

Multiple Sclerosis: Is Clinical Efficacy Sidetracked by Health Economics?

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Abstract: This study investigates the claim that clinical efficacy of drugs and related interventions for Multiple Sclerosis (MS) are side tracked by financial cost and economic efficiency considerations. In addressing this central question and its practical implications, the study reviewed relevant pharmacoeconomic studies generated from online medical/scientific databases with attention devoted to the literature on discontinued/failed clinical trials. A survey of these trials was also conducted using registries from the National Institutes of Health (NIH) and National Multiple Sclerosis Society in the United States. Survey results were tabulated and analyzed. The study sustains the validity of the initial claim concerning financial and economic considerations only to the extent that theoretical debates have extended and departed from the traditional scope and objectives of clinical efficacy. However, the same claim should be substantively qualified where it concerns actual applications and impact of cost and efficiency studies on discontinuing (or initiating) clinical testing and efficacy data collection for MS. The study suggests that expanded notions of clinical efficacy do not necessarily affect decisions to initiate or discontinue clinical trials for MS drugs but could help broaden or enhance our understanding of disease management options for MS sufferers.

Key words: Clinical trial, disease management, efficiency, financial cost, intervention, medical/scientific, pharmacoeconomic, risk, transaction cost

INTRODUCTION

Multiple Sclerosis (MS) is a disease of the central nervous system in which the affected individual's brain, spinal cord and optic nerves progressively deteriorate over time. Inflammation in MS causes the protective covering and insulation for these nerves known as myelin to disappear (demyelination). As a result, the electrical impulses traveling along the nerves decelerate; the nerves may also be damaged. When these occur, the vital functions controlled by the nervous system including vision, speech, memory, mobility and writing experience increased interference over time (Ryan, 2008).

Single and multiple MS symptoms vary in intensity and duration. They include visual disturbances, limb weakness, loss of sensation and muscle control, plain and manic depression, dizziness, speech impediments, paranoia and uncontrolled emotional tendencies. Over 80% of affected individuals begin with the Relapsing Remitting form of MS (RRMS) characterized by flare-ups such as relapses, attacks and bouts (MacLean and Freedman, 2001).

While, the causes of MS remain unknown disorders of the immune system and genetic explanations have been advanced by some scientists. MS predominantly affects adults (>20-50 years old) globally although some children <15 and the elderly are known to have been afflicted.

Women are 2-3 times as likely to contract MS. In terms of afflicted by MS compared to other racial groups. In the United States alone, about 400,000 suffer from MS (Noseworthy *et al.*, 2000; Inglese, 2006). The figure is estimated to be >2.1 million worldwide. For most of its sufferers, MS may not be fatal but will be seriously debilitating and harmful to their quality of life (Hauser, 1994).

Medical/scientific research has developed various interventions in the form of drugs (especially biologics), devices and procedures to slow down MS progression, reduce its severity and achieve recovery from related disabilities. Recent immunobiological findings and current pathophysiological theories along with advances in biotechnology, improvements in clinical trial design and development of Magnetic Resonance Imaging (MRI) have made a variety of these interventions evaluable. However, there is also growing concern within the medical/scientific community that debates over (their) clinical efficacy (are) often being sidelined by issues of health economics (Fuller and Bone, 2001). This concern has been raised to some extent in the American and international media. How valid is this assertion is the key question that underlies this study.

In addressing it, the study also considers how the medical/scientific community has responded to the cost and efficiency implications of MS drug interventions.

MATERIALS AND METHODS

Review of pharmacoeconomic literature: In view of the quantity and variety of clinically tested MS interventions, researchers surveyed the relevant pharmacoeconomic literature available from the major online medical/scientific databases. Employing pre-defined query terms and inclusion/exclusion criteria, systematic searches were conducted in MedLine, PubMed, NCBI, EMBASE, PsycINFO and Health Economic Evaluations Database (HEED) as well as conference abstracts. The references cited by Fuller and Bone (2001) whose original concern provided the central question for this study were automatically included in this review. Special attention was devoted to the available literature on discontinued MS clinical trials to determine the extent to which issues of health economics could affect clinical efficacy beyond the scholarly debates noted by Fuller and Bone (2001).

