Drugs for Neurodegenerative Disease

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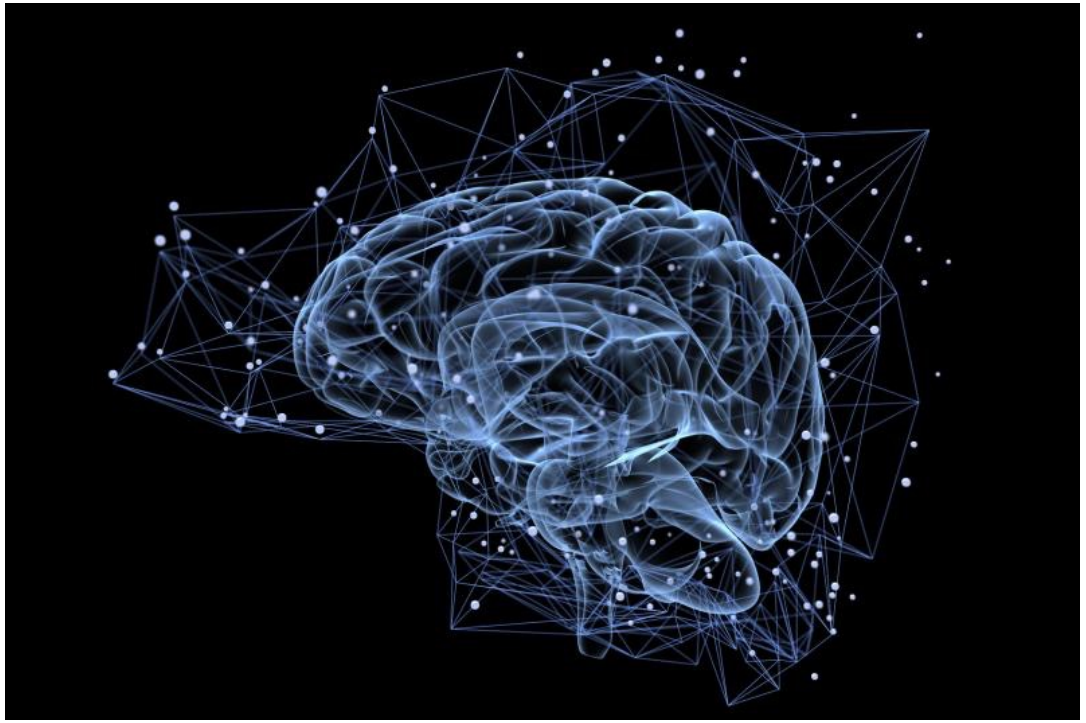


Synaptic Potentials

- In the CNS, receptors at most synapses are coupled to ion channels.

- Binding of the neurotransmitter to the postsynaptic membrane receptors results in a rapid but transient opening of ion channels. Open channels allow specific ions inside and outside the cell membrane to flow down their concentration gradients.

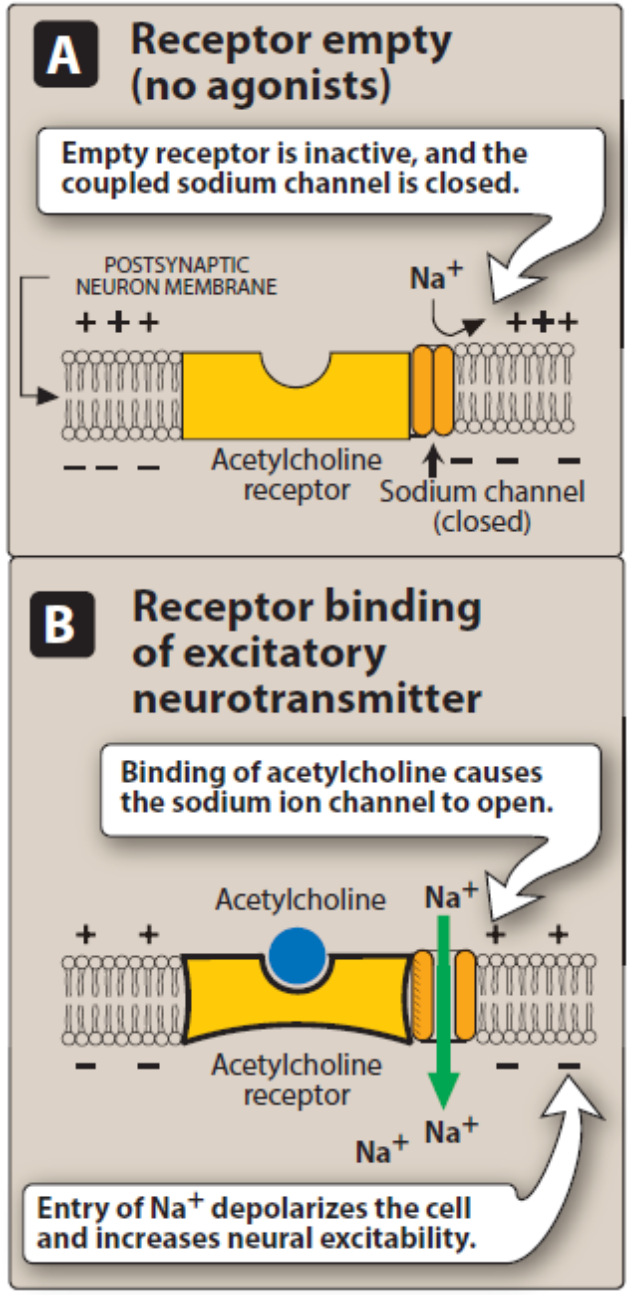
- The resulting change in the ionic composition across the membrane of the neuron alters the postsynaptic potential, producing either depolarization or hyperpolarization of the postsynaptic membrane, depending on the specific ions and the direction of their movement.

