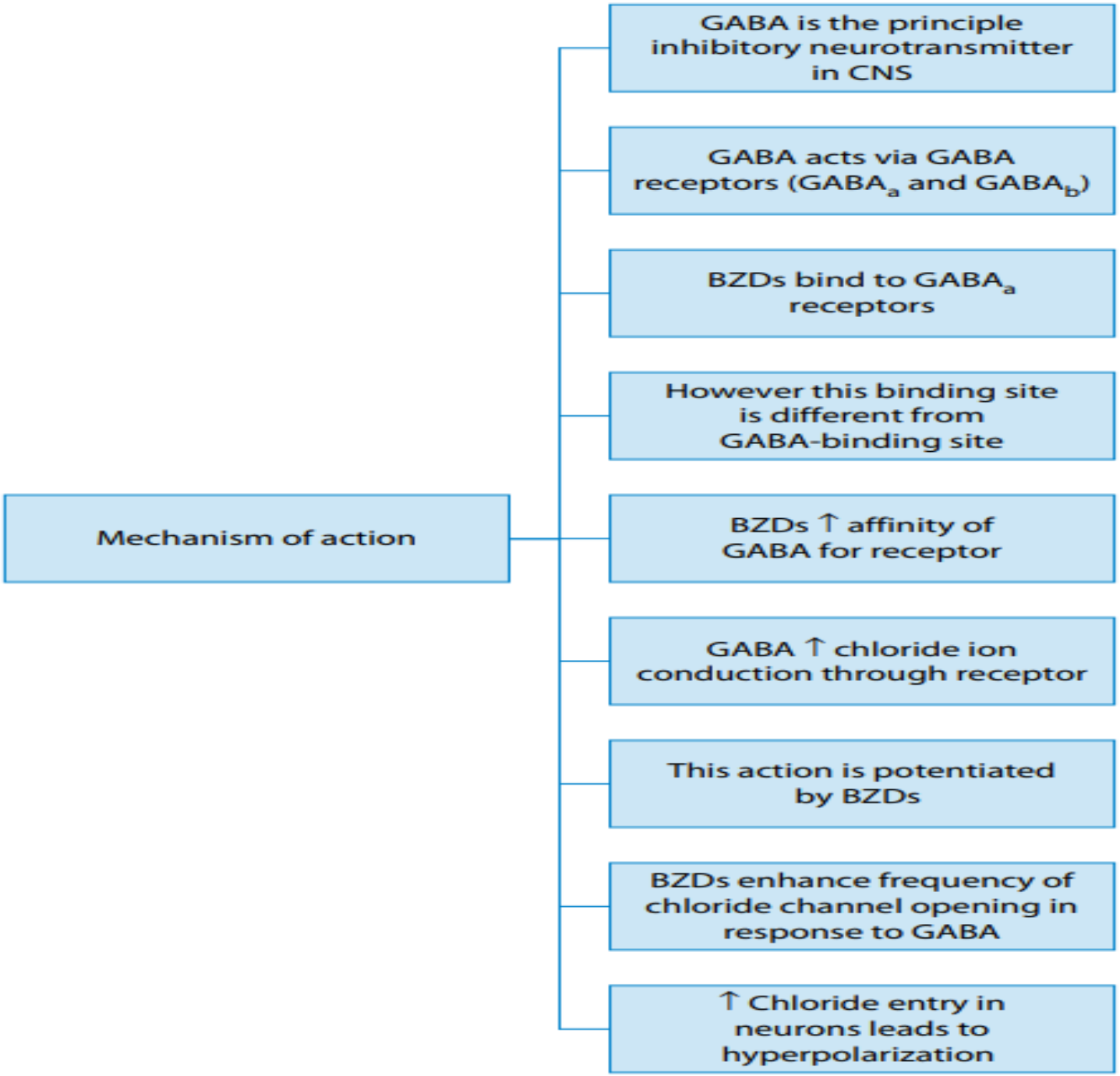
When someone abuses high doses of an addictive substance, they may develop a dependence. Drug dependence refers to someone feeling like they cannot function normally without the use of the substance. A drug dependence can be either physical or psychological and can have many negative effects on someone's life.

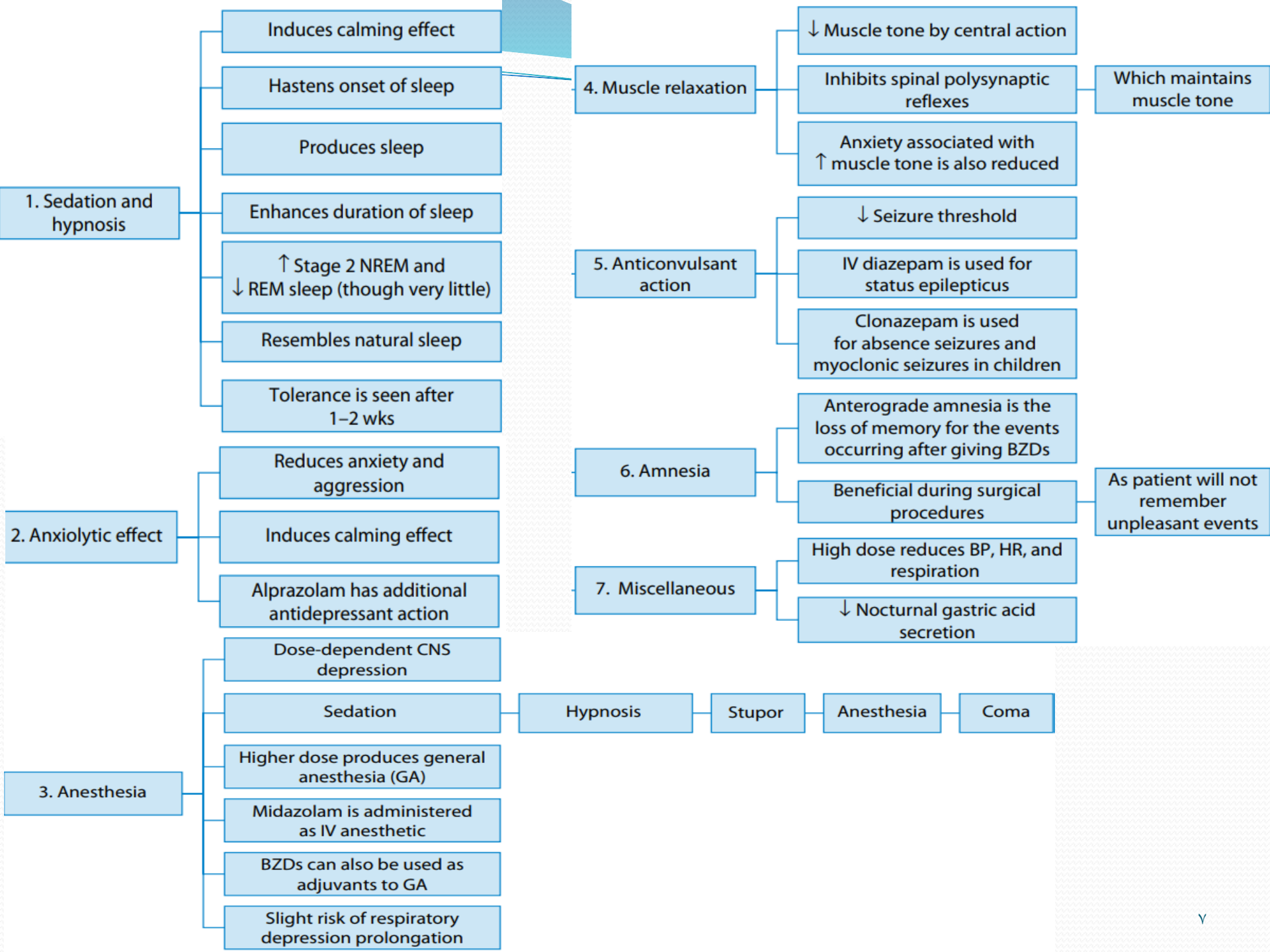
Addiction

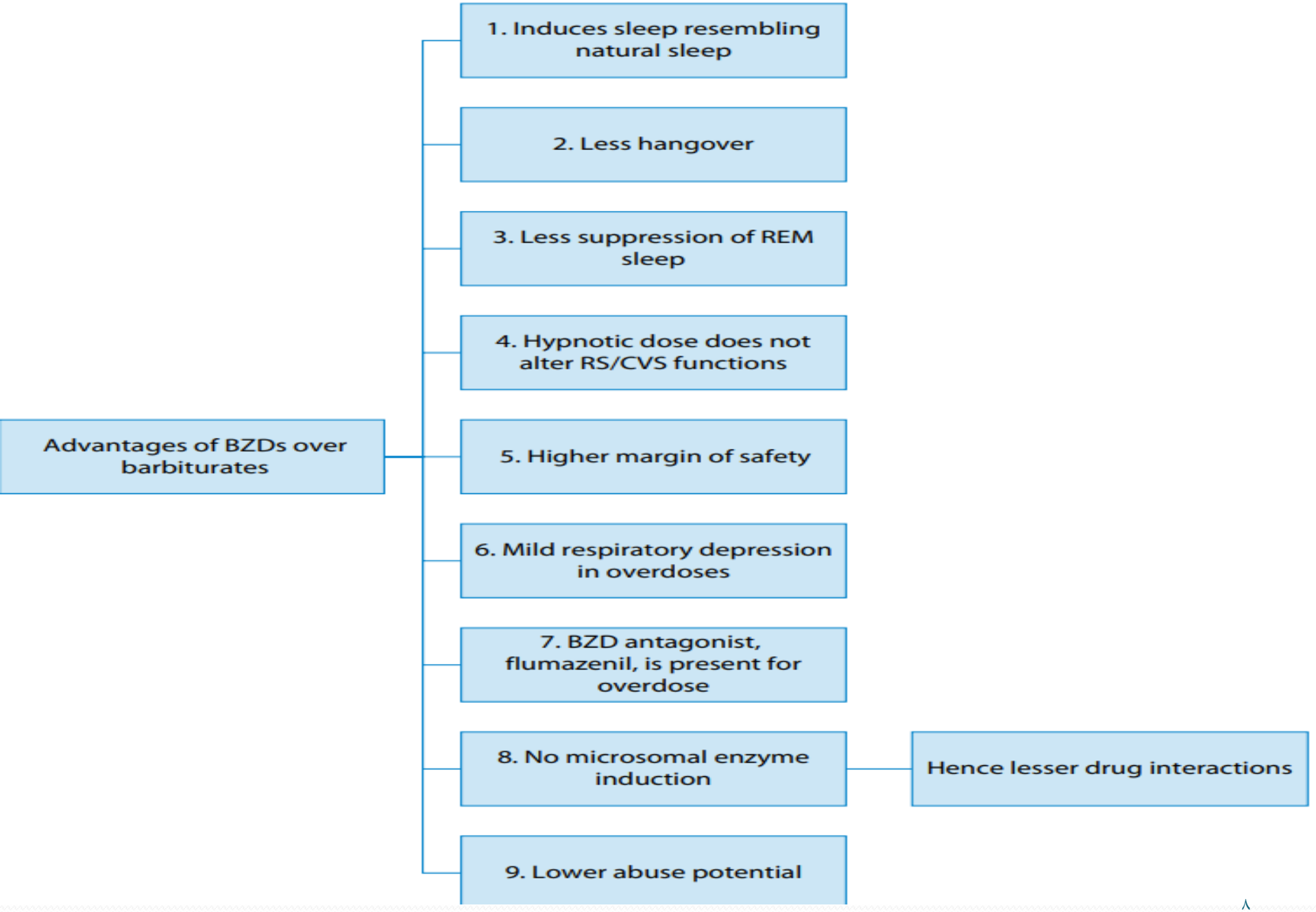
Drug addiction affects someone's mind and behavior. Addiction refers to the inability to control the use of drugs or alcohol. Those who struggle with addiction may try to stop using the substance but will feel like they cannot stop even though they may be experiencing negative consequences from it. Those struggling with addiction must receive the proper help and support needed to stop.

