



Disease-Modifying Agents in the Treatment of Relapsing-Remitting Multiple Sclerosis

Learning Objectives

1. Identify the symptoms and types of multiple sclerosis (MS).
2. Describe the measures to monitor disease progression of MS.
3. Discuss the disease-modifying agents approved by the FDA to treat relapsing-remitting MS (RRMS).
4. List the side effects of the disease-modifying agents.

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Introduction

Recently the treatment of multiple sclerosis (MS) has received much attention in the healthcare community and the public. In November 2004, the drug natalizumab (Tysabri®), a disease-modifying agent, received accelerated Food and Drug Administration (FDA) approval for the treatment of relapsing-remitting MS (RRMS) based on very promising results of 2 clinical trials. In February 2005, the co-manufacturers of natalizumab (Elan and Biogen) voluntarily suspended marketing after 2 reported cases of fatal multi-focal leukoencephalopathy were attributed to the drug.¹ The manufacturers and FDA are evaluating the safety data and it is unknown whether the drug will return to the market.¹ This article will review the use of the disease-modifying agents currently marketed for the treatment of RRMS.

Background

MS is a chronic neurological disease that affects 400,000 Americans and 2.5 million people worldwide. In the U.S., approximately 200 new cases are diagnosed every week.² It is estimated that the annual economic cost of MS in the U.S. is approximately \$20 billion.² The average age at onset of MS is 30 years³ with the majority of patients presenting with clinical symptoms between the ages of 20 and 40 years.⁴ MS has been reported rarely in patients younger than 15 years or older than 50 years. It is twice as prevalent in women as in men.⁵

Pathogenesis

MS is a chronic inflammatory disease of the central nervous system that leads to discrete areas of neuronal demyelination plaques and results in axonal loss. The pathogenesis of MS is not completely elucidated. Common symptoms include: fatigue; cognitive changes; sensory disturbances in the limbs, optic nerve, pyramidal tract, bladder or bowel; sexual dysfunction; ataxia and diplopia.⁶ These symptoms vary based on the area of the plaques within the central nervous system. Relapse attacks can include any of the symptoms or a combination of them.⁵

Types and Progression of Multiple Sclerosis

There are 4 main types of MS. The most common type is RRMS, which occurs in 85% of patients.⁷ RRMS has a clinical pattern of defined acute attacks of symptoms followed by full or partial recovery to the pre-existing level of disability without disease progression during the time between the attacks. Primary progressive MS (PPMS) presents with disease progression from the onset and may or may not have temporary small improvements or plateaus. Secondary progressive MS (SPMS) starts with a relapsing-

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remitting phase followed by disease progression with or without occasional relapses or minor improvements. Progressive relapsing MS (PRMS) is characterized by disease progression from the onset with acute relapses that are followed by full or partial recovery to the pre-existing disability level.^{4,8} The rate at which disability progresses and relapse frequency occurs is highly variable. Relapses are defined as new or worsening neurological symptoms. MS is a chronic disease that typically results in significant disability and has a negative impact on a patient's quality of life.

The progression of MS is measured with disability scales evaluating neurological impairment. The most common scale used is the Kurtzke Expanded Disability Status Scale (EDSS). The EDSS is an ordinal scale from 0 (normal exam) to 10 (death due to MS). The EDSS score range of 4 to 7 indicates the patient is able to walk; patients with scores greater than 7 are no longer able to walk. A score greater than 8.5 indicates the patient has no ability to use his or her arms or legs.⁷ Magnetic resonance imaging (MRI) scans are an important part of diagnosis of MS and monitoring disease progression by showing enhanced lesions indicative of blood brain barrier breakdown and active inflammation.

Treatment with Disease-Modifying Agents

Major advances have been made in the past decade in the treatment of MS with the development of disease-modifying therapies. Prior to these advances, patients were treated with glucocorticoids, cyclophosphamide, methotrexate, azathioprine, cladribine and cyclosporine.⁶ However, these drugs did not have long term benefits to modify the disease course of MS. The disease-modifying agents act on the immune system at the inflammatory stage of the disease process attempting to lessen neurological impairment and subsequent significant physical disability. They have demonstrated promising results in RRMS by reducing the frequency and severity of relapses, decreasing the number of brain lesions and lessening future disability.⁶

The disease-modifying agents are divided into 2 classes: immunomodulators and immunosuppressants. The first therapeutic agents approved by the FDA for the treatment of MS were the immunomodulators.^{2,6} This class includes 3 different beta-interferons and glatiramer acetate (GA), all of which are currently approved for the treatment of RRMS only. The results of several large clinical studies have shown that treatment with any of the

interferon beta (IFN- β) drugs or GA decreases both the clinical and MRI disease activity and delays MS progression.⁹⁻¹⁷ Mitoxantrone, an immunosuppressant with immunomodulator properties, is indicated for slowing the progression of disability in patients with worsening RRMS, SPMS and PRMS.¹ The medical advisory board of the National Multiple Sclerosis Society recommends that therapy with an immunomodulator be initiated as soon as possible in patients with RRMS. The Board has also recommended that the treatment be continued indefinitely unless there are no clear benefits, intolerable side effects develop or better therapy becomes available.²

Beta Interferons

Three different beta interferon products are approved by the FDA for treatment of RRMS, each having a different route of administration, dosage recommendations and frequencies of administration. Interferon β -1b (Betaseron[®]) was approved by the FDA in 1993 to be administered subcutaneously (SQ) every other day at a dose of 250 micrograms (μ g).¹⁸ In 1996 the FDA approved interferon β -1a (Avonex[®]) administered intramuscularly (IM) once weekly at a dose of 30 μ g.¹⁹ A year later a second interferon β -1a (Rebif[®]) was approved for SQ administration 3 times a week at a dosage of 22 or 44 μ g.²⁰

The most common side effects with the 3 IFN- β agents are flu-like symptoms, injection site reactions and elevated liver function tests. MS patients are at a higher risk to develop depression and should be monitored for its occurrence during interferon treatment.⁷ A treatment challenge with the IFN- β drugs is the development of neutralizing antibodies (Nabs) occurring in different proportions of patients depending on the IFN- β used. Nabs occur in 45% of patients treated with Betaseron[®], in 24-31% of patients treated with Rebif[®] and in 5% of patients treated with Avonex[®].¹⁸⁻²⁰ The clinical relevance of Nabs is uncertain, but their presence may be associated with a reduction in clinical effectiveness of IFN- β treatment. The efficacy of the IFN- β for RRMS has been demonstrated in several clinical trials.

