Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis (Review)

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[Intervention Review]

Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis

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ABSTRACT

Background

Different therapeutic strategies are available for treatment of multiple sclerosis (MS) including immunosuppressants, immunomodulators, and monoclonal antibodies. Their relative effectiveness in the prevention of relapse or disability progression is unclear due to the limited number of direct comparison trials. A summary of the results, including both direct and indirect comparisons of treatment effects, may help to clarify the above uncertainty.

Objectives

To estimate the relative efficacy and acceptability of interferon ß-1b (IFNß-1b) (Betaseron), interferon ß-1a (IFNß-1a) (Rebif and Avonex), glatiramer acetate, natalizumab, mitoxantrone, methotrexate, cyclophosphamide, azathioprine, intravenous immunoglobulins, and long-term corticosteroids versus placebo or another active agent in participants with MS and to provide a ranking of the treatments according to their effectiveness and risk-benefit balance.

Search methods

We searched the Cochrane Database of Systematic Reviews, the Cochrane MS Group Trials Register, and the Food and Drug Administration (FDA) reports. The most recent search was run in February 2012.

Selection criteria

Randomized controlled trials (RCTs) that studied one of the 11 treatments for use in adults with MS and that reported our pre-specified efficacy outcomes were considered for inclusion.

Data collection and analysis

Identifying search results and data extraction were performed independently by two authors. Data synthesis was performed by pairwise meta-analysis and network meta-analysis that was performed within a Bayesian framework. The body of evidence for outcomes within the pairwise meta-analysis was assessed according to GRADE, as very low, low, moderate, or high quality.

Main results

Forty-four trials were included in this review, in which 17,401 participants had been randomised. Twenty-three trials included relapsing-remitting MS (RRMS) (9096 participants, 52%), 18 trials included progressive MS (7726, 44%), and three trials included both RRMS and progressive MS (579, 3%). The majority of the included trials were short-term studies, with the median duration being 24 months. The results originated mostly from 33 trials on IFNß, glatiramer acetate, and natalizumab that overall contributed outcome data for 9881 participants (66%).

From the pairwise meta-analysis, there was high quality evidence that natalizumab and IFNß-1a (Rebif) were effective against recurrence of relapses in RRMS during the first 24 months of treatment compared to placebo (odds ratio (OR) 0.32, 95% confidence interval (CI) 0.24 to 0.43; OR 0.45, 95% CI 0.28 to 0.71, respectively); they were more effective than IFNß-1a (Avonex) (OR 0.28, 95% CI 0.22 to 0.36; OR 0.19, 95% CI 0.06 to 0.60, respectively). IFNß-1b (Betaseron) and mitoxantrone probably decreased the odds of the participants with RRMS having clinical relapses compared to placebo (OR 0.55, 95% CI 0.31 to 0.99; OR 0.15, 95% CI 0.04 to 0.54, respectively) but the quality of evidence for these treatments was graded as moderate. From the network meta-analysis, the most effective drug appeared to be natalizumab (median OR versus placebo 0.29, 95% credible intervals (CrI) 0.17 to 0.51), followed by IFNß-1a (Rebif) (median OR versus placebo 0.44, 95% CrI 0.24 to 0.70), mitoxantrone (median OR versus placebo 0.43, 95% CrI 0.20 to 0.87), glatiramer acetate (median OR versus placebo 0.48, 95% CrI 0.38 to 0.75), IFNß-1b (Betaseron) (median OR versus placebo 0.48, 95% CrI 0.29 to 0.78). However, our confidence was moderate for direct comparison of mitoxantrone and IFNB-1b vs placebo and very low for direct comparison of glatiramer vs placebo. The relapse outcome for RRMS at three years' follow-up was not reported by any of the included trials.

Disability progression was based on surrogate markers in the majority of included studies and was unavailable for RRMS beyond two to three years. The pairwise meta-analysis suggested, with moderate quality evidence, that natalizumab and IFNß-1a (Rebif) probably decreased the odds of the participants with RRMS having disability progression at two years' follow-up, with an absolute reduction of 14% and 10%, respectively, compared to placebo. Natalizumab and IFNß-1b (Betaseron) were significantly more effective (OR 0.62, 95% CI 0.49 to 0.78; OR 0.35, 95% CI 0.17 to 0.70, respectively) than IFNß-1a (Avonex) in reducing the number of the participants with RRMS who had progression at two years' follow-up, and confidence in this result was graded as moderate. From the network meta-analyses, mitoxantrone appeared to be the most effective agent in decreasing the odds of the participants with RRMS having progression at two years' follow-up, but our confidence was very low for direct comparison of mitoxantrone vs placebo. Both pairwise and network meta-analysis revealed that none of the individual agents included in this review were effective in preventing disability progression over two or three years in patients with progressive MS.

There was not a dose-effect relationship for any of the included treatments with the exception of mitoxantrone.

Authors' conclusions

Our review should provide some guidance to clinicians and patients. On the basis of high quality evidence, natalizumab and IFNß-1a (Rebif) are superior to all other treatments for preventing clinical relapses in RRMS in the short-term (24 months) compared to placebo. Moderate quality evidence supports a protective effect of natalizumab and IFNß-1a (Rebif) against disability progression in RRMS in the short-term compared to placebo. These treatments are associated with long-term serious adverse events and their benefit-risk balance might be unfavourable. IFNß-1b (Betaseron) and mitoxantrone probably decreased the odds of the participants with RRMS having relapses, compared with placebo (moderate quality of evidence). The benefit-risk balance with azathioprine is uncertain, however this agent might be effective in decreasing the odds of the participants with RRMS having relapses and disability progression over 24 to 36 months, compared with placebo. The lack of convincing efficacy data shows that IFNß-1a (Avonex), intravenous immunoglobulins, cyclophosphamide and long-term steroids have an unfavourable benefit-risk balance in RRMS. None of the included treatments are effective in decreasing disability progression in patients with progressive MS. It is important to consider that the clinical effects of all these treatments beyond two years are uncertain, a relevant point for a disease of 30 to 40 years duration. Direct head-to-head comparison(s) between natalizumab and IFNß-1a (Rebif) or between azathioprine and IFNß-1a (Rebif) should be top priority on the research agenda and follow-up of the trial cohorts should be mandatory.

PLAIN LANGUAGE SUMMARY

Comparative efficacy and risk-benefit balance of modulator and suppressant drugs of the immune system in people with multiple sclerosis (MS)

Several immunotherapies have been used to treat MS, but their relative effectiveness is unclear due to the limited number of direct comparison studies. The authors of this review tried to assess the efficacy and the extent of adverse events of immunotherapies commonly used in people with MS. Eleven agents were studied, interferon ß-1b (IFNß-1b) (Betaseron), IFNß-1a (Rebif and Avonex), glatiramer acetate, natalizumab, mitoxantrone, methotrexate, cyclophosphamide, azathioprine, immunoglobulins, and long-term corticosteroids.

Forty-four studies up to 2010 have been included in this review, comprising a total of 17,401 adults suffered from the relapsing-remitting (RRMS) and the progressive types (PrMS) of MS. The treatments were short-term, the median duration being 24 months.

The results show that:

- there is high quality evidence that both natalizumab and IFNß-1a (Rebif) can reduce relapses and disability progression compared to placebo; and they are also more effective than IFNß-1a (Avonex) in people with RRMS. Natalizumab can induce progressive multifocal leukoencephalopathy, especially with more than two years of treatment;

- IFNß-1b (Betaseron), glatiramer acetate, and mitoxantrone may also prevent relapse and disability progression in people with RRMS. These treatments are associated with possible medium and long-term side effects, and the risk-benefit balance might be unfavourable;

- IFNß-1a (Avonex), intravenous immunoglobulins, cyclophosphamide, and long-term corticosteroids have an unfavourable risk-benefit balance for people with RRMS;

- there are insufficient high quality data to clarify whether there is a favourable risk-benefit balance using azathioprine;

- nine drugs (IFNß-1b (Betaseron), IFNß-1a (Avonex and Rebif), glatiramer acetate, mitoxantrone, methotrexate, cyclophosphamide, intravenous immunoglobulins, and long-term corticosteroids) were also studied in people with PrMS. Few studies were of high quality and no drug was shown to be effective in preventing disability progression in people with PrMS.

It is important to consider that the efficacy and the risk-benefit of all these treatments beyond two years are uncertain, and this is a very relevant point for a lifetime disease such as MS. Thus, studies on the long-term efficacy and safety of immunotherapies for MS are urgently needed. It is also worth considering that more than 70% of the included studies were sponsored by pharmaceutical companies. This could have affected the results of this review.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Immunomodulators and immunosuppressants for multiple sclerosis

Intervention	Comparison intervention	Illustrative comparative risks*		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
		Assumed risk with comparator	Corresponding risk with intervention (95% CI)			
CHANCE OF DISABILITY GETTING WORSE OVER 24 MONTHS						
IFNß-1b (Betaseron)	**placebo**	**MS of all types**				
		34 per 100	**32 per 100** (24 to 42)	**OR 0.89** (0.59 to 1.36)	445 (2 studies)	⊕◯◯◯ **very low**[1,2,3]
		RRMS				
		34 per 100	**33 per 100** (24 to 44)	**OR 0.96** (0.61 to 1.52)	372 (1 study)	⊕◯◯◯ **very low**[1,2,3]
		SPMS/PRMS/PPMS				
		35 per 100	**25 per 100** (11 to 48)	**OR 0.62** (0.22 to 1.69)	73 (1 study)	⊕◯◯◯ **very low**[1,2,3]
IFNß-1a (Avonex)	**placebo**	**MS of all types**				
		48 per 100	**46 per 100** (39 to 53)	**OR 0.94** (0.71 to 1.25)	787 (3 studies)	⊕◯◯◯ **very low**[1,2,3]
		RRMS				
		59 per 100	**58 per 100** (46 to 68)	**OR 0.93** (0.59 to 1.47)	301 (1 study)	⊕◯◯◯ **very low**[1,2,3]

		SPMS/PRMS/PPMS				
		41 per 100	**39 per 100** (31 to 48)	**OR 0.95** (0.66 to 1.36)	486 (2 studies)	⊕○○○ **very low**[1,2,3]
IFNß-1a (Rebif)	**placebo**	**MS of all types**				
		53 per 100	**44 per 100** (39 to 51)	**OR 0.71** (0.56 to 0.92)	1178 (2 studies)	⊕⊕⊕○ **moderate**[1]
		RRMS				
		42 per 100	**32 per 100** (25 to 40)	**OR 0.65** (0.45 to 0.93)	560 (1 study)	⊕⊕⊕○ **moderate**[1]
		SPMS/PRMS/PPMS				
		62 per 100	**56 per 100** (48 to 65)	**OR 0.78** (0.55 to 1.10)	618 (1 study)	⊕○○○ **very low**[1,2,3]
Glatiramer acetate	**placebo**	**MS of all types**				
		39 per 100	**33 per 100** (24 to 43)	**OR 0.76** (0.49 to 1.17)	1350 (4 studies)	⊕○○○ **very low**[1,2,4,5]
		RRMS				
		29 per 100	**17 per 100** (5 to 42)	**OR 0.50** (0.14 to 1.74)	301 (2 studies)	⊕○○○ **very low**[1,2,3,4,5]
		SPMS/PRMS/PPMS				
		44 per 100	**42 per 100** (36 to 49)	**OR 0.94** (0.73 to 1.23)	1049 (2 studies)	⊕○○○ **very low**[1,2,3]
Methotrexate	**placebo**	*SPMS/PPMS*				

