Neurotransmitters from clinical point of view

Parkinson's Disease

- First described by James Parkinson in his classic 1817 monograph, "An Essay on the Shaking Palsy"

- Parkinson's disease (PD) is a neurological disorder characterized by a progressive degeneration of dopaminergic neurons located in the substantia nigra pars compacta (SNc)

Epidemiology

- Worldwide prevalence of PD is approximately 0.3 percent in the general population 40 years of age and older
- Estimates of the incidence of PD range from 8 to 18.6 per 100,000 person-years
- A global prevalence of 6.1 million people with PD in the year 2016

Pathophysiology

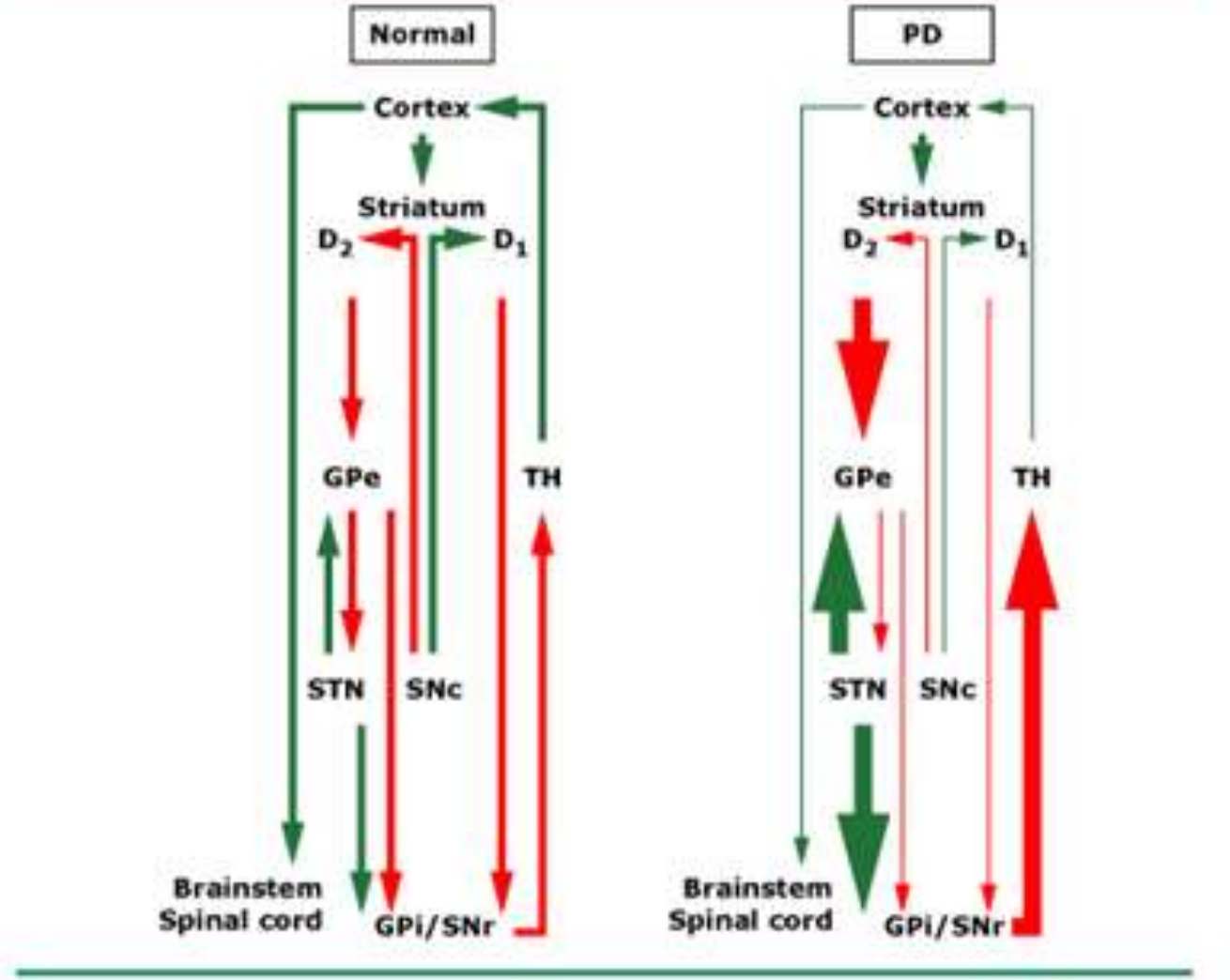
- The cortical input to the basal ganglia is excitatory, mediated by the neurotransmitter glutamate

- Neurons in the substantia nigra pars compacta (SNc) provide major dopaminergic input to the striatum and exert both excitatory and inhibitory influences on the striatal output neurons.