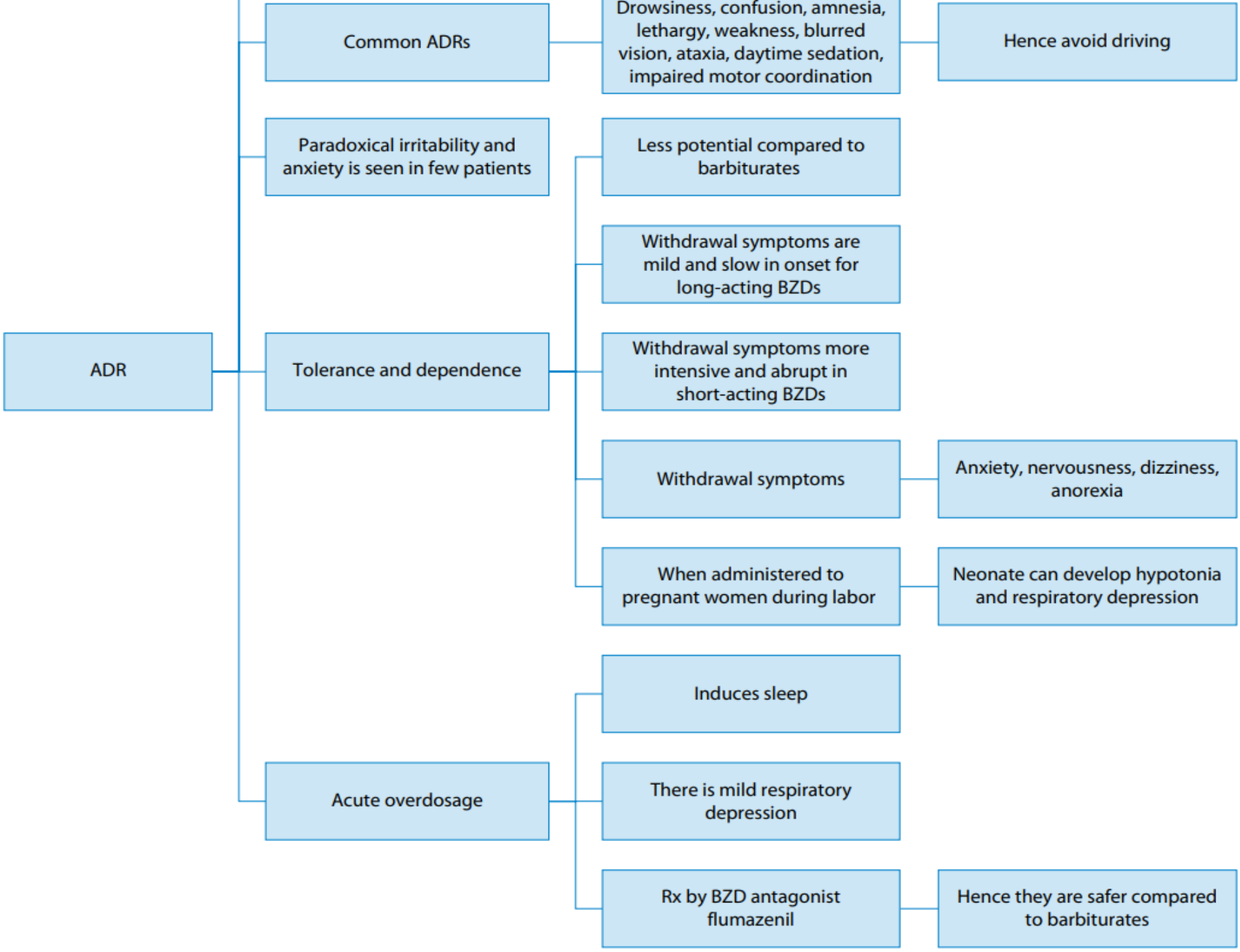

Introduction
Sedative
Produces calming/quieting actions, ↓excitement, produces drowsiness
Hypnotic
Induces sleep, mimicking natural sleep
Both sedation and hypnosis are different grades of CNS depression
Classification of sleep
NREM (non-rapid eye movement)
REM (rapid eye movement) (associated with dreaming)
Alternating NREM and REM sleep, cycles are present for short duration
Stages/levels of NREM sleep
Stage 0
From lying down to falling asleep
Stage 1
Less eye movement, neck muscles are relaxed
Stage 2
Still less eye movement, but person easily aroused
Stage 3
Minimal eye movement, deeper sleep, person not arousable
Stage 4
Deepest level of sleep, slow wave sleep, lowest metabolic rate, highest growth hormone secretion

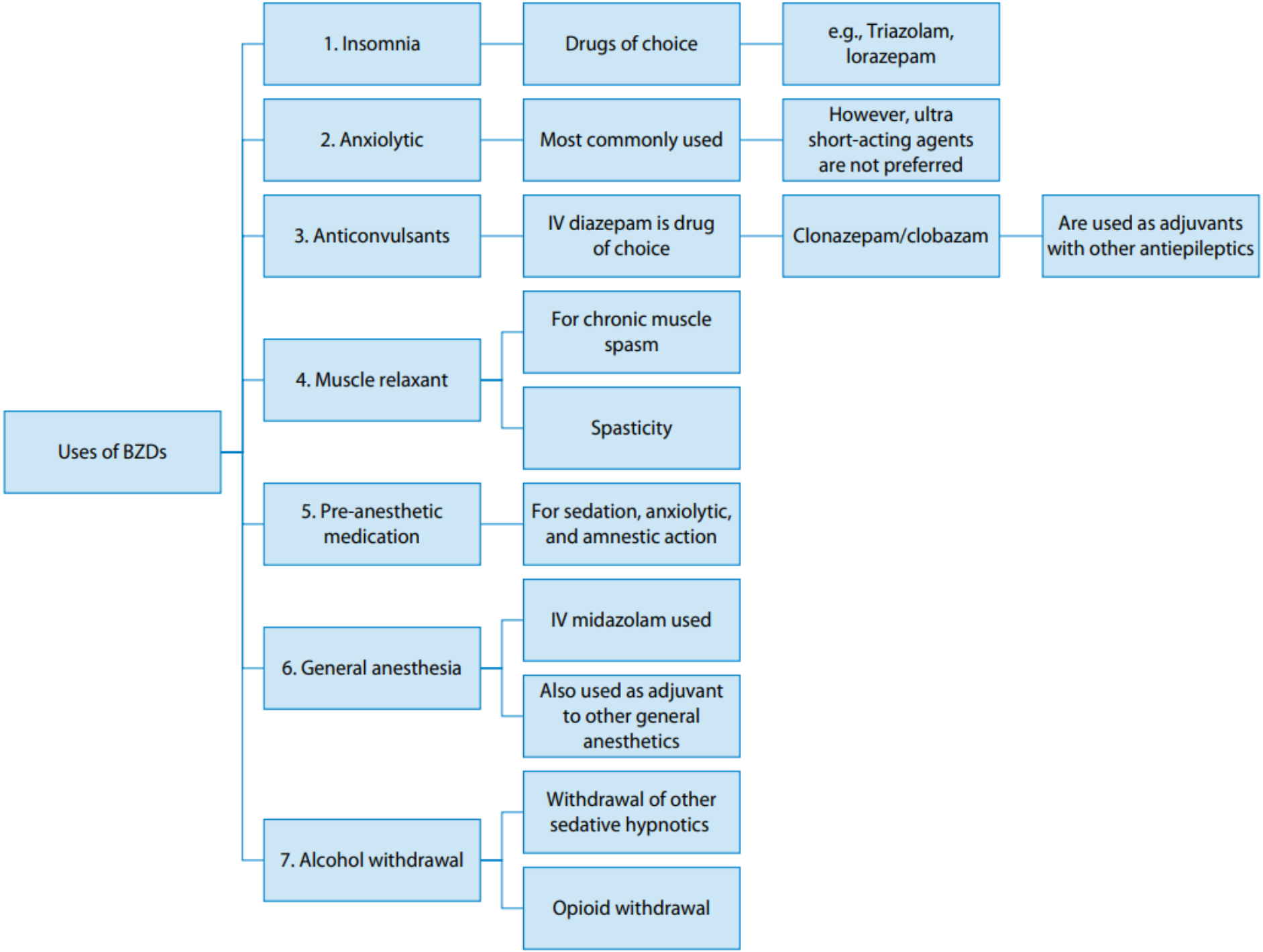

Classification
1. Benzodiazepines
a. Ultra short-acting (<6 h)
Triazolam, midazolam
b. Short-acting (12–24 h)
Alprazolam, lorazepam, nitrazepam
c. Long-acting (24–48 h)
Diazepam, clonazepam, flurazepam, chlordiazepoxide
2. Barbiturates
a. Ultra short-acting
Thiopentone
b. Short-acting
Pentobarbitone
c. Long-acting
Phenobarbitone
3. New agents
Zolpidem, zopiclone, zaleplon
4. Miscellaneous
Paraldehyde, chloralhydrate, meprobamate (rarely used)

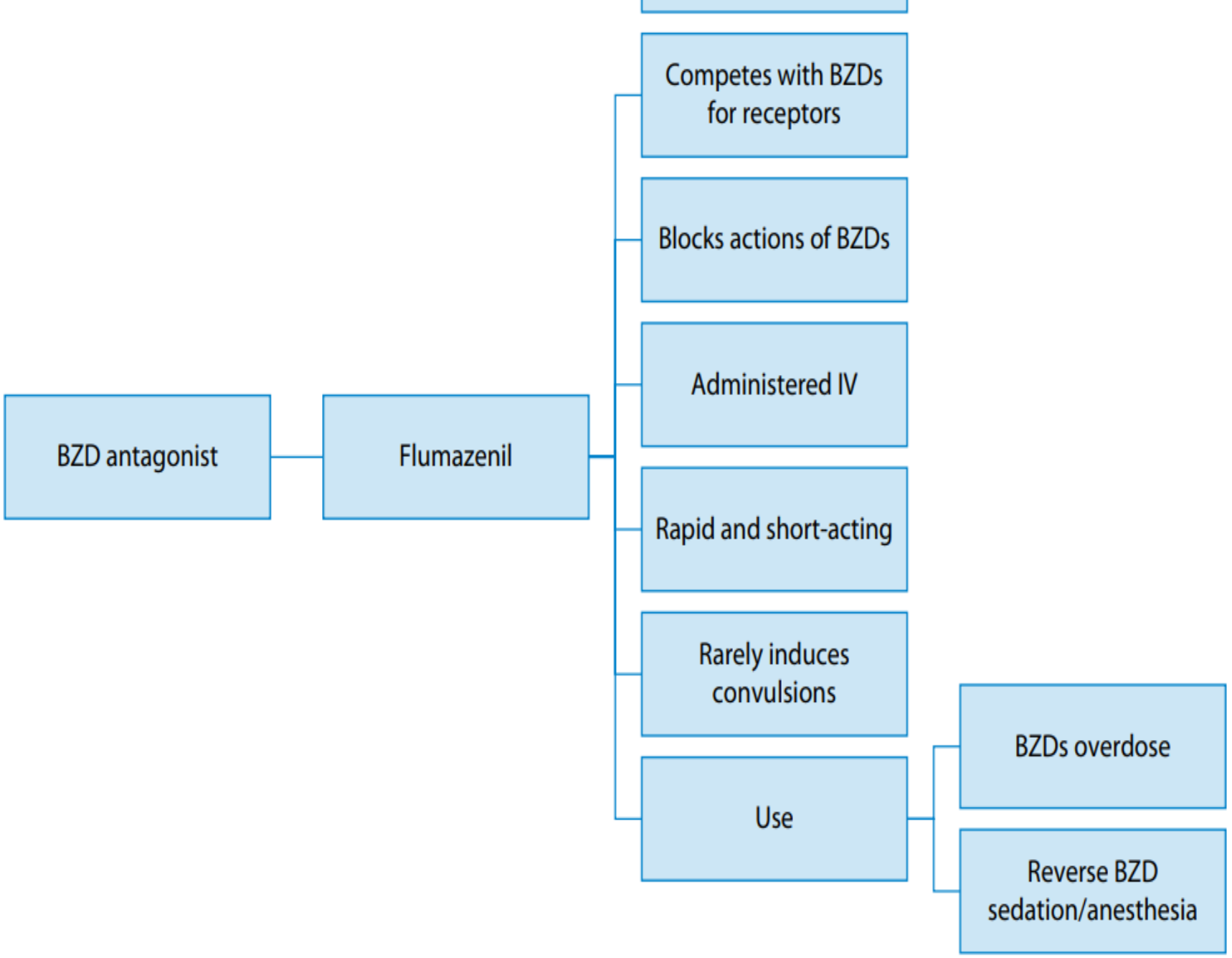

Mechanism of action
GABA is the principle inhibitory neurotransmitter in CNS
GABA acts via GABA receptors ($GABA_a$ and $GABA_b$)
BZDs bind to $GABA_a$ receptors
However this binding site is different from GABA-binding site
BZDs ↑ affinity of GABA for receptor
GABA ↑ chloride ion conduction through receptor
This action is potentiated by BZDs
BZDs enhance frequency of chloride channel opening in response to GABA
↑ Chloride entry in neurons leads to hyperpolarization


1. Sedation and hypnosis
Induces calming effect
Hastens onset of sleep
Produces sleep
Enhances duration of sleep
↑ Stage 2 NREM and ↓ REM sleep (though very little)
Resembles natural sleep
Tolerance is seen after 1–2 wks
2. Anxiolytic effect
Reduces anxiety and aggression
Induces calming effect
Alprazolam has additional antidepressant action
3. Anesthesia
Dose-dependent CNS depression
Sedation
Hypnosis
Stupor
Anesthesia
Coma
Higher dose produces general anesthesia (GA)
Midazolam is administered as IV anesthetic
BZDs can also be used as adjuvants to GA
Slight risk of respiratory depression prolongation
4. Muscle relaxation
↓ Muscle tone by central action
Inhibits spinal polysynaptic reflexes
Which maintains muscle tone
Anxiety associated with ↑ muscle tone is also reduced
5. Anticonvulsant action
↓ Seizure threshold
IV diazepam is used for status epilepticus
Clonazepam is used for absence seizures and myoclonic seizures in children
6. Amnesia
Anterograde amnesia is the loss of memory for the events occurring after giving BZDs
Beneficial during surgical procedures
As patient will not remember unpleasant events
7. Miscellaneous
High dose reduces BP, HR, and respiration
↓ Nocturnal gastric acid secretion