Interferon Beta-1b

IFN- β -1b (Betaseron[®]) was the first disease-modifying agent shown to be effective in treating RRMS. The Interferon Multiple Sclerosis Study group¹⁶ conducted a 24-month randomized, double-blind, placebo-controlled study of 372 patients with RRMS (EDSS score \leq 5.5). Subjects were randomized to placebo, IFN- β -1b 50 μ g or 250 μ g SQ every other day. By the

end of two years of treatment the annual relapse rate in the placebo group was 1.27 compared to 1.17 in the low dose IFN- β -1b group and 0.84 in the 250 μ g group. The reduction in relapse rate was statistically significant for both treatment groups compared to placebo and the 250 μ g dose was significantly more effective than the 50 μ g dose. The severity of the relapses was also significantly reduced with the 250 μ g dose. At the end of two years the mean lesion area seen on cranial MRI was reduced by 0.1% in the 250 μ g group compared to increases of 20% and 10.5% in the placebo and 50 μ g groups, respectively.²¹ Considering that the EDSS scores changed little in the treated as well as placebo groups, this study was not able to demonstrate a benefit in terms of disability. This study was the first large multi-center randomized trial to show the effectiveness of IFN- β -1b in reducing relapse rates and MRI activity to treat RRMS.

The Interferon Multiple Sclerosis Study group²² conducted a 36-month continuation of the study described above with 286 patients. The primary endpoints of the extension study of time to worsening of the EDSS by at least 1 point and the mean change in EDSS from baseline, did not show a statistically significant benefit from treatment. With the small sample size and with a drop out rate of over 40% by year 5, the study was underpowered for these endpoints. The results showed that both doses of IFN- β -1b had a significant beneficial effect on the pooled annual relapse rates for the entire study which were 1.12, 0.96, and 0.78 for the placebo, 50 μ g dose, and 250 μ g dose respectively. There was no significant change compared to baseline in the MRI lesion area in the 250 μ g dose group over the duration of the study; however, there was a significant increase in both the placebo and low-dose groups.

Interferon Beta-1a

Studies have shown that treating RRMS early is crucial to minimize the axon loss and subsequent disability progression. Jacobs and co-workers²³ conducted the Controlled High-Risk Avonex[®] Multiple Sclerosis Prevention Study (CHAMPS) to quantify the benefit of early treatment with IFN- β -1a after the first clinical demyelinating event. This was a 36-month randomized, double-blind study in 383 patients treated with IFN- β -1a 30 μ g IM once weekly or placebo. The rate ratio for developing clinically definite multiple sclerosis (CDMS) in the IFN- β -1a treated patients compared to placebo was 0.56 (95% CI 0.38-0.81). The actual cumulative probability of CDMS at three years was 50% in the placebo group and 35% in the

IFN- β -1a group. Patients receiving IFN- β -1a also had only a 1% median increase in the volume brain lesions seen on MRI at 18 months compared to a 16% increase with placebo ($p < 0.001$). The IFN- β -1a treated patients also had fewer lesions on MRI scans.

Jacobs and colleagues¹² had previously conducted a multi-center randomized double-blind trial to determine if IFN- β -1a could slow the disease progression of RRMS. The 24-month study in 301 patients compared IFN- β -1a 30 μ g IM weekly injections to placebo. The primary endpoint of this study was the time to onset of disease progression, which was defined as at least a 1.0 point increase on the EDSS score. IFN- β -1a compared to placebo showed a statistically significant increase in time to sustained disease progression ($p = 0.02$). Progression of disability occurred in 34.9% of placebo treated patients and 21.9% of interferon treated patients. Interferon also produced beneficial effects on the disease activity measured by the number and volume of lesions on the brain MRI ($p = 0.02$).¹⁴ The annual relapse rate was 0.67 with IFN- β -1a compared to 0.82 with placebo. This study showed evidence that IFN- β -1a (Avonex[®]) is effective in prolonging the time to disability and reducing the relapse rate in patients with RRMS. These results were later confirmed by Rudick and colleagues¹⁵ post-hoc analysis of the data to examine the impact of more stringent definitions of disability, the magnitude of change in the EDSS, and the proportion of subjects reaching EDSS scores of ≥ 4.0 or ≥ 6.0 . The implication of this analysis is that the clinical significance of the benefits of therapy were under expressed by the definitions of the outcomes used in the original analysis.

Ebers and associates²⁴ in 1998 published the results of the Prevention of Relapses and Disability by IFN- β -1a Subcutaneously in Multiple Sclerosis (PRISMS) study. This randomized, double-blind, placebo-controlled trial with 560 RRMS patients (EDSS score ≤ 5.0) assessed the efficacy of subcutaneous IFN β -1a (Rebif[®]) at 22 and 44 μ g 3 times weekly for 24 months. Neurological exams were conducted every 3 months and an MRI every 6 months. The results showed that the relapse rates were significantly lower ($p < 0.005$) with IFN- β -1a 22 and 44 μ g dose compared to placebo (relapse rates per patient over 2 years 1.82, 1.73 and 2.56, respectively). The number of patients who were relapse-free during the study was significantly increased ($p < 0.05$), and the time to first relapse was longer by 3 and 5 months in the 22 μ g and 44 μ g

groups, respectively. The time to progression of disability (EDSS increase of ≥ 1.0 sustained for 3 months) was also greater in the treated groups. The first quartile time (in months) to confirmed progression was 11.9, 18.5, and 21.3 in the placebo, 22 μ g and 44 μ g groups. Disease burden assessed by MRI also showed benefit from treatment.