		52 per 100	**42 per 100** (20 to 67)	**OR 0.67** (0.24 to 1.87)	60 (1 study)	⊕○○○ **very low**[1,2,3]
Azathioprine	**placebo**	**MS of all types**				
		54 per 100	**47 per 100** (36 to 59)	**OR 0.77** (0.48 to 1.24)	284 (3 studies)	⊕○○○ **very low**[1,2,3]
		RRMS				
		41 per 100	**27 per 100** (11 to 52)	**OR 0.52** (0.17 to 1.54)	59 (1 study)	⊕○○○ **very low**[1,2,3]
Mitoxantrone	**placebo**	**MS of all types**				
		25 per 100	**10 per 100** (3 to 32)	**OR 0.34** (0.08 to 1.44)	245 (2 studies)	⊕○○○ **very low**[1,2,5,6]
		RRMS				
		38 per 100	**7 per 100** (2 to 30)	**OR 0.13** (0.03 to 0.70)	51 (1 study)	⊕⊕○○ **low**[1,6]
		SPMS/PRMS/PPMS				
		20 per 100	**13 per 100** (6 to 25)	**OR 0.61** (0.27 to 1.34)	194 (1 study)	⊕⊕○○ **low**[2,3]
Cyclophosphamide	**placebo**	*SPMS/PRMS/PPMS*				
		73 per 100	**68 per 100** (37 to 89)	**OR 0.80** (0.22 to 2.94)	44 (1 study)	⊕○○○ **very low**[1,2,3]
Immunoglobulins	**placebo**	**MS of all types**				
		44 per 100	**38 per 100** (28 to 50)	**OR 0.78** (0.48 to 1.25)	739 (4 studies)	⊕○○○ **very low**[1,2,3]

		RRMS				
		23 per 100	**16 per 100** (8 to 28)	**OR 0.62** (0.30 to 1.29)	190 (2 studies)	⊕◯◯◯ **very low**[1,2,3]
		SPMS/PRMS/PPMS				
		52 per 100	**47 per 100** (30 to 65)	**OR 0.83** (0.39 to 1.74)	549 (2 studies)	⊕◯◯◯ **very low**[1,2,3]
Corticosteroids	**placebo**	*SPMS/PRMS/PPMS*				
		44 per 100	**52 per 100** (30 to 58)	**OR 1.37** (0.56 to 1.74)	86 (1 study)	⊕◯◯◯ **very low**[1,2,3]
Natalizumab	**placebo**	*RRMS*				
		47 per 100	**33 per 100** (27 to 39)	**OR 0.56** (0.42 to 0.74)	942 (1 study)	⊕⊕⊕◯ **moderate**[1]
Natalizumab	**IFNß-1a (Avonex)**	*RRMS*				
		57 per 100	**46 per 100** (40 to 51)	**OR 0.62** (0.49 to 0.78)	1171 (1 study)	⊕⊕⊕◯ **moderate**[1]
IFNß-1b (Betaseron)	**IFNß-1a (Avonex)**	*RRMS*				
		35 per 100	**16 per 100** (8 to 27)	**OR 0.35** (0.17 to 0.70)	188 (1 study)	⊕⊕⊕◯ **moderate**[7]
IFNß-1b (Betaseron)	**IFNß-1a (Rebif)**	*RRMS*				
		48 per 100	**49 per 100** (34 to 56)	**OR 1.02** (0.54 to 1.38)	301 (1 study)	⊕◯◯◯ **very low**[1,2,3,8]
Glatiramer acetate	**IFNß-1b (Betaseron)**	*RRMS*				

		41 per 100	**37 per 100** (32 to 42)	**OR 0.86** (0.69 to 1.06)	2244 (1 study)	⊕⊕◯◯ **low**[1,2]
Glatiramer acetate	**IFNß-1a (Rebif)**	*RRMS*				
		16 per 100	**9 per 100** (6 to 14)	**OR 0.53** (0.34 to 0.83)	764 (1 study)	⊕⊕◯◯ **low**[1,3]
CHANCE OF DISABILITY GETTING WORSE OVER 36 MONTHS						
IFNß-1b (Betaseron)	**placebo**	*SPMS*				
		68 per 100	**65 per 100** (55 to 74)	**OR 0.87** (0.57 to 1.33)	1657 (2 studies)	⊕◯◯◯ **very low**[2,3,5]
IFNß-1a (Rebif)	**placebo**	*SPMS*				
		63 per 100	**66 per 100** (54 to 76)	**OR 1.10** (0.68 to 1.80)	989 (2 studies)	⊕◯◯◯ **very low**[1,2,3,5]
Azathioprine	**placebo**	*SPMS/PRMS/PPMS*				
		67 per 100	**49 per 100** (28 to 71)	**OR 0.47** (0.19 to 1.17)	139 (2 studies)	⊕◯◯◯ **very low**[1,2,3]
Cyclophosphamide	**placebo**	*SPMS/PRMS/PPMS*				
		41 per 100	**53 per 100** (35 to 70)	**OR 1.60** (0.76 to 3.39)	111 (1 study)	⊕◯◯◯ **very low**[1,2,3]
CHANCE OF EXPERIENCING ONE OR MORE RELAPSES OVER 12 MONTHS						
IFNß-1b (Betaseron)	**placebo**	*RRMS*				
		57 per 100	**44 per 100** (12 to 82)	**OR 0.60** (0.10 to 3.49)	25 (1 study)	⊕⊕◯◯ **low**[2,3]
IFNß-1a (Avonex)	**placebo**	**RRMS**				

		64 per 100	**56 per 100** (44 to 67)	**OR 0.72** (0.45 to 1.14)	301 (1 study)	⊕⊕◯◯ **low**[2,3]
IFNß-1a (Rebif)	**placebo**	*RRMS*				
		74 per 100	**66 per 100** (42 to 84)	**OR 0.66** (0.25 to 1.78)	853 (2 studies)	⊕⊕◯◯ **low**[2,5]
Glatiramer acetate	**placebo**	**RRMS**				
		55 per 100	**30 per 100** (7 to 72)	**OR 0.34** (0.06 to 2.05)	289 (2 studies)	⊕◯◯◯ **very low**[2,3,4,5]
Azathioprine	**placebo**	**MS of all types**				
		57 per 100	**45 per 100** (36 to 54)	**OR 0.63** (0.44 to 0.89)	547 (4 studies)	⊕⊕⊕⊕ **high**
		RRMS				
		68 per 100	**62 per 100** (35 to 83)	**OR 0.77** (0.25 to 2.38)	54 (1 study)	⊕⊕◯◯ **low**[2,3]
		SPMS/PRMS/PPMS				
		32 per 100	**17 per 100** (7 to 35)	**OR 0.43** (0.16 to 1.12)	99 (1 study)	⊕⊕◯◯ **low**[2,3]
Mitoxantrone	**placebo**	**RRMS**				
		75 per 100	**30 per 100** (11 to 59)	**OR 0.14** (0.04 to 0.48)	51 (1 study)	⊕⊕⊕◯ **moderate**[6]
Immunoglobulins	**placebo**	**MS of all types**				
		42 per 100	**29 per 100** (13 to 54)	**OR 0.56** (0.20 to 1.60)	537 (4 studies)	⊕◯◯◯ **very low**[2,3,5]

		RRMS				
		61 per 100	**55 per 100** (43 to 56)	**OR 0.67** (0.38 to 1.21)	219 (3 studies)	⊕○○○ **very low**[2,3,5]
		SPMS/PRMS/PPMS				
		35 per 100	**33 per 100** (24 to 44)	**OR 0.95** (0.59 to 1.50)	318 (1 study)	⊕⊕○○ **low**[2,3]
Corticosteroids	**placebo**	**RRMS**				
		71 per 100	**52 per 100** (22 to 82)	**OR 0.46** (0.12 to 1.84)	36 (1 study)	⊕⊕○○ **low**[2,3]
Natalizumab	**placebo**	**RRMS**				
		40 per 100	**20 per 100** (16 to 25)	**OR 0.38** (0.28 to 0.51)	942 (1 study)	⊕⊕⊕⊕ **high**
Natalizumab	**IFNß-1a (Avonex)**	**RRMS**				
		49 per 100	**28 per 100** (24 to 33)	**OR 0.40** (0.32 to 0.51)	1171 (1 study)	⊕⊕⊕⊕ **high**
IFNß-1b (Betaseron)	**IFNß-1a (Avonex)**	**RRMS**				
		52 per 100	**41 per 100** (29 to 56)	**OR 0.65** (0.37 to 1.16)	188 (1 study)	⊕○○○ **very low**[2,3,7]
IFNß-1a (Rebif)	**IFNß-1a (Avonex)**	**RRMS**				
		61 per 100	**56 per 100** (48 to 63)	**OR 0.79** (0.58 to 1.07)	677 (1 study)	⊕⊕○○ **low**[2,3]
CHANCE OF EXPERIENCING ONE OR MORE RELAPSES OVER 24 MONTHS						
IFNß-1b (Betaseron)	**placebo**	*RRMS*				

		85 per 100	**76 per 100** (64 to 85)	**OR 0.55** (0.31 to 0.99)	372 (1 study)	⊕⊕⊕○ **moderate**[3]
IFNß-1a (Avonex)	**placebo**	**MS of all types**				
		61 per 100	**55 per 100** (47 to 62)	**OR 0.76** (0.56 to 1.05)	737 (2 studies)	⊕⊕○○ **low**[2,3]
		RRMS				
		83 per 100	**80 per 100** (70 to 88)	**OR 0.83** (0.46 to 1.49)	301 (1 study)	⊕⊕○○ **low**[2,3]
		SPMS				
		47 per 100	**40 per 100** (31 to 49)	**OR 0.74** (0.51 to 1.08)	436 (1 study)	⊕⊕○○ **low**[2,3]
IFNß-1a (Rebif)	**placebo**	*RRMS*				
		85 per 100	**72 per 100** (61 to 80)	**OR 0.45** (0.28 to 0.71)	560 (1 study)	⊕⊕⊕⊕ **high**
Glatiramer acetate	**placebo**	*RRMS*				
		74 per 100	**58 per 100** (33 to 79)	**OR 0.49** (0.18 to 1.36)	301 (2 studies)	⊕○○○ **very low**[2,3,4,5]
Methotrexate	**placebo**	**SPMS/PPMS**				
		17 per 100	**19 per 100** (6 to 47)	**OR 1.15** (0.31 to 4.28)	60 (1 study)	⊕○○○ **very low**[2,3,9]
Azathioprine	**placebo**	**MS of all types**				
		68 per 100	**58 per 100** (48 to 67)	**OR 0.64** (0.44 to 0.94)	737 (5 studies)	⊕⊕⊕⊕ **high**

		RRMS				
		83 per 100	**63 per 100** (35 to 85)	**OR 0.36** (0.11 to 1.21)	59 (1 study)	⊕⊕◯◯ **low**[2,3]
		SPMS/PRMS/PPMS				
		52 per 100	**48 per 100** (33 to 64)	**OR 0.85** (0.45 to 1.64)	284 (2 studies)	⊕⊕◯◯ **low**[2,3]
Mitoxantrone	**placebo**	**MS of all types**				
		69 per 100	**43 per 100** (16 to 76)	**OR 0.35** (0.09 to 1.42)	245 (2 studies)	⊕◯◯◯ **very low**[2,3,5,6]
		RRMS				
		79 per 100	**36 per 100** (13 to 67)	**OR 0.15** (0.04 to 0.54)	51 (1 study)	⊕⊕⊕◯ **moderate**[6]
		SPMS/PRMS				
		65 per 100	**54 per 100** (40 to 69)	**OR 0.65** (0.35 to 1.20)	194 (1 study)	⊕⊕◯◯ **low**[2,3]
Immunoglobulins	**placebo**	**MS of all types**				
		53 per 100	**44 per 100** (31 to 58)	**OR 0.70** (0.40 to 1.22)	705 (4 studies)	⊕◯◯◯ **very low**[2,3,5]
		RRMS				
		73 per 100	**37 per 100** (7 to 83)	**OR 0.22** (0.03 to 1.90)	190 (2 studies)	⊕⊕◯◯ **low**[2,5]
		SPMS				

