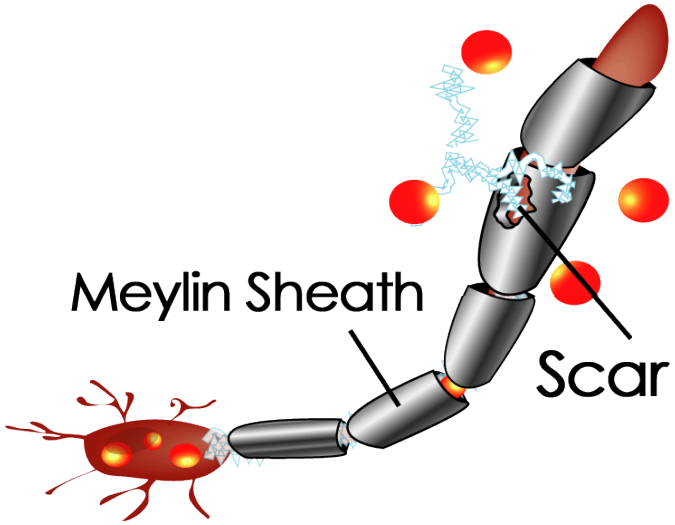
Cairo University
Faculty of Pharmacy

Therapeutics-2 (PO007)

Faculty of Pharmacy Cairo University

Department of Pharmacology and Toxicology

Multiple sclerosis



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At the time of diagnosis, the most common form of multiple sclerosis (MS) is:	
	A) Primary-progressive
	B) Relapsing-progressive
	C) Relapsing-remitting
	D) Secondary-progressive

Which of the following is used in the treatment of an acute attack/relapse of MS?	
	A) Oral immunoglobulin
	B) High-dose intravenous methylprednisolone
	C) High-dose oral prednisone
	D) Mitoxantrone

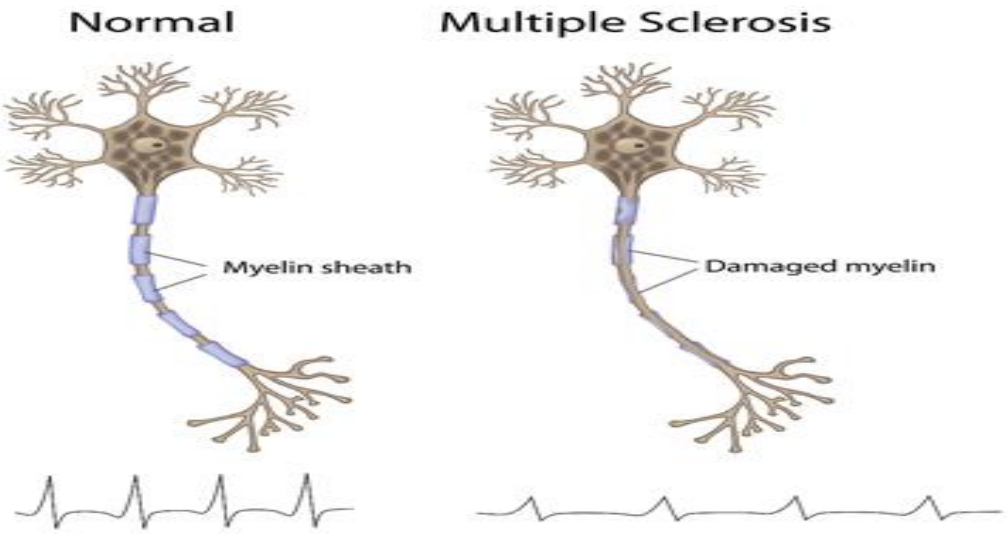
Efficacy of the interferons can be attributed to which mechanism of action?	
	A) ß1-blockade
	B) ß- and ß1-blockade
	C) Immune system dysregulation in the central nervous system
	D) Immune system modulation in the periphery and at the blood–brain barrier