Survey of discontinued trials: To empirically inquire into the net impact of cost and efficiency factors on clinical testing for MS interventions, researchers surveyed the profiles of controlled drug trials that were withdrawn (i.e., halted prematurely prior to enrollment of first participant (s) suspended (participant recruitment, examination or treatment halted prematurely but would potentially resume) or terminated (permanent cancellation of ongoing clinical trial (s) and participant recruitment).

MS clinical trials in the United States were initially identified from registries provided by the United States National Institutes of Health and National Multiple Sclerosis Society which were in turn gathered from principal investigators public presentations and published literature. Researchers analyzed discontinued trials based on the following: drug/intervention type and purpose; clinical trial design and objectives (as specified by the trial protocol) trial phase at the time of withdrawal, suspension or termination causes of withdrawal suspension or termination and decision makers decision making level involved.

Clinical efficacy objectives are typically assessed by the medical/scientific community and prescribed by the national regulating authority through randomized and controlled trials that are conducted in 4 distinct phases:

- Phase 1 tests a new drug/intervention in a small group of participants
- Phase 2 expands the trial to a larger group of participants
- Phase 3 expands the trial to an even larger group of participants

- Phase 4 takes place after the drug/intervention has been licensed and marketed

The discontinued MS treatments researchers surveyed underwent some or all of these phases to meet standards of patient safety and tolerability and therapeutic effectiveness including the ability to delay the progression of neurological and cognitive disability, reduce the frequency of relapses and inflammatory lesion burden preserve cognitive function, create positive effects on conventional and non-conventional measures of Magnetic Resonance Imaging (MRI) and reduce progression of brain atrophy. Safety, tolerability and effectiveness are assessed by the national regulating authority for new treatments already marketed treatments, differentiated treatment doses (e.g., 10 mg instead of 5 mg), comparisons of new treatments with existing or standard treatments (the gold standard) or comparisons in patients with a specific symptom of 2 or more already approved or common interventions.

RESULTS AND DISCUSSION

Pharmacoeconomic findings: There is consensus in the pharmacoeconomic literature under review that medical and pharmaceutical costs associated with the treatment of MS are substantial while price inflation tends to erode treatment cost effectiveness. In addition, the studies identified by Fuller and Bone (2001) and later ones represented by Bainbridge (2007) and Kobelt *et al.* (2006) found that direct monetary cost of illness increases in proportion to the frequency of exacerbations and severity of MS among individuals afflicted by the disease. There are also significant indirect and hidden costs (e.g., lost productivity, early retirement, limited mobility) particularly when quality of life issues are taken into account. Cost estimation methods abound and vary in the literature. They can also contradict each other as Schafer *et al.* (2010) have pointed out.

Many cost utility and cost effectiveness models have been advanced to establish the net effects and implications of MS treatments. In what could have been the first systematic review of disease-modifying (immunomodulatory) drugs, Bryant *et al.* (2001) found their cost effectiveness a problematic concept because of methodological limitations including the use of different treatment regimes, patient groups and outcome measures in clinical trials. Others like Chilcott *et al.* (2003) have suggested that the key determinants of cost effectiveness are time horizon, progression of patients after stopping treatment, differential discount rates and the actual price of the interventions with price as the key modifiable

determinant of cost effectiveness. Similarly, Bell *et al.* (2007) found that incremental cost per Quality Adjusted Life Year (QALY) results a popular cost metric are sensitive to changes in time horizon, disease progression and drug costs. Using a Markov Model, researchers concluded that biologics particularly Glatiramer Acetate (GA) and Natalizumab (NZ) offer greater long term benefits than symptom management, albeit at significantly higher costs. In contrast, studies such as those of Goldberg *et al.* (2009) found interferon beta preparations (specifically, IFN β -1a SC and IFN β -1b SC) to be far more cost effective. Yet, Forbes *et al.* (1999) in validating Parkin *et al.* (1998) concluded that the cost per QALY gained from IFN β -1b is high because drug cost is also very expensive while its clinical effect is modest. They suggested restricting access to IFN β -1b given its limited efficiency. Vigorous methodological debates of this nature have prompted Curtiss (2007) to liken many pharmacoeconomic studies of MS to building houses on sand.

