Drugs for Neurodegenerative Diseases

- Most drugs that affect the central nervous system (CNS) act by altering some step in the neurotransmission process.
- Drugs affecting the CNS may act presynaptically by influencing the production, storage, release, or termination of action of neurotransmitters.
- Other agents may activate or block postsynaptic receptors.
- The neurodegenerative disorders that respond to drug therapy include :
  - ✓ **Parkinson disease,**
  - ✓ **Alzheimer disease,**
  - ✓ **multiple sclerosis (MS), and**
  - ✓ **amyotrophic lateral sclerosis (ALS)** (Figure 8.1).

Neurotransmission in the CNS

- The basic functioning of neurons in the CNS is similar to that of the autonomic nervous system (ANS) described in last year.
- For example, transmission of information in both the CNS and in the periphery involves the release of neurotransmitters that diffuse across the synaptic cleft to bind to specific receptors on the postsynaptic neuron.
- In both systems, the recognition of the neurotransmitter by the membrane receptor of the postsynaptic neuron triggers intracellular changes.
- However, several major differences exist between neurons in the peripheral ANS and those in the CNS.
- The circuitry of the CNS is more complex than that of the ANS, and the number of synapses in the CNS is far greater.
- The CNS, unlike the peripheral ANS, contains networks of inhibitory neurons that are constantly active in modulating the rate of neuronal transmission.
- In addition, the CNS communicates through the use of multiple neurotransmitters, whereas the ANS uses only two primary neurotransmitters, acetylcholine, and norepinephrine.

Synaptic Potentials

- In the CNS, receptors in 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.

A. 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 neurotransmitters, 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.
- [Note: The generation of a nerve impulse typically reflects the activation of synaptic receptors by thousands of excitatory neurotransmitter molecules released from many nerve fibers.] Figure 8.2 shows an example of an excitatory pathway.

B. 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 neurotransmitters, 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. Figure 8.3 shows an example of an inhibitory pathway.

C. Combined effects of the EPSP and IPSP

- Most neurons in the CNS receive both EPSP and IPSP input.
- Thus, several different types of neurotransmitters may act on the same neuron, but each binds to its own specific receptor.
- The overall action is the summation of the individual actions of the various neurotransmitters on the neuron.
- The neurotransmitters are not uniformly distributed in the CNS but are localized in specific clusters of neurons, the axons of which may synapse with specific regions of the brain.
- Many neuronal tracts, thus, seem to be chemically coded, and this may offer greater opportunity for selective pharmacological modulation of certain neuronal pathways.

Neurodegenerative Diseases

- Neurodegenerative diseases of the CNS include Parkinson disease, Alzheimer disease, MS, and ALS.

- These devastating illnesses are characterized by the progressive loss of selected neurons in discrete brain areas, resulting in characteristic disorders of movement, cognition, or both.

Overview of Parkinson Disease

Parkinsonism is a progressive neurological disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia, and postural and gait abnormalities. Most cases involve people over the age of 65, among
whom the incidence is about 1 in 100 individuals.

Etiology

The cause of Parkinson 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 (shown in *red* in Figure 8.4) 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

- Normally, the neostriatum is connected to the substantia nigra by neurons (shown in *orange* in Figure 8.4) 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 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 (shown in *green* in Figure 8.4). This triggers a chain of abnormal signaling, resulting in loss of the control of muscle movements.

3. 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 disease.

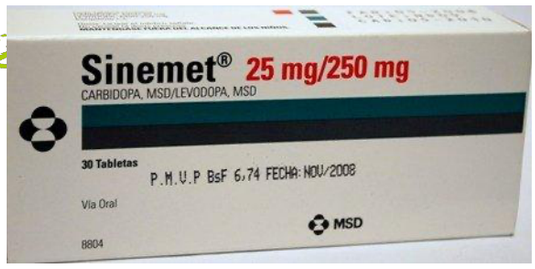
Strategy of treatment

- ✓ In addition to an abundance of inhibitory dopaminergic neurons, the neostriatum is also rich in excitatory cholinergic neurons that oppose the action of dopamine (Figure 8.4).
- ✓ Many of the symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons.

✓ Therapy is aimed at restoring dopamine in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance.

- ✓ Many currently available drugs aim to maintain CNS dopamine levels, or signaling, as constant as possible.
- ✓ These agents offer temporary relief from the symptoms of the disorder, but they do not arrest or reverse the neuronal degeneration caused by the disease.