Excitatory pathways

- Neurotransmitters can be classified as either excitatory or inhibitory, depending on the nature of the action they elicit. Stimulation of excitatory neurons causes a movement of ions that results in a depolarization of the postsynaptic membrane.
- These excitatory postsynaptic potentials (EPSP) are generated by the following:

1. Stimulation of an excitatory neuron causes the release of neurotransmitter molecules, such as glutamate or acetylcholine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of sodium (Na^+) ions.
2. The influx of Na^+ causes a weak depolarization, or EPSP, that moves the postsynaptic potential toward its firing threshold.
3. If the number of stimulated excitatory neurons increases, more excitatory neurotransmitter is released. This ultimately causes the EPSP depolarization of the postsynaptic cell to pass a threshold, thereby generating an all-or-none action potential.

- The generation of a nerve impulse typically reflects the activation of synaptic receptors by thousands of excitatory neurotransmitter molecules released from many nerve fibers.



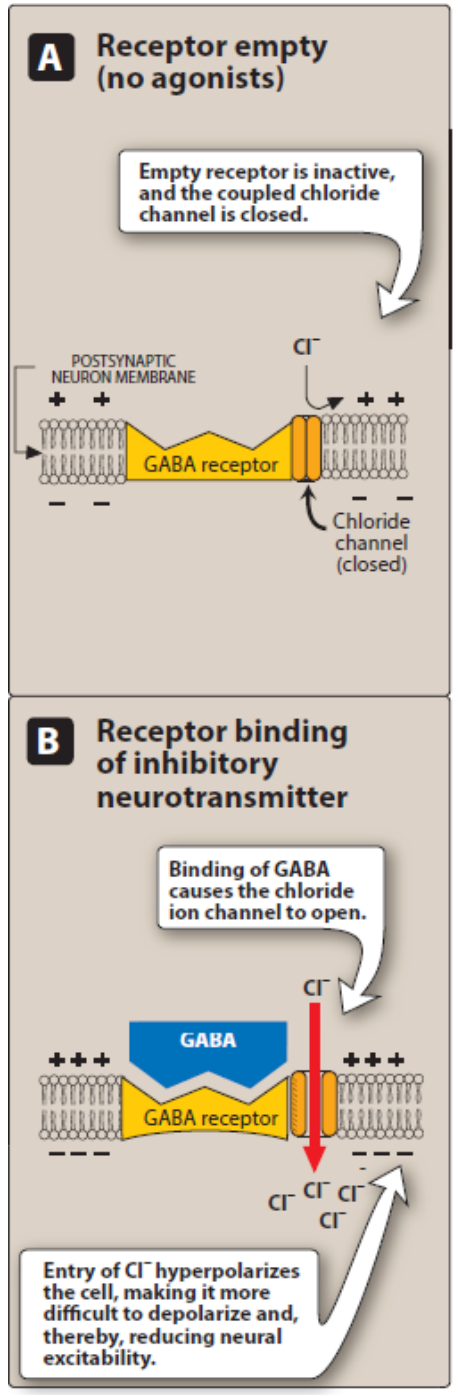
Inhibitory pathways

- Stimulation of inhibitory neurons causes movement of ions that results in a hyperpolarization of the postsynaptic membrane.

- These inhibitory postsynaptic potentials (IPSP) are generated by the following:

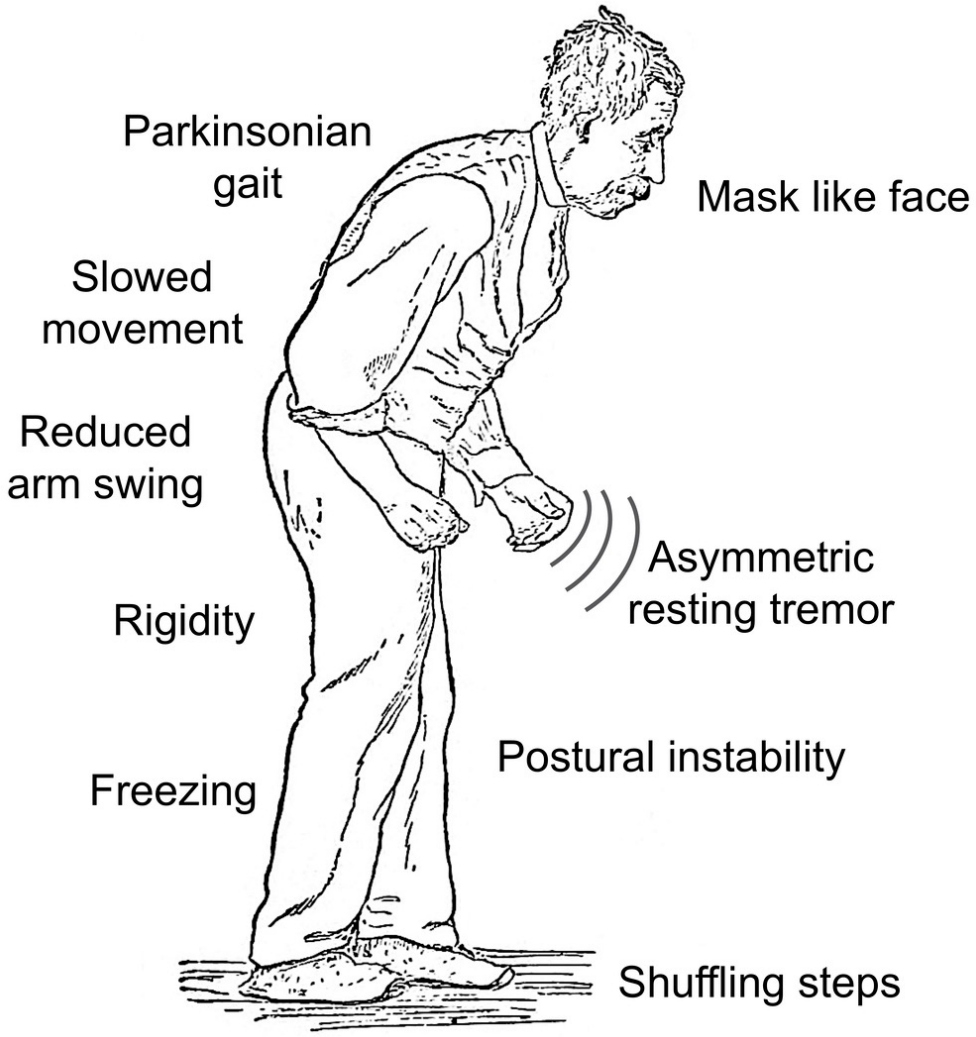
1. Stimulation of inhibitory neurons releases neurotransmitter molecules, such as γ-aminobutyric acid (GABA) or glycine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of specific ions, such as potassium (K^+) and chloride (Cl^-).