Others approach cost utility and cost-effectiveness from a broader and long term perspective. Kendrick and Johnson (2000), for example employed resource utilization costs (from an economic evaluation of RRMS) to calculate the longer term benefits of delaying disease progression and reducing brain atrophy in terms of better quality of life, improved health service and lower societal costs. Their pioneering model challenges earlier pharmacoeconomic research that considered only the short term impact of extremely expensive treatments, like IFN β preparations and excluded societal costs. However, Holmoy and Celius (2008) have found that cost effectiveness modeled from a societal or public goods perspective rests on several uncertain or tenuous assumptions.

A subset of the economic efficiency literature relates MS expenditure impact to output or production losses following disease occurrence. Loss expenditure frontier studies generally locate the economic optimum of disease control by evaluating both production losses and control expenditures for each of the available methods of treatment. For instance, Ziemssen and Hoffman (2008) discovered that RRMS treatment with GA for no <12 consecutive months was associated with significant improvements in fatigue symptoms and ability to work and a marked reduction in employee absenteeism. Judicibus *et al.* (2007) on the other hand, call attention to the financial strain of MS relative to its impact on the subjective aspects of quality and productivity of life of MS sufferers including their partnership and family roles, social involvement, physical activity and employment.

Finally, risk management studies identify opportunities and measures to optimize clinical and

service outcomes at the lowest cost. Asche *et al.* (2010) agree that price inflation remains as the primary driver of increased pharmacy costs for MS patients. However, they often disagree on the risk management and cost control approaches to adopt, *ceteris paribus* (e.g., preferring select agents on formulary, developing utilization management programs to promote patient safety, encouraging use of preferred agents, specialty pharmacies, etc).

The researchers find no clear indication from the prevailing pharmacoeconomic literature that financial cost and economic efficiency considerations have side tracked or tend to side track, clinical efficacy of MS drugs/interventions. What is evident is the extent to which pharmacoeconomic studies have uncovered the uneasy and multi dimensional relationship between utility, cost, risk and effectiveness of MS drugs/interventions whether on a short or longer term basis. The varying and sometimes conflicting, frameworks, methods and strategies offered by the literature, illustrate the breadth and uncertainty of the potential economic impact of MS drugs/interventions. Specifically, the preponderance of pharmacoeconomic studies and the debates surrounding them arise as a natural response to the excessive level of transaction costs (particularly search and information costs) associated with the health care of MS sufferers. For one, there are many unknown or uncertain variables in the development of MS interventions including the exact causes of MS, uniformly accepted MS Model, complete therapy/cure, uniform consensus guidelines and sufficient efficacy measures. Secondly, the costs of these interventions are very high and increase dramatically over time.

Cost and uncertainty offer the stimuli to the estimation of the efficiency advantages of MS interventions. Efficiency advantages are expectedly greatest where longer term benefits are realized in much the same way that Coasean Theory prefers long term contracts where transaction costs are high (Coase, 1937). Consequently, the option to choose it or choose something else to contain heavy search and information costs are implicit from these studies. They may deviate from but arguably broaden and enrich, the traditional, medical/scientific scope and concerns of clinical efficacy.

Studies of discontinued trials: Although, researchers do not strictly constitute a subset of the pharmacoeconomic literature, researchers also searched the online databases for studies of discontinued MS trials to determine how financial and economic considerations (if any) could affect actual clinical testing for efficacy. Available studies are limited but they shed light on the causes of many premature trial discontinuations. These include the

absence of expected benefits or significant positive effects from the tested intervention, lack of placebo efficacy (i.e., absence of statistically significant differences between treatment and placebo groups), unacceptable or unexpected side effects on trial participants, increased disease activity and participation related setbacks.

Scholarly debate was equally limited and focused on efficacy endpoints, especially the point in which a trial phase may be deemed worth discontinuing. There is barely any finding of lack of clinical interest or aborted testing due to unprofitability (e.g., funding constraints) and economic efficiency issues other than with respect to some orphan drugs. These refer to drugs used to treat diseases and conditions that occur rarely and hence, offer little financial incentive for the pharmaceutical industry to develop. Orphan drug status is usually granted by the national regulating authority (such as the United States Food and Drug Administration) to give a manufacturer specific financial incentives to develop and market such medications.