Advantages of BZDs over barbiturates
1. Induces sleep resembling natural sleep
2. Less hangover
3. Less suppression of REM sleep
4. Hypnotic dose does not alter RS/CVS functions
5. Higher margin of safety
6. Mild respiratory depression in overdoses
7. BZD antagonist, flumazenil, is present for overdose
8. No microsomal enzyme induction
Hence lesser drug interactions
9. Lower abuse potential

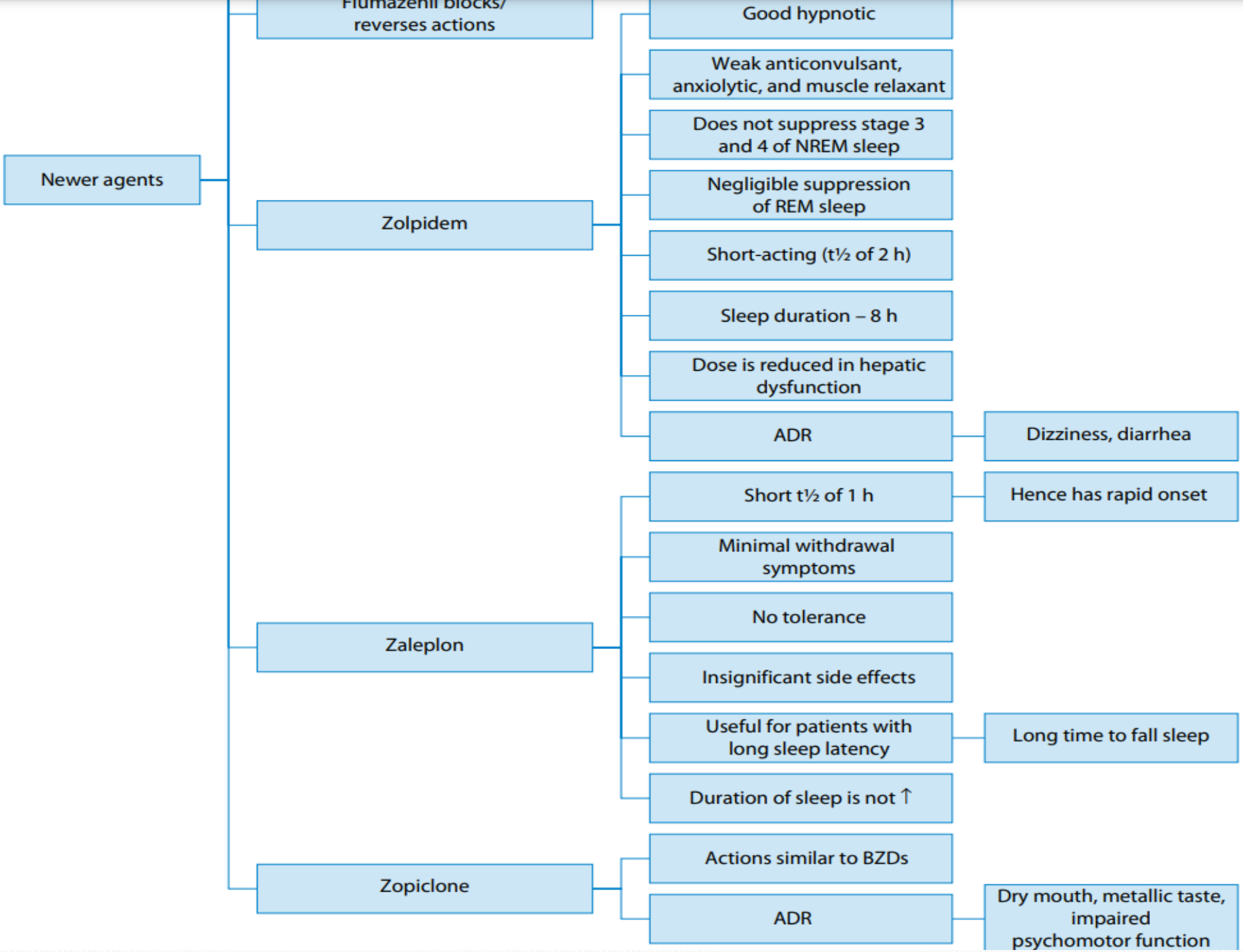

ADR
Common ADRs
Drowsiness, confusion, amnesia, lethargy, weakness, blurred vision, ataxia, daytime sedation, impaired motor coordination
Hence avoid driving
Paradoxical irritability and anxiety is seen in few patients
Tolerance and dependence
Less potential compared to barbiturates
Withdrawal symptoms are mild and slow in onset for long-acting BZDs
Withdrawal symptoms more intensive and abrupt in short-acting BZDs
Withdrawal symptoms
Anxiety, nervousness, dizziness, anorexia
When administered to pregnant women during labor
Neonate can develop hypotonia and respiratory depression
Acute overdosage
Induces sleep
There is mild respiratory depression
Rx by BZD antagonist flumazenil
Hence they are safer compared to barbiturates

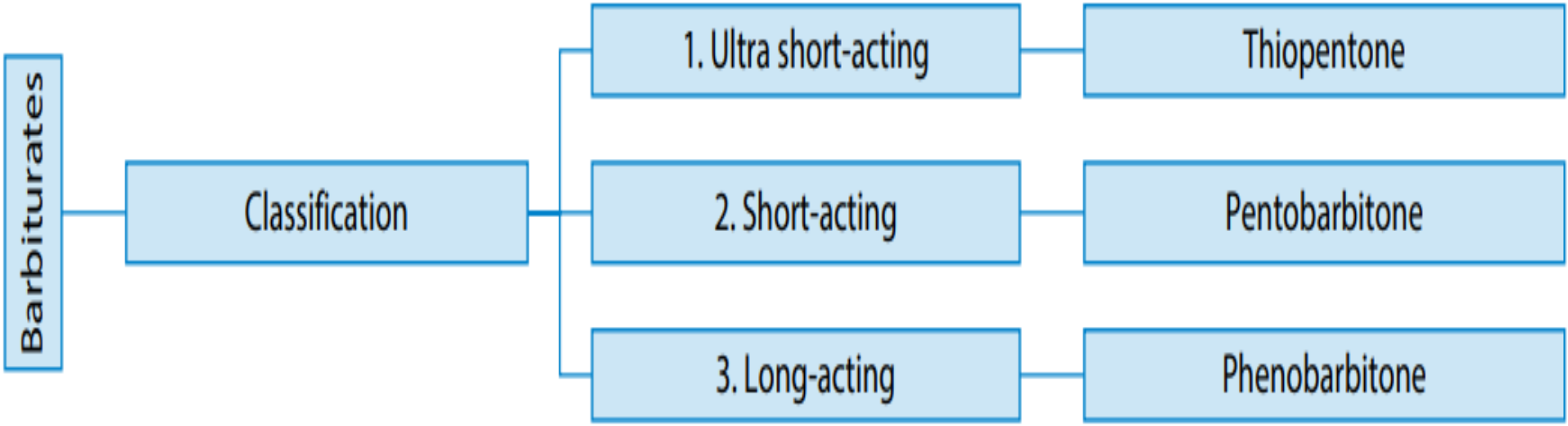

Uses of BZDs
1. Insomnia
Drugs of choice
e.g., Triazolam, lorazepam
2. Anxiolytic
Most commonly used
However, ultra short-acting agents are not preferred
3. Anticonvulsants
IV diazepam is drug of choice
Clonazepam/clobazam
Are used as adjuvants with other antiepileptics
4. Muscle relaxant
For chronic muscle spasm
Spasticity
5. Pre-anesthetic medication
For sedation, anxiolytic, and amnestic action
6. General anesthesia
IV midazolam used
Also used as adjuvant to other general anesthetics
7. Alcohol withdrawal
Withdrawal of other sedative hypnotics
Opioid withdrawal

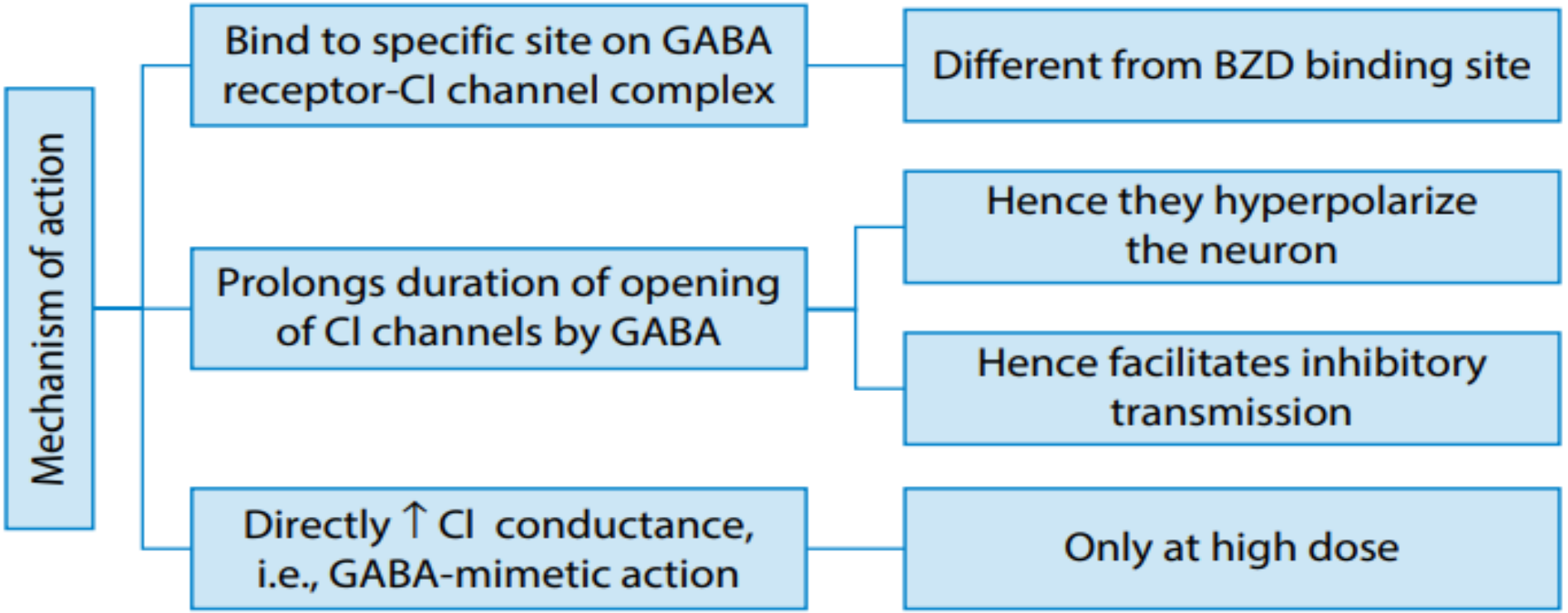

BZD antagonist
Flumazenil
Competes with BZDs for receptors
Blocks actions of BZDs
Administered IV
Rapid and short-acting
Rarely induces convulsions
Use
BZDs overdose
Reverse BZD sedation/anesthesia