The PRISMS investigators¹³ extended the trial another 24 months (PRISMS-4) in 506 patients. Patients originally on active treatment continued with the same dose for 24 more months and patients originally allocated to placebo were re-randomized to IFN- β -1a 22 or 44 μ g SQ 3 times weekly. The results indicated the clinical benefits noted after 2 years continued to be seen at 4 years, and the most clinical benefit was seen in patients receiving IFN- β -1a for 4 years compared to 2 years active treatment. There was also an indication of a dose response effect and that starting therapy at diagnosis is preferred to waiting, although the evidence for these effects is not consistent for all outcomes assessed.

Studies have shown that both formulations of IFN- β -1a are beneficial for patients with neurological impairments prior to definite RRMS and in patients with active RRMS. The most effective dose regimen and preparation remains controversial. Panitch and collaborators²⁵ conducted a 24-week, randomized, single-blind, comparative study of IFN- β -1a (Rebif[®]) 44 μ g SQ 3 times weekly and IFN- β -1a (Avonex[®]) 30 μ g IM once weekly in 677 patients with RRMS (EDSS scores of ≤ 5.5) who were IFN naïve. The percentage of patients who were relapse free at 24 weeks was significantly greater in the Rebif[®] cohort (74.9 %) compared to those in the Avonex[®] group (63.3%). The MRI showed fewer active lesions in the Rebif[®] group compared to the Avonex[®] group ($p < 0.001$). The investigators concluded that Rebif[®] is slightly more effective than Avonex[®] in improving relapse rates and MRI lesions in RRMS. However this is not definitive because of the study's short duration, lack of patient blinding, and lack of evidence of a difference in progression of disability. In addition, adverse effects of injection site reactions, (83% vs. 28%), abnormalities of liver enzymes (18% vs. 9%), altered leukocyte counts (11% vs. 5%), and development of neutralizing antibodies (25% vs. 2%) were all significantly higher in the patients treated with Rebif[®].

Glatiramer Acetate

Glatiramer acetate (GA) (Copaxone[®]- previously called co-polymer-1) was approved by the FDA in 1997 for the treatment of RRMS.² GA is a polypeptide composed of the amino acids L-glutamine, L-alanine, L-tyrosine and L-lysine. The mechanism of action is unclear, but it is believed to act via immunomodulating action. The side effects of GA are transient and include injection-site reactions, flushing, chest tightness, nausea, anxiety, arthralgia and hypertension.^{7,25}

GA was approved for treatment of RRMS based on 2 studies. Bornstein and co-authors²⁶ reported the results of a 24-month randomized, double-blind pilot trial of 50 patients with RRMS receiving GA 20 mg SQ daily compared to placebo. The results showed that fewer patients treated with GA had exacerbations of MS symptoms (44% vs. 74% for GA and placebo, respectively). The two year average exacerbation rate was 2.7 for placebo treated patients and 0.6 per patient in the GA treated group.

Johnson and colleagues²⁷ conducted a 24-month phase-III trial of 251 patients with RRMS randomized to GA 20 mg daily or placebo. GA therapy produced a statistically significant 29% relapse reduction rate compared to placebo ($p = 0.007$). The 2 year mean relapse rate was 1.19 in GA treated patients and 1.68 in the placebo group. When comparing baseline and 24 months, more patients treated with GA than those treated with placebo, showed a 1 point improvement on the EDSS, and more patients treated with placebo worsened by 1 point or more. However there was not a reduction in disease progression measured by the proportion of patients who had an increase of one point or more in the EDSS maintained for more than 90 days. By this definition the proportion of progression-free patients treated with GA was 78.4% compared to 75.4% in the placebo group. Johnson and colleagues²⁸ reported an extension of their original trial. The extension was for a mean period of approximately 6 months with a range of 1 to 11 months to allow all patients an opportunity to complete at least 24 months on study drug. The results showed that patients on GA had fewer relapses. There were significantly more patients in the placebo group who had an increase of the EDSS of ≥ 1.5 by the end of the study (41.6%), compared to those treated with GA (21.6%, $p = 0.001$). Sustained progression of disability based on an increase of EDSS of

≥ 1 for a period of 3 months or more was seen in 29.3% of subjects receiving placebo and 23.2% in the GA group, but this was not significant ($p=0.199$).

Mitoxantrone

In 2000 the FDA approved mitoxantrone (Novantrone®) for treatment of patients with worsening RRMS, SPMS and PRMS²⁹. If patients experience accumulating residual disability from repeated relapses or rapid progression of disability with evidence of continued inflammatory lesions, mitoxantrone therapy should be considered. Mitoxantrone is an immunosuppressive agent with immunomodulating properties. Its mechanism of action is inhibition of cellular DNA repair and synthesis by inhibiting DNA topoisomerase II.²⁹ It has also been shown to inhibit B cell, T cell, and macrophage proliferation and impair antigen presentation as well as the secretion of interferon gamma, TNFalpha and IL-2.²⁹ The side effects most commonly seen are nausea, fatigue, hair loss and menstrual disorder. Recently, the FDA issued a black-box warning about possible cardiotoxicity with mitoxantrone. It is recommended that patients have a baseline evaluation of left ventricular ejection fraction (LVEF). Patients with a LVEF lower than 50% should not receive mitoxantrone. LVEF should be tested prior to each dose, and if the LVEF falls below 50% the drug should be discontinued. The cardiotoxicity appears to be a cumulative effect, so the lifetime dose of the drug should not exceed 140 mg/m².³⁰ Also, a warning has been included in the labeling for the potential development of secondary acute myelogenous leukemia.²⁹

Mitoxantrone efficacy in worsening RRMS was studied by Hartung and co-workers in the mitoxantrone in multiple sclerosis study group (MIMS)³¹. They conducted a randomized, double-blind, placebo-controlled trial of 194 subjects with worsening RRMS (EDSS score 3.0-6.0 at baseline) or secondary progressive multiple sclerosis (SPMS). Patients were randomized to placebo or mitoxantrone 5mg/m² or 12 mg/m² IV every 3 months for 24 months. The mitoxantrone dose was reduced for individual patients based on white blood cell counts, platelet counts, and for non-hematological toxic effects. The results of this trial showed that patients in the mitoxantrone groups had less neurological deterioration from baseline compared to the changes from baseline seen with placebo. Patients receiving 12 mg/m² mitoxantrone had less disease progression than the placebo group as measured by the change in mean EDSS score at 24 months

minus the baseline score (-0.13 , +0.23, respectively; $p=0.0194$). The 12 mg/m² group also had a significantly lower mean number of relapses over two years compared to placebo (0.40 versus 1.20, respectively; $p=0.0002$). Subjects treated with 12 mg/m² also experienced fewer lesions on MRI, fewer hospitalizations, and better results on the quality of life measurement. The 5mg/m² dose demonstrated significant improvement compared to placebo in some outcomes but not all, and the results generally showed less benefit than the higher dose. These results indicate mitoxantrone is potentially effective in slowing disease progression in patients with worsening RRMS.