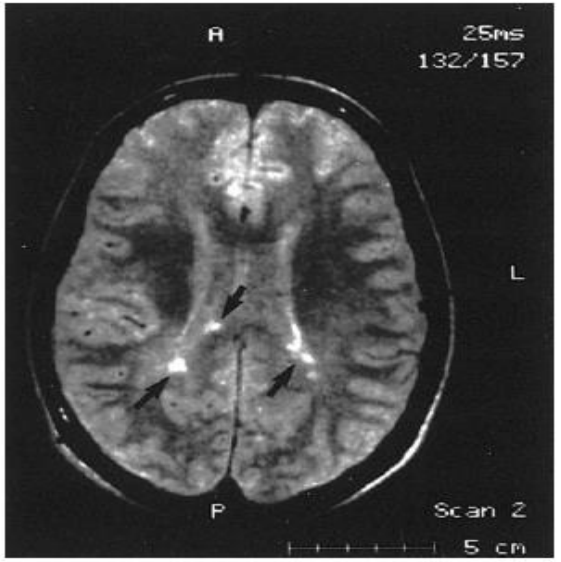
What is multiple sclerosis?

Multiple sclerosis

Multiple sclerosis (MS) is a disease characterized by multiple areas of **demyelination** within the brain and spinal cord. The myelin is the protective fatty sheath for nerves; its damage **disrupts communication between the central nervous system (CNS) and peripheral tissues** leading to **multiple neurological signs** and symptoms.

"Multiple" refers to the numerous affected areas of the brain and spinal cord, "sclerosis" refers to the characteristic plaques or sclerosed areas which are characteristic of the disease.





Etiology

Not confirmed!

Hypothesized that a **viral/ bacterial infections** triggers an **autoimmune response** leading to the destruction of the myelin sheath.

This hypothesis is supported by the increase in the level of **immunoglobulin G** detected in the **cerebrospinal fluids of MS** patients

Genetic factors also contribute!

Association between MS and the **human leukocyte antigen region** on the **6th chromosome** that is implicated in immunity mechanisms. **Scandinavian white people** are the most susceptible ethnic groups to develop MS

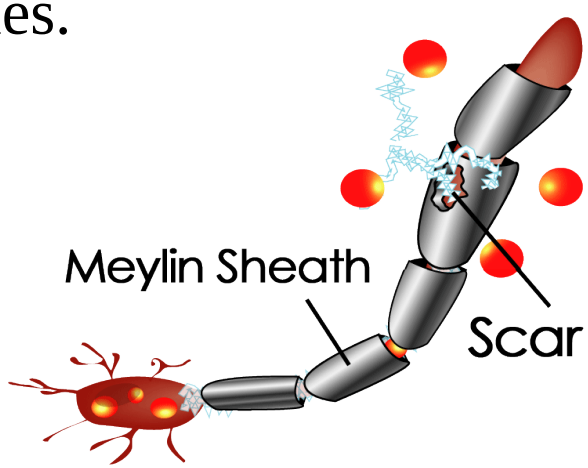
Environmental factors Disease prevalence is higher in **colder climates**; the greater the distance from the equator, the higher the prevalence

Smoking cigarettes is associated with both an increased risk of MS and with more severe progression

Progression of the disease

In the **early stage** of the disease, the **myelin sheath is damaged** but the nerve axon is intact. This damage is mediated by an array of immune cells and mediators including lymphocytes, macrophages, antibodies and the complement system.

As the **disease progress**, the **axons are also irreversibly damaged** leading to disabilities.



MS patients are classified into **four categories**:

1. Relapsing-remitting MS
2. Secondary-progressive MS
3. Primary-progressive MS
4. Progressive-relapsing MS

Patients' categories

1. Relapsing-remitting MS: Patients develop new symptoms (relapse) that last for days or weeks and usually subside partially or completely, followed by remission periods that last for months or years. Certain factors including infections, fever, heat, sleep deprivation, stress, malnutrition, anemia, exertion, and childbirth have been reported to aggravate symptoms or ead to an acute attack.

2. Secondary-progressive MS: Eventually, most of the patients develop a steady progression of signs and symptoms, with or without periods of remission.

3. Primary-progressive MS: Some people experience a gradual onset and steady progression of signs and symptoms with no remission. In general, these patients have a worse prognosis than those who with relapsing-remitting MS.

4. Progressive-relapsing MS*:* A small percentage of patients may have a mixture of both progression (gradual neurological deterioration) and relapses .