		46 per 100	**44 per 100** (36 to 53)	**OR 0.93** (0.66 to 1.32)	515 (2 studies)	⊕⊕◯◯ **low**[2,3]
Corticosteroids	**placebo**	**RRMS**				
		95 per 100	**94 per 100** (47 to 100)	**OR 0.89** (0.05 to 15.40)	36 (1 study)	⊕⊕◯◯ **low**[2,3]
Natalizumab	**placebo**	*RRMS*				
		63 per 100	**36 per 100** (29 to 43)	**OR 0.32** (0.24 to 0.43)	942 (1 study)	⊕⊕⊕⊕ **high**
Natalizumab	**IFNß-1a (Avonex)**	*RRMS*				
		79 per 100	**51 per 100** (45 to 58)	**OR 0.28** (0.22 to 0.36)	1171 (1 study)	⊕⊕⊕⊕ **high**
IFNß-1b (Betaseron)	**IFNß-1a (Avonex)**	*RRMS*				
		71 per 100	**52 per 100** (39 to 65)	**OR 0.44** (0.26 to 0.75)	248 (2 studies)	⊕⊕⊕◯ **moderate**[7]
IFNß-1b (Betaseron)	**Glatiramer acetate**	*RRMS*				
		58 per 100	**57 per 100** (52 to 62)	**OR 0.96** (0.78 to 1.18)	2244 (1 study)	⊕⊕◯◯ **low**[2,3]
Glatiramer acetate	**IFNß-1a (Rebif)**	*RRMS*				
		37 per 100	**35 per 100** (29 to 42)	**OR 0.93** (0.69 to 1.25)	764 (1 study)	⊕⊕◯◯ **low**[2,3]
IFNß-1a Rebif	**IFNß-1b (Betaseron)**	**RRMS**				
		57 per 100	**43 per 100** (22 to 68)	**OR 0.58** (0.21 to 1.62)	60 (1 study)	⊕⊕◯◯ **low**[2,3]

IFNß-1a (Rebif)	**IFNß-1a Avonex**	**RRMS**				
		80 per 100	**43 per 100** (19 to 71)	**OR 0.19** (0.06 to 0.60)	60 (1 study)	⊕⊕⊕⊕ **high**
CHANCE OF EXPERIENCING ONE OR MORE RELAPSES OVER 36 MONTHS						
IFNß-1b (Betaseron)	**placebo**	*SPMS*				
		78 per 100	**71 per 100** (66 to 76)	**OR 0.71** (0.56 to 0.90)	1657 (2 studies)	⊕⊕⊕⊕ **high**
IFNß-1a (Rebif)	**placebo**	*SPMS*				
		60 per 100	**64 per 100** (55 to 69)	**OR 1.22** (0.82 to 1.48)	371 (1 study)	⊕⊕◯◯ **low**[2,3]
Azathioprine	**placebo**	*SPMS*				
		81 per 100	**66 per 100** (54 to 77)	**OR 0.45** (0.27 to 0.76)	493 (3 studies)	⊕⊕⊕⊕ **high**

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;**NNT:** number needed to treat. **RRMS:** participants with a relapsing remitting form of MS; **SPMS/PRMS/PPMS:** participants with a secondary progressive or progressive relapsing or primary progressive form of MS

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Control event rates based on the number of events in the included studies
[1] Disability getting worse confirmed at 3 months' follow-up.
[2] The 95% confidence interval around the pooled effect included both no effect and appreciable benefit or harm
[3] The optimal information size (OIS) criterion was not met (small sample size, very few events).
[4] Out of two studies, one (Bornstein 1987) had inadequate allocation concealment.
[5] Widely differing estimates of the treatment effect (i.e. heterogeneity in results) across the studies

[6] The study (Millefiorini 1997) reported no blinding of outcome assessment.
[7] The INCOMIN (INCOMIN 2002) study reported no blinding of personnel, participants and outcome assessment
[8] The Koch-Henriksen (Koch-Henriksen 2006) study reported no blinding of personnel, participants and outcome assessment
[9]The study (Goodkin 1995) had inadequate allocation concealment.

BACKGROUND

Description of the condition

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) resulting from the effect of an interaction between unidentified environmental factors and susceptibility genes (Milo 2010). Several pathological processes occur in MS, including engagement of the immune system, T cell-mediated and B cell-mediated mechanisms, demyelination, inflammatory injury of axons and glia, post-inflammatory gliosis, and neurodegeneration (Bennett 2009; Vercellino 2009). The sequential involvement of these processes influences the clinical course, characterized by attacks with recovery, attacks leaving persistent deficits, and progression that causes fixed physical and cognitive disability (Compston 2002).

MS is among the commonest causes of neurological disability in young people, with an annual incidence ranging from 2 to 10 cases/100,000 persons/year and a north-south gradient, with a lower incidence closer to equator. Its clinical manifestations typically occur between 20 and 40 years of age, with symptoms and signs involving different CNS regions (optic nerve, brainstem, cerebellum, cerebral hemispheres, spinal cord) (Compston 2002).

MS has a chronic course evolving over 30 to 40 years. The clinical phenotypes include relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive-relapsing MS (PRMS) (Lublin 1996). The development of disease progression (SPMS, PRMS, PPMS) is responsible for permanent long-term disability and it supervenes in about 80% of RRMS participants after 20 to 25 years. After 15 to 18 years, about 50% of participants need assistance to walk, are confined to a wheelchair, bed, or have died (Kremenchutzky 2006). PPMS (approximately 10% of all participants with MS) is characterized, from the beginning, by a slow worsening of neurological deficits without experiencing attacks, and PRMS by a progressive course from onset with attacks and continuing progression (Lublin 1996). Natural history studies provide little support for the concept that progression is related primarily to a succession of attacks, indicating that attacks do not play a major role in long-term disability (Filippini 2007; Kremenchutzky 2006). Preventing progressive disability is the key therapeutic goal for MS.

Description of the intervention

Recombinant interferon ß-1b (IFNß-1b) (Betaseron), IFNß-1a (Rebif and Avonex) and glatiramer acetate were approved by many national regulatory agencies (FDA 1993; FDA 1996; FDA 2001; EMEA 2002; FDA 2002; FDA 2003) and are available for use in MS free of charge from many national health services. Natalizumab is a recombinant monoclonal antibody that was approved for the treatment of RRMS (FDA 2004). Following the recognition of two cases of progressive multifocal leukoencephalopathy (PML) in patients who had been receiving natalizumab, its commercialisation was suspended. In July 2006 marketing of natalizumab resumed after an investigation of patients included in clinical trials (including trials carried on in patients with Crohn's disease) (Yousry 2006). Natalizumab was commercialised worldwide from that year on. Mitoxantrone was approved in 2000 (FDA 2000) under the description "for reducing neurological disability and/or the frequency of clinical relapses in patients with SPMS, PRMS or worsening RRMS". In March 2005, the US Food and Drug Administration (FDA 2005) warned about cardiotoxicity and therapy-related acute leukaemia in mitoxantrone-treated patients. In many countries azathioprine is used for the treatment of MS, however since the approval of IFNß for the same indication, azathioprine has not been recommended as a first line therapy (Goodin 2002). Intravenous immunoglobulins may have a role in patients with severe and frequent relapses for whom other treatments are contraindicated, but they should not be used routinely (Association of British Neurologists 2005). Severe adverse events leading to discontinuation of the treatment with intravenous immunoglobulins were noted in 4% of 84 treatment courses with a total 341 infusions under routine clinical conditions. These included thrombosis of the jugular vein, an allergic reaction, and retrosternal pressure (Elovaara 2008). Cyclophosphamide and methotrexate might benefit patients with progressive MS (Goodin 2002) but these agents are less commonly used because their toxicity is severe. Long-term pulsed regimens of corticosteroids may be effective for MS owing to their long-lasting immunosuppressive effect, and they are reported to be well-tolerated and safe with only minor, dose-related side effects (Pozzilli 2004).

How the intervention might work

Immunomodulator or immunosuppressive effects are common to all treatments included in this review. The exact mode of action of immunomodulators is unknown, but they are thought to target various immune cells or cytokines important in MS pathogenesis. The IFNß family have effects on the production of cytokines by T helper lymphocytes, on migration of leukocytes across the blood-brain barrier, and have antiviral activity (Billiau 2004). Glatiramer acetate has a combined effect on anti-inflammatory T-cell populations and regulatory type II antigen-presenting cells (Lalive 2011). Natalizumab is a monoclonal antibody targeting an integrin that blocks adhesion and transmigration of lymphocytes through the vascular endothelium, thus avoiding inflammation (Fontoura 2010).

Immunosuppressant agents suppress immune function by one of several mechanisms of action; they also have anti-inflammatory activity. Azathioprine, cyclophosphamide, mitoxantrone, and methotrexate are classical cytotoxic immunosuppressants that act

by inhibiting DNA synthesis. Azathioprine inhibits T-cell function (Tiede 2003); cyclophosphamide suppresses both cell-mediated and humoral immunity (Calabresi 1991); mitoxantrone reduces the number of B-cells, inhibits T-cells, and enhances T-cell suppressor activity (Fox 2004); methotrexate inhibits T-cell activation and suppresses intercellular adhesion molecule expression by T-cells (Johnston 2005). Corticosteroids have many immunological effects, they inhibit lymphocyte proliferation and the synthesis of most pro-inflammatory cytokines and cell surface molecules required for immune function (Sloka 2005). The mechanism of action of intravenous Immunoglobulins remains unclear although, through the mediation of the effects of cytokines, remyelination of demyelinated CNS axons may occur (Stangel 1999).

Why it is important to do this review

Although there is consensus that immunotherapies reduce the frequency of relapses in MS, their relative effectiveness in the prevention of new attacks or delaying disability progression remains unclear. This uncertainty is due to the limited number of direct comparison trials, which provide the most rigorous and valid research evidence on the relative efficacy and safety of different treatments for MS. A summary of the results of trials, including both direct and indirect comparisons, may help to clarify the above uncertainty (Caldwell 2005; Glenny 2005).

OBJECTIVES

To compare immunomodulators and immunosuppressants against placebo or against one another in terms of response and acceptability. Given the wide spectrum of available comparisons, we aimed to use the methodology of network meta-analysis, a method that allows the integration of data from direct comparisons (when treatments are directly compared within a randomised trial) and indirect comparisons (when treatments are compared between trials by combining results against a common comparator treatment) (Lu 2004; Caldwell 2005; Salanti 2008).

In summary, the aims of this overview were:

1. to estimate the relative effectiveness and acceptability of immunomodulators and immunosuppressants for MS;

2. to provide a ranking of the treatments according to their effectiveness and acceptability in order to inform clinical practice.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) that studied one of the agents for use in MS and that reported our pre-specified outcomes were evaluated for inclusion. Trials for which it was unclear whether the method of randomisation provided adequate allocation concealment or open label studies were also included, but the quality of these studies was taken into account. RCTs with follow-up less than six months were excluded. Quasi-randomised trials and non-randomised studies were excluded.

Types of participants

Participants 18 years age or older with a diagnosis of MS were included. Only RCTs adopting the Poser (Poser 1983) or McDonald diagnostic criteria (McDonald 2001; Polman 2005) were selected. We included all phenotypes: relapsing-remitting MS (RRMS); secondary progressive MS (SPMS); progressive-relapsing MS (PRMS); and primary progressive MS (PPMS), regardless of age, sex, degree of disability, and duration of the disease.

Types of interventions

Interferon ß-1b (IFNß-1b), IFNß-1a (Rebif, Avonex), glatiramer acetate, natalizumab, mitoxantrone, methotrexate, cyclophosphamide, azathioprine, immunoglobulins, and long-term corticosteroids versus placebo or versus another active agent. Regimens were included irrespective of their dose as long as it was within therapeutic range. IFNß-1b, IFNß-1a (Rebif) and glatiramer acetate are administered by subcutaneous injection; IFNß-1a (Avonex) by intramuscular injection; natalizumab, mitoxantrone, cyclophosphamide, immunoglobulins by the intravenous route; methotrexate and azathioprine orally. Corticosteroids are administered intravenously or by the oral route.