Millefiorini and co-workers³² also found mitoxantrone to be effective in reducing the exacerbation rate and possibly the progression of disease in patients with RRMS. The 24-month randomized trial of 51 patients compared mitoxantrone 8 mg/m² IV monthly to placebo. Therapy was given for one year and monitoring of outcomes continued for two years. Of the patients assigned to mitoxantrone 7% showed disease progression based on a one point increase in EDSS compared to 37% receiving placebo ($p=0.02$). However there was not a significant difference in mean EDSS change between the two groups at the end of the first or second year. Mitoxantrone showed a significantly lower mean relapse rate over the study period compared to placebo (0.89 and 2.62, respectively; $p=0.0002$). A greater proportion of mitoxantrone patients remained relapse-free after 24 months compared to placebo (63% and 21%, respectively; $p=0.006$). Benefits were also seen with mitoxantrone on the number of new or enlarging lesions seen on MRI.

These studies showed that mitoxantrone is potentially effective in patients with worsening RRMS. However, each patient's healthcare team will need to determine the risk versus benefit for mitoxantrone.

Therapeutic Selection

The choice of which agent is best for each patient depends on the clinician's expectation of clinical benefit and the patient's anticipated tolerance of side effects. The subcommittee of the American Academy of Neurology MS council published practice guidelines for disease modifying therapies in multiple sclerosis. The recommendations, based on several studies, have shown that the three IFN- β products, GA and mitoxantrone reduce the attack rate measured clinically and on MRI, in RRMS patients. There is no known

clinical difference between the different types of IFN- β agents based on current trials, and more studies are needed to confirm this finding. Mitoxantrone's potential cardiac toxicity may outweigh the clinical benefits of its use in some patients.⁶

Conclusion

The disease modifying agents currently approved for use in RRMS show promising results in the inflammatory period of disease progression and provide hope to patients who previously only had symptomatic therapy available. MS remains a challenging disease to treat because the cause is unknown and the unpredictable course of the disease makes it difficult to determine if the benefits gained by short-term results can be continued long term. The challenges for future MS research will be to address: long-term benefits of therapy on disability; adverse effects and risks of treatment; drug therapy after inflammatory progression; optimization of dose, schedule and route of administration; possible combination therapies, and the cost-effectiveness of these agents.

Accreditation Information



The University of Iowa College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider for continuing pharmacy education. The ACPE program number is 020-000-05-094-H01. The University of Iowa will award 1 contact hour (0.1 CEU) of continuing pharmacy education for satisfactory completion of this monograph.

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Disease-Modifying Agents in the Treatment of Relapsing-Remitting Multiple Sclerosis

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1. Which of the following is a common symptom of MS?
 - a. optic nerve dysfunction
 - b. bladder or bowel dysfunction
 - c. sensory disturbances in the limbs
 - d. all of the above
2. Secondary progressive multiple sclerosis clinical pattern presents as _____.
 - a. defined acute attacks of symptoms followed by full or partial recovery to the pre-existing level
 - b. disease progression from the onset with or without temporary small improvements
 - c. disease progression from the onset with acute relapses followed by full or partial recovery to the pre-existing disability level
 - d. relapsing-remitting phase followed by disease progression with or without temporary small improvements
3. In the Kurtzke Expanded Disability Status Scale of neurological impairment of MS, a score of 5 would indicate what level of impairment?
 - a. patient is unable to use his or her arms or legs
 - b. patient is no longer able to walk
 - c. patient is able to walk
 - d. patient has a normal exam
4. Which of the following statements is true?
 - a. The average age at onset of MS is 15 years
 - b. The worldwide prevalence of MS is estimated at 4 million people
 - c. The prevalence of MS is higher in men than in women
 - d. In the U.S., approximately 200 new cases of MS are diagnosed every week
5. What is the approved dose of Interferon β -1a (Rebif®) for the treatment of RRMS?
 - a. 30 μ g IM once weekly
 - b. 22 or 44 μ g SQ 3 times weekly
 - c. 250 μ g SQ every other day
 - d. 20 μ g SQ daily
6. The CHAMPS study was able to quantify the benefit of early treatment of which disease-modifying agent?
 - a. INF- β -1a (Avonex®)
 - b. INF- β -1b (Betaseron®)
 - c. INF- β -1a (Rebif®)
 - d. GA (Copaxone®)
7. Which of the following statements is true?
 - a. GA has been proven to be less effective than the IFN- β drugs in treating RRMS
 - b. GA is a polypeptide composed of the amino acids L-glutamine, L-alanine, L-tyrosine and L-lysine

- c. GA mechanism of action is inhibition of cellular DNA repair and synthesis by inhibiting DNA topoisomerase II
 - d. GA side effects include nausea, anxiety, cardiotoxicity and secondary leukemia
8. The prescribing information for mitoxantrone carries a black-box warning for _____.
 - a. liver failure
 - b. renal failure
 - c. ototoxicity
 - d. cardiotoxicity
9. Natalizumab (Tysabri®) was withdrawn from the market after reported deaths attributed to the use of the drug causing _____.
 - a. congestive heart failure
 - b. secondary leukemia
 - c. liver failure progressive
 - d. progressive multi-focal leukoencephalopathy
10. Which of the following drugs is approved for use in treating worsening RRMS, SPMS and PRMS?
 - a. Novantrone®
 - b. Rebif®
 - c. Avonex®
 - d. Copaxone®

Please Note: The CE processing fee has increased to \$7.50

PROGRAM EVALUATION

	Excellent				Poor
Overall quality	5	4	3	2	1
Relevance to practice	5	4	3	2	1
Value of content	5	4	3	2	1
Important to pharmacists	Agree		Disagree		
	5	4	3	2	1
Increased my knowledge	5	4	3	2	1
Achieved stated objectives	5	4	3	2	1
Was educational and not promotional	5	4	3	2	1

It took me _____ hours and _____ minutes to read this article and complete the assessment questions.