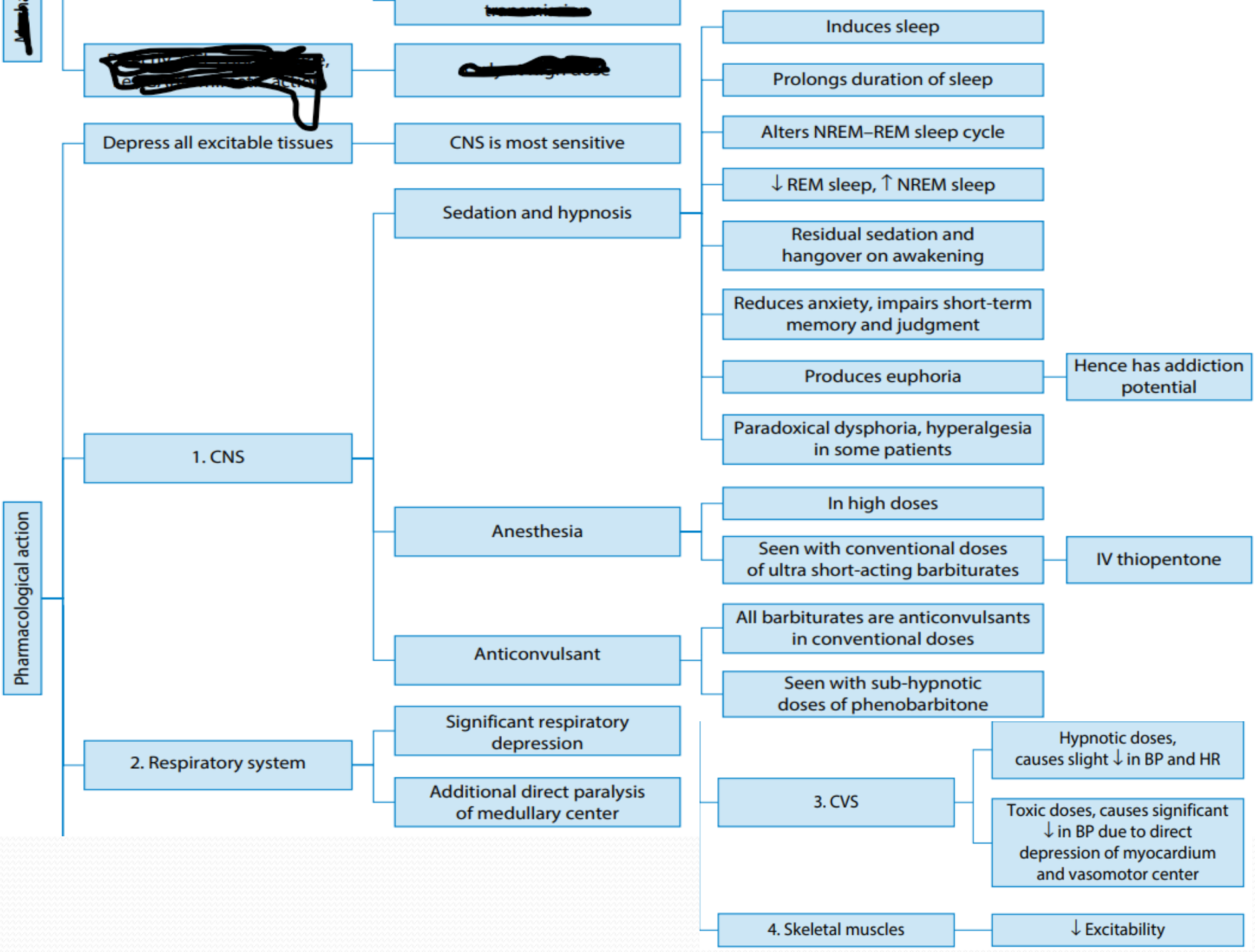
NEWER AGENTS

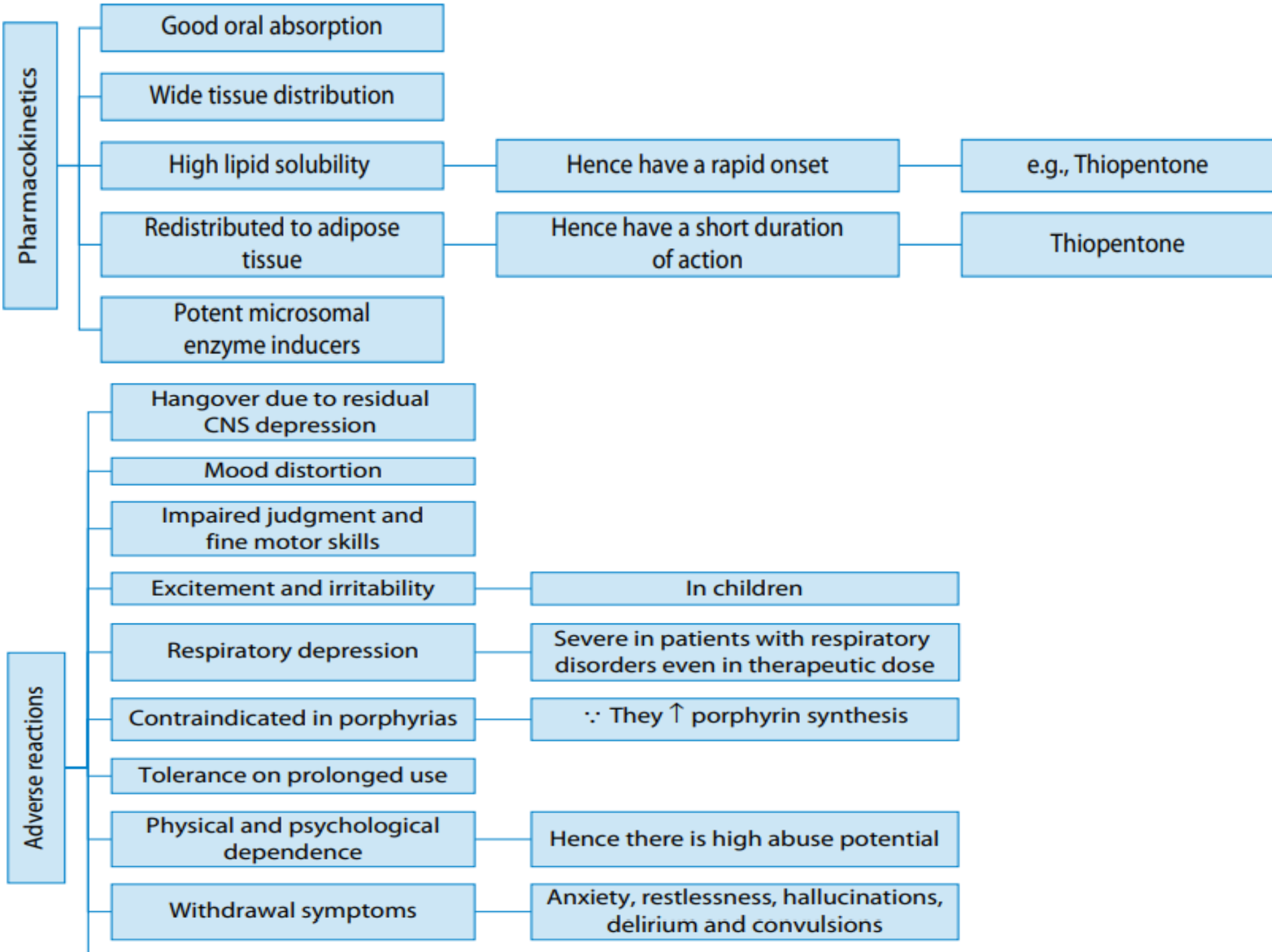
- e.g., Zolpidem, zopiclone, zaleplone
- Non-BZDs
- But produce their effects
- Bind to $GABA_a$ receptor
- Facilitate inhibitory transmission
- Lesser incidence of dependence and tolerance compared to BZDs
- Insignificant alteration of sleep pattern
- Used for short duration in insomnia
- Rapid onset and short duration of action
  - Hence there is less hangover
- Flumazenil blocks/ reverses actions
  - [redacted]

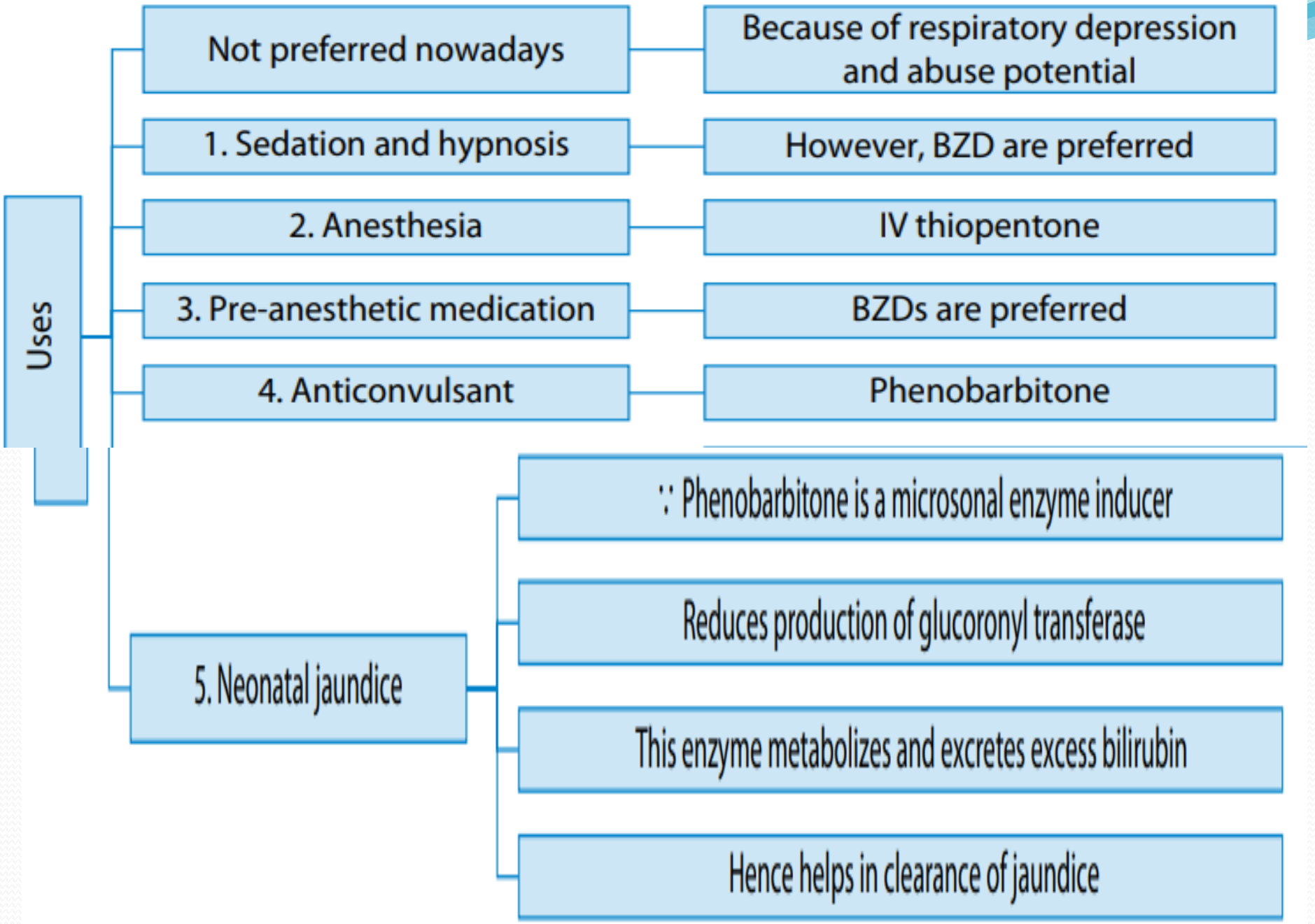

Flumazenil blocks/ reverses actions
Good hypnotic
Weak anticonvulsant, anxiolytic, and muscle relaxant
Does not suppress stage 3 and 4 of NREM sleep
Newer agents
Negligible suppression of REM sleep
Zolpidem
Short-acting (t½ of 2 h)
Sleep duration – 8 h
Dose is reduced in hepatic dysfunction
ADR
Dizziness, diarrhea
Short t½ of 1 h
Hence has rapid onset
Minimal withdrawal symptoms
No tolerance
Zaleplon
Insignificant side effects
Useful for patients with long sleep latency
Long time to fall sleep
Duration of sleep is not ↑
Actions similar to BZDs
Zopiclone
ADR
Dry mouth, metallic taste, impaired psychomotor function


Barbiturates
Classification
1. Ultra short-acting
Thiopentone
2. Short-acting
Pentobarbitone
3. Long-acting
Phenobarbitone


Mechanism of action
Bind to specific site on GABA receptor-Cl channel complex
Different from BZD binding site
Prolongs duration of opening of Cl channels by GABA
Hence they hyperpolarize the neuron
Hence facilitates inhibitory transmission
Directly ↑ Cl conductance, i.e., GABA-mimetic action
Only at high dose


Pharmacological action
Depress all excitable tissues
CNS is most sensitive
1. CNS
Sedation and hypnosis
Induces sleep
Prolongs duration of sleep
Alters NREM–REM sleep cycle
↓ REM sleep, ↑ NREM sleep
Residual sedation and hangover on awakening
Reduces anxiety, impairs short-term memory and judgment
Produces euphoria
Hence has addiction potential
Paradoxical dysphoria, hyperalgesia in some patients
Anesthesia
In high doses
Seen with conventional doses of ultra short-acting barbiturates
IV thiopentone
Anticonvulsant
All barbiturates are anticonvulsants in conventional doses
Seen with sub-hypnotic doses of phenobarbitone
2. Respiratory system
Significant respiratory depression
Additional direct paralysis of medullary center
3. CVS
Hypnotic doses, causes slight ↓ in BP and HR
Toxic doses, causes significant ↓ in BP due to direct depression of myocardium and vasomotor center
4. Skeletal muscles
↓ Excitability


Pharmacokinetics
Good oral absorption
Wide tissue distribution
High lipid solubility
Hence have a rapid onset
e.g., Thiopentone
Redistributed to adipose tissue
Hence have a short duration of action
Thiopentone
Potent microsomal enzyme inducers
Adverse reactions
Hangover due to residual CNS depression
Mood distortion
Impaired judgment and fine motor skills
Excitement and irritability
In children
Respiratory depression
Severe in patients with respiratory disorders even in therapeutic dose
Contraindicated in porphyrias
∵ They ↑ porphyrin synthesis
Tolerance on prolonged use
Physical and psychological dependence
Hence there is high abuse potential
Withdrawal symptoms
Anxiety, restlessness, hallucinations, delirium and convulsions


Uses
Not preferred nowadays
Because of respiratory depression and abuse potential
1. Sedation and hypnosis
However, BZD are preferred
2. Anesthesia
IV thiopentone
3. Pre-anesthetic medication
BZDs are preferred
4. Anticonvulsant
Phenobarbitone
5. Neonatal jaundice
∵ Phenobarbitone is a microsonal enzyme inducer
Reduces production of glucoronyl transferase
This enzyme metabolizes and excretes excess bilirubin
Hence helps in clearance of jaundice