Drugs Used in Parkinson Disease



A. Levodopa *and* carbidopa

- ➢ *Levodopa* [lee-voe-DOE-pa] is a metabolic precursor of dopamine (Figure 8.5).
- ➢ It restores dopaminergic neurotransmission in the neostriatum by enhancing the synthesis of dopamine in the surviving neurons of the substantia nigra.
- ➢ In early disease, the number of residual dopaminergic neurons in the substantia nigra (typically about 20% of normal) is adequate for conversion of *levodopa* to dopamine.
- ➢ Thus, in new patients, the therapeutic response to *levodopa* is consistent, and the patient rarely complains that the drug effects "wear off."
- ➢ Unfortunately, with time, the number of neurons decreases, and fewer cells are capable of converting exogenously administered *levodopa* to dopamine.
- ➢ Consequently, motor control fluctuation develops.
- ➢ Relief provided by *levodopa* is only symptomatic, and it lasts only while the drug is present in the body.

Mechanism of action

Levodopa

- ➢ Dopamine does not cross the blood–brain barrier, but its immediate precursor, *levodopa*, is actively transported into the CNS and converted to dopamine (Figure 8.5).
- ➢ *Levodopa* must be administered with *carbidopa* [kar-bi-DOE-pa].
- ➢ Without *carbidopa*, much of the drug is decarboxylated to dopamine in the periphery, resulting in diminished effect, nausea, vomiting, cardiac arrhythmias, and hypotension.

Carbidopa

- ➢ *Carbidopa*, a dopamine decarboxylase inhibitor (a peripheral dopa decarboxylase inhibitor), diminishes the metabolism of *levodopa* in the periphery, thereby increasing the availability of *levodopa* to the CNS.

- The addition of *carbidopa* lowers the dose of *levodopa* needed by four- to five-fold and, consequently, decreases the severity of adverse effects arising from peripherally formed dopamine.

Therapeutic uses

- *Levodopa* in combination with *carbidopa* is an efficacious drug regimen for the treatment of Parkinson disease.
- It decreases rigidity, tremors, and other symptoms of parkinsonism.
- In approximately two-thirds of patients with Parkinson disease, *levodopa–carbidopa* substantially reduces the severity of symptoms for the first few years of treatment.
- Patients typically experience a decline in response during the 3rd to 5th year of therapy.
- Withdrawal from the drug must be gradual.

Absorption and metabolism

- The drug is absorbed rapidly from the small intestine (when empty of food).
- *Levodopa* has an extremely short half- life (1 to 2 hours), which causes fluctuations in plasma concentration.
- This may produce fluctuations in motor response, which generally correlate with the plasma concentration of *levodopa*, or perhaps give rise to the more troublesome "on–off" phenomenon, in which the motor fluctuations are not related to plasma levels in a simple way.
- Motor fluctuations may cause the patient to suddenly lose normal mobility and experience tremors, cramps, and immobility.
- Ingestion of meals, particularly if high in protein, interferes with the transport of *levodopa* into the CNS.
- Thus, *levodopa* should be taken on an empty stomach, typically 30 minutes before a meal.

Adverse effects

a. Peripheral effects

- Anorexia, nausea, and vomiting occur because of stimulation of the chemoreceptor trigger zone (Figure 8.6).
- Tachycardia and ventricular extrasystole result from dopaminergic action on the heart.
- Hypotension may also develop.
- Adrenergic action on the iris causes mydriasis.
- In some individuals, blood dyscrasias and a positive reaction to the Coombs test are seen.
- Saliva and urine may turn brownish color because of the melanin pigment produced from catecholamine oxidation.

b. CNS effects

- Visual and auditory hallucinations and abnormal involuntary movements (dyskinesias) may occur.
- These effects are the opposite of parkinsonian symptoms and reflect overactivity of dopamine in the basal ganglia.
- *Levodopa* can also cause mood changes, depression, psychosis, and anxiety.

Interactions

- The vitamin **pyridoxine (B_6)** increases the peripheral breakdown of *levodopa* and diminishes its effectiveness (Figure 8.7).
- Concomitant administration of *levodopa* and nonselective **monoamine oxidase inhibitors (MAOIs),** such as ***phenelzine*,** can produce a hypertensive crisis caused by enhanced catecholamine production. Therefore, concomitant administration of these agents is contraindicated.
- In many psychotic patients, *levodopa* exacerbates symptoms, possibly through the buildup of central catecholamines.

- Cardiac patients should be carefully monitored for the possible development of arrhythmias.
- Antipsychotic drugs are generally contraindicated in Parkinson disease, because they potently block dopamine receptors and may augment parkinsonian symptoms. However, low doses of atypical antipsychotics, such as *quetiapine* or *clozapine*, are sometimes used to treat *levodopa*-induced psychotic symptoms.