New Molecular Entities & Biologicals

An *IDIS* search retrieved articles relevant to the new drugs and their approved uses. These articles provide a selection of key critical studies and reviews. Additional information on these newly approved drugs will be available in the FDA Approval Package [an official United States Food and Drug Administration (FDA) document] that is compiled for new drugs following approval. The FDA Approval Package includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are selectively indexed and included as part of the *IDIS* database as they become available. Use the descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the database.

Therapeutic Potentials:

P = Priority Review, significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease.

S = Standard Review, the drug appears to have therapeutic qualities similar to those of one or more already marketed drugs.

O = Orphan drug.

FDA Approvals
April – August 2005

Evidence of Safety and Efficacy

Exenatide Synthetic

Byetta™ Injectable,
subcutaneous, Amylin
(P)

Degn KB, Brock B, Juhl CB, Djurhuus CB, et al. Effect of intravenous infusion of **exenatide** (Synthetic Exendin-4) on glucose-dependent insulin secretion and counterregulation during hypoglycemia. *Diabetes*. 2004; 53:2397-2403. (*IDIS* Article Number 522868)

Approved 28Apr2005 for
treatment of diabetes

This was a randomized, triple-blind crossover study with 12 healthy volunteers who received either 0.066 pmol · kg⁻¹ · min⁻¹ of exenatide intravenously or placebo during a stepwise hyperinsulinemic-hypoglycemic clamp that found the glucose-dependent insulin secretory response and counterregulatory response were preserved during hypoglycemia with use of exenatide.

Calara F, Taylo K, Han J, Zabala E, et al. A randomized, open-label, crossover study examining the effect of injection site on bioavailability of **exenatide** (Synthetic Exendin-4). *Clin Ther*. 2005; 27:210-215. (*IDIS* Article Number 531337)

The goal of this open-label, randomized crossover study with 28 type 2 DM patients was to discover the relative bioavailability of exenatide subcutaneously injected into either the abdomen, arm or thigh. Investigators found that the AUC (geometric LS mean ratio for relative bioavailability) was 0.93 (geometric 90% CI, 0.82-1.05) for arm versus abdomen, and 0.97 (geometric 90% CI 0.86-1.10) for thigh versus abdomen.

IDIS Search Terms [9 IDIS citations]

Exenatide	68200001
Diabetes Mellitus	250.

Galsulfase

Naglazyme™ Injection,
Biomarin
(O), (P) Biological
Approved 31May2005 for
treatment of
Mucopolysaccharidosis
VI (MPS VI).

The FDA approved **galsulfase** with an Orphan Drug Status and Priority Review classification. No published human studies have been found for entry into the *IDIS* database.

IDIS Search Terms [0 IDIS citations]

Mucopolysaccharidosis	277.5
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Thank you in advance for your prompt attention to your subscription renewal and your continued support of the *Iowa Drug Information Service*.

Insulin Detemir

*Levemir*TM sc injection,
Norvo Nordisk
(P)
Approved 16Jun2005
for treatment of Type 1
or Type 2 diabetes long
acting control of
hyperglycemia

Home P, Bartley P, Russell-Jones D, Hanaire-Broutin H, et al. **Insulin detemir** offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. *Diabetes Care*. 2004; 27:1081-1087. (IDIS Article Number 524410)

An open-label, parallel group, 16-week trial with 408 type 1 diabetic patients randomized participants to insulin detemir, twice daily either before breakfast and at bedtime (IDetmorn+bed) or every 12 hours (IDet12h), or to NPH insulin twice daily, before breakfast and at bedtime. Investigators found clinic fasting plasma glucose was lower in both insulin detemir groups than in the NPH insulin group, mean difference (IDet12h = -1.5 mmol/l vs. NPH, p=0.004; IDetmorn+bed = -2.3 mmol/l vs. NPH, p<0.001), and also the self-measured pre-breakfast plasma glucose was lower, p=0.006 and p=0.004 respectively. The NPH group gained weight during the trial, while neither the IDet12h nor the IDetmorn+bed group gained weight, p=0.006 and p=0.040 respectively.

IDIS Search Terms [13 IDIS citations]

Insulin Detemir	68200824
Diabetes Mellitus	250.

Tigecycline

*Tygacil*TM Injection,
Wyeth Pharms, Inc.
(P)
Approved 15Jun2005
for treatment of
complicated skin and
skin structure
infections, and
complicated abdominal
infections.

Postier RG, Green SL, Klein SR, Ellis-Grosse EJ, et al. Results of a multicenter, randomized, open-label efficacy study of two doses of **tigecycline** for complicated skin and skin-structure infections in hospitalized patients. *Clin Ther*. 2004; 26:704-714. (IDIS Article Number 516633)

Investigators compared the efficacy, tolerability and pharmacokinetic properties of two dosing regimens, 25mg or 50mg intravenously every 12 hours for 7 to 14 days of tigecycline, in this randomized, multicenter, open-label study of 160 patients, and found that tigecycline was safe and efficacious with a favorable pharmacokinetic profile. The clinical cure rates and eradication rates were 74% and 69% respectively for patients who received 50mg doses, and 67% and 56% for patients who received the 25mg doses.

IDIS Search Terms [8 IDIS citation]

Tigecycline	8122407
Infection, Skin/SQ NEC	686.
Peritonitis	567.

Tipranavir

*Aptivus*TM Capsule, oral
Boehringer Ingelheim
(S)
Approved 22Jun2005
For use in conjunction
with ritonavir for HIV-1
infection.