Types of outcome measures

Primary outcomes

Efficacy

Two primary outcomes were considered.

1. Clinical relapses: proportion of participants who experienced new relapses over 12, 24, or 36 months after randomisation or at the end of the study. A relapse is defined as newly developed or recently worsened symptoms of neurologic dysfunction that last more than 24 hours, occurring in the absence of fever or other acute diseases, and separated in time from any previous episode by more than 30 days (McDonald 2001). A relapse resolves either partially or completely.
2. Disability progression: proportion of participants who experienced disability progression over 24 or 36 months after randomisation or at the end of the study. Disability progression

is defined as at least 1 point Expanded Disability Status Scale (EDSS) (Kurtzke 1983) increase, or a 0.5 point increase if the baseline EDSS was ≥ 5.5, confirmed during two subsequent neurological examinations separated by an interval of at least six months free of attacks. The EDSS is a common measure of MS disability (where 0 is normal, 3 mild disability, 6 care requirement, 7 wheelchair use, and 10 is death from MS). It is frequently used to measure disability progression in clinical trials.

Acceptability

Treatment discontinuation was used to assess acceptability and was measured by the dropout rate, that is the proportion of participants who were lost to follow-up or definitely discontinued treatment (withdrawals) but completed follow-up, out of the total number of participants randomly assigned to each treatment arm.

Secondary outcomes

Adverse events (AE)

Number of participants with:
a) at least one AE;
b) at least one serious AE (SAE), as defined by the authors of the primary study;
c) withdrawal due to AE at any time during the follow-up period;
d) serious infections, as defined by the authors of the primary study;
e) a new diagnosis of leukaemia, lymphoma, or any other type of cancer during the follow-up period.

Search methods for identification of studies

No language restrictions were applied.

Electronic searches

1. We searched the Cochrane Database of Systematic Reviews (CDSR) (Issue 1 of 12, 2012) (Appendix 1).
Cochrane Multiple Sclerosis Systematic Reviews (SRs) retrieved:
1. Azathioprine for multiple sclerosis (Casetta 2007);
2. Corticosteroids for the long term treatment in multiple sclerosis (Ciccone 2008);
3. Cyclophosphamide for multiple sclerosis (La Mantia 2007);
4. Glatiramer acetate for multiple sclerosis (La Mantia 2010);
5. Interferon in relapsing-remitting multiple sclerosis (Rice 2001);
6. Interferon beta for primary progressive multiple sclerosis (Rojas 2010);
7. Interferon beta for secondary progressive multiple sclerosis (La Mantia 2012);
8. Intravenous immunoglobulins for multiple sclerosis (Gray 2003);
9. Methotrexate for multiple sclerosis (Gray 2004);
10. Mitoxantrone for multiple sclerosis (Martinelli 2005);
11. Natalizumab for relapsing-remitting multiple sclerosis (Pucci 2011).

Updated searches were run, for out of date reviews to retrieve primary RCTs, which were limited from the date of their most recent search to February 2012. The search strategies used are those reported in the published reviews.
2. We searched the Cochrane Multiple Sclerosis Specialised Register (February 2012) for direct comparison trials. Keywords for each comparison are listed in Appendix 2. For information about the Cochrane Multiple Sclerosis Review Group Trials Register please see: Cochrane Multiple Sclerosis Group.
3. We searched the Food and Drug Administration (FDA) reports on all the treatments included in this review (www.fda.gov) (February 2012).

Searching other resources

Reference lists of published reviews and retrieved articles were checked for additional trials.

Data collection and analysis

Selection of studies

The reference lists of selected SRs were screened. If a review was not published in the CDSR, or it was incomplete or not updated, titles and abstracts from the search results were independently assessed by the two review authors to identify relevant trials for inclusion. The full text of the study was obtained, when necessary, to confirm inclusion. Trials were selected if they met the pre-specified eligibility criteria. Discrepancies in judgements were resolved by discussion among the two review authors (LV, GF).

Data extraction and management

Two review authors (GF, LV) independently extracted data using a predefined data extraction form. If outcomes were not reported at the predefined time points, we extracted data as close as possible to that time point. Trial arms involving the same agent at different fixed doses within the therapeutic range were converted into a single arm by summing the number of events and the sample size. Disagreements were resolved by discussion between the two review authors. Data were extracted from:
1) the Cochrane SRs and additional information from the original RCT reports, when necessary;
2) the original RCTs for treatments that were not included in published Cochrane SRs or for direct comparison trials;

3) FDA reports, which were consulted in order to obtain further details on study characteristics or outcomes if these data were unclearly presented in the original articles.

Assessment of risk of bias in included studies

The risk of bias (RoB) was assessed for each included study using the Cochrane Collaboration criteria (Higgins 2011). These included: random sequence generation, allocation concealment, blinding of participants and outcome assessment, incomplete outcome data, and selective outcome reporting. Other potential sources of RoB were: sustained disability progression measured after only three months' follow-up, that is a surrogate marker for unremitting disability (Ebers 2008), and role of the sponsor. The RoB of each study was explicitly judged on each criterion and classified as 'low', 'high', or 'unclear'. Complete outcome data were judged as 'low risk' when the percentage of participants lost to follow-up was low (arbitrarily set at values lower than 15%) and when numbers and causes of losses to follow-up were balanced between arms. Regarding selective outcome reporting bias, we assigned 'high risk' when one or more outcomes of interest were not reported or were presented incompletely and they could not be analysed quantitatively.

To summarize the RoB overall for a study, we considered allocation concealment, blinding of outcome assessment, and incomplete outcome data in order to classify each study as: 'low risk of bias' when all three criteria were met; 'high risk of bias' when at least one criterion was unmet; and 'moderate risk of bias' in the remaining cases. Allocation concealment, blinding of outcome assessment, and incomplete outcome data were not expected to vary in importance across the two primary efficacy outcomes (relapses and progression), and therefore we summarized the RoB of each study considering the two outcomes together.

We assessed RoB for adverse events (AE) by considering specific factors that may have had a large influence on the adverse events data. We evaluated methods for monitoring and detecting an AE for each study: did the researchers actively monitor for AEs (low risk of bias), or did they simply provide spontaneous reporting of AEs that arose (high risk of bias)? Did the authors define serious AE according to an accepted international classification and report the number of SAEs?

The RoB of each study was assessed independently by the two review authors (GF, LV) and any disagreement was resolved by discussion to reach consensus.

Measures of treatment effect

For each pairwise comparison and each outcome at each time point, we used odds ratio (OR) with 95% confidence interval (95% CI) as a measure of the association between the treatment used and efficacy. As the outcomes are negative, ORs < 1 correspond to beneficial treatment effects of the first treatment compared with the second treatment.

Unit of analysis issues

Our unit of data extraction, evaluation, and analysis was the primary randomised trial.

Dealing with missing data

In order to assess the effect of patient withdrawal or loss to follow-up on primary outcomes, we extracted data according to a likely scenario, that is we assumed that the treated- and control-group participants who dropped out and were not included in the study analysis both had the outcome (relapse or disability progression).

Assessment of heterogeneity

Heterogeneity or inconsistency can be the result of an uneven distribution of important clinical and methodological effect modifiers across studies (heterogeneity) or across comparisons (inconsistency). The presence of statistical heterogeneity was assessed by visual inspection of the forest plots and by calculating the I^2 statistic and its confidence limits. Potential sources of heterogeneity or inconsistency include: different participant baseline characteristics (MS phenotype), different treatment dose, influence of funders. We investigated the distribution of these characteristics and carried out a subgroup analysis for the efficacy outcomes at each time point.

Assessment of reporting biases

The possibility of reporting bias in network meta-analysis was evaluated by means of an adaptation of the funnel plot for pairwise meta-analysis, the 'comparison-adjusted' funnel plot (Chaimani 2012). In a network of interventions each study estimates the relative effect of different interventions, so asymmetry in the funnel plot could not be judged. To account for this, we subtracted from each study-specific log odds-ratio of an active treatment versus placebo the mean of the meta-analysis for the same comparison and plotted it against the study's standard error. We drew funnel plots for the efficacy outcomes at 24 and 36 months and acceptability for all interventions versus placebo. As with regular funnel plots, asymmetry might be caused by publication bias but other reasons such as true heterogeneity are also possible. We used the STATA routines available in www.mtm.uoi.gr to create the comparison-adjusted funnel plots.

Data synthesis

First, conventional pairwise meta-analyses was conducted for all outcomes and comparisons, provided that at least two studies were available, using a random-effects model (DerSimonian 1986). We then performed a network meta-analysis for primary outcomes (relapses, progression, and dropouts). Network meta-analysis is a method of synthesizing information from a network of

trials addressing the same question but involving different interventions. For a given comparison, say A versus B, direct evidence is provided by studies that compare these two treatments directly. In addition, indirect evidence for the A versus B comparison can be provided by synthesizing studies that compare A versus C and B versus C (Higgins 1996; Caldwell 2005). Network meta-analysis combines direct and indirect evidence across a network of randomised trials into a single effect size, and under certain assumptions it can increase the precision in the estimates while randomisation is respected. We performed network meta-analyses within a Bayesian framework, assuming an equal heterogeneity parameter τ across all comparisons, and we accounted for correlations induced by multi-arm studies (Lu 2006; Salanti 2009). The analysis was performed using WinBUGS (MRC Biostatistics Unit, Cambridge, UK) (http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml); the codes and description of the methodology can be found at www.mtm.uoi.gr/howtodoanmtm.html. We used a normal prior with zero mean and variance one restricted to positive values for the common heterogeneity standard deviation τ and non-informative vague priors for all mean parameters, otherwise referred as treatment effects. As a measure that reflects ranking and the uncertainty, we used the Surface Under the Cumulative RAnking curve (SUCRA) as described in Salanti 2011. This measure, expressed as percentage, showed the relative probability of an intervention being among the best options.

The adequacy of each model was evaluated by comparing the posterior deviance to the number of data points (they should be close for models that fit the data well) and by calculating the Deviance Information Criterion (DIC), which is a measure equivalent to Akaike's Information Criterion and penalizes model fit for complexity (lower values indicate better models) (Spiegelhalter 2002). There are limitations in the use of the network meta-analysis methodology and it is essential to check the assumptions of the analysis before drawing conclusions. The most important assumption is that the network of comparisons is consistent, meaning that direct and indirect evidence on the same comparisons agree. Joint analysis can be misleading if the network is substantially inconsistent. Inconsistency can be present if the trials in the network have very different protocols and their inclusion and exclusion criteria are not comparable, or may result from an uneven distribution of effect modifiers across groups of trials that compare different treatments.

In order to estimate network inconsistency we calculated the difference between indirect and direct estimates in each closed loop formed by the network of trials (using the Bucher method) and their relative 95% confidence interval (CI). Then we examined whether there were any material discrepancies; if the 95% CI did overlap with 0 the hypothesis of consistency was not rejected, as described in Salanti (Salanti 2009). The code to assess consistency is available at www.mtm.uoi.gr/howtodoanmtm.html. Further, we compared the DIC between the models with and without the consistency assumption; a lower DIC for the consistency model indicates that the consistency assumption is statistically supported. In the case of important clinical or statistical inconsistency being identified, we planned to investigate this further and possibly to adjust for potential effect modifiers using network meta-regression or relaxing the consistency assumption and extending the model as described in Lu and Ades (Lu 2006).

Subgroup analysis and investigation of heterogeneity

Subgroup analysis for the efficacy outcomes at each time point were based on the following.