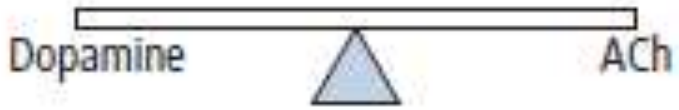
- The striatal output system is mediated by the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).

- The connection between the STN and the internal (medial) globus pallidus (GPi) and between STN and the lateral (or external) globus pallidus (GPe) is excitatory, mediated by glutamate.

Model of basal ganglia dysfunction

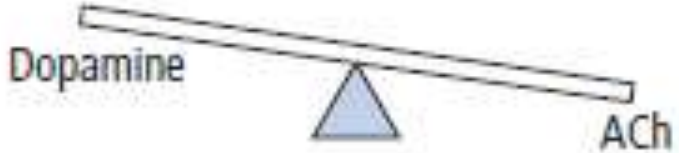


(a)



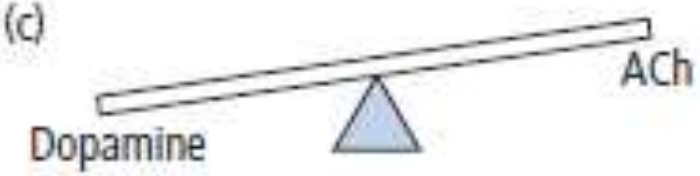
Normal-dopaminergic pathways balanced by those utilizing other neurotransmitters, predominantly acetylcholine (ACh).

(b)



Dopaminergic deficiency or cholinergic excess, resulting in an akinetic–rigid syndrome, e.g. idiopathic Parkinson's disease or drug-induced Parkinsonism (NB phenothiazines and related drugs are dopamine antagonists).

(c)



Dopaminergic excess or cholinergic deficiency, resulting in excessive involuntary movements – dyskinesia, e.g. due to overtreatment of Parkinson's disease with dopaminergic drugs, or to degenerative disease of non-dopaminergic pathways, as in Huntington's disease.

Risk factors

- Older age and family history of PD are associated with an increased risk of developing PD
- Cigarette smoking is associated with a decreased risk

PD and Smoking

- There is an inverse correlation between PD and smoking
- A neuroprotective effect of nicotine has been proposed as one possible explanation for these observations
- An alternative hypothesis is that patients who develop PD are less likely to smoke in the first place, or more likely to quit smoking than those who do not develop PD. This alternative explanation posits that since dopamine is an integral component of the brain's reward system, people who will later develop signs of PD do not engage in reward-seeking behaviors, such as smoking, because dopamine is significantly depleted in the basal ganglia years before symptoms of PD appear