2. The influx of Cl^- and efflux of K^+ cause a weak hyperpolarization, or IPSP, that moves the postsynaptic potential away from its firing threshold. This diminishes the generation of action potentials.



Parkinson disease

- Parkinsonism is a progressive neurological disorder of muscle movement.
- It is characterized by tremors, muscular rigidity, bradykinesia (slowness in initiating and carrying out voluntary movements), and postural and gait abnormalities.
- Most cases involve people over the age of 65, among whom the incidence is about 1 in 100 individuals.



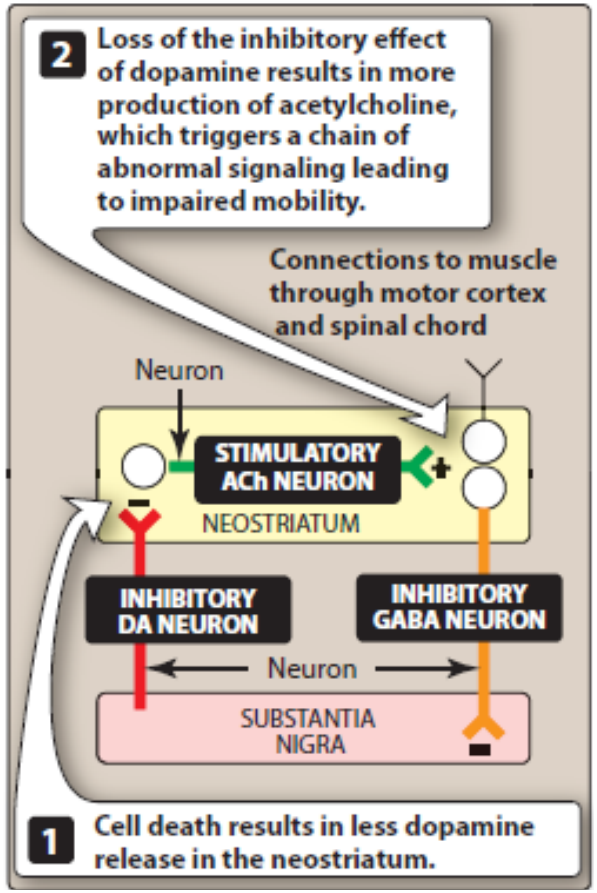
Parkinson disease - Etiology

- The cause of Parkinson's disease is unknown for most patients. The disease is correlated with destruction of dopaminergic neurons in the substantia nigra with a consequent reduction of dopamine actions in the corpus striatum, parts of the basal ganglia system that are involved in motor control.

1. **Substantia nigra:** The substantia nigra, part of the extrapyramidal system, is the source of dopaminergic neurons that terminate in the neostriatum. Each dopaminergic neuron makes thousands of synaptic contacts within the neostriatum and, therefore, modulates the activity of a large number of cells. These dopaminergic projections from the substantia nigra fire tonically rather than in response to specific muscular movements or sensory input. Thus, the dopaminergic system appears to serve as a tonic, sustaining influence on motor activity, rather than participating in specific movements.

2. **Neostriatum:** the neostriatum is connected to the substantia nigra by neurons that secrete the inhibitory transmitter GABA at their termini. In turn, cells of the substantia nigra send neurons back to the neostriatum, secreting the inhibitory transmitter dopamine at their termini. This mutual inhibitory pathway normally maintains a degree of inhibition of both areas.

- In Parkinson's disease, destruction of cells in the substantia nigra results in the degeneration of the nerve terminals that secrete dopamine in the neostriatum. Thus, the normal inhibitory influence of dopamine on cholinergic neurons in the neostriatum is significantly diminished, resulting in overproduction or a relative overactivity of acetylcholine by the stimulatory neurons. This triggers a chain of abnormal signaling, resulting in loss of the control of muscle movements.



Parkinson disease - Etiology

- **Secondary parkinsonism:** Drugs such as the phenothiazines and haloperidol, whose major pharmacologic action is blockade of dopamine receptors in the brain, may produce parkinsonian symptoms (also called pseudoparkinsonism).

- These drugs should be used with caution in patients with Parkinson's disease.

Levodopa and carbidopa

- Levodopa is a metabolic precursor of dopamine. It restores dopaminergic neurotransmission in the neostriatum by enhancing the synthesis of dopamine in the surviving neurons of the substantia nigra.

- Carbidopa is a dopamine decarboxylase inhibitor, diminishes the metabolism of *levodopa* in the periphery, thereby increasing the availability of *levodopa* to the CNS.

- Levodopa must be administered with *carbidopa*. Without *carbidopa*, much of the drug is decarboxylated to dopamine in the periphery, resulting in side effects.

- Side effects: gastric upset, nausea, vomiting, cardiac arrhythmias, orthrostatic hypotension, dyskinesia, hallucination, confusion.
- Pharmacokinetic: must be taken on empty stomach ! WHY?

- What is the “wearing off” effect?
- What is the on-off fluctuation effect?

Dopamine receptor agonists

Bromocriptine, Ropinirole, Pramipexole, Rotigotine, Apomorphine

- These agents have a longer duration of action than that of Levodopa and are effective in patients exhibiting fluctuations in response to Levodopa.
- *Bromocriptine, pramipexole, and ropinirole* are effective in patients with Parkinson's disease complicated by motor fluctuations and dyskinesias.
- These drugs are ineffective in patients who have not responded to Levodopa.
- *Apomorphine* is an injectable dopamine agonist that is used in severe and advanced stages of the disease to supplement oral medications.