1. Clinical phenotype, distinguishing two groups of participants: RRMS and SPMS, PRMS, PPMS.
2. Treatment dose: as we previously said, many immunotherapies exist for the management of MS and some of them are administered at different doses. However, it is still unclear whether the relative efficacy of the MS agents depends on the dose used and, in particular, whether some agents given at higher doses are more effective. For that reason, we explored whether the agent's efficacy on disability progression at 24 months was modulated by dose administration. For this purpose we considered the network formed of agents administered at different doses (so that each node in the network was a treatment at a different dose). Any specific dose used for each agent was transformed into a unique measure unit (mg) 'dose per week' (for example 0.02 mg three times a week corresponded to a 'dose per week' equal to 0.06). The network was re-analysed and posterior ORs were summarized for each drug and dose. We compared the DICs between models where doses of the same agent were assumed to be equally effective with the DIC from models where each dose was assumed to be a different intervention. We also applied different assumptions regarding the association between dose effects, such as linear and monotonic.
3. Funders: sponsorship from pharmaceutical companies or independent trials.

Sensitivity analysis

The RoB in included studies was taken into account in the interpretation of evidence using the GRADE approach.

Summary of findings table

The main results of the review are presented in a summary of findings (SoF) table, as recommended by The Cochrane Collaboration (Schünemann 2011a). The SoF table was provided for the direct estimates only and included an overall grading of the evidence for relapses over 12, 24, and 36 months, and disability getting worse over 24 and 36 months. For each treatment, data were pooled across all types of MS, and the subgroups of RRMS and progressive MS. The SoF table includes an overall grading of the quality of evidence related to each of the outcomes, using the GRADE approach (Schünemann 2011b). Quality of evidence was graded

as high, moderate, low, or very low, considering within-study RoB, directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias. The control event rates used in the calculation of absolute risks were based on the number of events in the included studies.

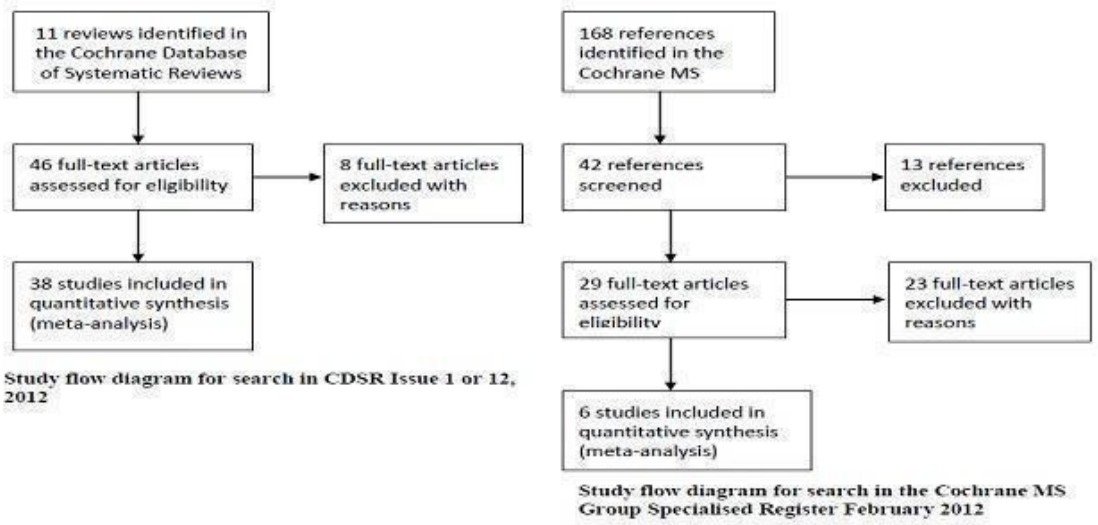
RESULTS

Description of studies

Results of the search

Flow charts describe the results of the electronic search (Figure 1). Thirty-eight studies were identified in 11 reviews available from the Cochrane Database of Systematic Reviews (CDSR) and six studies were identified in the Cochrane Multiple Sclerosis Review Group Specialised Register.

Figure 1. Study flow diagrams



Included studies

Forty-four trials in which 17,401 participants had been randomised were included in this review. Twenty-three trials included RRMS (9096 participants, 52%), 18 trials included progressive MS (7726, 44%), and three trials included both RRMS and progressive MS (579, 3%). The table Characteristics of included studies provides details on the characteristics of the included studies. The duration of the trials ranged from six to 36 months with the median duration being 24 months. The findings presented in this review originated mostly from trials on the IFNβ family, glatiramer acetate, and natalizumab that overall contributed outcome data for 12,275 patients (71%) included in 33 trials (Table 1).
Eleven Cochrane reviews of active treatments versus placebo were included: IFNß for RRMS (Rice 2001), SPMS (La Mantia 2012) or PPMS (Rojas 2010); glatiramer acetate (La Mantia 2010); natalizumab (Pucci 2011); mitoxantrone (Martinelli 2005); methotrexate (Gray 2004); cyclophosphamide (La Mantia 2007); azathioprine (Casetta 2007); intravenous immunoglobulins (Gray 2003), and corticosteroids for long-term treatment (Ciccone 2008). Thirty-eight studies were included from the Cochrane reviews (Achiron 1998; AFFIRM 2006; Andersen 2004; Bornstein 1987; Bornstein 1991; BPSM 1995; British and Dutch 1988; CCMSSG 1991; Comi 2001; Edan 1997; Ellison 1989; European Study Group 1998; Fazekas 1997; Fazekas 2008; Ghezzi 1989; Goodkin 1991; Goodkin 1995; Hartung 2002; Hommes 2004; IFNB MS Group 1993; IMPACT 2002; Johnson 1995; Knobler 1993; Leary 2003; Lewanska 2002; Likosky 1991; Milanese 1993; Millefiorini 1997; Miller 1961; Montalban 2009; MSCRG 1996; NASP 2004; OWIMS 1999; Pohlau 2007; PRISMS 1998; SENTINEL 2006;

SPECTRIMS 2001; Wolinsky 2007). The two arms of calcium aspirin and placebo in the Miller (Miller 1961) study were grouped as a single placebo arm by summing the number of events and the sample size.

Six trials of treatments directly compared to each other (BEYOND 2009; Etemadifar 2006; EVIDENCE 2007; INCOMIN 2002; Koch-Henriksen 2006; REGARD 2008) were retrieved by searching the Cochrane Multiple Sclerosis Review Group Specialised Register.

Excluded studies

Eight studies were excluded from the Cochrane reviews: two trials of IFNα (Durelli 1994; Myhr 1999); one because active treatment with natalizumab was confounded by glatiramer acetate (GLANCE 2009); one of oral glatiramer acetate (Filippi 2006); one of mitoxantrone in which the inclusion criteria were not described (Van de Wyngaert 2001); two trials because treatment with cyclophosphamide was confounded by other treatments (Hauser 1983; Wender 1988); and a dose comparison trial of long-term corticosteroids without a control group (Zivadinov 2001). In one study (CCMSSG 1991) one arm with combined cyclophosphamide, plasmapheresis, and prednisone was excluded. Another 23 studies were excluded from the 29 full-text articles identified through the Cochrane MS Review Group Specialised Register (see Characteristics of excluded studies).

Risk of bias in included studies

The RoB of the included studies is summarized (Figure 2; Figure 3). Considering our predefined criteria (allocation concealment, blinding of outcome assessment, and complete outcome data) to assess RoB overall for a study, five out of 44 (11%) trials (Achiron 1998; AFFIRM 2006; British and Dutch 1988; Leary 2003; PRISMS 1998) were judged at low RoB, 21 (48%) (Bornstein 1991; CCMSSG 1991; Comi 2001; Ellison 1989; Etemadifar 2006; EVIDENCE 2007; Fazekas 2008; Goodkin 1991; Hartung 2002; Hommes 2004; IFNB MS Group 1993; Johnson 1995; Knobler 1993; Lewanska 2002; Likosky 1991; Montalban 2009; Pohlau 2007; REGARD 2008; SENTINEL 2006; SPECTRIMS 2001; Wolinsky 2007) were evaluated at moderate RoB, and 18 (41%) (Andersen 2004; BEYOND 2009; Bornstein 1987; BPSM 1995; Edan 1997; European Study Group 1998; Fazekas 1997; Ghezzi 1989; Goodkin 1995; IMPACT 2002; INCOMIN 2002; Koch-Henriksen 2006; Milanese 1993; Millefiorini 1997; Miller 1961; MSCRG 1996; NASP 2004; OWIMS 1999) were judged at high RoB.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

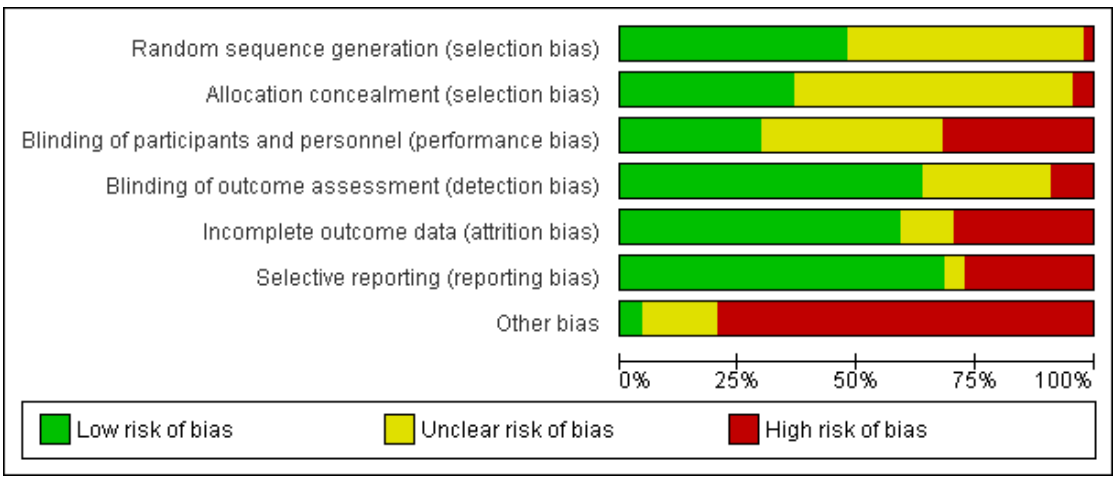
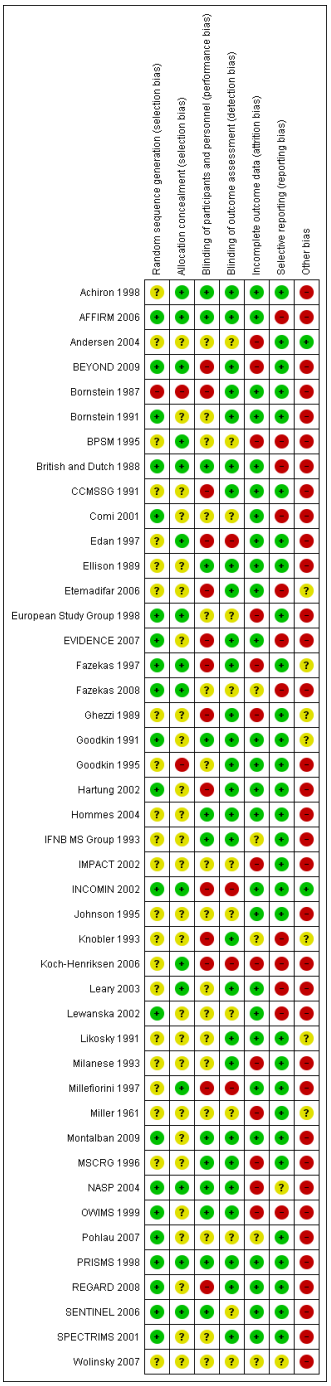


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sixteen of 44 trials (36%) reported adequate methods for allocation concealment (low risk). Twenty-six trials (59%) did not provide enough information to assess allocation concealment (unclear). Two trials (Bornstein 1987; Goodkin 1995) used an unconcealed procedure (high risk).