Types of benzodiazepines

Based on drug elimination (metabolism + kidney filtration),
3 category of benzodiazepines exist

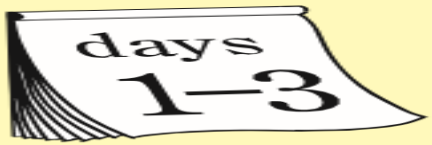
	Half life	example
Long acting	> 24 hrs	Diazepam,Nitrazepam chlordiazepoxide, flurazepam
Intermediate acting	12-24 hrs	alprazolam, lorazepam clonazepam, flunitrazepam,
Short acting	< 1-12 hrs	midazolam and triazolam.

longer-acting benzodiazepines are recommended for the treatment of anxiety

Short- and intermediate-acting are preferred for the treatment of insomnia;

DURATION OF ACTION OF BENZODIAZEPINES

Long-acting



Clorazepate
Chlordiazepoxide
Diazepam
Flurazepam
Quazepam

Intermediate-acting

10–20 Hours

Alprazolam
Estazolam
Lorazepam
Temazepam

Short-acting

3–8 Hours

Oxazepam
Triazolam

Ramelteon and Tasimelteon

are a selective agonist at the MT1 and MT2 subtypes of melatonin receptors. Melatonin is a hormone secreted by the pineal gland that helps to maintain the circadian rhythm underlying the normal sleep–wake cycle. Stimulation of MT1 and MT2 receptors by ramelteon is thought to induce and promote sleep. Ramelteon is indicated for the treatment of insomnia characterized by difficulty falling asleep (increased sleep latency). It has minimal potential for abuse, and no evidence of dependence or withdrawal effects has been observed. Therefore, ramelteon can be administered long term. Common adverse effects of ramelteon include dizziness, fatigue, and somnolence. Ramelteon may also increase prolactin levels. Tasimelteon is indicated for non 24-hour sleep–wake disorder, often experienced by patients who are blind. The most common adverse effects of tasimelteon are headache, abnormal dreams, increase in liver function tests, and possible upper respiratory tract infections.

Antihistamines

Some antihistamines with sedating properties, such as diphenhydramine, hydroxyzine, and doxylamine, are effective in treating mild types of situational insomnia. However, they have undesirable side effects (such as anticholinergic effects) that make them less useful than the benzodiazepines and the nonbenzodiazepines.

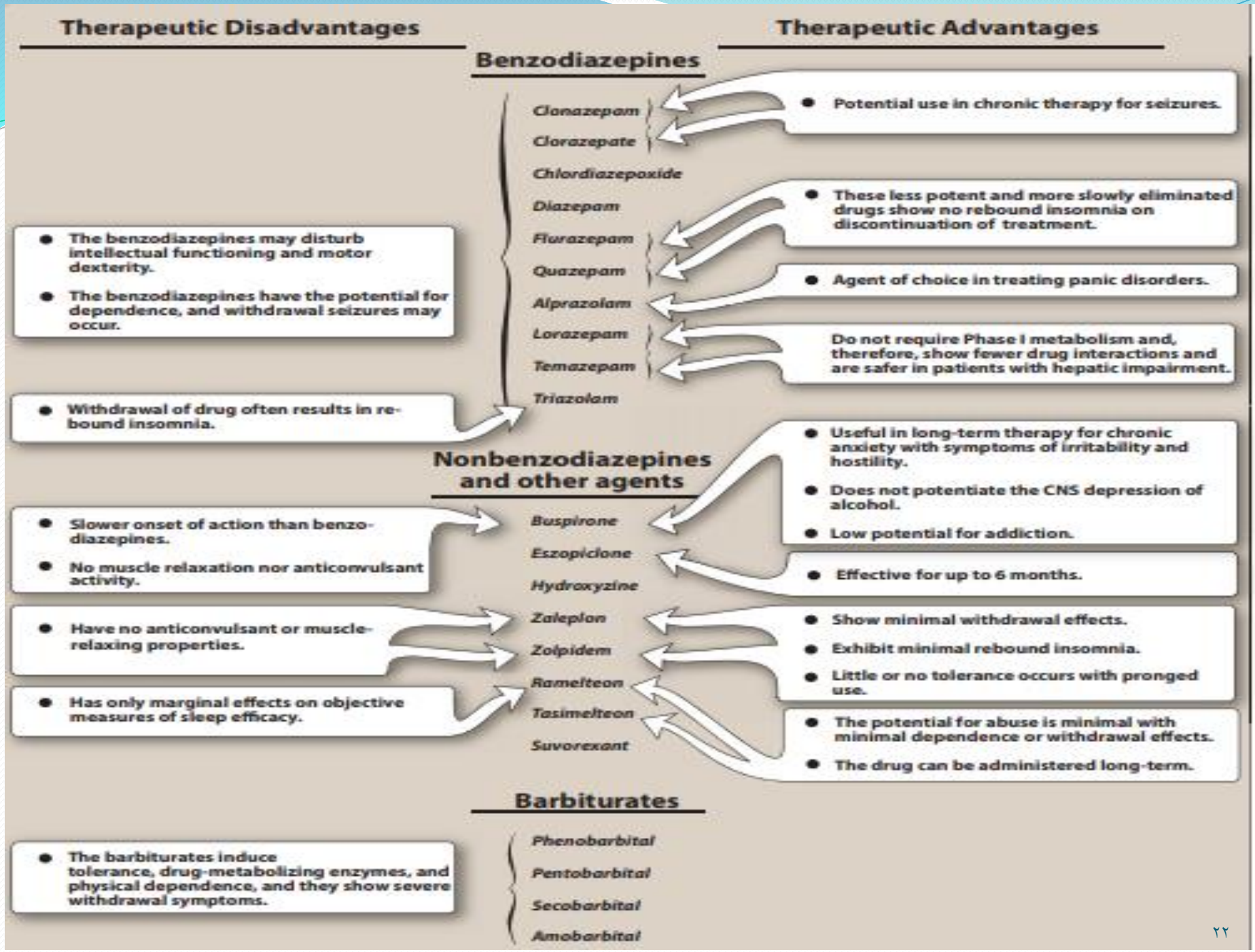
Antidepressants

Doxepin, an older tricyclic agent with SNRI mechanisms of antidepressant and anxiolytic action, was recently approved at low doses for the management of insomnia. Other antidepressants, such as trazodone, mirtazapine, and other older tricyclic antidepressants with strong antihistamine properties are used off-label for the treatment of insomnia.

Buspirone is a nonbenzodiazepine partial agonist at serotonin receptors. The actions of buspirone appear to be mediated by serotonin (5-HT1A) receptors, although it also displays some affinity for D2 dopamine receptors and 5-HT2A serotonin receptors. Thus, its mode of action differs from that of the benzodiazepines. Buspirone is useful for the chronic treatment of generalized anxiety disorder (GAD) and has an efficacy comparable to that of benzodiazepines as it is devoid of sedation, hypnosis, and general CNS depression or drug abuse liability of benzodiazepines. It has a slow onset of action and is not effective for short-term or "as-needed" treatment of acute anxiety. In addition, buspirone lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines. Buspirone usually requires therapy of 3 to 6 weeks to demonstrate efficacy. The frequency of adverse effects is low, with the most common effects being headache, dizziness, nervousness, nausea, and light-headedness. Sedation and psychomotor and cognitive dysfunction are minimal, and dependence is unlikely, a benefit that is particularly important in elderly patients. Buspirone does not potentiate the CNS depression of alcohol.

Suvorexant

Suvorexant is an antagonist of the orexin receptor. Orexin is a neuropeptide that promotes wakefulness. Antagonism of the effects of orexin suppresses the wake drive from this neuropeptide. This antagonism may also explain the adverse events that are similar to signs of narcolepsy and cataplexy. The loss of orexin producing neurons is believed to be an underlying pathology for narcolepsy. Daytime somnolence and increased suicidal ideation are other reported adverse effects.


Therapeutic Disadvantages
Therapeutic Advantages
Benzodiazepines
Clonazepam
Clorazepate
Chlordiazepoxide
Diazepam
Flurazepam
Quazepam
Alprazolam
Lorazepam
Temazepam
Triazolam
Potential use in chronic therapy for seizures.
These less potent and more slowly eliminated drugs show no rebound insomnia on discontinuation of treatment.
Agent of choice in treating panic disorders.
Do not require Phase I metabolism and, therefore, show fewer drug interactions and are safer in patients with hepatic impairment.
The benzodiazepines may disturb intellectual functioning and motor dexterity.
The benzodiazepines have the potential for dependence, and withdrawal seizures may occur.
Withdrawal of drug often results in re-bound insomnia.
Nonbenzodiazepines and other agents
Buspirone
Eszopiclone
Hydroxyzine
Zaleplon
Zolpidem
Ramelteon
Tasimelteon
Suvorexant
Useful in long-term therapy for chronic anxiety with symptoms of irritability and hostility.
Does not potentiate the CNS depression of alcohol.
Low potential for addiction.
Effective for up to 6 months.
Show minimal withdrawal effects.
Exhibit minimal rebound insomnia.
Little or no tolerance occurs with pronged use.
The potential for abuse is minimal with minimal dependence or withdrawal effects.
The drug can be administered long-term.
Slower onset of action than benzo-diazepines.
No muscle relaxation nor anticonvulsant activity.
Have no anticonvulsant or muscle-relaxing properties.
Has only marginal effects on objective measures of sleep efficacy.
Barbiturates
Phenobarbital
Pentobarbital
Secobarbital
Amobarbital
The barbiturates induce tolerance, drug-metabolizing enzymes, and physical dependence, and they show severe withdrawal symptoms.

DRUG	PEAK BLOOD LEVEL (HOURS)	ELIMINATION HALF-LIFE (HOURS)[1]	DURATION OF ACTION	COMMENTS
Benzodiazepines (short-acting):				
Oxazepam	2–4	10–40	3–8 hours	No active metabolites; useful in sleep onset
Triazolam	1	2–3	3–8 hours	Rapid onset; short duration of action
Benzodiazepines (intermediate-acting):				
Alprazolam	1–2	12–15	10–20 hours	Rapid oral absorption; useful in sleep maintenance
Lorazepam	1–6	10–20	10–20 hours	No active metabolites; useful in sleep maintenance
Temazepam	2–3	10–40	10–20 hours	Slow oral absorption
Estazolam	1–6	8–31	10–20 hours	Useful in sleep maintenance
Benzodiazepines (long-acting):				
Chlordiazepoxide	2–4	15–40	1–3 days	Active metabolites; erratic bioavailability from injection
Clorazepate	1–2 (*nordiazepam*)	50–100	1–3 days	Prodrug; hydrolyzed to active form in stomach
Diazepam	1–2	20–80	1–3 days	Active metabolites; erratic bioavailability from injection; useful in sleep maintenance
Flurazepam	1–2	40–100	1–3 days	Active metabolites with long half-lives; useful in sleep maintenance
Nonbenzodiazepines:				
Eszopiclone	<1	6	7 hours	Minor active metabolites; fast acting (20 min); useful in sleep maintenance
Zaleplon	<1	1–2	2–3 hours	Metabolized via aldehyde dehydrogenase; ultra short-acting; useful for sleep onset
Zolpidem[2]	1–3	1.5–3.5	5 hours	No active metabolites; fast acting (10–15 min of oral administration); short duration of action
Ramelteon	<1	1–3	7 hours	Promotes sleep initiation and maintenance

[1]Include half-lives of active metabolites

CNS Stimulants

PSYCHOMOTOR STIMULANTS
Methylxanthines
Caffeine
Theophylline
Nicotine
Varenicline
Cocaine
Amphetamine
Methamphetamine
Dextroamphetamine
Lisdexamfetamine
Methylphenidate or mixed amphetamine salts
Methylphenidate
Dexmethylphenidate
Modafinil
Armodafinil
Selective norepinephrine (noradrenaline) reuptake inhibitor
Atomoxetine
Hallucinogens
Lysergic acid diethyamide (LSD)
Tetrahydrocannabinol (Marihuana)

CNS stimulants:

drugs that act primarily to stimulate the central nervous system (CNS) are two groups :

1. Psychomotor stimulants:

stimulants cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity.

2. Hallucinogens:

produce profound changes in thought patterns and mood, with little effect on the brainstem and spinal cord.

A. Methylxanthines:

- include theophylline (tea); theobromine, (cocoa); and caffeine (coffee, tea, cola drinks, energy drinks, chocolate candy, and cocoa).

Mechanism: Several mechanisms have been proposed:

1. Including translocation of extracellular calcium.
2. Increase in CAMP and CGMP caused by inhibition of PDE.
3. Blockade of adenosine receptors. (most likely accounts for the actions achieved by the usual consumption of caffeine-containing beverages).

Actions:

a. **CNS:** The caffeine contained in one to two cups of coffee (100 - 200 mg) causes a decrease in fatigue and increased mental alertness as a result of stimulating the cortex and other areas of the brain.