B. Selegiline, rasagiline, and safinamide

- ***Selegiline*** [seh-LEDGE-ah-leen], also called *deprenyl* [DE-pre-nill], selectively inhibits monoamine oxidase (MAO) type B, the enzyme that metabolizes dopamine.
- It does not inhibit MAO type A (metabolizes norepinephrine and serotonin) unless given above recommended doses, where it loses its selectivity.
- By decreasing the metabolism of dopamine, *selegiline* increases dopamine levels in the brain (Figure 8.8).
- When *selegiline* is administered with *levodopa*, it enhances the actions of *levodopa* and substantially reduces the required dose.
- Unlike nonselective MAOIs, *selegiline* at recommended doses has little potential for causing hypertensive crises. However, the drug loses selectivity at high doses, and there is a risk for severe hypertension.
- *Selegiline* is metabolized to *methamphetamine* and *amphetamine*, whose stimulating properties may produce insomnia if the drug is administered later than mid-afternoon.
- ***Rasagiline*** [ra-SA-gi-leen], 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.
- ***Safinamide*** [sa-FIN-a-mide] is also a selective inhibitor of MAO type B indicated for use as an adjunct to *levodopa–carbidopa*.

C. Catechol-*O*-methyltransferase inhibitors

- Normally, the methylation of *levodopa* by catechol-*O*-methyltransferase (COMT) to 3-*O*-methyldopa is a minor pathway for *levodopa* metabolism.
- However, when peripheral dopamine decarboxylase activity is inhibited by *carbidopa*, a significant concentration of 3-*O*-methyldopa is formed that competes with *levodopa* for active transport into the CNS (Figure 8.9).

- ***Entacapone*** [en-TAK-a-pone] and ***tolcapone*** [TOLE-ka-pone] selectively and reversibly inhibit COMT.
- Inhibition of COMT by these agents leads to decreased plasma concentrations of 3-*O*-methyldopa, increased central uptake of *levodopa*, and greater concentrations of brain dopamine.
- Both of these agents 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.

Pharmacokinetics

- Oral absorption of both drugs occurs readily and is not influenced by food.

- They are extensively bound to plasma albumin, with a limited volume of distribution.
- *Tolcapone* has a relatively long duration of action (probably due to its affinity for the enzyme) compared to *entacapone*, which requires more frequent dosing.
- Both drugs are extensively metabolized and eliminated in feces and urine.
- The dosage may need to be adjusted in patients with moderate or severe cirrhosis.

Adverse effects

- Both drugs exhibit adverse effects that are observed in patients taking *levodopa–carbidopa*, including diarrhea, postural hypotension, nausea, anorexia, dyskinesias, hallucinations, and sleep disorders.
- Most seriously, fulminating hepatic necrosis is associated with *tolcapone* use. Therefore, it should be used, along with appropriate hepatic function monitoring, only in patients in whom other modalities have failed.
- *Entacapone* does not exhibit this toxicity and has largely replaced *tolcapone* in clinical practice.

D. Dopamine receptor agonists

- This group of antiparkinsonian compounds includes ***bromocriptine*** [broe-moe-KRIP-teen], **an ergot derivative,** and the **nonergot drugs**, ***ropinirole*** [roe-PIN-i-role], ***pramipexole*** [pra-mi-PEX-ole], ***rotigotine*** [ro-TIG-oh-teen], and ***apomorphine*** [A-poe-more-feen].
- These agents have a longer duration of action than that of *levodopa* and are effective in patients exhibiting fluctuations in response to *levodopa*.
- Initial therapy with these drugs is associated with less risk of developing dyskinesias and motor fluctuations as compared to patients started on *levodopa*.
- *Bromocriptine*, *pramipexole*, and *ropinirole* are effective in patients with Parkinson disease complicated by motor fluctuations and dyskinesias.
- However, 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.
- Adverse effects severely limit the utility of the dopamine agonists (Figure 8.10).

Bromocriptine

- The actions of the ergot derivative *bromocriptine* are similar to those of *levodopa*, except that hallucinations, confusion, delirium, nausea, and orthostatic hypotension are more common, whereas dyskinesia is less prominent.
- In psychiatric illness, *bromocriptine* may cause the mental condition to worsen.
- It should be used with caution in patients with a history of myocardial infarction or peripheral vascular disease due to the risk of vasospasm.
- Because *bromocriptine* is an ergot derivative, it has the potential to cause pulmonary and retroperitoneal fibrosis.