Blinding

Twenty-eight of 44 trials (64%) reported adequate methods for blinding of outcome assessment (low risk). Twelve trials (27%) did not provide enough information to assess it (unclear). This bias was judged at 'high risk' for four open label trials (Edan 1997; INCOMIN 2002; Koch-Henriksen 2006; Millefiorini 1997). We suspected that most participants and treating physicians had become aware of the treatment they were receiving during the course of the trial because all the agents included in this review have well-documented side effects, for example injection-site reactions and influenza-like symptoms after IFNß injection.

Incomplete outcome data

Twenty-six of 44 (59%) included studies were judged to meet this criterion because missing outcome data were less than 15% and were balanced in numbers across intervention groups with similar reasons for missing data across groups. In 13 (29%) trials (Andersen 2004; BEYOND 2009; BPSM 1995; European Study Group 1998; Fazekas 1997; Ghezzi 1989; IMPACT 2002; Koch-Henriksen 2006; Milanese 1993; Miller 1961; MSCRG 1996; NASP 2004; OWIMS 1999) more than 15% of participants were lost to follow-up, or incomplete outcome data were not balanced in numbers or the reasons across groups (high risk). In five studies insufficient information was provided (unclear).

Selective reporting

Just half the studies (22 of 44; 50%) reported outcomes of interest at two years' follow-up, and only eight (18%) (Andersen 2004; British and Dutch 1988; CCMSSG 1991; Ellison 1989; European Study Group 1998; Milanese 1993; NASP 2004; SPECTRIMS 2001) reported outcomes at three years. One or more outcomes of interest were not reported or were presented incompletely in 12 studies (27%) (AFFIRM 2006; BPSM 1995; British and Dutch 1988; Comi 2001; Etemadifar 2006; EVIDENCE 2007; Fazekas 2008; Knobler 1993; Koch-Henriksen 2006; Leary 2003; Lewanska 2002; OWIMS 1999) that were considered at high risk of reporting bias.

Other potential sources of bias

Sequence generation : 22 trials (50%) did not provide enough information to assess sequence generation (unclear), and 21 (48%) reported adequate methods (low risk). One of the trials (Bornstein 1987) used a sequence generated by alternation and was assigned 'high risk'.

Other bias : 24 (54.5%) of 44 studies used an inadequate definition of sustained disability progression (confirmed at three months' follow-up) and 31 (70.5%) were pharmaceutical industry-funded studies.

Method of adverse event (AEs) monitoring (Table 2): in 20 (45%) trials, AEs were actively monitored and the RoB was judged to be low. Nineteen trials (43%) reported insufficient information about the method of AEs monitoring so that it was uncertain whether or not AEs were monitored appropriately. RoB was judged to be unclear in these studies. Spontaneous reporting of AEs as they occurred was reported in four studies (Bornstein 1987; Bornstein 1991; EVIDENCE 2007; Goodkin 1991); one study (Etemadifar 2006) was lacking in safety assessment. These five trials (16%) were judged at high RoB.

Serious adverse event (SAEs) definition and reporting: neither the definitions nor methods of quantification were specified for most of the included studies. In 23 (52%) trials SAEs were not reported and the RoB was judged to be high. In 20 (45%) trials SAEs were reported but insufficient information on their definition was given and we judged the RoB to be unclear. Only one study (BEYOND 2009) provided a definition of SAEs and the RoB was judged to be low.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings table

1. Efficacy

1.1 Pairwise meta-analysis (direct comparisons)

Summary of findings for the main comparison provides a summary of the risk estimates for each major outcome and the grading of the evidence.

Recurrence of relapses over 12 months

See: Summary of findings for the main comparison; Analysis 1.1; Analysis 1.2; Analysis 1.3

a) *Treatments compared to placebo*: 17 studies with 3581 participants (21% of those included in this review) were available.

Data for RRMS was provided in 13 out of 17 trials, with 2770 (77%) participants (Achiron 1998; AFFIRM 2006; Bornstein 1987; BPSM 1995; Comi 2001; Fazekas 2008; Goodkin 1991; Knobler 1993; Lewanska 2002, Millefiorini 1997; MSCRG 1996; OWIMS 1999; PRISMS 1998). Nine agents (IFNß-1b, IFNß-1a (Avonex, Rebif), glatiramer acetate, natalizumab, azathioprine, mitoxantrone, intravenous immunoglobulins, and long-term corticosteroids) were assessed.

Data for progressive MS was provided in only two trials. One assessed azathioprine (Ellison 1989) in 99 participants and the other (Hommes 2004) evaluated intravenous immunoglobulins in 318 participants. Two studies of azathioprine (British and Dutch 1988; Milanese 1993) presented grouped data as RRMS or progressive MS (394 participants, 11%).

The following results for participants with RRMS were found.

- Natalizumab reduced the odds (OR 0.38, 95% CI 0.28 to 0.51), a 62% reduction in the number of participants who had relapses compared with placebo.
- Mitoxantrone probably reduced the odds (OR 0.14, 95% CI 0.04 to 0.48), a 86% reduction in the number of participants who had relapses compared with placebo, but the quality of evidence for this treatment was moderate.
- Azathioprine reduced slightly the odds (OR 0.63, 95% CI 0.44 to 0.89) when data across all trials that studied this agent were pooled, but meaningful odds estimates, specific for RRMS and progressive MS, were uncertain since there was only one small study for each of the two phenotypes (Ellison 1989; Goodkin 1991). The two studies (British and Dutch 1988; Milanese 1993) that included grouped data for participants with RRMS or progressive MS were excluded from the analysis.
- IFNß-1b (Betaseron), IFNß-1a (Avonex), IFNß-1a (Rebif) and long-term corticosteroids might have slightly reduced the odds (OR 0.60, 95% CI 0.10 to 3.49; OR 0.72, 95% CI 0.45 to 1.14; OR 0.66, 95% CI 0.25 to 1.78; OR 0.46, 95% CI 0.12 to 1.84) of the participants with RRMS, but the quality of evidence for all these treatments was low.
- There was uncertainty regarding the effect of glatiramer acetate and intravenous immunoglobulins for RRMS since the quality of the evidence for these two treatments was very low.

The study of intravenous immunoglobulins (Hommes 2004) reporting relapse outcome in progressive MS stated that the numbers of participants who had experienced relapses over 12 months were not statistically significantly different from those observed in the placebo group.

b) *Treatments compared to each other*: three studies with 2036 RRMS participants (14% of those included in this review) compared natalizumab with IFNß-1a (Avonex) (SENTINEL 20066), IFNß-1a (Avonex) with IFNß-1b (Betaseron) (INCOMIN 2002), and IFNß-1a (Rebif) versus IFNß-1a (Avonex) (EVIDENCE 2007).

- Natalizumab reduced the odds compared with IFNß-1a (Avonex) (OR 0.40, 95% CI 0.32 to 0.51), a 60% reduction in the number of RRMS participants who had relapses over 12 months.
- IFNß-1a (Rebif) also might have decreased the odds compared to IFNß-1a (Avonex) (OR 0.79, 95% CI 0.58 to 1.07).
- INCOMIN 2002 was judged to have very low quality evidence to allow a meaningful comparison between IFNß-1b (Betaseron) and IFNß-1a (Avonex).

Mitoxantrone might have decreased the odds of the participants with progressive MS, compared to long-term corticosteroids (OR 0.25, 95% CI 0.07 to 0.90) but the CI around the estimate of treatment effect was very wide (Edan 1997).

Recurrence of relapses over 24 months

See: Summary of findings for the main comparison; Analysis 2.1; Analysis 2.2; Analysis 2.3

a) *Treatments compared to placebo*: 20 studies with 4695 participants (27% of those included in this review) were available.

Eleven trials in RRMS (2812 participants, 60% of those compared to placebo) (Achiron 1998; AFFIRM 2006; Bornstein 1987; BPSM 1995; Fazekas 1997; Goodkin 1991; IFNB MS Group 1993; Johnson 1995; Millefiorini 1997; MSCRG 1996; PRISMS 1998) assessed 10 agents, IFNß-1b (Betaseron), IFNß-1a (Avonex), IFNß-1a (Rebif), glatiramer acetate, natalizumab, azathioprine, methotrexate, mitoxantrone, intravenous immunoglobulins, and long-term corticosteroids.

Six trials in progressive MS (1304 participants, 28% of those compared to placebo) (Ellison 1989; Goodkin 1995; Hartung 2002; Hommes 2004; IMPACT 2002; Pohlau 2007) evaluated five agents, IFNß-1a (Avonex), azathioprine, methotrexate, mitoxantrone, and intravenous immunoglobulins. Three trials (British and Dutch 1988; Ghezzi 1989; Milanese 1993) assessed azathioprine in 579 (12%) participants with RRMS and progressive MS combined.

The following results for participants with RRMS were found.

- Both natalizumab and IFNß-1a (Rebif) reduced the odds (OR 0.32, 95% CI 0.24 to 0.43; OR 0.45, 95% CI 0.28 to 0.71, respectively), a 68% and 55% reduction in the number of participants who had relapses over 24 months compared with placebo.
- IFNß-1b (Betaseron) and mitoxantrone probably decreased the odds (OR 0.55, 95% CI 0.31 to 0.99; OR 0.15, 95% CI 0.04 to 0.54, respectively) compared with placebo, but the quality of evidence for these treatments was moderate.
- Azathioprine reduced the odds (OR 0.64, 95% CI 0.44 to 0.94) when all the included trials of azathioprine were aggregated, but this treatment was not statistically significantly different from control when data for RRMS and progressive MS were analysed separately. Azathioprine might have decreased slightly the odds of the participants with RRMS (OR 0.36, 95% CI 0.11 to 1.21).

- For the other five treatments (IFNß-1a (Avonex), glatiramer acetate, methotrexate, intravenous immunoglobulins, and long-term corticosteroids), the numbers of RRMS participants experiencing new relapses were not statistically significantly different from the numbers in the placebo groups.

IFNß-1a (Avonex), methotrexate, azathioprine, mitoxantrone, and intravenous immunoglobulins were not effective for progressive MS.

b) *Treatments compared to each other:* four trials in RRMS (4427, 25% of those included in this review) provided direct comparisons between treatments, natalizumab versus IFNß-1a (Avonex) (SENTINEL 2006), IFNß-1b (Betaseron) versus IFNß-1a (Avonex) (INCOMIN 2002), IFNß-1b (Betaseron) versus glatiramer acetate (BEYOND 2009), and glatiramer acetate versus IFNß-1a (Rebif) (REGARD 2008). One three-arm trial (Etemadifar 2006) compared IFNß-1b (Betaseron), IFNß-1a (Avonex), and IFNß-1a (Rebif).

- Natalizumab, IFNß-1b (Betaseron), and IFNß-1a (Rebif) were significantly more effective than IFNß-1a (Avonex) (OR 0.28, 95% CI 0.22 to 0.36; OR 0.44, 95% CI 0.26 to 0.75; OR 0.19, 95% CI 0.06 to 0.60, respectively) for RRMS participants.
- The quality of the evidence was too low to allow meaningful comparisons of glatiramer acetate with IFNß-1b (Betaseron) or IFNß-1a (Rebif).

Relapses over 36 months

See: Summary of findings for the main comparison; Analysis 3.1

Information on this outcome was not available for RRMS. Four trials in 2127 progressive MS participants (14% of those included in this review) compared IFNß-1b (Betaseron) (European Study Group 1998; NASP 2004), IFNß-1a (Rebif) (Andersen 2004), azathioprine (Ellison 1989) versus placebo. Two studies (British and Dutch 1988; Milanese 1993) assessed azathioprine in 394 participants with RRMS and progressive MS combined.