CARDINAL MANIFESTATIONS

- Tremor
- Bradykinesia
- Rigidity
- Postural instability

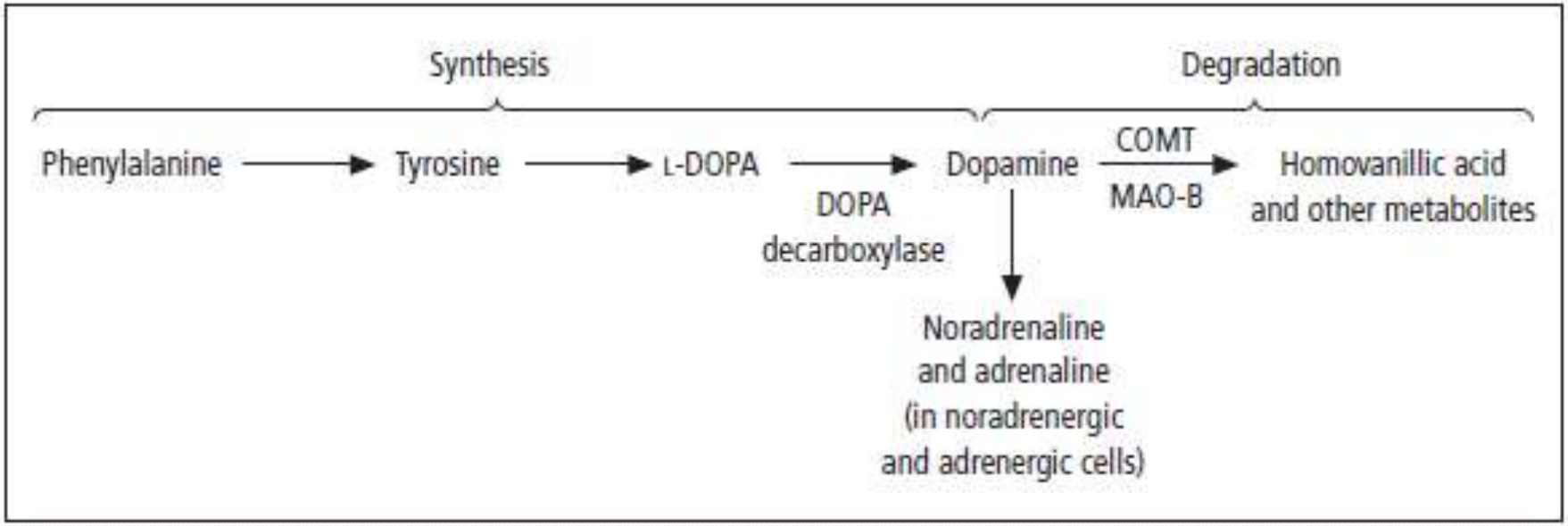
Other features

- Hypomimia (masked facial expression)
- Hypophonia
- Sialorrhea
- Micrographia
- Stooped posture
- Difficulty turning in bed
- Gait:
  - Shuffling, short-stepped gait
  - Freezing

Non motor manifestations

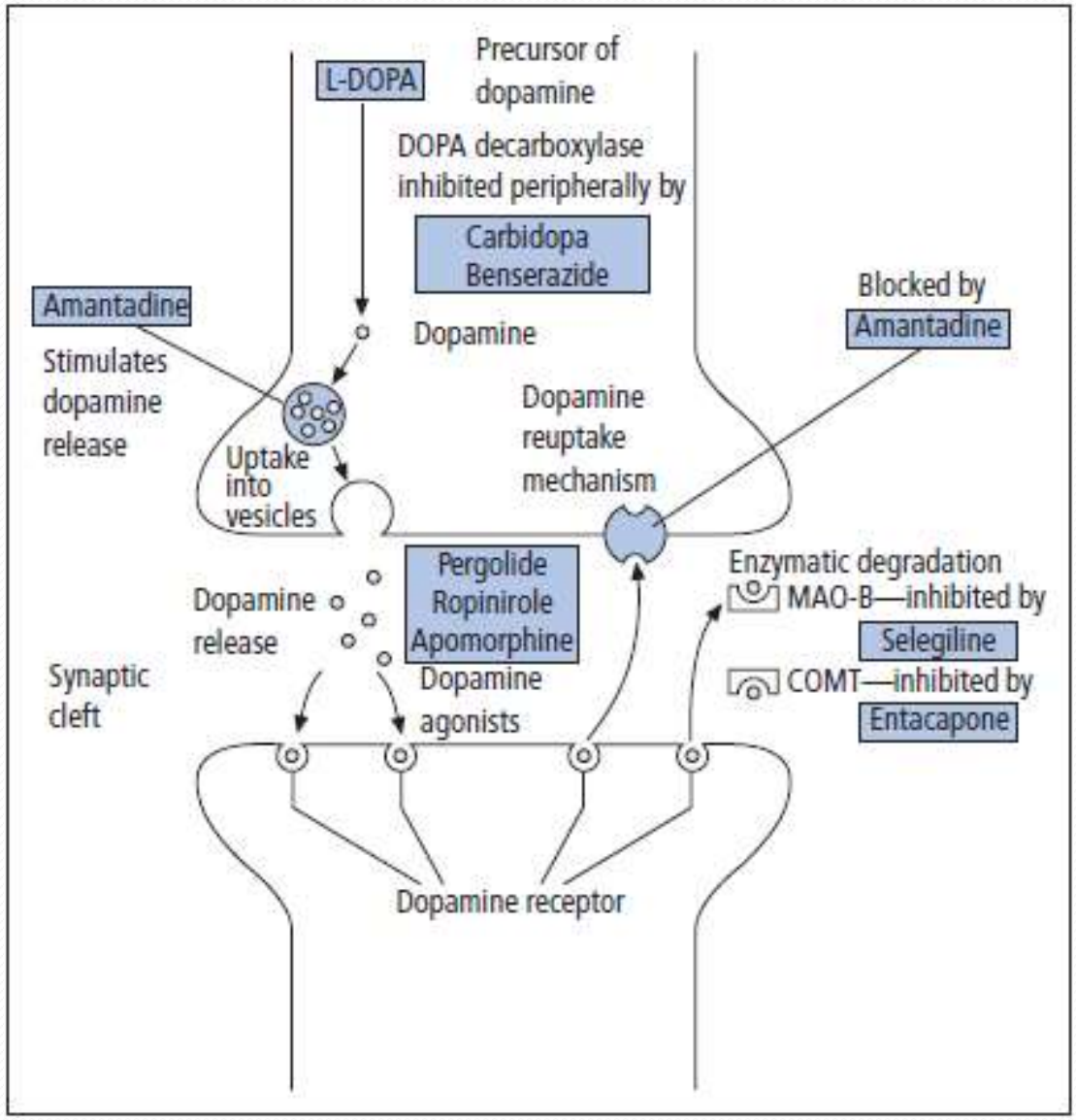
- Cognitive dysfunction
- Psychosis
- Mood disorders
- Sleep disturbances
- Fatigue
- Autonomic dysfunction
- Olfactory dysfunction