Symptoms and diagnosis

MS patients may develop visual complaints/optic neuritis, gait problems, paresthesias (tickling, pricking, or burning of a person's skin), pain, spasticity, fatigue, ataxia, bowel/bladder dysfunction, sexual dysfunction, paralysis, tremors, seizures, speech difficulty, psychological and cognitive changes, and/or depression.

Diagnosis relies on excluding other neurologic diseases that might produce similar signs and symptoms e.g. tumors. The hallmark of MS is "**lesions separated in space and time**" meaning the occurrence of **at least two episodes of neurologic disturbance** attributed to **different sites of damage in the CNS** that cannot be explained by another mechanism.

There is no specific test but clinicians rely on **magnetic resonance imaging** (MRI) of the brain and spine to detect lesions, **cerebrospinal fluid evaluation** to measure levels of antibodies and immune cells and, **visual or electrical evoked potential** to measure nerve conduction in establishing the diagnosis of MS in conjunction with the **physical examination** and **medical history**.

Treatment

Currently there is **no cure for MS**, but treatments aim to **speed recovery from relapses**, to **manage symptoms** in order to maintain the patient's quality of life, or to **slow the progression of the disease**.

There is no consensus regarding treatment regimens; therefore, treatment decisions should be based on the conditions and goals of individual patients

A. **Treatments of acute attacks**
B. **Treatments to slow progression of the disease**
C. **Treatments for symptomatic management**

A. Treatments of acute attacks

Intravenous injection of **high-dose corticosteroids** e.g. methylprednisolone has been shown to shorten the duration of acute exacerbations, probably by reducing inflammation and edema in the area of demyelination.
Corticosteroids are known to cause a long list of adverse effects so the patient should be closely monitored.

If a patient suffers from very severe attacks, manifested by hemiplegia, paraplegia, or quadriplegia and fails to improve with steroid therapy, **plasma exchange** **every other day for seven treatments** can be used

B. Treatments to slow progression of the disease

Interferon β_{1b} and Interferon β_{1a}: Interferon β_{1b} is a non-glycosylated synthetic analog of interferon β and is produced in *Escherichia coli*. Interferon β_{1a} is a natural-sequence glycosylated interferon produced in Chinese hamster ovary cells.

Use of interferon β_{1a} or interferon β_{1b} was associated with reduced severity and frequency of relapses. The exact **mechanism of action is unknown**, but it may be caused by the **immunomodulating** properties of interferons at the blood brain barrier and periphery.

Adverse effects: flu-like symptoms, injection-site inflammation, shortness of breath, tachycardia, thyroid dysfunction, and depression.

Patients receiving interferons should be monitored for **blood cells count, liver function and depressive symptoms**.

Intramuscular interferon β_{1a} offers several advantages:
Fewer local injection site reactions and once-weekly administration versus subcutaneous injection every other day with interferon β_{1b}

B. Treatments to slow progression of the disease

Glatiramer Acetate: **a synthetic polypeptide** consisting of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine that is administered subcutaneously.

The precise mechanism of action of is unknown, but glatiramer acetate appears to **mimic the antigenic properties of myelin basic protein** and hence may block immune system's attack on myelin.

Adverse effects: milder than interferons including mild pain and pruritus at the injection site, and less frequently chest tightness, flushing, and dyspnea.

B. Treatments to slow progression of the disease

Natalizumab is a partially humanized **monoclonal antibody** that binds to the cell surface **adhesion molecule$_{\alpha 4\beta}$-integrin**, thus blocking its interaction with endothelium vascular cell adhesion molecule and inhibiting the infiltration of immune cells from the bloodstream to the CNS.

Adverse effects: Natalizumab may increase the risk for **progressive multifocal leukoencephalopathy**; therefore, its use is reserved for patients with severe, active MS, or who do not respond to or can't tolerate other treatments

B. Treatments to slow progression of the disease

Mitoxantrone: An **immunosuppressant** drug used to reduce neurologic disability and the frequency of relapses in **patients with severe, advanced MS**.

Adverse effects: The use of this drug may cause severe cardiac dysfunction, nausea, alopecia, menstrual disorder, amenorrhea, upper respiratory tract infection, urinary tract infection, and leukopenia.

The maximum allowable lifetime cumulative dose of mitoxantrone is **140 mg/m^2.**

Body surface area [m^2] = 0.007184 * Height [cm]$^{0.725}$ * Weight [kg]$^{0.4}$

C. Treatments for symptomatic management

Spasticity tends to affect the legs more than the arms and can result in falls.