- Azathioprine (OR 0.45, 95% CI 0.27 to 0.76) and IFNß-1b (Betaseron) decreased slightly (OR 0.71, 95% CI 0.56 to 0.90) the odds of experiencing new relapses over three years in progressive MS, compared with placebo.
- IFNß-1a (Rebif) may have resulted in little or no difference in this outcome compared to participants with progressive MS who took placebo, but the quality of evidence was low so our confidence in this result was low.

Disability progression over 24 months

See: Summary of findings for the main comparison; Analysis 4.1; Analysis 4.2; Analysis 4.3

a) *Treatments compared to placebo:* 24 studies with 6160 participants (41% of those included in this review) were available.

Ten studies in RRMS (2776 participants, 45%) (Achiron 1998; AFFIRM 2006; Bornstein 1987; Fazekas 1997; Goodkin 1991; IFNB MS Group 1993; Johnson 1995; Millefiorini 1997; MSCRG 1996; PRISMS 1998) assessed eight agents, IFNß-1b (Betaseron), IFNß-1a (Avonex), IFNß-1a (Rebif), glatiramer acetate, natalizumab, azathioprine, mitoxantrone, and intravenous immunoglobulins versus placebo.

Twelve studies in progressive MS (3159 participants, 51%) (Bornstein 1991; Goodkin 1995; Hartung 2002; Hommes 2004; IMPACT 2002; Leary 2003; Likosky 1991; Miller 1961; Montalban 2009; Pohlau 2007; SPECTRIMS 2001; Wolinsky 2007) evaluated nine agents, IFNß-1b (Betaseron), IFNß-1a (Avonex), IFNß-1a (Rebif), glatiramer acetate, methotrexate, mitoxantrone, cyclophosphamide, intravenous immunoglobulins, and long-term corticosteroids. Two studies of azathioprine (Ghezzi 1989; Milanese 1993) reported the outcome in 225 (4%) RRMS and progressive MS participants combined.

The following results for participants with RRMS were found.

- Natalizumab and IFNß-1a (Rebif) probably reduced the odds (OR 0.56, 95% CI 0.42 to 0.74; OR 0.65, 95% CI 0.45 to 0.93, respectively) by 44% and 35% compared with placebo.
- Mitoxantrone might have reduced the odds (OR 0.13, 95% CI 0.03 to 0.70) but the CI around the estimate of treatment effect was very wide.
- None of the other treatments were statistically significantly different from placebo in terms of the number of RRMS participants experiencing disability progression over 24 months.

There was no effect of all these treatments for progressive MS.

b) *Treatments compared to each other:* direct comparisons of active agents were available from five two-arm studies with 4668 RRMS participants (31% of those included in this review) comparing natalizumab versus IFNß-1a (Avonex) (SENTINEL 2006), IFNß-1b (Betaseron) versus IFNß-1a (Avonex) (INCOMIN 2002), IFNß-1b (Betaseron) versus IFNß-1a (Rebif) (Koch-Henriksen 2006), glatiramer acetate versus IFNß-1b (Betaseron) (BEYOND 2009), and glatiramer acetate versus IFNß-1a (Rebif) (REGARD 2008).

- Natalizumab and IFNß-1b (Betaseron) were significantly more effective (OR 0.62, 95% CI 0.49 to 0.78; OR 0.35, 95% CI 0.17 to 0.70, respectively) than IFNß-1a (Avonex) for RRMS.
- The quality of the evidence was too low to allow meaningful comparisons of IFNß-1b (Betaseron) with IFNß-1a (Rebif), and glatiramer acetate with IFNß-1b (Betaseron) or with IFNß-1a (Rebif).

One small trial (Edan 1997) comparing mitoxantrone with long-term corticosteroids in progressive MS patients did not find a difference between the two treatments.

Disability progression over 36 months

See: Summary of findings for the main comparison; Analysis 5.1

This outcome was not reported in trials for RRMS. Data for this outcome were available from seven two-arm studies in 2896

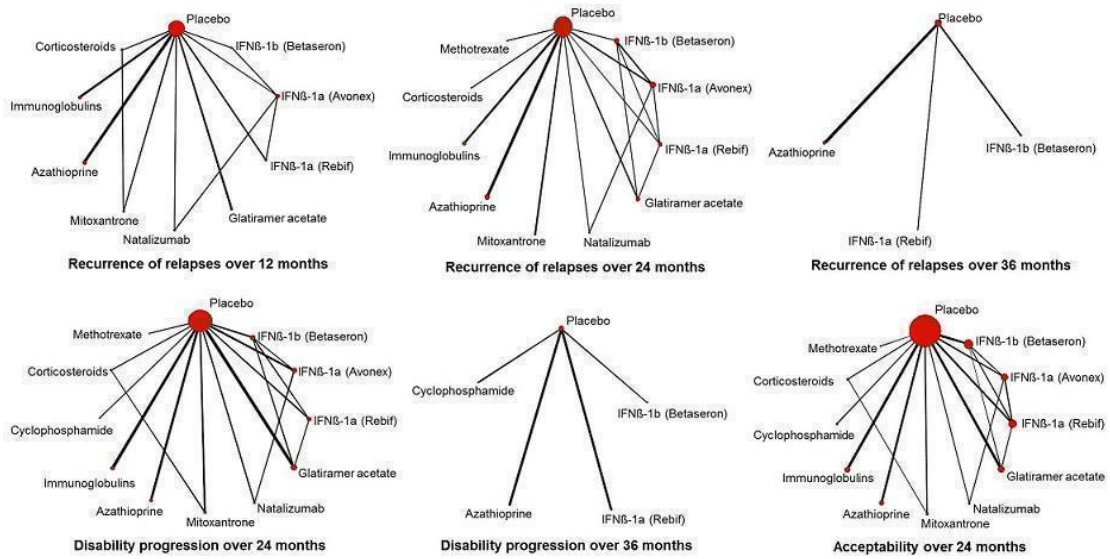
progressive MS participants (19% of those included in this overview). The trials compared IFNß-1b (Betaseron) (European Study Group 1998; NASP 2004), IFNß-1a (Rebif) (Andersen 2004; SPECTRIMS 2001), azathioprine (Ellison 1989; Milanese 1993), cyclophosphamide (CCMSSG 1991) versus placebo.

Although results for these four agents did not reach statistical significance, azathioprine was associated with the least number of participants experiencing disability progression (OR 0.47, 95% CI 0.19 to 1.17) and cyclophosphamide was associated with the most number of participants who had disability progression in comparison to placebo (OR 1.60, 95% CI 0.76 to 3.39). However, we judged the quality of these studies as very low, so our confidence in these results was very low.

1.2 Network meta-analysis (combination of direct and indirect comparisons)

Figure 4 shows the networks of the treatments for recurrence of relapses and disability progression at each time point, and acceptability of treatments over 24 months of follow-up. Each line links treatments directly compared in trials. The thickness of the line is proportional to the number of comparisons included in the network; the width of the circle is proportional to the number of studies involving the specific treatment.

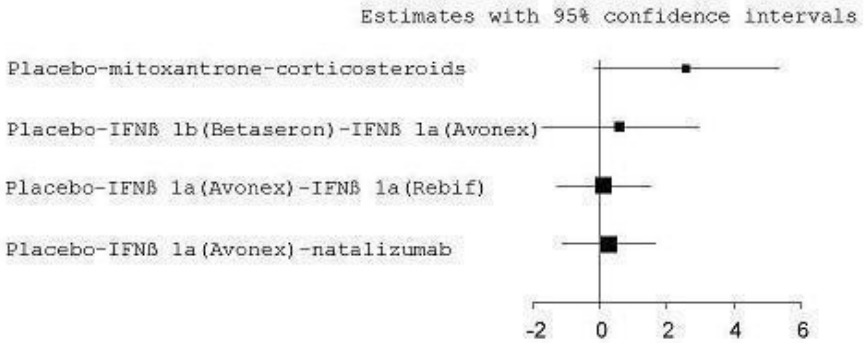
Figure 4. Networks of the treatments for recurrence of relapses and disability progression at each time point and acceptability of treatments over 24 months of follow-up



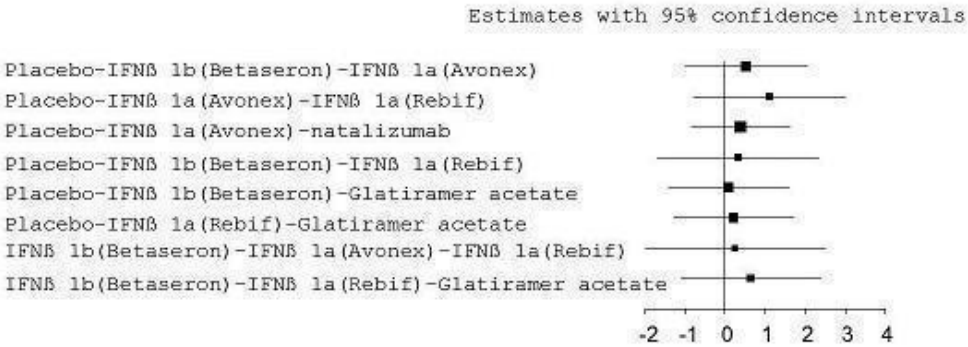
There was no statistical or clinical indication that the assumption of consistency was inappropriate. No loop was found to be statistically inconsistent (Figure 5), the DIC of the consistency model was always lower compared to the inconsistency models, and the pairwise meta-analyses were not dissimilar in trial methods and populations. Table 3 reports model fit and parsimony measures for all the primary outcomes along with the DIC values for the consistency and inconsistency models.

Summary ORs (posterior values and their 95% credible intervals (CrI)) of all active interventions versus placebo and SUCRA values expressed as a percentage are reported in Table 4 for relapses over 12, 24, and 36 months; in Table 5 for disability progression over 24 and 36 months; in Table 6 for relapses over 12 and 24 months and progression over 24 months in the subgroup of participants with RRMS. In the subgroup of progressive MS, only pairwise meta-analyses were done as the number of studies was small for each outcome and time point.

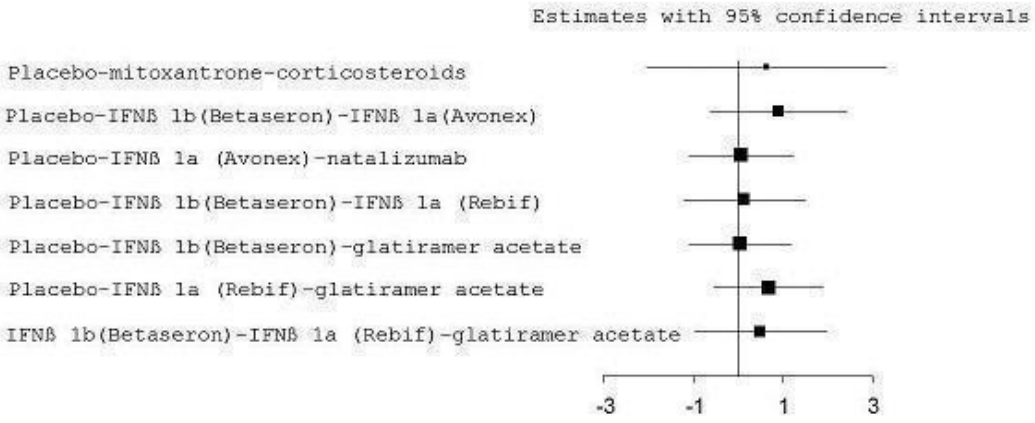
Figure 5. Evaluation of consistency within first order closed loops for recurrence of relapses and disability progression at each time point. Difference in log odds ratios between indirect and direct evidence is reported on x-axis.



