Clinician Summary
Disease Modifying Drugs for Multiple Sclerosis
June 2011

Based on the DERP report of August 2010

Produced by:
The Health Resources Commission
Office for Oregon Health Policy & Research
1225 Ferry Street SE Salem, OR 97301 Phone: 503.373.1629
HRC.info@state.or.us
http://www.oregon.gov/OHPPR/HRC/index.shtml

Clinician Summary: Drugs for MS

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Included Drugs

Glatiramer Acetate (Copaxone®), Interferon β 1a (Avonex®), Interferon β 1a (Rebif®), Interferon β 1b (Betaseron®), Interferon β 1b (Extavia®), Mitoxantrone (Novantrone®), Natalizumab (Tysabri®)

Limitations of the Evidence:

1. End points were relapse prevention, disease progression and change in Expanded Disability Status Score (EDSS.)
2. No study was classified as an effectiveness study. Applicability to patients seen in usual care may be limited.
3. All studies looked primarily at relapsing-remitting MS. There was no direct evidence in patients with primary or secondary progressive multiple sclerosis, or progressive relapsing multiple sclerosis.
4. Adverse event reporting was incomplete.

Progression of relapsing-remitting MS

Fair evidence: interferon beta-1b (Betaseron®) was more efficacious than interferon beta-1a IM (Avonex®) in relapse outcomes in patients with relapsing remitting MS.
Insufficient evidence: To determine a difference in efficacy for all other drug comparisons for all other forms of MS.

Preventing progression of clinically isolated syndrome to clinically definite MS

Fair evidence: glatiramer (Copaxone®), interferon beta-1a IM (Avonex®), interferon beta-1a SC (Rebif®) and interferon beta-1b (Betaseron®) are more effective than placebo
No studies: of natalizumab or mitoxantrone for this condition.

Harms

1. Discontinuation rate due to adverse events was low and similar among the interferons.
2. Interferon beta-1b SC (Avonex®) had the lowest rates of injection site reactions (8.5%)
3. Interferon beta-1b SC (Betaseron®) and Interferon beta-1b SC (Rebif®) had similar rates 58-61%

Case studies:

1. glatiramer - lipoatrophy with prolonged use
2. mitoxantrone - rare incidence of acute leukemia and cardiotoxicity

Observational studies: mitoxantrone - permanent amenorrhea in older women receiving high total doses

Development of drug antibodies

Subcutaneous administration of interferon appears to be more antigenic than IM administration. About half of patients who develop antibodies will become antibody negative over time. The clinical significance of antibody development is unknown.

Black box warnings

Mitoxantrone for cardiotoxicity.
Natalizumab for Progressive Multifocal Leukoencephalopathy (PML.) Rate 1/1000

Subgroups

Insufficient evidence: to determine a comparative difference in subgroups.

Table 1. Pharmacology and dosing of included drugs

Agent	Dosage and Administration	Black Box Warning?	Indication	Clinical Pharmacology
Glatiramer Acetate Copaxone®	20 mg Subcutaneously qd		RRMS	Interferes with antigen presentation by mimicking and competing with MBP, a selfantigen, for binding to the MHC on the APC. The glatiramer-MHC complex competes with the MBP-MHC complex for binding to the TCR on T helper cells, which down-regulates Th1 activity and promotes a Th2 cell response, leading to increased anti-inflammatory cytokine production.
Interferon β 1a Avonex®	30 mcg Intramuscularly 1x/wk		RRMS	Modulates the immune system by reducing T cell migration from the periphery into the CNS by decreasing the production of adhesion molecules and increasing the production of metalloproteases on the vascular endothelium that constitutes the blood brain barrier.12 These agents may also inhibit the proliferation of proinflammatory cytokines from Th1 cells (TNFα, IFNγ, IL-12).
Interferon β 1a Rebif®	22 or 44 mcg Subcutaneously 3x/wk		RRMS	
Interferon β 1b Betaseron®	0.25 mg Subcutaneously Every other day		RRMS, SPMS ,CIS	
Interferon β 1b Extavia®	0.25 mg Subcutaneously Every other day		Treatment of relapsing forms of MS to reduce frequency of clinical exacerbations. Effective in patients who experienced a first clinical episode and have MRI features consistent with MS	
Mitoxantrone Novantrone®	12 mg/m2 Intravenously Every 3 mos (Max cumulative	Y (cardiotoxicity)	SPMS, PRMS, or Worsening RRMS	Inhibits cell division and impairs the proliferation of T cells, B cells and macrophages by intercalating and crosslinking DNA, thus inhibiting DNA replication and

	dose is 140 mg/m2)			RNA synthesis of these cells. Impairs antigen presentation by causing apoptosis of APCs and other cells that associate with APCs.
Natalizumab Tysabri®	300 mg Intravenously Every 4 wks	Y (PML)	RRMS	Binds to α4 integrins expressed on leukocytes, which prevents binding to adhesion cells VCAM-1 and MAdCAM-1 on the vascular endothelium and prevents migration of leukocytes from the periphery into the CNS.

APC = antigen-presenting cell, CNS = central nervous system, IL = interleukin, IFN = interferon, MAdCAM-1 = mucosal vascular addressin cell adhesion molecule-1, MBP = myelin basic protein, MHC = major histocompatibility complex, PRMS = progressive relapsing multiple sclerosis, RRMS = relapsing-remitting multiple sclerosis, SPMS = secondary progressive multiple sclerosis, TCR = T cell receptor, Th = T-helper, TNF = Tumor Necrosis Factor, VCAM-1 = vascular cell adhesion molecule-1, CIS = clinically isolated syndrome.