Apomorphine, pramipexole, ropinirole, and rotigotine

- These are nonergot dopamine agonists that are approved for the treatment of Parkinson disease.
- *Ropinirole* is also indicated for the treatment of restless legs syndrome.
- *Pramipexole* and *ropinirole* are orally active agents.
- *Apomorphine* and *rotigotine* are available in injectable and transdermal delivery systems, respectively.
- *Apomorphine* is used for acute management of the hypomobility "off" phenomenon in advanced Parkinson disease.
- *Rotigotine* is administered as a once-daily transdermal patch that provides even drug levels over 24 hours.
- These agents alleviate the motor deficits in patients who have never taken *levodopa* and also in patients with advanced Parkinson disease who are treated with *levodopa*.
- Dopamine agonists may delay the need to use *levodopa* in early Parkinson disease and may decrease the dose of *levodopa* in advanced Parkinson disease.
- Unlike the ergotamine derivatives, these agents do not exacerbate peripheral vascular disorders or cause fibrosis.
- Nausea, hallucinations, insomnia, dizziness, constipation, and orthostatic hypotension are adverse effects of these drugs, but dyskinesias are less frequent than with *levodopa* (Figure 8.11).
- *Pramipexole* is mainly excreted unchanged in the urine, and dosage adjustments are needed in renal dysfunction.
- The fluoroquinolone antibiotics and other inhibitors of the cytochrome P450 (CYP450) 1A2 isoenzyme (for example, *fluvoxamine*) may inhibit the metabolism of *ropinirole*, requiring an adjustment in *ropinirole* dosage.
- Figure 8.12 summarizes some properties of dopamine agonists.

E. Amantadine

- It was accidentally discovered that the antiviral drug *amantadine* [a-MAN-ta-deen] has an antiparkinsonian action.
- *Amantadine* has several effects on a number of neurotransmitters implicated in parkinsonism, including increasing the release of dopamine, blocking cholinergic receptors, and inhibiting the *N*-methyl-D-aspartate (NMDA) type of glutamate receptors.
- The drug may cause restlessness, agitation, confusion, and hallucinations, and, at high doses, it may induce acute toxic psychosis.
- Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur.
- *Amantadine* is less efficacious than *levodopa*, and tolerance develops more readily.
- However, *amantadine* has fewer adverse effects.

F. Antimuscarinic agents

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

- The actions of ***benztropine*** [BENZ-troe-peen] and ***trihexyphenidyl*** [tri-hex-ee-FEN-i-dill] are similar, although individual patients may respond more favorably to one drug or the other.
- Blockade of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission, since it helps to correct the imbalance in the dopamine/acetylcholine activity (Figure 8.4).
- These agents can induce mood changes and confusion, and produce xerostomia, 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.

Drugs Used in Alzheimer Disease

- **Alzheimer's disease** is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills, and, eventually, the ability to carry out the simplest tasks. In most people with Alzheimer's, symptoms first appear in their mid-60s.
- Alzheimer's is the most common cause of **dementia** among older adults.
- **Dementia** is the loss of cognitive functioning—thinking, remembering, and reasoning—and behavioral abilities to such an extent that it interferes with a person's daily life and activities

- Dementia of the Alzheimer type has three distinguishing features:
  1) Accumulation of senile plaques (β-amyloid accumulations),
  2) Formation of numerous neurofibrillary tangles, and
  3) Loss of cortical neurons, particularly cholinergic neurons.
- Current therapies aim to either improve cholinergic transmission within the CNS or prevent excitotoxic actions resulting from overstimulation of NMDA-glutamate receptors in selected areas of the brain.
- Pharmacologic intervention for Alzheimer disease is only palliative and provides modest short-term benefit.
- None of the available therapeutic agents alter the underlying neurodegenerative process.

A. ACETYLCHOLINESTERASE INHIBITORS

- Numerous studies have linked the progressive loss of cholinergic neurons and, presumably, cholinergic transmission within the cortex to the memory loss that is a hallmark symptom of Alzheimer disease.
- It is postulated that inhibition of acetylcholinesterase (AChE) within the CNS improves cholinergic transmission, at least at those neurons that are still functioning.
- The reversible AChE inhibitors approved for the treatment of Alzheimer disease include ***donepezil*** [doe-NE-peh-zil], ***galantamine*** [ga-LAN-ta-meen], and ***rivastigmine*** [ri-va-STIG-meen].
- These agents 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. At best, these compounds may provide a modest reduction in the rate of loss of cognitive functioning in Alzheimer patients.
- *Rivastigmine* is the only agent approved for the management of dementia associated with Parkinson disease and also the only AChE inhibitor available as a transdermal formulation.