Monoamine oxidase (MAO) inhibitors

Selegiline and Rasagiline

- They selectively inhibits MAO type B at low to moderate doses.
- Selegiline is metabolized to *methamphetamine* and *amphetamine,* whose stimulating properties may produce insomnia if the drug is administered later than mid-afternoon.
- Rasagiline is an irreversible and selective inhibitor of brain MAO type B, has five times the potency of Selegiline.
- Unlike Selegiline, Rasagiline is not metabolized to an *amphetamine*-like substance

Antimuscarinic drugs

benztropine trihexyphenidyl, procyclidine, biperiden

- The antimuscarinic agents are much less efficacious than *levodopa* and play only an adjuvant role in anti-parkinsonism therapy.

- Blockage of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission, since it helps to correct the imbalance in the dopamine/acetylcholine ratio.

- These agents can induce mood changes and produce xerostomia (dryness of the mouth), constipation, and visual problems typical of muscarinic blockers.

- They interfere with gastrointestinal peristalsis and are contraindicated in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis.

Catechol-O-methyltransferase (COMT) inhibitors

Entacapone and Tolcapone

- They selectively and reversibly inhibit COMT and leads to decreased plasma concentrations of 3-*O*-methyldopa, increased central uptake of *levodopa,* and greater concentrations of brain dopamine.

- They reduce the symptoms of “wearing-off” phenomena seen in patients on levodopa−carbidopa.

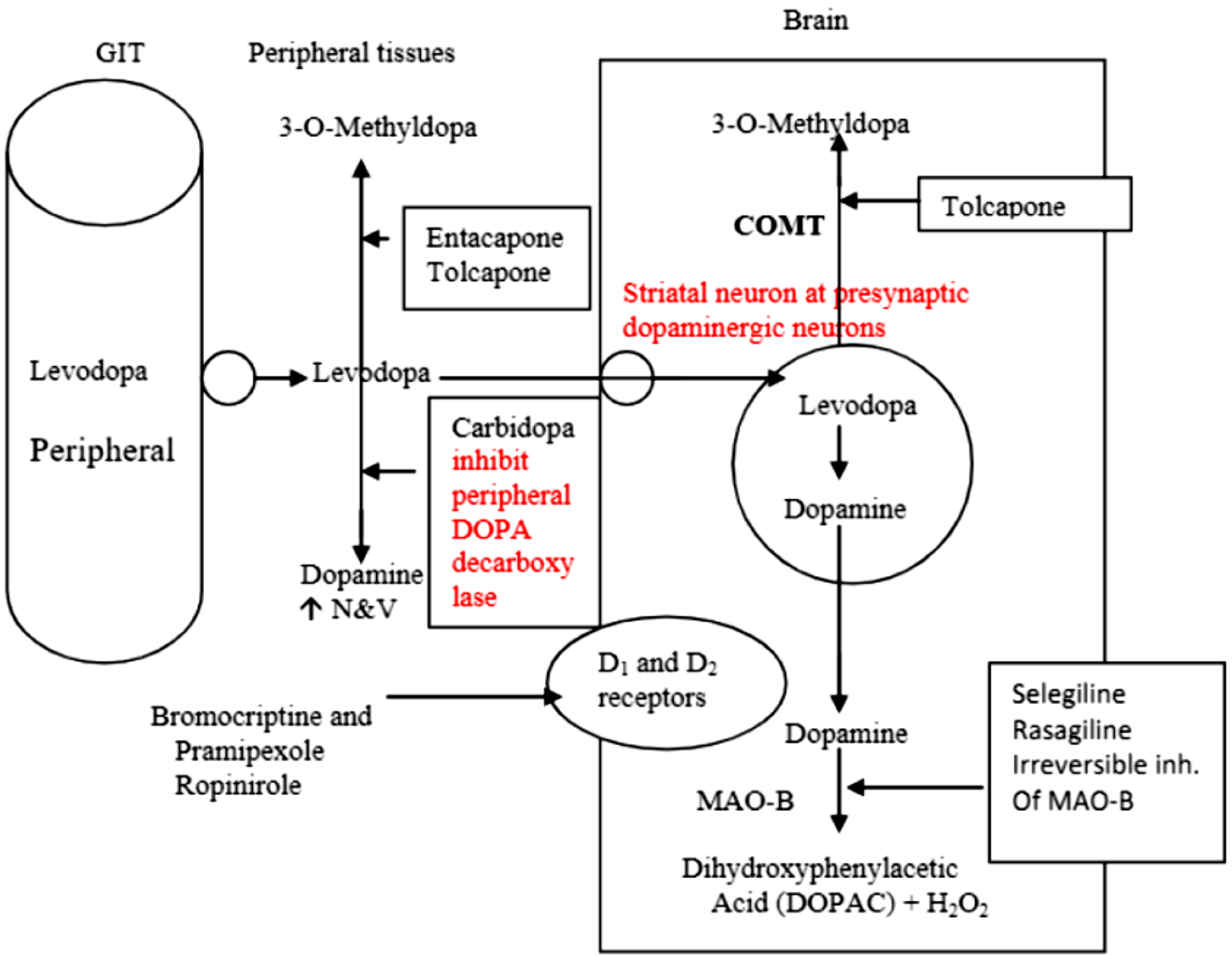
- The two drugs differ primarily in their pharmacokinetic and adverse effect profiles.