- Consumption of 1.5 g of caffeine (12 - 15 cups of coffee) produces anxiety and tremors. The spinal cord is stimulated only by very high doses (2 - 5 g) of caffeine.
- Tolerance can rapidly develop to the stimulating properties of caffeine,
- Withdrawal consists of feelings of fatigue and sedation.

b. Cardiovascular system:

- A high dose of caffeine has positive inotropic and chronotropic effects on the heart. (Increased contractility can be harmful to patients with angina pectoris. In others, an accelerated heart rate can trigger premature ventricular contractions).

c. Diuretic action:

- Caffeine has a mild diuretic action that increases urinary output of sodium, chloride, and potassium.

d. Gastric mucosa:

- stimulate secretion of gastric acid, individuals with peptic ulcers should avoid foods and beverages containing methylxanthines.

Therapeutic uses:

- Caffeine and its derivatives relax the smooth muscles of the bronchioles. (replaced by β2 agonists and corticosteroids).
- Caffeine is also used in combination with the analgesics acetaminophen and aspirin for the management of headaches in both prescription and OTC products.

Adverse effects:

- Moderate doses of caffeine cause insomnia, anxiety, and agitation.
- A high dosage is required for toxicity, which is manifested by emesis and convulsions.
- The lethal dose is 10 g of caffeine (about 100 cups of coffee), which induces cardiac arrhythmias. Death from caffeine is, therefore, highly unlikely.
- Lethargy, irritability, and headache occur in users who routinely consume more than 600 mg of caffeine per day (roughly six cups of coffee per day) and then suddenly stop.

B. Nicotine

- the active ingredient in tobacco. Although this drug is not currently used therapeutically (except in smoking cessation therapy).
- nicotine is second only to caffeine as the most widely used CNS stimulant, and it is second only to alcohol as the most abused drug.
- In combination with the tars and carbon monoxide found in cigarette smoke, nicotine represents a serious risk factor for lung and cardiovascular disease, various cancers, and other illnesses.
- Dependency on the drug is not easily overcome.

Mechanism of action:

- In low doses: nicotine causes ganglionic stimulation by depolarization.
- At high doses, nicotine causes ganglionic blockade.
- Nicotine receptors exist at a number of sites in the CNS, which participate in the stimulant attributes of the drug.

Actions:

a. CNS:

- Nicotine is highly lipid soluble and readily crosses the BBB. Cigarette smoking or administration of low doses of nicotine produces some degree of euphoria and arousal, as well as relaxation. It improves attention, learning, problem solving, and reaction time.
- High doses of nicotine result in central respiratory paralysis and severe hypotension caused by medullary paralysis.
- Nicotine is also an appetite suppressant.

b. Peripheral effects: complex.

- Stimulation of sympathetic ganglia as well as of the adrenal medulla increases blood pressure and heart rate. Thus, use of tobacco is particularly harmful in hypertensive patients.
- Many patients with peripheral vascular disease experience an exacerbation of symptoms with smoking.
- Nicotine-induced vasoconstriction can decrease coronary blood flow, adversely affecting a patient with angina.
- At higher doses, blood pressure falls and activity ceases in both the gastrointestinal (GI) tract and bladder musculature as a result of a nicotine-induced block of parasympathetic ganglia.

Adverse effects:

- The CNS effects of nicotine include irritability and tremors.
- Intestinal cramps, diarrhea, and increased heart rate and blood pressure.

Withdrawal syndrome:

- Nicotine is an addictive substance, and physical dependence develops rapidly and can be severe .
- Withdrawal is characterized by irritability, anxiety, restlessness, difficulty concentrating, headaches, and insomnia. Appetite is affected, and GI upset often occurs.
- Smoking cessation programs that combine pharmacologic and behavioral therapy are the most successful in helping individuals to stop smoking. The transdermal patch and chewing gum containing nicotine have been shown to reduce nicotine withdrawal symptoms and to help smokers stop smoking.

- For example, the blood concentration of nicotine obtained from nicotine chewing gum is typically about one-half the peak level observed with smoking.
- Other forms of nicotine replacement used for smoking cessation include the inhaler, nasal spray, and lozenges.
- Bupropion, an antidepressant can reduce the craving for cigarettes.

C. Varenicline:

- A partial agonist at neuronal nicotinic acetylcholine receptors in the CNS.
- It produces less euphoric effects than nicotine. Thus, it is useful as an adjunct in the management of smoking cessation in patients with nicotine withdrawal symptoms.
- Attenuate the rewarding effects of nicotine if a person relapses and uses tobacco.
- AE: Patients taking varenicline should be monitored for suicidal thoughts, vivid nightmares, and mood changes.

D. Cocaine:

- widely available and highly addictive drug.
- Because of its abuse potential, cocaine is classified as a Schedule II drug.

Mechanism:

- blockade of reuptake of the monoamines (norepinephrine, serotonin, and dopamine) into the presynaptic terminals. This potentiates and prolongs the CNS and peripheral actions of these monoamines.
- Prolongation of dopaminergic effects in the brain's pleasure system (limbic system) produces the intense euphoria that cocaine initially causes.

- Chronic intake of cocaine depletes dopamine. This depletion triggers the vicious cycle of craving for cocaine that temporarily relieves severe depression.

E. Amphetamine:

- Sympathetic amine that shows neurologic and clinical effects quite similar to those of cocaine.
- Dextroamphetamine is the major member of this class of compounds.
- Methamphetamine (also known as “speed”) is a derivative of amphetamine available for prescription use. It can also be smoked and is preferred by many abusers.
- 3,4-Methylenedioxymethamphetamine (also known as MDMA, or Ecstasy) is a synthetic derivative of methamphetamine with both stimulant and hallucinogenic properties.

Mechanism:

- elevation of the level of catecholamine neurotransmitters in synaptic spaces. This is achieved by :

1. Releasing intracellular stores of catecholamines.
2. Inhibits monoamine oxidase (MAO) and
3. A weak reuptake transport inhibitor,

- Despite different mechanisms of action, the behavioral effects of amphetamine and its derivatives are similar to those of cocaine.

Actions:

a. CNS:

- Amphetamine stimulates the entire cerebrospinal axis, cortex, brainstem, and medulla. This leads to increased alertness, decreased fatigue, depressed appetite, and insomnia.
- Hyperactivity in children, for narcolepsy, and for appetite control.
- At high doses, psychosis and convulsions can ensue.

b. Sympathetic nervous system:

Acts on the adrenergic system, indirectly stimulating the receptors through norepinephrine release.

- **Therapeutic uses:**

a. Attention deficit hyperactivity disorder (ADHD):

Some young children are hyperkinetic and lack the ability to be involved in any one activity for longer than a few minutes.

- Dextroamphetamine, methamphetamine, the mixed amphetamine salts, and methylphenidate can help improve attention span and alleviate many of the behavioral problems associated with this syndrome, in addition to reducing hyperkinesia.
- Lisdexamfetamine is a prodrug that is converted to the active component dextroamphetamine after GI absorption and metabolism.
- Atomoxetine is a nonstimulant drug approved for ADHD in children and adults. [Note: This drug should not be taken by individuals on MAO inhibitors and by patients with angle-closure glaucoma.]
- is more selective for inhibition of norepinephrine reuptake. Therefore, it is not considered habit forming and is not a controlled substance.

b. Narcolepsy:

- a relatively rare sleep disorder that is characterized by uncontrollable bouts of sleepiness during the day. It is sometimes accompanied by catalepsy, a loss in muscle control, and even paralysis brought on by strong emotions such as laughter.
- The sleepiness can be treated with drugs, such as the mixed amphetamine salts or methylphenidate.
- Modafinil and its R-enantiomer derivative, armodafinil are considered first-line agents for the treatment of narcolepsy.
- Modafinil promotes wakefulness, but it produces fewer psychoactive and euphoric effects and fewer alterations in mood, perception, thinking, and feelings typical of other CNS stimulants.
- The mechanism of action remains unclear, but may involve the adrenergic and dopaminergic systems.
- AE: Headaches, nausea, and nervousness .
- Modafinil and armodafinil may have some potential for abuse and physical dependence, and both are classified as controlled substances.

c. Appetite suppression:

- Phentermine and diethylpropion are sympathomimetic amines that are related structurally to amphetamine.
- These agents are used for their appetite-suppressant effects in the management of obesity .

Pharmacokinetics:

- Amphetamine abusers often administer the drugs by IV injection and/or by smoking.
- The euphoria caused by amphetamine lasts 4 - 6 hrs, or 4 - 8 fold longer than the effects of cocaine.

AE:

- The amphetamines may cause addiction, leading to dependence, tolerance, and drug-seeking behavior.
- In addition, they have the following undesirable effects:

a. CNS effects:

- Insomnia, irritability, tremor, and hyperactive reflexes ,confusion, delirium, panic states, and suicidal tendencies, especially in mentally ill patients. Benzodiazepines, such as lorazepam, are often used in the management of agitation and CNS stimulation secondary to amphetamine overdose.
- Chronic amphetamine use produces a state of “amphetamine psychosis” that resembles the psychotic episodes associated with schizophrenia.
- Long-term amphetamine use is associated with psychic and physical dependence.
- Tolerance to its effects may occur within a few weeks.
- The anorectic effect of amphetamine is due to its action in the lateral hypothalamic feeding center.

b. Cardiovascular effects:

- Palpitations, cardiac arrhythmias, hypertension, anginal pain, and circulatory collapse.
- Headache, chills, and excessive sweating may also occur.

c. GI system effects:

Anorexia, nausea, vomiting, abdominal cramps, and diarrhea.

C/I:

Patients with hypertension, cardiovascular disease, hyperthyroidism, glaucoma, or a history of drug abuse or those taking MAO inhibitors should not be treated with amphetamine.

F. Methylphenidate

- CNS-stimulant properties similar to those of amphetamine and may also lead to abuse.
- Methylphenidate is presently one of the most prescribed medications in children.

Mechanism:

- Children with ADHD may produce weak dopamine signals.
- Methylphenidate is a dopamine and norepinephrine transport inhibitor and may act by increasing both dopamine and norepinephrine in the synaptic space.
- Methylphenidate may have less potential for abuse than cocaine, because it enters the brain much more slowly and, thus, does not increase dopamine levels rapidly.

Therapeutic uses:

- ADHD.
- narcolepsy.

AE:

- GI: abdominal pain, nausea& anorexia.
- Insomnia, nervousness, and fever.
- In seizure patients, methylphenidate may increase seizure frequency, especially if the patient is taking antidepressants.

C/I: glaucoma.

Hallucinogens:

- Induce altered perceptual states reminiscent of dreams, accompanied by visions of bright, colorful changes in the environment and by a plasticity of constantly changing shapes and color.
- The individual under the influence of these drugs is incapable of normal decision making because the drug interferes with rational thought.
- lysergic acid diethylamide (LSD) and tetrahydrocannabinol (from marijuana) are

examples of agents in this class.

Introduction to CNS

Tikrit University
College of Pharmacy
Department of Pharmacology & Toxicology
By:- Ass. Lec. Rabei Abdullah Salih

Pharmacology- II

Theory: 3 hours/week **Practical: 2 hours/week**
Units:4 **Course number: 414**

No.	Lecture title	Hours
1.	Introduction to CNS pharmacology	2
2.	CNS stimulants	2
3.	Anxiolytic and Hypnotic drugs	3
4.	General and Local Anesthetics	3
5.	Antidepressant drugs	3
6.	Antipsychotic (neuroleptic) drugs	2
7.	Opioid analgesics and antagonists	3
8.	Treatment of neurodegenerative diseases	3
9.	Antiepileptic Drugs	2
10.	Diuretics	2
11	The treatment of heart failure (HF)	2
12	Antiarrhythmic drugs	2
13.	Antianginal Drugs	2
14.	Antihypertensive drugs	3
15.	Drugs affecting the blood	3
16.	Antihyperlipidemic drugs	2
17.	Gastrointestinal and antiemetic drugs	3
18.	Drugs acting on the respiratory system	3

Reference text

Howland RD, Mycek MJ. Lipincotts Illustrated Reviews Pharmacology, 6th edition, 2013, Lippincott William and Wilkins, Philadelphia.