McCallister S, Valdez H, Curry K, MacGregor T, et al. A 14-day dose-response study of the efficacy, safety, and pharmacokinetics of the nonpeptidic protease inhibitor **tipranavir** in treatment-naïve HIV-1-infected patients. *J Acquir Immune Defic Syndr*. 2004; 35:376-382. (IDIS Article Number 513269)

A total of 31 HIV-1 infected patients participated in this randomized, open-label, multicenter, parallel-group study that tested the safety, efficacy and pharmacokinetics of tipranavir 1200mg twice daily (TPV 1200), tipranavir 300mg plus ritonavir 200mg twice daily (TPV/r 300/200) or tipranavir 1200mg plus ritonavir 200mg twice daily (TPV/r 1200/200). After 14 days of treatment, investigators found that tipranavir was safe, effective and well tolerated with a median decrease in viral load of -0.77 log₁₀ in the TPV 1200 group, -1.43 log₁₀ in the TPV/r 300/200 group and -1.64 log₁₀ in the TPV/r 1200/200 group, and that TPV exposure increased 24- and 70-fold in the combination groups as compared with TPV alone.

IDIS Search Terms [83 IDIS citations]

Tipranavir	8180808
Syn-Acq Immune Deficiency	042.
Infection, HIV, Asymptomatic	V08.

Nicola Sarrazin is a 1984 graduate of the University of Iowa (B.A. in Anthropology and Asian Studies) and a 1997 graduate of the University of Iowa College of Pharmacy (Pharm.D.). Since that time she has been a pharmacist in the College of Pharmacy's Division of Drug Information Service. Nickie's responsibilities include indexing articles for the IDIS database, overseeing the Drug vocabulary and contributing articles for the *World of Drug Information* newsletter.



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Hilton San Francisco, San Francisco, CA
October 23-26, 2005
Booth #244

40th American Society of Health-System
Pharmacists (ASHP) Midyear Meeting and Exhibit
Las Vegas, NV
December 4-8, 2005
Booth #618

Constipation and laxative use in the elderly: Misconceptions

Perspective from an



IDIS Subscriber

The following discussion is intended to provide background information to those working directly with institutionalized elderly patients. It does not apply to young children or populations with special needs such as spinal cord injury patients. The use of surgical procedures for refractory chronic constipation or laxative abuse is beyond the scope of this article.⁸

Definition

There is no consensus definition of constipation for use in practice. Patients typically define constipation by the following symptoms: hard stools, the need for excessive straining, sensation of incomplete evacuation, infrequent stools, and increased time spent on the toilet or in unsuccessful attempts at defecation. The American Gastroenterological Association (AGA) technical report¹ on constipation states: “self-reported constipation is just as likely to refer to straining or hard stools as it is to focus on infrequent stooling.” In an effort to introduce uniform standards into clinical research on constipation, an international panel of experts developed a consensus definition of constipation, the Rome II criteria.² One of the components of the Rome II criteria, less than 3 bowel movements per week, is controversial. Traditionally it has been taught that bowel patterns vary widely among healthy people, the following definitions are representative of those in standard texts:

“... average normal person passes one well formed stool daily, although people in the best of health may defecate only one, two or three times a week.”³

“...normal bowel habit ranges from one bowel movement daily to every 3 or 4 days to 3 or 4 stools per day...some people have only one stool per week or longer for many years.”⁴

The role of the frequency criteria for constipation, less than 3 times weekly, from the Rome consensus conference in general practice is limited, as it is well known that bowel movement patterns vary widely among healthy individuals.

In one of the largest published prospective surveys of bowel movement frequency in the adult British population, Heaton and colleagues⁵ surveyed almost 2000 people for information on their bowel movement history, information on the timing and a description of their next three bowel movements. Only 38% of men and 36% of women claimed to have a history of 7 daily bowel movements per week. The time lapse between bowel movements was around 24 hours for almost 51% of men and 46% of women. However intervals longer than 51 hours occurred in about 4% of men and 11% of women. Three women in their 20's or 30's had intervals of over 1 week. They concluded that the regular once daily pattern of bowel movements was a minority practice in their subjects. **Public belief about the need for “regularity” = daily bowel movement for good gastrointestinal health**

Sonnenberg and Koch⁷ estimated that constipation was responsible for 2.5 million patient visits per year in the United States. The rate of such visits was described as stable from 1958 to 1986. Over 1% of the United States population presented to a physician with the complaint of constipation in any year studied. Only 4% (100,000 patients) were referred to gastroenterologists. Laxative sales in the United States are estimated to be in the range of several hundred million dollars each year.⁸ Proprietary cathartics are widely advertised to the public. It is

suggested that to miss a bowel movement is of serious consequence.

“..... from earliest times man has been conscious of his bowel and purges have long been considered a panacea for many ills.”⁹ Johanson and colleagues¹⁰ cite work by Rubin indicating that over 60% of the public surveyed still believes “a bowel movement each day is necessary for good digestive health”.

There apparently has never been any data consistent with the proposition that regular laxative use will prevent constipation.

Public belief that having less than a daily bowel movement may be dangerous

The belief that diseases might be caused by poisonous substances produced from undigested food in the intestine named “autointoxication” dates from ancient Egyptian manuscripts.¹¹ The concept of autointoxication was related to the local stasis of colonic contents, increased residence time of stool in the colon and its claimed systemic effect(s). With increased residence time in the colon bacterial flora were thought to be altered and result in the growth of bacteria capable of toxin production. This theory contributed to the public's belief that daily and often unnecessary evacuation of stools was needed. Toxins absorbed from the bowel were never demonstrated.

According to Muller-Lissner and colleagues¹¹ this theory was most widely accepted in the early 20th century when autointoxication was advocated by a famous surgeon at Guy's Hospital in London as “the most widespread illness in

the developed world.” He stated “auto-intoxication is the cause of all the chronic diseases of civilization, I have no doubt.” Even though there was never any evidence to support this theory, now long discarded by the scientific community, regular colonic cleansing with laxatives and or enemas is not uncommon to this day. Almost unbelievably, this theory and belief led to the use of subtotal or total colectomy to cure chronic constipation, a practice which resulted in many unnecessary deaths.