Representative studies of discontinued trials include those of Wiendl *et al.* (2000) who found that MS clinical studies typically failed or were abandoned due to the absence of positive effects and the presence of unexpected side effects. The researchers also raised critical questions concerning the hypothetical pathogenesis of MS lesions and the value of MRI in the assessment of clinically relevant therapeutic drug effects. A further study by Wiendl and Hohlfeld (2002) showed that theoretically promising agents may paradoxically increase disease activity (e.g., lenercept, infliximab) be associated with unforeseen adverse effects (roquinimex) while short term favorable trends could reverse with prolonged follow up (sulfasalazine). Greater selectivity, according to this study may also imply lower efficacy as antigen related therapies can stimulate rather than inhibit encephalitogenic cells.

Other researches shows how failed or discontinued testing assisted in a critical revision of assumed immunopathological mechanisms as well as future trial design or redesign. Tan *et al.* (2000) inquired specifically into the discontinuation of several phase 3 trials for linomide, a synthetic immunomodulator. Lack of placebo efficacy and the unexpected increase in serious cardiovascular events in MS patients accounted for their termination. Coles *et al.* (2008) found that randomized blinded phase 2 trials of alemtuzumab, a humanized monoclonal antibody had to be suspended after autoimmunity (immune thrombocytopenic purpura) developed in early RRMS patients, one of whom died; IFN β -1a treatments for trial subjects nonetheless

continued. O'Connor *et al.* (2009) reported on 946 patients who were enrolled in the largest controlled trials of NZ to assess its long term safety. The early phase trials were suspended and the drug was temporarily withdrawn from the market in 2005 due to the detection of initial cases of Progressive Multifocal Leukoencephalopathy (PML). This has encouraged various risk management approaches such as the 3-4 months drug suspension/holiday policy of many MS centers following one year of NZ treatment to restore immune surveillance. Participation related setbacks were underscored by Sorensen *et al.* (2009) who examined the NORMIMS trial for oral methylprednisolone, an add-on therapy to subcutaneous IFN β -1a whose testing was terminated due to slow recruitment and high dropout rate of MS patients. The researchers suggest caution in interpreting the significant relapse reducing effects of supplements along with the need for empirical corroboration in larger cohorts. The NINDS (2007) listed inadequate allocation concealment, unreported and underreported percentages of treatment dropouts as participation issues, along with the failure to calculate treatment effects in intent-to-treat analyses.

A few studies explain how economic and political considerations figure more prominently and undermine clinical and scientific investigations of drug efficacy. Among these is Couzin (2005)'s analysis of the development of IDEC-131, a monoclonal antibody whose initially suspended phase 2 testing was resumed and strongly encouraged in 2003 after the United States Food and Drug Administration found that adverse effects (thromboembolism) owed to pre-existing, patient based risk factors. Despite positive clinical results and a clear pathogenically driven mechanism of drug action, the distributing company ended any further trials since an unfavorable risk-to-profit calculation (which could amount to lawsuits) was expected. IDEC-131's termination underscores the divergent interests of the pharmaceutical industry and those of the medical/scientific communities and MS patients.

The converse is represented by drug compounds like anti-CD52 mAb alemtuzumab (Campath-1H) which may be ineffective, harmful or at least suspect when tested but whose trials remain supported by pharmaceutical firms given its multi billion dollar projected sales. In spite of several identified serious complications, Kleinschmitz *et al.* (2008) found that Campath-1H trials also continue because of its assumed extraordinary efficacy and the possibility to timely recognize specific side effects but alluded to the lack of risk-to-benefit ratio evaluation for long lasting immunosuppression that could keep patients prone to serious infections. A variant of the

Campath-1H effect is a group of drugs/interventions that achieved popularity due to considerable but unfounded media attention based on limited or unscientific case observations. Baumhackl *et al.* (2005) studied Hydrolytic Enzymes (HE) which were well tolerated by MS patients but clearly failed to show any treatment effect on clinical or MRI parameters. They noted that continued HE use is helped by its uncritical prescription by physicians.