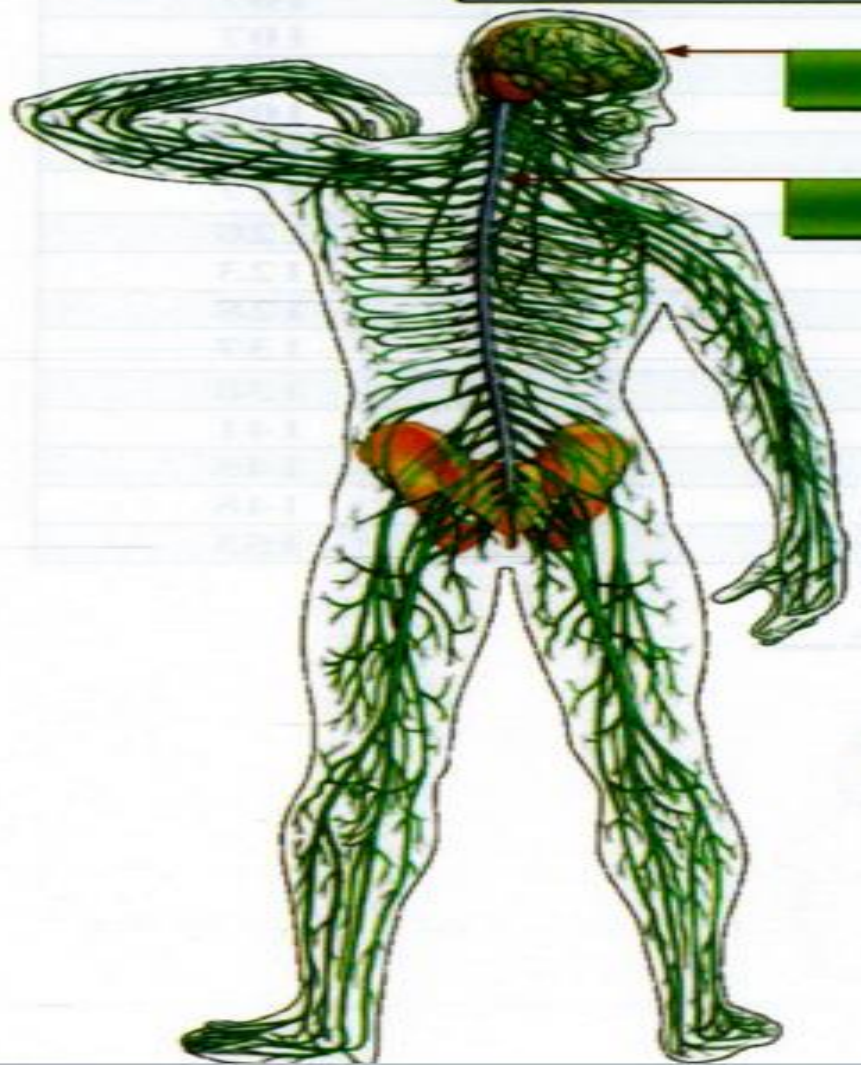
Nervous system

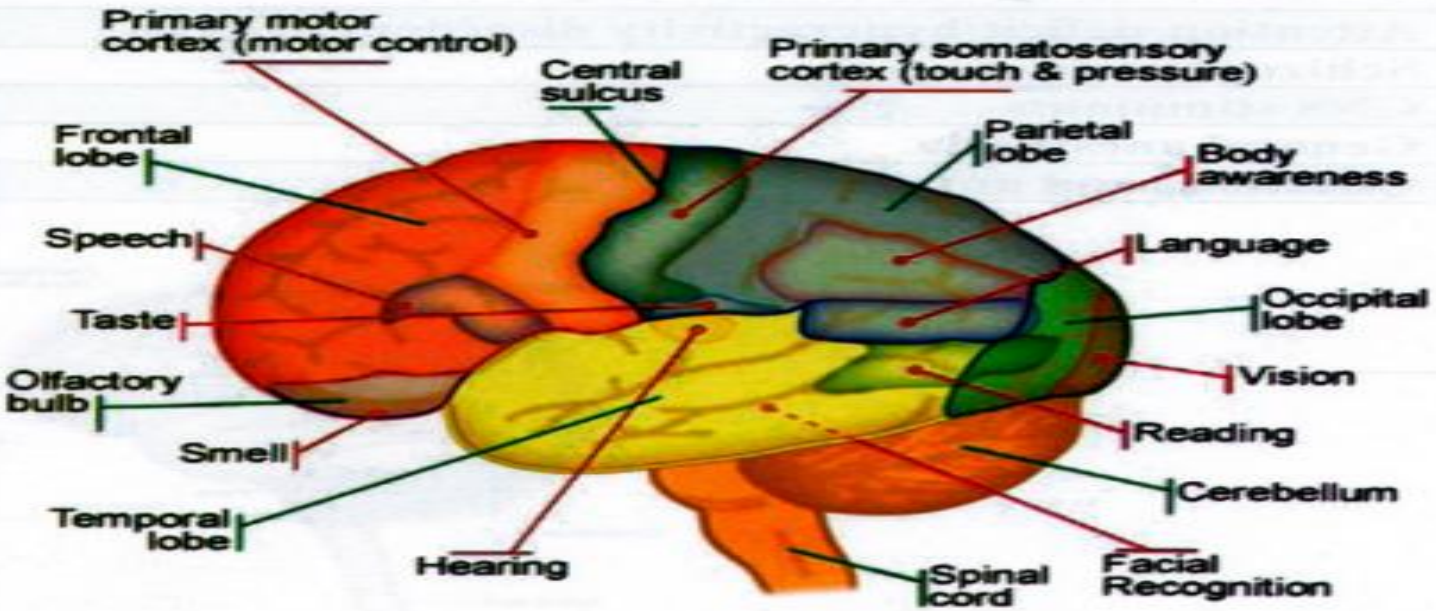
(CNS)
Central Nervous System

(PNS)
Peripheral Nervous System

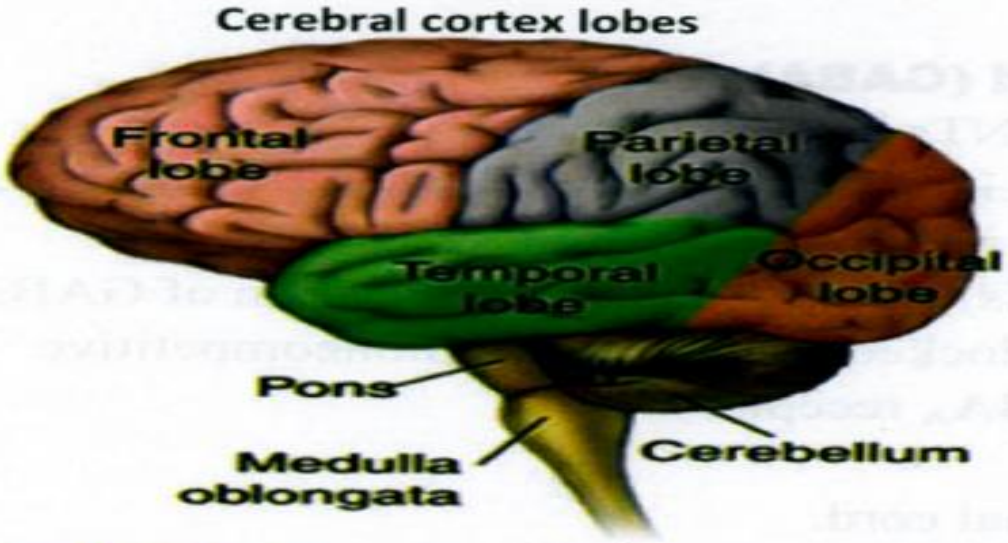
Brain

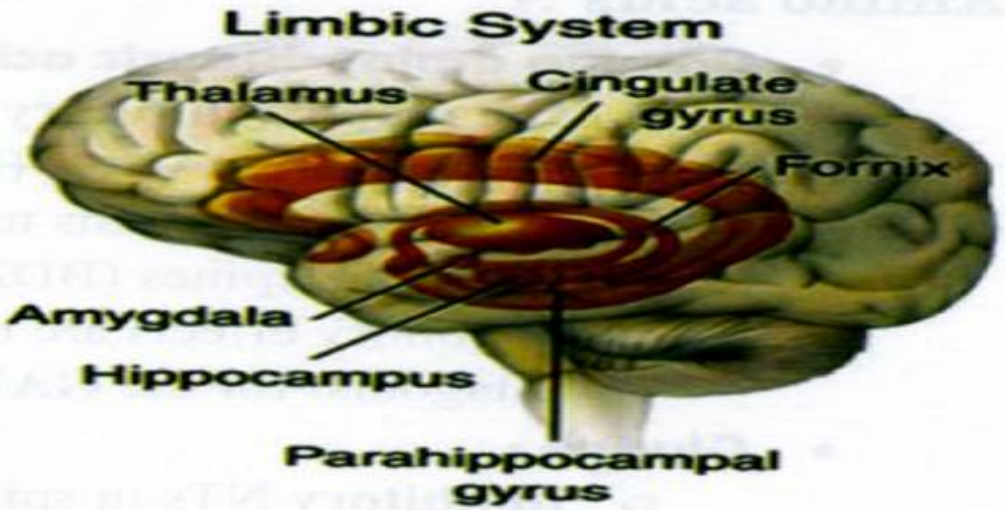
Spinal cord





Anatomical subdivision of the brain





- **Forebrain :-**
  - **Cerebral cortex :**
    - ***Function***: Thought, speech, perception and reasoning (Receives and processes sensory information).
  - **Basal ganglia :**
    - ***Function***: Voluntary movement.
  - **Limbic system :**
    - ***Function***: Behavior, Emotional reaction, Learning and memory.
  - **Thalamus :**
    - ***Function***: Sensory processing (Pain sensation).
  - **Hypothalamus :**
    - ***Function***: Regulation of body temperature, emotions, sleeping, hunger, thirst and sexual response

- **Midbrain :-**
  - *Function:* Vision and hearing (due to presence of their centers in it).
- **Hindbrain :-**
  - **Cerebellum :**
    - *Function:* Movement, balance and posture.
  - **Pons :**
    - *Function:* Respiration (due to respiratory center) and Relays sensory information between the cerebrum down to the cerebellum and medulla oblongata.
  - **Medulla oblongata :**
    - *Function:* Heart rate and blood pressure regulation (Autonomic function).

Central (brain) neurotransmitter (NTs)

➢ Amino acids :-

- **Gamma amino-butyric acid (GABA) :**
  - The **major inhibitory** NTs in the CNS.
  - Act on both $GABA_A$ (Ligand gated ion channel (Cl^- channel)) and $GABA_B$ (G-proteins to potassium channels) receptors.
  - Benzodiazepines (BDZs) act by enhancing the action of GABA.
  - Inhibitory effects are blocked by Picrotoxin (noncompetitive antagonist for the **$GABA_A$** receptor).
- **Glycine :**
  - **Inhibitory** NTs in spinal cord.
  - Act on Glycine receptor (GlyR) → opening Cl^- channels.
  - Strychnine selective glycine receptor blocker.
- **Aspartate and glutamate :**
  - Both are **excitatory** NTs in CNS.
  - They act on N-methyl-D-aspartate (NMDA) receptor.

➢ Acetylcholine :-

- It is excitatory NT in the basal ganglia (Act on M_1 receptor).
- Loss of cholinergic neurons in the bran results in Alzheimer's disease
- Its excitatory effects are blocked by Atropine.

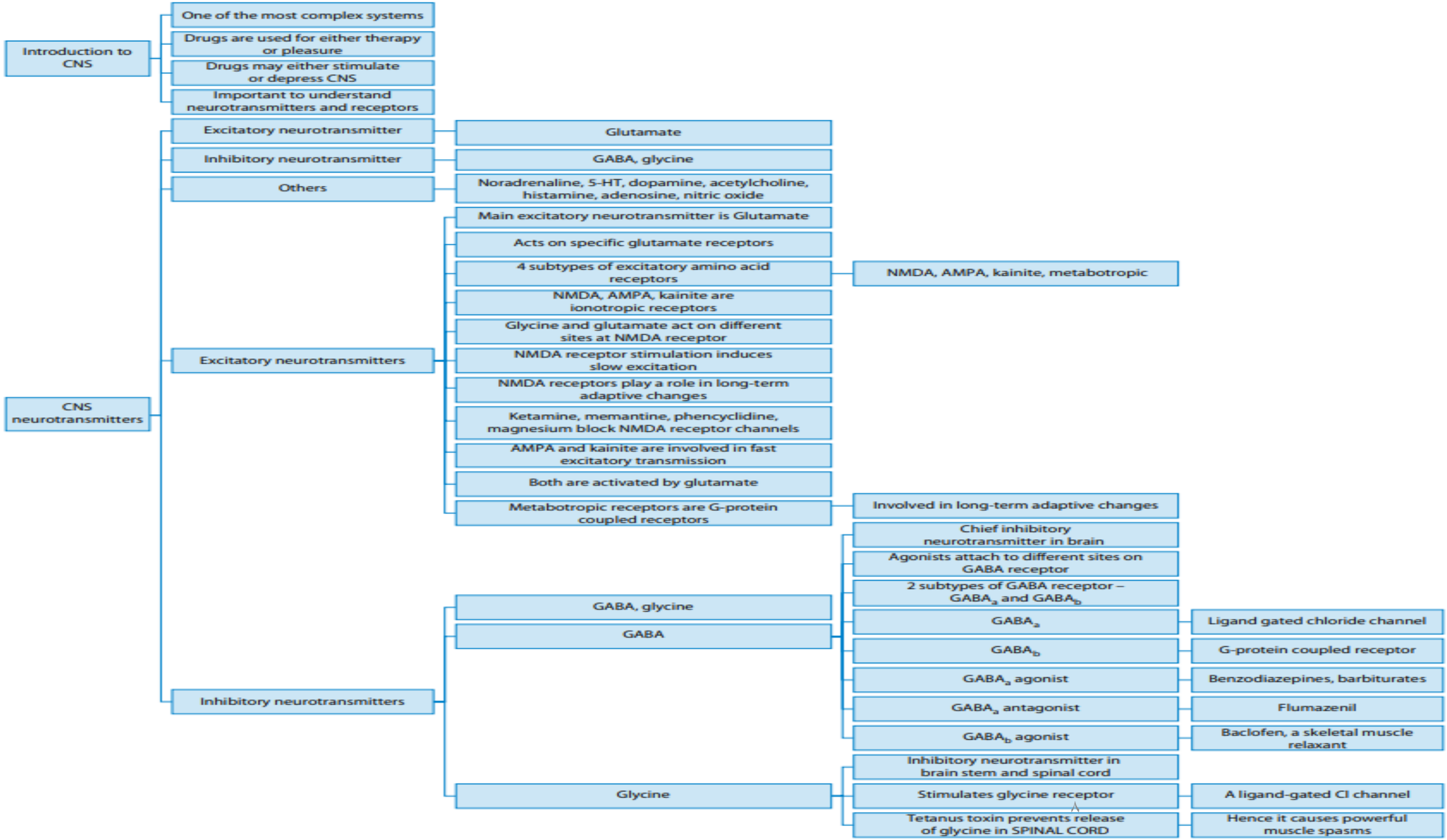
➢ Monoamines :-

- **Dopamine :**
  - Generally exerts a slow inhibitory action on the CNS.
  - Dysfunction of the dopamine system is also implicated in Parkinson's disease and schizophrenia.
- **Norepinephrine (NE) :**
  - Mainly located in the locus coeruleus and the lateral tegmental field.
  - May be involved in regulation of mood and blood pressure.
- **5-Hydroxy tryptamine (5-HT) (Serotonin) :**
  - It has both excitatory (5-HT_3) and inhibitory (5-HT_{1A}) effects.
  - It is secreted by neurons in pons and mid brain.
  - It is responsible for regulation of mood, sleep, appetite and temperature

➢ Peptides :-

- **Opioids :** → E.g. Endorphins, Enkephalins and Dynorphins.
- **Non-oipoids :** → E.g. Neurotensin, Neuropeptide and Substance-P.