Is an elongated colon (dolichocolon) associated with constipation?

This theory related to gravitational forces associated with upright posture resulting in “unnatural kinking” of the colon and presumably slowed passage of stool. In the early 20th century total colectomy was recommended often for trivial symptoms, similar to those occurring in irritable bowel syndrome, and reported to be effective.¹¹ It has never been demonstrated that an elongated bowel is a cause of constipation nor are there pre-clinical or clinical studies correlating colonic transit time with colonic length. Except in patients with a demonstrated volvulus (intestinal obstruction due to a knotting or twisting of the bowel) there is no evidence to support surgical intervention.

Is lack of physical activity associated with constipation and is exercise an effective treatment?

Muller-Lissner and colleagues¹¹ report “that physical activity does affect colonic motor function, with changes in function probably proportional to the extent of the activity.” In spite of the association between inactivity and constipation, exercise has not definitely been shown to be an effective treatment.^{1,12} Muller-Lissner and colleagues¹¹ comment on a study by Kinnunen in 439 geriatric hospital patients, 78 patients visiting a geriatric day hospital and 183 people living in

physical activity periods. There was no correlation between daily activity and constipation. According to the authors, the exercise program in their study was the best that could be expected from average elderly people. More intense and or more frequent physical activity may have an impact on colon transit time and on chronic constipation. Bingham and colleagues¹³ reported that athletic activity such as training for marathon running can lead to “dramatic increases in large bowel function.” Apparently even if normal daily exercise can not improve chronic constipation, prolonged bed rest seems to be associated with increased rates of constipation. The level of activity achieved by the elderly in typical rehabilitation programs has not been shown to be an effective treatment for chronic constipation.

Is low fluid intake associated with constipation and can drinking fluids improve constipation?

Schiller⁶ reminds us that the human intestine receives from 7 to 10 liters of fluid daily, 1 to 1.5 liters of which enters the colon. The average 100 grams of stool produced daily contains 70 ml of water. Aichbichler and colleagues¹⁴ studied stool characteristics from working people who ate a normal diet. When the percent of insoluble solids in the stool exceed 25% they reported a dramatic increase in actual stool hardness. Normal subjects rarely perceived their stools as hard. On the other hand 56% of constipated subjects perceived their stools as hard or very hard. Muller-Lissner and colleagues¹¹ mention some interview data in the elderly and nursing home patients which purports to show no relationship between fluid intake and constipation. However, no details are given on how daily fluid intake was measured in any of the groups. They concluded that “..... available data do not suggest that stools can be manipulated to a clinically relevant extent by modifying fluid ingestion.”

What is the role of lack of fiber causing constipation, and the role of dietary or other fiber in treating constipation?

Dietary fiber is well known to increase stool bulk in healthy people. The AGA¹ recommends a gradual increase in fiber intake as the first step in the medical management of constipation. Patients should gradually increase the fiber content of their diet with a target of around 20 grams of fiber daily. This may be accomplished over several weeks with morning and evening doses of fiber with fluids or meals. They should not expect an immediate response and should be warned about abdominal pain and or increased flatus. The 2005 USDA dietary guidelines¹⁵ for Americans recommends 14

grams of fiber per 1000 kcal of the daily diet. A local clinical dietitian (M. Pawlik-Perevarski, personal communication July 2005) who works exclusively with geriatric patients, suggests that the typical free living elderly patient ingests less than 10 grams of fiber daily. Her experience is that increased fiber and fluid may be effective in the management of constipation.

Does chronic stimulant laxative use damage the GI tract?

A recent clinical review has concluded that the “risks of laxative abuse have been overemphasized, and this has minimized their rational use by physicians.”¹⁶ Anthraquinone laxatives cause the development of *melanosis coli*, a brown discoloration of the colonic mucosa. Muller-Lissner¹¹ and Wald¹⁶ report that it can occur within a few months of use and can last for almost one year after discontinuing laxative use. The functional impact of *melanosis coli* is uncertain, but in any event it does not extend into the muscle layers of enteric plexuses of the colon.¹⁶

The original concern that laxatives might damage the colon came from uncontrolled observations of 12 patients who had abused laxatives and whose colons had been removed in an attempt to relieve severe constipation. Damage to enteric nerves and smooth muscle atrophy were described in those 12 colon sections. Current expert opinion cannot decide whether those findings were due to an undiagnosed primary motility disorder, to laxatives no longer available, or to use of laxatives currently available.^{11,16} Those patients had used laxatives for longer than ten years in daily doses that were 18 times the recommended daily dose.¹¹ Similar findings have also been described in patients with diabetic autonomic neuropathy and chronic inflammatory bowel disease by Riemann and Schmidt, according to Muller-Lissner.¹¹

Recent findings that patients with colonic inertia have a decreased number or volume of enteric neurons raises the possibility that previous problems may have been improperly attributed to the chronic use of stimulant laxatives. Muller-Lissner¹¹ believes it appears unlikely that chronic use of stimulant laxatives at recommended doses are harmful to the colon.

Does chronic use of stimulant laxatives cause cathartic colon?

Muller-Lissner¹⁷ recently addressed this topic. He cited a review of 240 cases of laxative abuse in which no cases of cathartic colon were described. The author

(continued on page 11)

Factor	Relative Risk of Constipation
walking less than 0.5 km daily	1.7
walking with help	3.4
chairbound	6.9
bedbound	15.9

old-people’s homes. Kinnunen’s results were presented as follows:

Meshkinpour and colleagues¹² studied the effect of regular exercise in 8 patients with chronic idiopathic constipation. They followed the subjects for two weeks of rest and four weeks of regular exercise one hour five days a week at a “somewhat hard” level of exertion. The mean weekly distance was 1.9+/-0.33 miles and 3.2 +/-0.28 miles during the rest and

New Director takes helm of Division of Drug Information Service (DDIS)



Kevin Moores, Pharm.D.
Director, DDIS/Associate Professor (Clinical)

Kevin Moores, Pharm.D., joined the College of Pharmacy as the Director of the Division of Drug Information Service and an Associate Professor (Clinical) in the Clinical and Administrative Division. Dr. Moores' appointment began August 1. He returned to the Division from Creighton University School of Pharmacy and Allied Health Professions where he was an Associate Professor of Pharmacy Practice and the Director of Drug Informatics Services. Dr. Moores previously worked in the Division of Drug Information Service from 1996 to 2001 as an Assistant Professor (Clinical) and the Director of Iowa Drug Information Network (IDIN). The Division is pleased to welcome Dr. Moores back. Dr. Moores replaces Professor Hazel Seaba who has been appointed the Assistant Dean for Curriculum and Assessment in the College of Pharmacy.