Calculations of economic gain and loss by decision makers incorporate the transaction costs (e.g., market reach, negative drug publicity, potential lawsuits) of using or staying out of the MS drug market. For example, after supporting its trials, Novartis transformed Gilenya, a relatively cheap synthetic drug which was a market failure in organ transplant into an MS blockbuster by reducing information costs in determining Gilenya's global reach and multi billion sales volume despite the small number of patient users (Maggon, 2010). Similar economic and political considerations could compromise evidence of clinical and scientific efficacy. However, it is difficult to establish from the foregoing literature any trend that suggests health economics predominates over or actually subverts clinical testing or efficacy data collection. Whether financial cost and economic efficiency calculations account for the exception rather than the rule when testing is initiated or aborted for MS interventions is empirically verified in this study.

Pooled survey results: Primary data about MS trial results were obtained from registries of the National Institutes of Health and National Library of Medicine (2011) and (NMSS, 2011) as well as trial reports published in PubMed. The lists were cross checked to eliminate duplications and tabulated as a whole. Practically, each one of these trials which were held mostly in the United States, evaluated drugs/interventions by recruiting patients with predetermined MS symptoms and characteristics, administering treatment(s) and collecting efficacy data (on the patients' health and performance over a defined time frame). If participation setbacks were not encountered, investigators typically sent pooled data to the trial sponsor, investigator and collaborators for statistical analysis of technical capacity, diagnostic effects and therapeutic or patient outcome impacts. In most instances particularly in completed trials, data shows that efficacy ranges from efficacious through probably efficacious to possibly efficacious to not empirically supported. Table 1 shows pooled data on all reported MS trials. The subset of discontinued trials constitutes >9% of the base total and adjusted total (after discounting for unknown/unverified status) for MS trials. This figure lends empirical support to the finding of

Kleinschnitz *et al.* (2008) that many trials are discontinued but remain unpublished and hence under assessed. The vast majority of discontinued trials in Table 1 (>64% of the subset) were the result of their complete termination. Clinical trials were mostly discontinued during or after testing MS treatments on larger groups of participants (Phase 2 and 3) as shown in Table 2. Discontinuation appears to be essentially a consensual decision on the part of the investigator/s and collaborators. In following up on these discontinued trials, the researchers found only a relatively small number of instances (6.58%) where the drug manufacturer or distributor unilaterally opted for cancellation.

The stated causes of trial discontinuation are shown in Table 3. Financial problems and related cost issues count among the causes of discontinuation particularly if sponsor decisions (10.52%) are factored in. Sponsor discontinuations could be partly cost related.

Cost considerations can overlap with efficacy problems as exemplified by BioMs's discontinuation of all ongoing studies of dirucotide for failing to achieve its

Table 1: Clinical trial status as of July 11, 2011 (n = 841 trials)

Status	F (%)
Not started	25 (2.97)
Recruiting (including enrolling by invitation)	229 (27.23)
Active (not recruiting)	191 (22.71)
Completed (with/without results)	282 (33.53)
Terminated	49 (5.83)
Suspended	9 (1.07)
Withdrawn	18 (2.14)
Unknown status (in the last 2 years)	38 (4.52)
Totals	841 (100.00)

Table 2: Trial phase at discontinuation (n = 76 trials)

Phases	F (%)
1	9 (11.84)
2	28 (36.84)
3	26 (34.21)
4	13 (17.11)
Total	76 (100.00)

Pooled data from registries of US National Institutes of Health; National Library of Medicine (2011); National Multiple Sclerosis Society (2011)

Table 3: Causes of trial discontinuation* (n = 76 trials)

Reasons for discontinuation	F (%)
Lack of participants (no interest, poor/slow recruitment, high dropout rate, participant limitations/prohibitions, etc.)	22 (28.94)
Study redesign	4 (5.26)
Trial disapproval (by monitoring committee, regulator, etc.)	2 (2.63)
Funding constraints	10 (13.16)
Sponsor decision	8 (10.52)
Negative/lack of efficacy/expected benefits)	20 (26.32)
Adverse effects (including increased disease activity)	11 (14.47)
Unfavorable interim analysis (e.g., lack of placebo efficacy)	3 (3.95)
Others (e.g., departure of investigator, failure to meet timeline, unforeseen circumstances, etc.)	6 (7.89)