Baclofen, a $GABA_A$ receptor agonist, is used as muscle relaxant. Small doses of **diazepam** may be added to baclofen if optimal response has not been achieved.

Tizanidine stimulates presynaptic α-adrenoceptors in the CNS resulting in inhibition of motor neurons and reduced spasticity.

Gabapentin (voltage-gated calcium channels**)**

Tiagabine (GABA reuptake inhibitor), **pregabalin** (voltage-gated calcium channels)**,** and **botulinum toxin** may also be used for spasticity.

Tremors: Propranolol, primidone (anticonvulsant acting on GABA and Na channels), and **isoniazid** (anti tuberculosis) may be used to reduce tremors.

Bowel and Bladder incontinence: Anticholinergic agents e.g. **oxybutynin chloride** can be used.

C. Treatments for symptomatic management

Fatigue: **Amantadine hydrochloride** (enhance dopaminergic transmission and block NMDA receptors)
Methylphenidate (CNS stimulant)
Modafinil "wakefulness-promoting agent“ acting on DA and H transmission
Dextroamphetamine (CNS stimulant)

Depression: **Antidepressants** can be used to manage depressive symptoms. Interferon products should be used cautiously in depressed patients.

Treatment

Acute attacks

- High-dose corticosteroids
- Plasma exchange

Slow progression

- Interferons
- Glatiramer acetate
- Natalizumab
- Mitoxantrone

Symptomatic management

- Spasticity
- Tremors
- Bowel and Bladder incontinence
- Depression
- Fatigue

عقاقير الاكتئاب وأمراض القلب "قد تفيد" في علاج تصلب الأعصاب المتعدد

سارة بلوتشبي بي سي
قبل 4 ساعة•
شارك

قالت جامعات بريطانية إنها ستجري اختبارا على عقاقير الاكتئاب وأمراض القلب المتوفرة بهدف إيجاد علاجات لمرض التهاب الأعصاب المعروف باسم التصلب المتعدد من بين أدوية موجودة بالفعل.

ولا يوجد حاليا أي علاج للمرحلة الثانوية المتقدمة من هذا المرض الذي يصيب الشخص بحالة شديدة من التعب والإرهاق.

ويأمل الأطباء أن تكون الأدوية اللازمة لعلاج هذا المرض موجودة بالفعل، لكن لم تختبر من قبل على التصلب المتعدد.

وسيشارك أكثر من 400 شخص في هذه التجربة بجامعة لندن وجامعة أدنبرة.

وتؤثر المراحل المتقدمة لهذا المرض على المشي والتوازن والكلام والرؤية.

وهناك علاجات للمراحل المبكرة من مرض التصلب العصبي المتعدد لمنع تكرار الانتكاسات أو الحد من شدتها، لكن لا يوجد عقاقير لعلاج المراحل المتقدمة من المرض.

إعادة توظيف

ستعمل هذه "التجربة الذكية" على اختبار سلامة وفعالية ثلاثة عقاقير تستخدم في حالات أخرى:

- أميلوريد – مرخص لعلاج أمراض القلب
- فلوكستين – يستخدم في حالات الاكتئاب
- ريلوزول – يستخدم لعلاج الأمراض العصبية الحركية

وجرى تحديد هذه العقاقير بعد مراجعة بحث نشر سابقا حول العقاقير التي قد تعمل على حماية الأعصاب من التلف.

ويعتقد باحثون أن هذه العقاقير يمكن أن تبطئ تطور مرض التصلب العصبي، وستكون هذه التجربة هي الأولى من

At the time of diagnosis, the most common form of multiple sclerosis (MS) is:	
	A) Primary-progressive
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Which of the following is used in the treatment of an acute attack/relapse of MS?	
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B)	High-dose intravenous methylprednisolone
C)	High-dose oral prednisone
D)	Mitoxantrone

Which of the following is a serious adverse effect of mitoxantrone?	
	A) Hepatotoxicity
	B) Renal failure
	C) Skin site reactions
	D) Leukemia

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http://www.merckmanuals.com/

www.medscape.com

www.drugs.com

www.nccam.nih.gov

http://ods.od.nih.gov

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