Amantadine

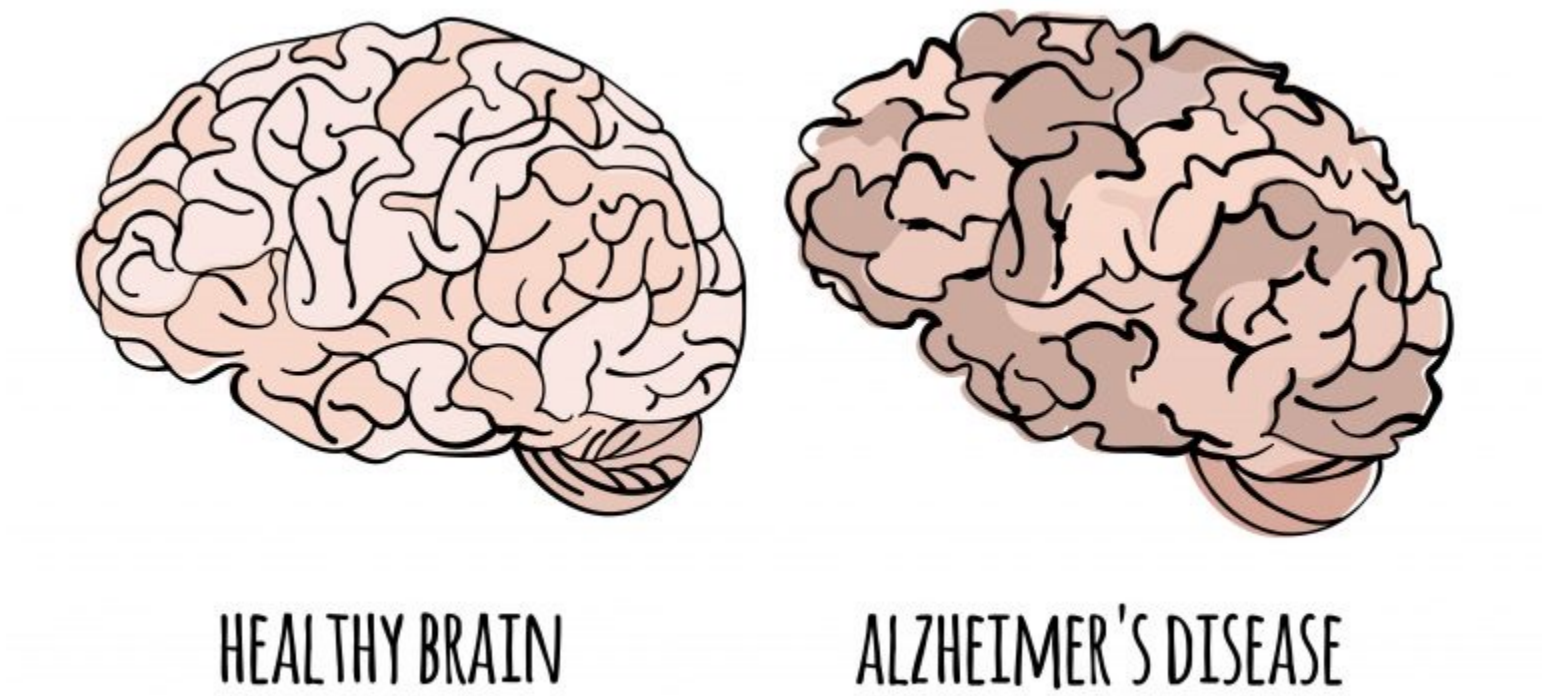
- It increases the release of dopamine, blocks cholinergic receptors, and inhibits the *N*-methyl-D-aspartate (NMDA) type of glutamate receptors.

- *Amantadine* is less efficacious than *levodopa,* and tolerance develops more readily.

- However, *amantadine* has fewer side effects.


Brain
GIT
Peripheral tissues
3-O-Methyldopa
3-O-Methyldopa
Tolcapone
COMT
Entacapone
Tolcapone
Striatal neuron at presynaptic dopaminergic neurons
Levodopa
Peripheral
Levodopa
Levodopa
Carbidopa
inhibit peripheral DOPA decarboxy lase
Dopamine
Dopamine
Dopamine
↑ N&V
D1 and D2 receptors
Bromocriptine and
Pramipexole
Ropinirole
Selegiline
Rasagiline
Irreversible inh.
Of MAO-B
MAO-B
Dihydroxyphenylacetic
Acid (DOPAC) + H2O2

Alzheimer Disease



Alzheimer disease (Dementia)

- Dementia has three distinguishing features:

1) Accumulation of senile plaques (β-amyloid accumulations).
2) Formation of numerous neurofibrillary tangles.
3) Loss of cortical neurons, particularly cholinergic neurons.

- Current therapies aim to either:

1. Improve cholinergic transmission within the CNS.
2. Prevent excitotoxic actions resulting from overstimulation of NMDA-glutamate receptors in selected areas of the brain.

Acetylcholinesterase inhibitors

Donepezil, Galantamine, Rivastigmine, Tolcapone

- They have some selectivity for AChE in the CNS, as compared to the periphery.

- Galantamine may also augment the action of acetylcholine at nicotinic receptors in the CNS.

- Rivastigmine is the only agent approved for the management of dementia associated with Parkinson's disease and also the only AChE inhibitor available as a transdermal formulation.