*Totals do not add up to 100% due to multiple causes for some trials
Pooled data from registries of US National Institutes of Health; National Library of Medicine in 2011; National Multiple Sclerosis Society in 2011

primary and secondary endpoints and causing company shares to plunge by well >50% in 2009. Funding on the other hand could be discontinued by sponsors and distributors for purely non economic reasons. Another example from our survey was the termination even before meeting primary and secondary endpoints of a study on the safety and efficacy of smoked cannabis in relieving spasticity/tremors in progressive MS (Agius, 2008). Both scientific review and safety monitoring boards recommended its discontinuation (and hence funding withdrawal) due to lack of feasibility including a prohibition on driving throughout the 16 weeks participants were enrolled in the study.

Nonetheless, over a quarter of surveyed MS trials were discontinued at various phases owing to lack of expected or adequate benefits to MS patients. Adverse/side effects and unfavorable interim test results when taken together, account for almost 20% of stated causes. These findings suggest that clinical efficacy (whether positive or negative) rather than cost and financial efficiency variables are the leading causes of trial termination suspension or withdrawal.

Finally, it is important to note from Table 3 that a variety of participation issues, more than economic decisions constitutes a key source of bottleneck in MS clinical trials. Participation problems represent approximately 30% of the discontinuation sources and were found by the survey team in all 4 phases.

By their nature, testing for existing and new MS treatments incur heavy search, information and compliance costs to determine their safety, tolerability, effectiveness and compliance with clinical and regulatory protocols. Once the financial viability and market potential of the drug is established along with its projected benefits, discontinuation of clinical trials may be expected to arise more as the result of negative efficacy and harms than an explicit cost calculus on the part of the sponsor, manufacturer and distributor. The considerable proportions of discontinued trials in the later clinical phases, typical sources of decision making and the non economic explanations for the vast majority of discontinued trials appear to support this point. Political and economic factors doubtless figure in several trials researchers have surveyed but they do not collectively offer any analytical trend.

CONCLUSION

Because MS drugs/interventions constitute market goods and services, cost and efficiency considerations inevitably exist in their proposal, development, testing, market introduction and promotion as well as their scholarly treatment. This study was initiated precisely to

determine the validity and extent of the assertion that these considerations do not simply exist but tend to sidetrack the clinical efficacy of MS drugs/interventions. The researchers find validity to this assertion in so far as the theoretical debates over clinical efficacy are concerned. In adopting a transaction cost approach, researchers review of related literature suggests why and how issues of risk and uncertainty of MS treatments generate questions about the legitimacy and sufficiency of both traditional concepts of efficacy and the diversity of costing approaches and methods. There may be setbacks from broadening traditional efficacy concepts and objectives. But, there are also gains to be derived from non-clinical approaches to assessing drug efficacy particularly when key factors about a disease are not known or well established. In the case of MS, these include its cause/s, a uniform model of disease progression, consensus guidelines and complete therapy/solution.

The claim concerning the sidetracking effect(s) of health economics needs to be qualified when it comes to clinical testing for efficacy. The literature review and pooled survey of discontinued trials suggest that premature discontinuation occurs in a comparatively smaller number of clinical trials, some of which command unscientific but significant media attention. In these instances, economic and political considerations are given considerable value and attention by sponsors and distributors to determine whether to push for or pull out from clinical trials those drugs where harms and risks figure prominently particularly in terms of search, information and compliance costs. Looking beyond and assigning a lower value to scientific proofs of clinical efficacy is a cornerstone of such decision making process. Given the excessive transaction costs associated with MS disease management, this process also stimulates incentives for physicians to uncritically prescribe or promote under investigated interventions for reasons beyond their clinical efficacy.

For the vast majority of clinical trials however researchers find that the choice of whether to initiate or discontinue them rests on predominantly scientific and clinical evidence. They include the lack of expected benefits, inadmissible adverse effects and risks, disease heterogeneity study design questions and subject selection problems. The theoretical debates that figure prominently in the literature seldom affect the decision to suspend withdraw or terminate trials in MS therapy. This study also showed the utility of failed or discontinued trials. To the medical/scientific community halted trials could still offer valuable insights about the disease itself patient selection and effects and design of future trials including their relative strengths and weaknesses.