- *Rivastigmine* is hydrolyzed by AChE to a carbamylated metabolite and has no interactions with drugs that alter the activity of CYP450 enzymes.
- The other agents are substrates for CYP450 and have a potential for such interactions.
- Common adverse effects include nausea, diarrhea, vomiting, anorexia, tremors, bradycardia, and muscle cramps (Figure 8.13).

B. NMDA receptor antagonist

- Stimulation of glutamate receptors in the CNS appears to be critical for the formation of certain memories.
- However, overstimulation of glutamate receptors, particularly of the NMDA type, 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* [meh-MAN-teen] is an NMDA receptor antagonist indicated for moderate to severe Alzheimer disease.
- It acts by blocking the NMDA receptor and limiting Ca^{2+} influx into the neuron, such that toxic intracellular levels are not achieved.
- *Memantine* is well tolerated, with few dose-dependent adverse events.
- Expected adverse effects, such as confusion, agitation, and restlessness, are often indistinguishable from the symptoms of Alzheimer disease.
- Given its different mechanism of action and possible neuroprotective effects, *memantine* is often given in combination with an AChE inhibitor.

Drugs Used in Multiple Sclerosis

- MS is an autoimmune inflammatory demyelinating disease of the CNS.
- The course of MS is variable. For some, MS may consist of one or two acute neurologic episodes. In others, it is a chronic, relapsing, or progressive disease that may span 10 to 20 years.
- Historically, corticosteroids (for example, *dexamethasone* and *prednisone*) have been used to treat acute exacerbations of the disease.
- Chemotherapeutic agents, such as *cyclophosphamide* and *azathioprine*, have also been used.

A. Disease-modifying therapies

Drugs currently approved for MS are indicated to decrease relapse rates or, in some cases, to prevent accumulation of disability. 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.

1. Interferon b_{1a} and interferon b_{1b}

The immunomodulatory effects of *interferon* [in-ter-FEER-on] help to diminish the inflammatory responses that lead to demyelination of the axon sheaths. Adverse effects of these medications may include depression, local injection site reactions, increases in hepatic enzymes, and flu-like symptoms.

2. Glatiramer

Glatiramer [gluh-TEER-a-mur] is a synthetic polypeptide that resembles myelin protein and may act as a decoy to T-cell attack. Some patients experience a postinjection reaction that includes flushing, chest pain, anxiety, and itching. It is usually self-limiting.

3. Fingolimod

Fingolimod [fin-GO-li-mod] 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

Teriflunomide [te-ree-FLOO-no-mide] is an oral pyrimidine synthesis inhibitor that leads to a lower concentration of active lymphocytes in the CNS. *Teriflunomide* may cause elevated liver enzymes. It should be avoided in pregnancy.

5. Dimethyl fumarate

Dimethyl fumarate [dye-METH-il FOO-ma-rate] is an oral agent that may alter the cellular response to oxidative stress to reduce disease progression. Flushing and abdominal pain are the most common adverse events.

6. Monoclonal antibodies

Alemtuzumab [AL-em-TOOZ-ue-mab], *daclizumab* [dah-KLIH-zyoo-mab], *natalizumab* [na-ta-LIZ-oo-mab], and *ocrelizumab* [OK-re-LIZ-ue-mab] are monoclonal antibodies indicated for the treatment of MS. *Ocrelizumab* is the first agent to be approved for primary progressive forms of the disease. These agents can be associated with significant toxicities, such as progressive multifocal leukoencephalopathy with *natalizumab*, serious infections with *daclizumab* and *alemtuzumab*, and autoimmune disorders with *alemtuzumab*. As such, these agents may be reserved for patients who have failed other therapies.

B. Symptomatic treatment

Many different classes of drugs are used to manage symptoms of MS such as spasticity, constipation, bladder dysfunction, and depression. *Dalfampridine* [DAL-fam-pre-deen], an oral potassium channel blocker, improves
walking speeds in patients with MS. It is the first drug approved for this use.

Drugs Used in Amyotrophic Lateral Sclerosis

- ✓ ALS is characterized by progressive degeneration of motor neurons, resulting in the inability to initiate or control muscle movement.
- ✓ ***Riluzole*** [RIL-ue-zole] and ***edaravone*** [e-DAR-a-vone] are indicated for the management of ALS.
- ✓ *Riluzole*, an oral NMDA receptor antagonist, is believed to act by inhibiting glutamate release and blocking sodium channels.
- ✓ *Riluzole* may improve survival time in patients suffering from ALS. *Edaravone* is an intravenous free radical scavenger and antioxidant that may slow the progression of ALS.

With best regards,

Dr. Waleed