Dopamine metbolism



Treatment

- Drug therapy:
  - L-dopa and dopa decarboxylase inbhibitor
  - MAO B inhibitors
  - Dopamine agonists
  - Amantidine
  - Anticholenergic drugs
- Stereotactic thalamotomy
- Deep brain Stimulation


L-DOPA
Precursor of dopamine
DOPA decarboxylase inhibited peripherally by
Carbidopa
Benserazide
Amantadine
Stimulates dopamine release
Dopamine
Blocked by
Amantadine
Uptake into vesicles
Dopamine reuptake mechanism
Pergolide
Ropinirole
Apomorphine
Dopamine release
Dopamine agonists
Synaptic cleft
Enzymatic degradation
MAO-B—inhibited by
Selegiline
COMT—inhibited by
Entacapone
Dopamine receptor

Huntington disease

- It is an inherited progressive neurodegenerative disorder characterized by:
  - choreiform movements,
  - psychiatric problems,
  - dementia.
- It is caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat expansion in the huntingtin (HTT) gene on chromosome 4p and inherited in an autosomal-dominant pattern.

- Huntingtin is present in a large number of tissues throughout the body. However, pathology mainly involves the central nervous system, with atrophy of the caudate and putamen (the neostriatum) being most prominent.
- In the early stages, Dopamine neurotransmission is increased leading to hyperkinetic movements .
- In contrast, in the late stages, Dopamone deficits produce hypokinesia

- The main determinant of age of onset is the number of CAG repeats in the HTT gene.
  - The normal number of repeats is 28 or less.
  - 28 - 35 will not develop symptoms but the next generation is at a small risk to develop expansion
  - 36 -39 are incompletely penetrant
  - equal or greater than 40, the disease is fully penetrant and symptoms of the disease will occur.

CLINICAL PROGRESSION

- Regardless of age of onset, HD is a chronic, slowly progressive disease .