Perhaps, the key challenge for the medical/scientific community is to actively participate in ongoing clinical efficacy debates and help establish the relevance, sufficiency and practicality of pharmacoeconomic models of MS drugs/interventions. Randomized trials test hypotheses and rigorously assess intervention effects to understand the pathophysiology and natural history of MS but not their net socio economic consequences which could be equally devastating to MS sufferers. Interdisciplinary approaches can foster vital professional collaborations between scientists and economists. They also enrich the understanding of the breadth and depth of disease management for MS sufferers and their families worldwide.

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REFERENCES

- Agius, M.D., 2008. Cannabis for Spasticity/Tremor in MS: Placebo Controlled Study. University of California, Clalifornia.
- Asche, C.V., M.E. Singer, M. Jhaveri, H. Chung and A. Miller, 2010. All-cause healthcare utilization and costs associated with newly diagnosed multiple sclerosis sin the United States. *J. Manag. Care Pharm.*, 16: 703-712.
- Bainbridge, J.L., 2007. Economics of multiple sclerosis and its treatment. *Adv. Stud. Pharmacy*, 4: 330-333.
- Baumhackl, U., L. Kappos, E.W. Radue, P. Freitag, A. Guseo, M. Daumer and J. Martin, 2005. A randomized, double-blind, placebo controlled study of oral hydrolytic enzymes in relapsing multiple sclerosis. *Mult. Scler.*, 11: 166-168.
- Bell, C., J. Graham, S. Earnshaw, M. Oleen-Burkey, J. Castelli-Haley and K. Johnson, 2007. Cost-effectiveness of four immunomodulatory therapies for relapsing-remitting multiple sclerosis: A Markov model based on long-term clinical data. *J. Manag. Care Pharm.*, 13: 245-261.
- Bryant, J., A. Clegg and R. Milne, 2001. Systematic review of immunomodulatory drugs for the treatment of people with multiple sclerosis: Is there good quality evidence on effectiveness and cost? *J. Neurol. Neurosurg. Psychiatry*, 70: 574-579.
- Chilcott, J., C. McCabe, P. Tappenden, A. O'Hagan, N.J. Cooper, K. Abrams and K. Claxton, 2003. Modelling the cost effectiveness of interferon beta and glatiramer acetate in the management of multiple sclerosis. *BMC*, 326: 522-526.
- Coase, R., 1937. The nature of the firm. *Economica*, 4: 386-405.
- Coles, A.J., D.A. Compston, K.W. Selmaj, S.L. Lake and S. Moran *et al.*, 2008. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *N. Engl. J. Med.*, 359: 1786-1801.
- Couzin, J., 2005. Drug discovery: Magnificent obsession. *Sci.*, 307: 1712-1715.
- Curtiss, F.R., 2007. Pharmacoeconomic modeling of drug therapies for multiple sclerosis--are we building houses on sand? *J. Manag. Care Pharm.*, 13: 245-261.
- Forbes, R.B., A. Lees, N. Waugh and R.A. Swingler, 1999. Population based cost utility study of interferon beta-1b in secondary progressive multiple sclerosis. *BMC*, 319: 1529-1533.
- Fuller, G.N. and I. Bone, 2001. Disease modifying treatment in multiple sclerosis. *J. Neurol. Neurosurg. Psychiatry*, 71: i20-ii21.
- Goldberg, L.D., N.C. Edwards, C. Fincher, Q.V. Doan, A. AL-Sabbagh and D.M. Meletiche, 2009. Comparing the cost-effectiveness of disease-modifying drugs for the first-line treatment of relapsing-remitting multiple sclerosis. *J. Manag. Care Pharm.*, 15: 543-555.
- Hauser, S., 1994. Multiple Sclerosis and Other Demyelinating Diseases. In: *Harrison's Principles of Internal Medicine*, Isselbacher, K.J., J.B. Martin and A.S. Fauci (Eds.), McGraw-Hill, New York, pp: 2287-2295.
- Holmoy, T and E.G. Celius, 2008. Cost-effectiveness of natalizumab in multiple sclerosis. *Expert Rev. Pharm. Outcomes. Res.*, 8: 11-21.
- Inglese, M., 2006. Multiple sclerosis: New insights and trends. *Am. J. Neurorad.*, 27: 954-957.
- Judicibus, De M.A. and M.P. McCabe, 2007. The impact of the financial costs of multiple sclerosis on quality of life. *Int. J. Behav. Med.*, 14: 3-11.
- Kendrick, M and K.I. Johnson, 2000. Long term treatment of multiple sclerosis with interferon-â may be cost effective. *Pharmacoeconomics*, 18: 45-53.
- Kleinschnitz, C., S.G. Meuth and H. Wiendl, 2008. The trials and errors in MS therapy. *Int. MS J.*, 15: 79-90.
- Kobelt, G., J. Berg, D. Atherly and O. Hadjimichael, 2006. Costs and quality of life in multiple sclerosis: A cross-sectional study in the United States. *Neurology*, 66: 1696-1702.
- MacLean, H.J. and M.S. Freedman, 2001. Immunologic therapy for relapsing-remitting multiple sclerosis. *Curr. Neurol. Neurosci. Rep.*, 1: 277-285.
- Maggon, K., 2010. Daclizumab (Biogen, Abbott) review: Multiple sclerosis. <http://www.scoop.it/t/daclizumab-biogen-abbott-multiple-sclerosis-review?page=4>.