NMDA receptor antagonist

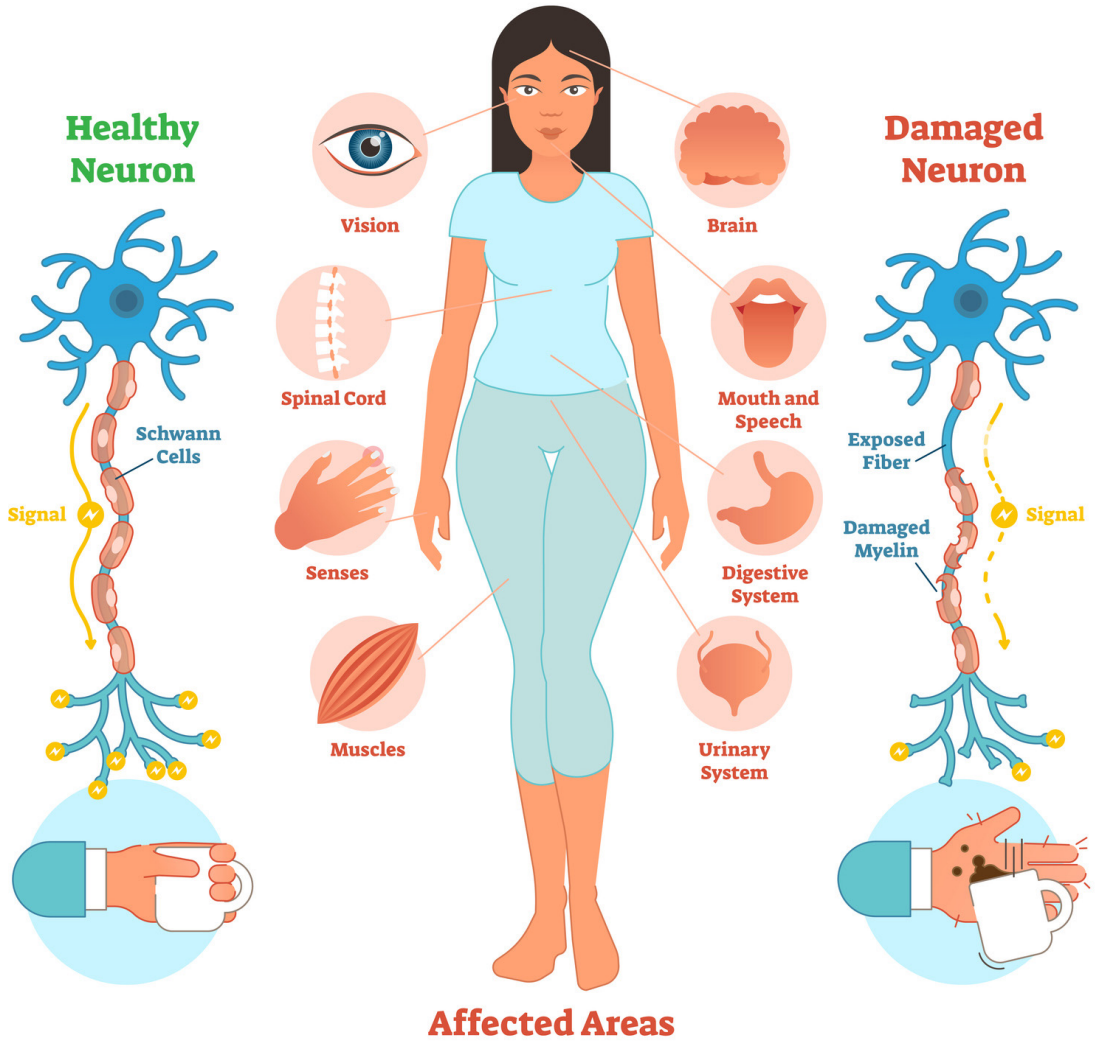
Memantine

- Overstimulation of glutamate receptors, particularly of the *N*-methyl-D-aspartate (NMDA) type of glutamate receptors, may result in excitotoxic effects on neurons and is suggested as a mechanism for neurodegenerative or apoptotic (programmed cell death) processes.

- Binding of glutamate to the NMDA receptor assists in the opening of an ion channel that allows Ca^{2+} to enter the neuron. Excess intracellular Ca^{2+} can activate a number of processes that ultimately damage neurons and lead to apoptosis.

- Memantine is an NMDA receptor antagonist indicated for moderate to severe Alzheimer's disease.

MULTIPLE SCLEROSIS



MULTIPLE SCLEROSIS

- Multiple sclerosis is an autoimmune inflammatory demyelinating disease of the CNS.

- The major target of these medications is to modify the immune response through inhibition of white blood cell–mediated inflammatory processes that eventually lead to myelin sheath damage and decreased or inappropriate axonal communication between cells.

Disease-modifying therapies

1. Interferon β1a and interferon β1b: help to diminish the inflammatory responses that lead to demyelination of the axon sheaths.

2. Glatiramer: is a synthetic polypeptide that resembles myelin protein and may act as a decoy to T-cell attack.

3. Fingolimod: is an oral drug that alters lymphocyte migration, resulting in fewer lymphocytes in the CNS. Fingolimod may cause first-dose bradycardia and is associated with an increased risk of infection and macular edema.

4. Teriflunomide: is an oral pyrimidine synthesis inhibitor that leads to a lower concentration of active lymphocytes in the CNS. It should be avoided in pregnancy.

5. Dimethyl fumarate: is an oral agent that may alter the cellular response to oxidative stress to reduce disease progression.