In normal Situation There is a balance between the excitatory NTs and the inhibitory NTs.


Introduction to CNS
One of the most complex systems
Drugs are used for either therapy or pleasure
Drugs may either stimulate or depress CNS
Important to understand neurotransmitters and receptors
CNS neurotransmitters
Excitatory neurotransmitter
Glutamate
Inhibitory neurotransmitter
GABA, glycine
Others
Noradrenaline, 5-HT, dopamine, acetylcholine, histamine, adenosine, nitric oxide
Excitatory neurotransmitters
Main excitatory neurotransmitter is Glutamate
Acts on specific glutamate receptors
4 subtypes of excitatory amino acid receptors
NMDA, AMPA, kainite, metabotropic
NMDA, AMPA, kainite are ionotropic receptors
Glycine and glutamate act on different sites at NMDA receptor
NMDA receptor stimulation induces slow excitation
NMDA receptors play a role in long-term adaptive changes
Ketamine, memantine, phencyclidine, magnesium block NMDA receptor channels
AMPA and kainite are involved in fast excitatory transmission
Both are activated by glutamate
Metabotropic receptors are G-protein coupled receptors
Involved in long-term adaptive changes
Inhibitory neurotransmitters
GABA, glycine
GABA
Chief inhibitory neurotransmitter in brain
Agonists attach to different sites on GABA receptor
2 subtypes of GABA receptor – GABA$_a$ and GABA$_b$
GABA$_a$
Ligand gated chloride channel
GABA$_b$
G-protein coupled receptor
GABA$_a$ agonist
Benzodiazepines, barbiturates
GABA$_a$ antagonist
Flumazenil
GABA$_b$ agonist
Baclofen, a skeletal muscle relaxant
Glycine
Inhibitory neurotransmitter in brain stem and spinal cord
Stimulates glycine receptor
A ligand-gated Cl channel
Tetanus toxin prevents release of glycine in SPINAL CORD
Hence it causes powerful muscle spasms

Acetylcholine

Approximately 5% of brain neurons have receptors for acetylcholine (ACh). Drugs affecting the activity of cholinergic systems in the brain include the acetylcholinesterase inhibitors used in Alzheimer's disease (e.g., rivastigmine) and the muscarinic blocking agents used in parkinsonism (e.g., benztropine).

Dopamine

The D2 receptor is the main dopamine subtype in basal ganglia neurons, other dopamine receptor subtypes have been identified (D3, D4, and D5). Drugs that block the activity of dopaminergic pathways include older antipsychotics (e.g., chlorpromazine, haloperidol), which may cause parkinsonian symptoms. Drugs that increase brain dopaminergic activity include CNS stimulants (e.g., amphetamine), and commonly used antiparkinsonism drugs (e.g., levodopa).

Norepinephrine

Excitatory effects are produced by activation of α1 and β1 receptors. Inhibitory effects are caused by activation of α2 and β2 receptors. CNS stimulants (eg, amphetamines [used in attention deficit hyperactivity disorder, ADHD], cocaine), monoamine oxidase inhibitors (eg, phenelzine), and tricyclic antidepressants (eg, amitriptyline) are examples of drugs that enhance the activity of noradrenergic pathways.

Serotonin

Most serotonin (5-hydroxytryptamine; 5-HT) pathways originate from cell bodies. Most of the agents used in the treatment of major depressive disorders affect serotonergic pathways to some degree (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors).

Glutamic Acid

Most neurons in the brain are excited by glutamic acid. High concentrations of glutamic acid in synaptic vesicles are achieved by the vesicular glutamate transporter (VGLUT). There are three major subtypes of glutamate receptors. The N-methyl d-aspartate (NMDA) receptor is blocked by phencyclidine (PCP) and ketamine. NMDA receptors appear to play a role in synaptic plasticity related to learning and memory. Memantine is an NMDA antagonist approved for treatment of Alzheimer's dementia. Excessive activation of NMDA receptors after neuronal injury may be responsible for cell death.

The second glutamate receptor type, the AMPA receptors, mediate an excitatory postsynaptic increase in both Na^+ and K^+ conductance. An important marine toxin, domoic acid, activates the third glutamate receptor type: kainate receptors, and causes excitatory toxicity. Activation of various glutamate metabotropic receptors can reduce presynaptic Ca^{2+} conductance, decrease cAMP, decrease K^+ conductance, and increase IP3 and DAG.

GABA and Glycine

GABA is the primary neurotransmitter mediating Inhibitory postsynaptic potential (IPSPs) in neurons in the brain; it is also important in the spinal cord. GABAA receptor activation opens chloride ion channels. GABAB receptors (activated by baclofen, a centrally acting muscle relaxant) are coupled to G proteins that either open a potassium channel that is shared with 5-HT1A receptors, or close calcium channels.

Fast IPSPs are blocked by GABAA receptor antagonists, and slow IPSPs are blocked by GABAB receptor antagonists. Drugs that influence GABAA receptor systems include sedative-hypnotics (eg, barbiturates, benzodiazepines, zolpidem) and some anticonvulsants (eg, gabapentin, tiagabine, vigabatrin). Glycine receptors, which are more numerous in the cord than in the brain, are blocked by strychnine, a spinal convulsant.

Peptide Transmitters

The best-defined peptides are the opioid peptides (beta-endorphin, met- and leu-enkephalin, and dynorphin). Some of the important therapeutic actions of opioid analgesics (eg, morphine) are mediated via activation of receptors for these endogenous peptides.
Another peptide, substance P, is a mediator of slow EPSPs in neurons involved in nociceptive sensory pathways in the spinal cord and brain stem. Orexins are peptides associated with sleep-wake cycling and promote wakefulness.
Peptide transmitters differ from nonpeptide transmitters in that
(1) the peptides are synthesized in the cell body and transported to the nerve ending via axonal transport, and
(2) no reuptake or specific enzyme mechanisms have been identified for terminating their actions.

Endocannabinoids

These are widely distributed brain lipid derivatives (eg, 2-arachidonyl-glycerol) that bind to receptors for the cannabinoids found in marijuana. They are synthesized and released postsynaptically after membrane depolarization but diffuse backward (retrograde), acting presynaptically to decrease transmitter release, via their interaction with a specific cannabinoid receptor.

Other Transmitters

Histamine receptors are widely distributed in the brain and appear to modulate arousal, appetite, and memory. Centrally acting antihistamines have significant sedative and anti-motion sickness effects.
Nitric oxide is not stored but synthesized on demand. Purines are cotransmitters in several types of transmitter vesicles and receptors for ATP, adenosine, UTP, and UDP are found in the CNS.
ATP acts on metabotropic A1 receptors to inhibit calcium channels and reduce the release of other transmitters. ATP also acts on P2X and P2Y receptors.

NEUROTRANSMITTER		POSTSYNAPTIC EFFECTS
	Acetylcholine	Excitatory: Involved in arousal, short-term memory, learning and movement.
BIOGENIC AMINES	Norepinephrine	Excitatory: Involved in arousal, wakefulness, mood, and cardiovascular regulation.
	Dopamine	Excitatory: Involved in emotion, reward systems and motor control.
	Serotonin	Excitatory/Inhibitory: Feeding behavior, control of body temperature, modulation of sensory pathways including nociception (stimulation of pain nerve sensors), regulation of mood and emotion, and sleep/wakefulness.
AMINO ACIDS	GABA	Inhibitory: Increases Cl^- flux into the postsynaptic neuron, resulting in hyperpolarization. Mediates the majority of inhibitory postsynaptic potentials.
	Glycine	Inhibitory: Increases Cl^- flux into the postsynaptic neuron, resulting in hyperpolarization.
	Glutamate	Excitatory: Mediates excitatory Na^+ influx into the postsynaptic neuron.
NEURO-PEPTIDES	Substance P	Excitatory: Mediates nociception (pain) within the spinal cord.
	Met-enkephalin	Generally inhibitory: Mediates analgesia as well as other central nervous system effects.

TABLE 21–1 Neurotransmitter pharmacology in the CNS.

Transmitter	Anatomical Distribution	Receptor Subtypes	Receptor Mechanisms
Acetylcholine	Cell bodies at all levels, short and long axons	Muscarinic, M_1; blocked by pirenzepine and atropine	Excitatory; ↓ K^+ conductance; ↑ IP_3 and DAG
		Muscarinic, M_2; blocked by atropine	Inhibitory; ↑ K^+ conductance; cAMP
	Motoneuron-Renshaw cell synapse	Nicotinic, N	Excitatory; ↑ cation conductance
Dopamine	Cell bodies at all levels, short, medium, and long axons	D_1; blocked by phenothiazines	Inhibitory; ↑ cAMP
		D_2; blocked by phenothiazines and haloperidol	Inhibitory (presynaptic); ↓ Ca^{2+} conductance
			Inhibitory (postsynaptic); ↑ K^+ conductance; ↓ cAMP
Norepinephrine	Cell bodies in pons and brain stem project to all levels	$Alpha_1$; blocked by prazosin	Excitatory; ↓ K^+ conductance; ↑ IP_3 and DAG
		$Alpha_2$; activated by clonidine	Inhibitory (presynaptic); ↓ Ca^{2+} conductance
			Inhibitory (postsynaptic); ↑ K^+ conductance; ↓ cAMP
		$Beta_1$; blocked by propranolol	Excitatory; ↓ K^+ conductance; ↑ cAMP
		$Beta_2$; blocked by propranolol	Inhibitory; ↑ electrogenic sodium pump
Serotonin (5-hydroxytryptamine)	Cell bodies in midbrain and pons project to all levels	$5\text{-}HT_{1A}$; buspirone is a partial agonist	Inhibitory; ↑ K^+ conductance
		$5\text{-}HT_{2A}$; blocked by clozapine, risperidone, and olanzapine	Excitatory; ↓ K^+ conductance; ↑ IP_3 and DAG
		$5\text{-}HT_3$; blocked by ondansetron	Excitatory; ↑ cation conductance
		$5\text{-}HT_4$	Excitatory; ↓ K^+ conductance; ↑ cAMP
GABA	Supraspinal interneurons; spinal interneurons involved in presynaptic inhibition	$GABA_A$; facilitated by benzodiazepines and zolpidem	Inhibitory; ↑ Cl^- conductance
		$GABA_B$; activated by baclofen	Inhibitory (presynaptic); ↓ Ca^{2+} conductance
			Inhibitory (postsynaptic); ↑ K^+ conductance
Glutamate, aspartate	Relay neurons at all levels	Four subtypes; NMDA subtype blocked by phencyclidine, ketamine, and memantine	Excitatory; ↑ Ca^{2+} or cation conductance
		Metabotropic subtypes	Inhibitory (presynaptic); ↓ Ca^{2+} conductance; ↓ cAMP
			Excitatory (postsynaptic); ↓ K^+ conductance; ↑ IP^3 and DAG
Glycine	Interneurons in spinal cord and brain stem	Single subtype; blocked by strychnine	Inhibitory; ↑ Cl^- conductance
Opioid peptides	Cell bodies at all levels	Three major subtypes: μ, δ, κ	Inhibitory (presynaptic); ↓ Ca^{2+} conductance; ↓ cAMP ١٤
			Inhibitory (postsynaptic); ↑ K^+ conductance; ↓ cAMP