- NINDS, 2007. Multiple sclerosis information page. National Institute of Neurological Disorders and Stroke, Bethesda, MD. http://www.ninds.nih.gov/disorders/multiple_sclerosis/multiple_sclerosis.htm.
- NMSS, 2011. Clinical trials in multiple sclerosis 2011: Planned, in progress, recently completed. National Multiple Sclerosis Society, New York. <http://www.nationalmssociety.org/download.aspx?id=224>.
- Noseworthy, J., C. Lucchinetti, M. Rodriguez and B. Weinshenker, 2000. Multiple sclerosis. *N. Eng. J. Med.*, 343: 938-952.
- O'Connor, P.S., A.D. Goodman, L. Kappos, F.D. Lublin and D.H. Miller *et al.*, 2009. Return of disease activity after cessation of natalizumab. *Mult. Scler.*, 15: S240-S240.
- Parkin, D., P. Miller, P. McNamee, S. Thomas, A. Jacoby and D. Bates, 1998. A cost utility study of interferon beta for multiple sclerosis. *Health Technol. Assess.*, 2: 1-65.
- Ryan, M., 2008. Multiple Sclerosis. In: *Pharmacotherapy A Pathophysiologic Approach*, Dipiro, J.T., R.L. Talbert, G.C. Yee, G.R. Matzke, B.G. Wells and L.M. Posey (Eds.), McGraw Hill, New York, pp: 431-441.
- Schafer, J.A., B.W. Gunderson and P.P. Gleason, 2010. Price increases and new drugs drive increased expenditures for multiple sclerosis. *J. Manage. Care Pharm.*, 16: 713-717.
- Sorensen, P.S., S.I. Mellgren, A. Svenningsson, I. Elovaara and J.L. Frederiksen *et al.*, 2009. NORDic trial of oral Methylprednisolone as add-on therapy to Interferon β -1a for treatment of relapsing-remitting Multiple Sclerosis (NORMIMS study): A randomised, placebo-controlled trial. *Lancet Neurol.*, 8: 519-529.
- Tan, I.L., G.J.L. Nijeholt, C.H. Polman, H.J. Ader and F. Barkhof, 2000. Linomide in the treatment of multiple sclerosis: MRI results from prematurely terminated phase-III trials. *Mult. Scler.*, 6: 99-104.
- Wiendl, H. and R. Hohlfeld, 2002. Therapeutic approaches in multiple sclerosis: Lessons from failed and interrupted treatment trials. *Bio. Drugs*, 16: 183-200.
- Wiendl, H., O. Neuhaus, L. Kappos and R. Hohlfeld, 2000. Multiple sclerosis: Current review of failed and discontinued clinical trials of drug treatment. *Nervenarzt*, 71: 597-610.
- Ziemssen, T. and J. Hoffman, 2008. Effects of glatiramer acetate on fatigue and days of absence from work in first-time treated relapsing-remitting multiple sclerosis. *Health Qual. Life Outcomes*, 6: 67-67.