- The average length of survival after clinical onset ranges from 10 to 20 years, and some affected individuals live for 30 to 40 years

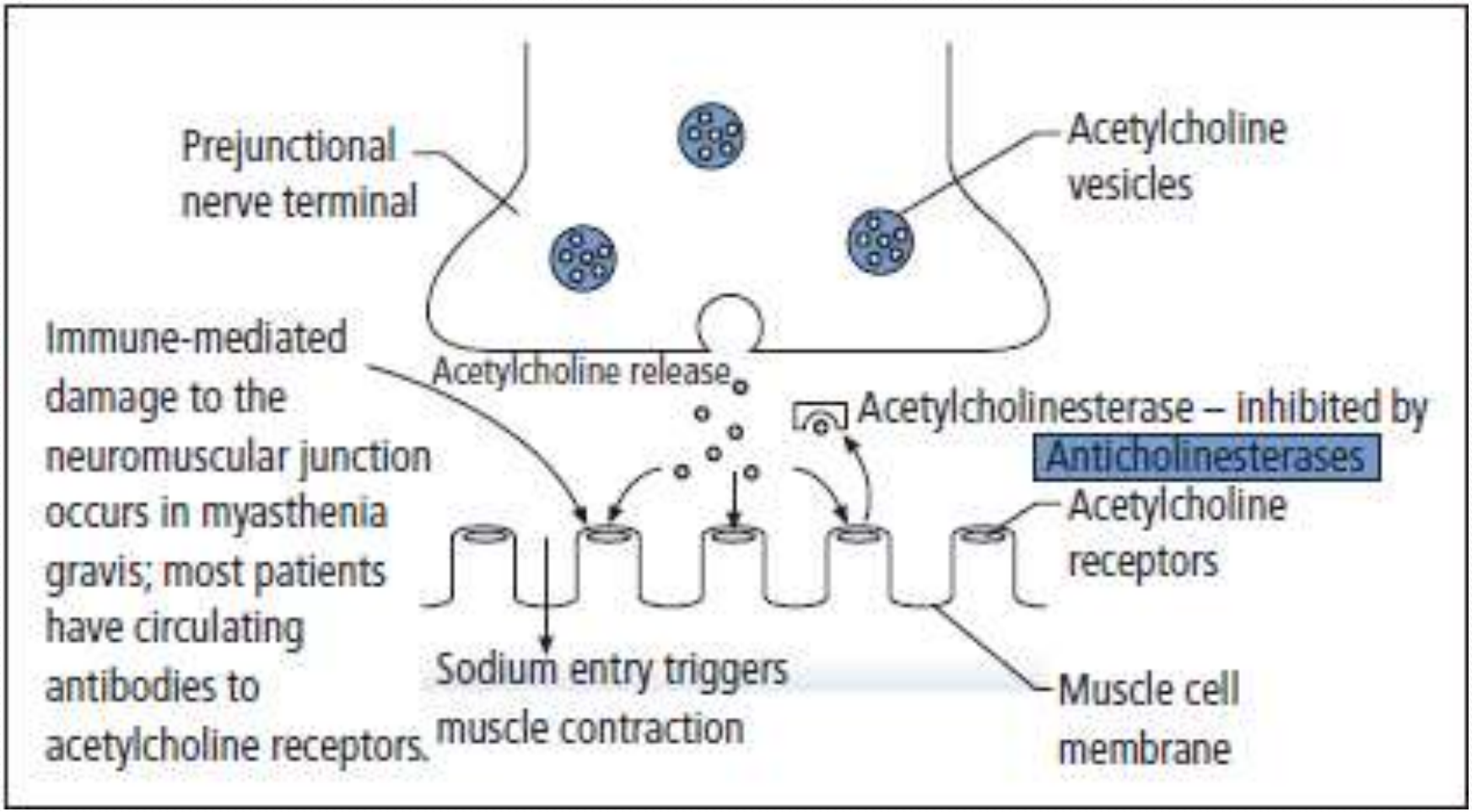
Anticipation

- Expansion of the repeat number between successive generations, which causes an earlier and more severe phenotype

Myasthenia Gravis

- Myasthenia gravis is an acquired autoimmune disorder of the neuromuscular junction characterized by weakness and fatigability of skeletal muscles

- It is the most common disorder of neuromuscular transmission.


Prejunctional nerve terminal
Acetylcholine vesicles
Immune-mediated damage to the neuromuscular junction occurs in myasthenia gravis; most patients have circulating antibodies to acetylcholine receptors.
Acetylcholine release
Acetylcholinesterase – inhibited by Anticholinesterases
Acetylcholine receptors
Sodium entry triggers muscle contraction
Muscle cell membrane

- AChR antibodies cause dysfunction at the neuromuscular junction by blocking ACh binding to the AChR, cross-linking and internalizing AChRs, and activating complement-mediated AChR destruction.