6. Natalizumab: is a monoclonal antibody indicated for MS in patients who have failed first-line therapies.

7. Mitoxantrone: is a cytotoxic anthracycline analog that kills T cells and may also be used for MS.

Symptomatic treatment

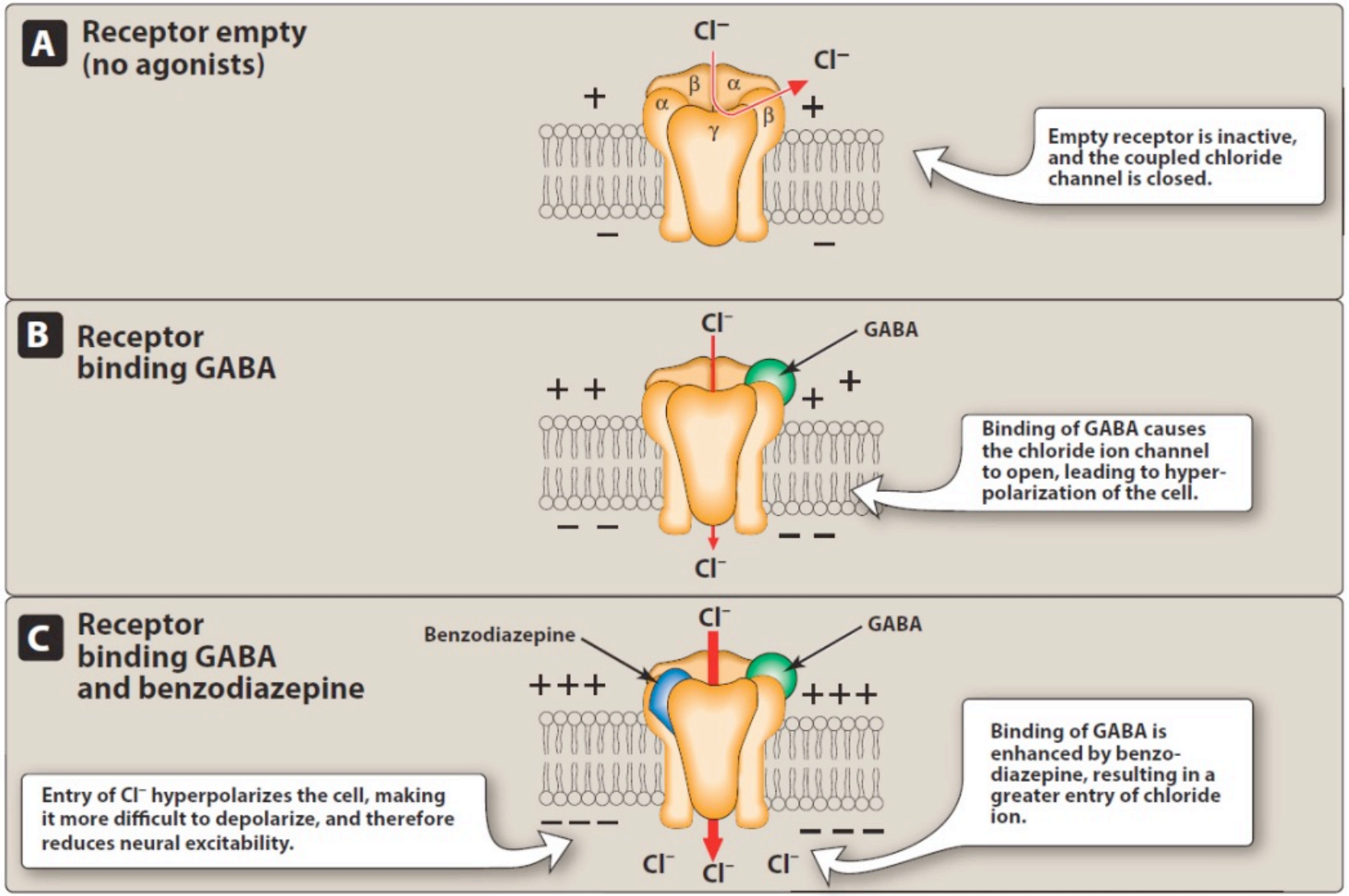
- *Dalfampridine* an oral potassium channel blocker, improves walking speeds in patients with MS.

- It is the first drug approved for this use.

Anxiolytic and Hypnotic Drugs

Benzodiazepines

Alprazolam, Chlordiazepoxide, Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam, Lorazepam, Midazolam, Oxazepam, Quazepam, Temazepam, Triazolam



Benzodiazepines

Alprazolam, Chlordiazepoxide, Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam, Lorazepam, Midazolam, Oxazepam, Quazepam, Temazepam, Triazolam

1- Anxiety disorders: including anxiety symptoms secondary to panic disorder, generalized anxiety disorder (GAD), social anxiety disorder, performance anxiety, posttraumatic stress disorder, obsessive–compulsive disorder, and extreme anxiety associated with phobias, such as fear of flying and anxiety related to depression and schizophrenia.

- The longer-acting agents, such as Clonazepam, Lorazepam, and Diazepam, are often preferred in those patients with anxiety that may require prolonged treatment.

- Tolerance? Cross-tolerance? Dependence?

Benzodiazepines

Alprazolam, Chlordiazepoxide, Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam, Lorazepam, Midazolam, Oxazepam, Quazepam, Temazepam, Triazolam

2- Sleep disorders:

a. Temazepam: This drug is useful in patients who experience frequent wakening. However, because the peak sedative effect occurs 1 to 3 hours after an oral dose, it should be given 1 to 2 hours before bedtime.

b. Triazolam: Whereas *temazepam* is useful for insomnia caused by the inability to stay asleep, short-acting *triazolam* is effective in treating individuals who have difficulty in going to sleep.

- Tolerance frequently develops within a few days, and withdrawal of the drug often results in rebound insomnia. Therefore, this drug is not a preferred agent, and it is best used intermittently.
- In general, hypnotics should be given for only a limited time, usually less than 2 to 4 weeks.

Benzodiazepines

Alprazolam, Chlordiazepoxide, Clonazepam, Clorazepate, Diazepam, Estazolam, Flurazepam, Lorazepam, Midazolam, Oxazepam, Quazepam, Temazepam, Triazolam

3- Amnesia: *Midazolam* is used to facilitate amnesia while causing sedation prior to anesthesia.

4- Seizures: *Clonazepam* is occasionally used as an adjunctive therapy for certain types of seizures, whereas *Lorazepam* and *Diazepam* are the drugs of choice in terminating status epilepticus.

5. Muscular disorders: *Diazepam* is useful in the treatment of skeletal muscle spasms, such as occur in muscle strain, and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.

Benzodiazepines Antagonist

- ***Flumazenil*** is a GABA receptor antagonist that can rapidly reverse the effects of benzodiazepines.
- The drug is available for intravenous (IV) administration only.
- Onset is rapid, but the duration is short, with a half-life of about 1 hour.

Other Anxiolytic Agents

1- Antidepressants (Selective serotonin reuptake inhibitors (SSRIs) or serotonin/norepinephrine reuptake inhibitors (SNRIs): should be considered as first-line agents, especially in patients with concerns for addiction or dependence.

2- Buspirone: is useful for the chronic treatment of generalized anxiety disorder (GAD) and has an efficacy comparable to that of the benzodiazepines.