Dr. Moores plans to invigorate the Division's quest for new and innovative patient care products to support health care providers at a local, regional, national and global level. DDIS's commitment to excellent products and user services for Iowa Drug Information Service (IDIS) subscribers and the Iowa Drug Information Network (IDIN) members remains a top priority – as does education.

(continued from page 10)

of the case series was unable to identify a published case of cathartic colon in which laxative use started after 1960. The clinical significance of the radiological finding including loss of haustrations has not been established. Muller-Lissner¹⁷ speculates about the possible role of oral podophyllin use in the past. He concludes, that whatever the cause, cathartic colon is apparently very rare in the recent period. Cappell¹⁸ considers the relationship between the chronic use of stimulant laxatives and numerous cases of cathartic colon to be well established. He describes *melanosis coli* not as a harmless mucosal discoloration but as the "possible deposition of degenerating cell components following laxative-induced apoptosis of colonocytes." The interested reader should review both the Muller-Lissner and Cappell papers.

Does chronic use of stimulant laxatives increase the risk of colorectal cancer?

The many issues related to the extrapolation of data derived from *in vitro* and animal studies which suggest tumorigenic potential for anthraquinone or diphenylmethane laxatives to humans are well beyond the scope of this discussion. The recent proposal by the FDA to reclassify phenolphthalein as "not generally safe and effective" after a 2 year rodent study found increased incidences of several tumors, resulted in the voluntary

withdrawal of most phenolphthalein containing laxatives in the United States. There are no similar studies with bisacodyl. Subsequently, a large case-control study did not find an increase in the risk of any type of tumor with daily or less frequent use of normal doses of phenolphthalein laxatives for up to 3 months.¹⁹

Are laxatives associated with tolerance?

Muller-Lissner and colleagues¹¹ cite a German language trial, in which bisacodyl was used from two to thirty-four years by spinal cord injury patients with no loss of effect. During a seven year period in which I was assigned to a spinal cord injury rehabilitation service, in which bisacodyl suppositories were the laxative used in the standard bowel regimen three times weekly, I was unaware of any cases of therapeutic failure.

Are laxatives effective for chronic constipation?

Ramkumar and Rao²⁰, from the University of Iowa, Division of Gastroenterology, have recently published a systematic review of the randomized controlled trials of medical therapies in adults with chronic constipation. They found good evidence to support the use of PEG, tegaserod, lactulose, and psyllium. For many of the other drugs which have been available over the counter, randomized controlled trials were not required. It is

generally agreed that there is insufficient data to guide laxative choices or doses. Laxative choice is based on experience, patient preference, side effects, and cost.

Other laxative safety issues

Repeated use of oral sodium phosphates oral solution (or the enema if previous doses are retained in the colon) in doses of more than 45 ml during a 24 hour period have resulted in serious electrolyte disturbances, dehydration, metabolic acidosis, renal failure, tetany, and death. Whether used as a bowel preparation for surgery, examinations, or as a laxative for refractory constipation, not more than 45 ml should be used in elderly patients in any 24 hour period. It would be prudent to obtain baseline and post treatment electrolyte values.²¹

Concluding thoughts

My view of the daily use of prune juice or other laxatives in the geriatric patients I serve has changed. I am no longer concerned that daily use of laxatives in standard doses might harm the bowel or could result in loss of effectiveness. I am uncertain whether or not the laxatives we use are in fact responsible for the changes in bowel habit we observe. I continue to be surprised about the patient's and staff's expectations of the need for a daily bowel movement. Expert opinion has traditionally been that a subset of the healthy population may have only one bowel

movement every 7 to 10 days. I have intentionally avoided any mention of specific laxative regimens for elderly institutionalized patients, references 1,6,8,20, and 22 will provide suggestions, for those wishing specific advice.

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Dave Mace, R.Ph., Drug Information Specialist, wrote this article. Mace graduated from the University of Iowa College of Pharmacy in 1967. Since 1982 he has served as the Director of the Drug Information Center at Bay Pines Veteran's Administration Medical Center, 10,000 Bay Pines Blvd., Bay Pines, FL 33744. His responsibilities include serving as a preceptor for drug information and Pharm.D. clerkship programs and responding to complex drug information requests from clinical staff.

EDITOR'S NOTE:

FROM TIME TO TIME, WE PUBLISH ARTICLES CONTRIBUTED BY IDIS SUBSCRIBERS. AN ARTICLE FROM DAVE MACE, B.S.PHARM., IS INCLUDED IN THIS ISSUE. DAVE MACE IS FROM AN INSTITUTION THAT IS A LONG-STANDING IDIS SUBSCRIBER, UTILIZING THE DATABASE ON A REGULAR BASIS. HIS ARTICLE ILLUSTRATES IDIS DATABASE USE CONTRIBUTING DIRECTLY TO PATIENT CARE OUTCOMES. THE RESPONSIBILITY FOR ERRORS IS THE AUTHOR'S ALONE. THE ARTICLE DOES NOT NECESSARILY REPRESENT HOSPITAL VIEWS AND RECOMMENDATIONS. WE HOPE YOU FIND THE INFORMATION INTERESTING AND USEFUL. WE WELCOME COMMENTS. IF YOU ARE INTERESTED IN SHARING YOUR EXPERIENCES USING THE IDIS DATABASE, PLEASE CONTACT DONNA-BRUS@UIOWA.EDU



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