The thymus and the origin of autoimmunity

- The majority of patients with AChR antibody-positive myasthenia gravis have thymic abnormalities:
  - hyperplasia in 60 to 70 percent
  - thymoma in 10 to 12 percent .

- Furthermore, the disease often improves or disappears after thymectomy

- The thymus contains a small number of "myoid" cells.
- These cells are distinguished by striations and the presence of AChR on their surface and are the only known cells to express intact AChR outside of muscle.

Clinical manifestations:

- The cardinal feature of myasthenia gravis is fluctuating skeletal muscle weakness, often with true muscle fatigue. The fatigue is manifest by worsening contractile force of the muscle, not a sensation of tiredness

- The weakness may fluctuate throughout the day, but it is most commonly worse later in the day or evening, or after exercise

There are two clinical forms of myasthenia gravis:

- Ocular myasthenia:
  - the weakness is limited to the eyelids and extraocular muscles.
- Generalized disease:
  - the weakness commonly affects ocular muscles, but it also involves a variable combination of bulbar, limb, and respiratory muscles.

- **Ocular symptoms:**
  - Weakness of the eyelid muscles can lead to ptosis
  - Weakness of extraocular muscles produces binocular diplopia that disappears when the patient closes or occludes one eye.

- **Bulbar muscles** :
  - Fatigable chewing
  - Dysarthria and dysphagia
  - Nasal speech

- **Facial muscles**
  - Patient appear expressionless.

- **Neck and limb muscles**
  - Neck extensor and flexor muscles are commonly affected.
  - Involvement of the limbs in myasthenia produces predominantly proximal weakness similar to other muscle diseases.

- **Respiratory muscles**
  - Involvement of the muscles of respiration produces the most serious symptoms in myasthenia gravis.
  - Respiratory muscle weakness that leads to respiratory insufficiency and pending respiratory failure is a life-threatening situation called "myasthenic crisis."

There are four basic therapies used to treat myasthenia gravis (MG):

- Smptomatic treatments (anticholinesterase agents)
- Chronic immunomodulating treatments (glucocorticoids and other immunosuppressive drugs)
- Rapid immunomodulating treatments (plasmapheresis and intravenous immune globulin)
- Surgical treatment (thymectomy)

Alzheimer disease

- AD is the most common cause of dementia in all age groups, occurring with markedly increased frequency in the elderly.

- It is a neurodegenerative disorder characterized pathologically by intracellular **neurofibrillary tangles** composed of 'paired helical filaments', and extracellular **neuritic plaques** containing an amyloid core, along with neuronal loss

- The cholinergic system is involved in critical physiological processes, such as attention, learning, memory, stress response, wakefulness and sleep, and sensory information

- Cholinergic neurones are particularly affected in AD, providing a rationale for the use of cholinergic-enhancing drugs to improve memory in this disease.

- The concentration of ammo acid transmitters, particularly of glutamate, is also reduced in cortical and subcortical areas

Risk factors

- Age
- Family history
- Hypertension
- Dyslipidemia
- Cerebrovascular disease
- Peripheral atherosclerosis
- Type 2 diabetes and obesity
- Lifestyle and activity

Clinical features

- Early in the course of the illness, *memory loss* is apparent, particularly for recent events. Patients have difficulty learning and retaining new information.
- Later, the impairment of memory, along with *attention deficits,* leads to disorientation in time. There are word-finding difficulties and loss of general knowledge.
- Finally, there is severe global loss of *cognitive function*:
  - amnesia, dysphasia, dyspraxia and agnosia.
- Death within 5–10 years.

Other symptoms

- **Apraxia** — Dyspraxia, or difficulty performing learned motor tasks
- **Olfactory dysfunction**
- **Sleep disturbances**
- **Seizures**
- **Motor signs**

Treatment

- Various cholinergic-enhancing drugs have been used to improve memory early in the disease, albeit for only a few months, most notably the cholinesterase inhibitors
- Memantine affects glutamate transmission and is licensed for use in moderate to severe AD

Thank you