- It has a slow onset of action and is not effective for short-term or "as-needed" treatment of acute anxiety states.

- 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

Barbiturates

- Mechanism of action: The sedative–hypnotic action of the barbiturates is due to their interaction with GABA receptors, which enhances GABAergic transmission.

***The binding site of barbiturates on the GABA receptor is distinct from that of the benzodiazepines. HOW?**

- **Therapeutic Uses:**

1- Anesthesia: The ultra–short-acting barbiturates, such as *thiopental,* have been used intravenously to induce anesthesia but have largely been replaced by other agents.

Barbiturates

2. Anticonvulsant: *Phenobarbital* has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression.

3. Sedative/hypnotic: Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia. When used as hypnotics, they suppress REM sleep more than other stages.

- However, the use of barbiturates for insomnia is no longer generally accepted, given their adverse effects and potential for tolerance.

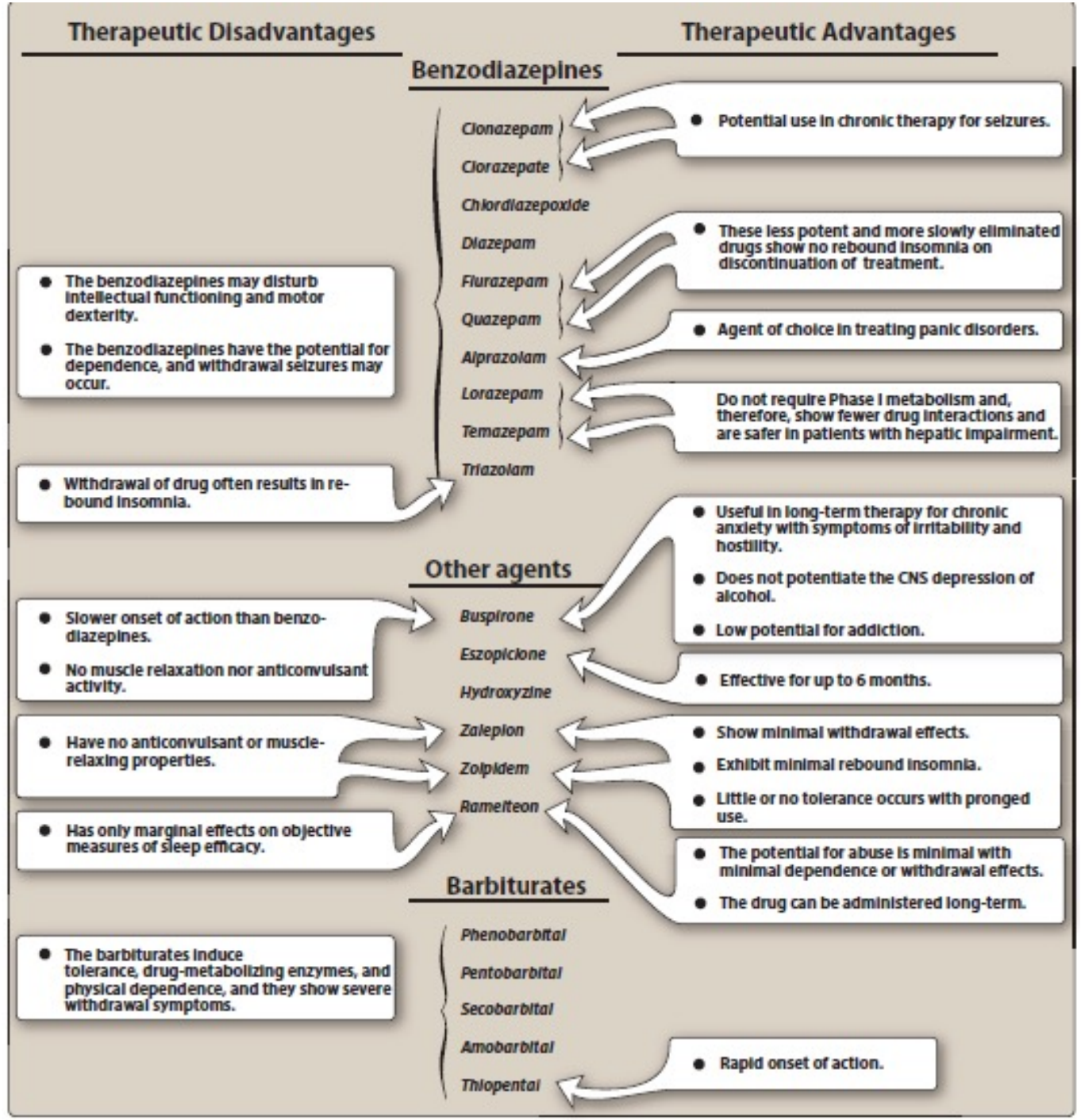
- ***Butalbital*** is commonly used in combination products (with *acetaminophen* and *caffeine* or *aspirin* and *caffeine*) as a sedative to assist in the management of tension-type or migraine headaches.

OTHER HYPNOTIC AGENTS

1- <u>Zolpidem:</u> it selectively binds to the benzodiazepine receptor subtype BZ_1. *Zolpidem* has no anticonvulsant or muscle-relaxing properties.

2- <u>Zaleplon:</u> is an oral nonbenzodiazepine hypnotic similar to zolpidem; however, it causes fewer residual effects on psychomotor and cognitive function compared to zolpidem or the benzodiazepines.

3- Ramelteon: is a selective agonist at the MT1 and MT2 subtypes of melatonin receptors. It is indicated for the treatment of insomnia characterized by difficulty falling asleep (increased sleep latency).


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.
Other agents
Buspirone
Eszopiclone
Hydroxyzine
Zaleplon
Zolpidem
Ramelteon
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
Thiopental
Rapid onset of action.
The barbiturates induce tolerance, drug-metabolizing enzymes, and physical dependence, and they show severe withdrawal symptoms.


Thank
you