Recurrence of relapses over 12 months



Recurrence of relapses over 24 months



Disability progression over 24 months

Relapses over 12, 24, and 36 months

See: Table 4

a) Relapses over 12 months were provided in 20 studies (Achiron 1998; AFFIRM 2006; Bornstein 1987; BPSM 1995; British and Dutch 1988; Comi 2001; Edan 1997; Ellison 1989; EVIDENCE 2007; Fazekas 2008; Goodkin 1991; Hommes 2004; INCOMIN 2002; Knobler 1993; Lewanska 2002; Milanese 1993; Millefiorini 1997; MSCRG 1996; OWIMS 1999; PRISMS 1998; SENTINEL 2006) and 5628 participants with MS (37.5% of those included in this review). Mitoxantrone was the best drug (median OR versus placebo 0.12, 95% CrI 0.03 to 0.55; SUCRA = 95%) followed by natalizumab (median OR versus placebo 0.35, 95% CrI 0.12 to 1.06; SUCRA = 72%). The heterogeneity standard deviation τ was 0.60 (95% CrI 0.22 to 1.18).

b) Relapses over 24 months were provided in 25 studies (Achiron 1998; AFFIRM 2006; BEYOND 2009; Bornstein 1987; BPSM 1995; British and Dutch 1988; Ellison 1989; Etemadifar 2006; Fazekas 1997; Ghezzi 1989; Goodkin 1991; Goodkin 1995; Hartung 2002; Hommes 2004; IFNB MS Group 1993; IMPACT 2002; INCOMIN 2002; Johnson 1995; Milanese 1993; Millefiorini 1997; MSCRG 1996; Pohlau 2007; PRISMS 1998; REGARD 2008; SENTINEL 2006) and 9186 participants with MS (61% of those included in this review). Different agents seemed to be significantly correlated to relapse at 24 months' follow-up. The most effective drug appeared to be natalizumab (median OR versus placebo 0.29, 95% CrI 0.17 to 0.51; SUCRA = 92%), followed by IFNß-1a (Rebif) (median OR versus placebo 0.44, 95% CrI 0.24 to 0.70; SUCRA = 73%), mitoxantrone (median OR versus placebo 0.43, 95% CrI 0.20 to 0.87; SUCRA = 71%), glatiramer acetate (median OR versus placebo 0.48, 95% CrI 0.38 to 0.75; SUCRA = 66%), IFNß-1b (Betaseron) (median OR versus placebo 0.48, 95% CrI 0.29 to 0.78; SUCRA = 65%). The heterogeneity standard deviation τ was 0.20 (95% CrI 0.01 to 0.53).

c) Relapses over 36 months were available from six studies (Andersen 2004; British and Dutch 1988; Ellison 1989; European Study Group 1998; Milanese 1993; NASP 2004) (2521, 17% of those included in this review) comparing each agent azathioprine, cyclophosphamide, IFNß-1b (Betaseron), IFNß-1a (Rebif) versus placebo. Only azathioprine appeared to be effective (mean OR 0.43, 95% CrI 0.17 to 0.88; SUCRA = 94%). The heterogeneity standard deviation τ was 0.30 (95% CrI 0.02 to 1.27).

Disability progression over 24 and 36 months

See: Table 5

a) Disability progression over 24 months was available from 30 studies (Achiron 1998; AFFIRM 2006; BEYOND 2009; Bornstein 1987; Bornstein 1991; Edan 1997; Fazekas 1997; Ghezzi 1989; Goodkin 1991; Goodkin 1995; Hartung 2002; Hommes 2004; IFNB MS Group 1993; IMPACT 2002; INCOMIN 2002; Johnson 1995; Koch-Henriksen 2006; Leary 2003; Likosky 1991; Milanese 1993; Millefiorini 1997; Miller 1961; Montalban 2009; MSCRG 1996; Pohlau 2007; PRISMS 1998; REGARD 2008; SENTINEL 2006; SPECTRIMS 2001; Wolinsky 2007) and 10,828 participants with MS (72%% of those included in this review). Mitoxantrone appeared to be the most effective agent at 24 months' follow-up (median OR versus placebo 0.42, 95% CrI 0.20 to 0.87; SUCRA = 89%). Natalizumab and glatiramer acetate showed a similar effect (median OR versus placebo 0.61, 95% CrI 0.41 to 0.91; 0.67, 95% CrI 0.49 to 0.88). The heterogeneity standard deviation was 0.20 (95% CrI 0.03 to 0.38).

b) Disability progression over 36 months was available in seven trials with IFNß-1b (Betaseron) (European Study Group 1998; NASP 2004), IFNß-1a (Rebif) (Andersen 2004; SPECTRIMS 2001), azathioprine (Ellison 1989; Milanese 1993), and cyclophosphamide (CCMSSG 1991) compared to placebo. None of the four agents was effective in preventing progression at this time. The heterogeneity standard deviation τ was 0.39 (95% CrI 0.05 to 1.33).

Subgroup and sensitivity analyses

• **Participants with RRMS** (Table 6)

a) Relapses over 12 months were provided in 16 trials (4817 participants, 32% of those included in this review) (Achiron 1998; AFFIRM 2006; Bornstein 1987; BPSM 1995; Comi 2001; EVIDENCE 2007; Fazekas 2008; Goodkin 1991; INCOMIN 2002; Knobler 1993; Lewanska 2002; Millefiorini 1997; MSCRG 1996; OWIMS 1999; PRISMS 1998; SENTINEL 2006) and nine treatments, IFNß-1b (Betaseron), IFNß-1a (Avonex), IFNß-1a (Rebif), glatiramer acetate, natalizumab, azathioprine, mitoxantrone, intravenous immunoglobulins, and long-term corticosteroids versus placebo. In the network meta-analysis there was no statistically significant effect of these treatments compared to the control groups.

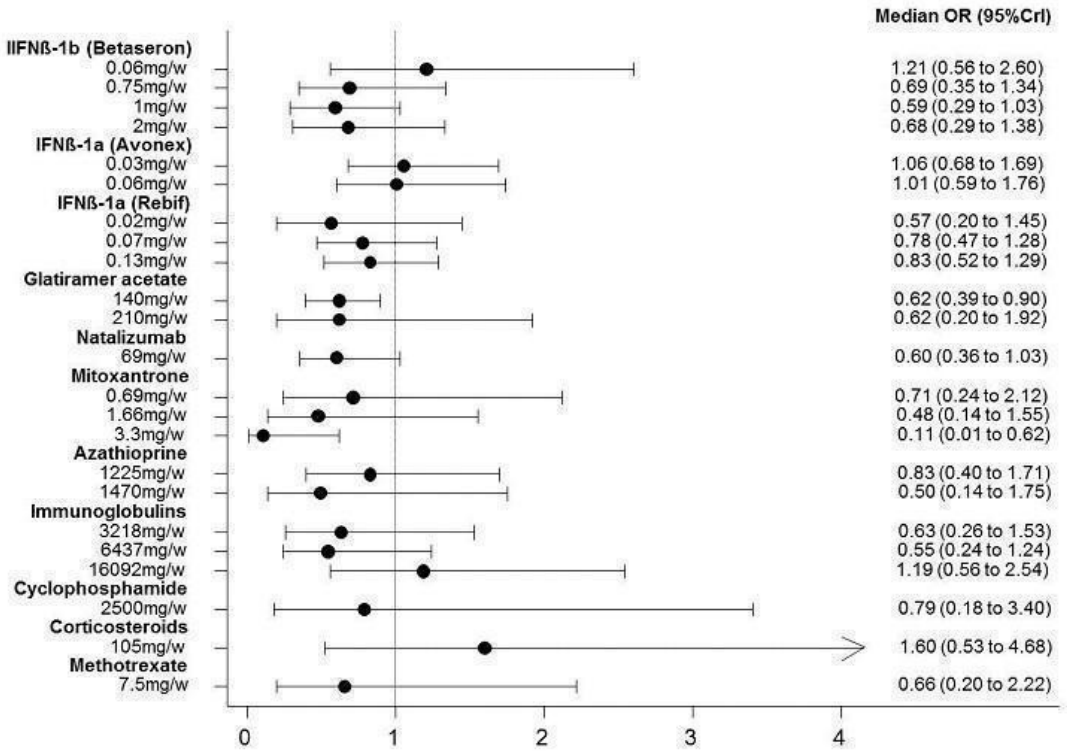
b) Relapses at 24 months were provided in 16 trials (7269, 48% of those included in this review) (Achiron 1998; AFFIRM 2006; BEYOND 2009; Bornstein 1987; BPSM 1995; Etemadifar 2006; Fazekas 1997; Goodkin 1991; IFNB MS Group 1993; INCOMIN 2002; Johnson 1995; Millefiorini 1997; MSCRG 1996; PRISMS 1998; REGARD 2008; SENTINEL 2006) and nine treatments, IFNß-1b (Betaseron), IFNß-1a (Avonex), IFNß-1a (Rebif), glatiramer acetate, natalizumab, mitoxantrone, azathioprine, intravenous immunoglobulins, long-term corticosteroids, and placebo. Mitoxantrone was the most effective agent

with a median OR of 0.14 (95% CrI 0.03 to 0.55; SUCRA = 92%) followed by natalizumab (median OR 0.31, 95% CrI 0.19 to 0.55; SUCRA = 75%), intravenous immunoglobulins (median OR 0.34, 95% CrI 0.13 to 0.69; SUCRA = 70%), azathioprine (median OR 0.34, 95% CrI 0.08 to 1.30; SUCRA = 65%), IFNß-1a (Rebif) (median OR 0.46, 95% CrI 0.25 to 0.71; SUCRA = 53%), IFNß-1b (Betaseron) (median OR 0.50, 95% CrI 0.31 to 0.82; SUCRA = 45%), and glatiramer acetate (median OR 0.50, 95% CrI 0.29 to 0.77; SUCRA = 46%). The heterogeneity standard deviation was 0.17 (95% CrI 0.01 to 0.73).

c) Progression at 24 months was provided in 15 two-arm studies (7444 participants, 50% of those included in this review) (Achiron 1998; AFFIRM 2006; BEYOND 2009; Bornstein 1987; Fazekas 1997; Goodkin 1991; IFNB MS Group 1993; INCOMIN 2002; Johnson 1995; Koch-Henriksen 2006; Millefiorini 1997; MSCRG 1996; PRISMS 1998; REGARD 2008; SENTINEL 2006) and eight treatments, IFNß-1b (Betaseron), IFNß-1a (Avonex), IFNß-1a (Rebif), glatiramer acetate, natalizumab, mitoxantrone, azathioprine, intravenous immunoglobulins, and placebo. Mitoxantrone seemed to be the most effective agent in reducing the number of participants with disability progression at 24 months (median OR 0.11, 95% CrI 0.01 to 0.65; SUCRA = 96%), followed by glatiramer acetate (median OR 0.52, 95% CrI 0.28 to 0.88; SUCRA = 70%). The heterogeneity standard deviation was 0.29 (95% CrI 0.03 to 0.80).

• **Dose effects** (Figure 6)

Figure 6. Forest plot: disability progression over 24 months in MS of all types according to each agent-dose compared to placebo.



Thirty studies were available comparing 24 agent doses for progression at 24 months. When each dose was assumed to be a different treatment the DIC was 125 compared to 117 when each dose had a fixed agent-specific effect, indicating that the dose did not alter the agent's effectiveness much. The dose by week analysis suggested that mitoxantrone was the most effective drug in delaying disability progression at 24 months when administered intravenously at 12 mg/m²/body surface area every three months (median OR 0.11, 95% CrI 0.01 to 0.62; SUCRA = 91%). Over-

all the ranking of the agents was consistent with this result obtained when the dose-effects were ignored, as presented in Table 5. Exploration of models that assumed a monotonic or linear dose-effect association did not improve fit or parsimony and similar observations were made for the analysis of relapses at 24 months (Del Giovane 2013).

• Priors for heterogeneity

We re-analysed the primary efficacy outcomes using a uniform prior between 0 and 3 for standard deviation; no important changes were observed in the results.

• Sponsoring

Thirty-one out of 44 (70.5%) studies were sponsored by pharmaceutical companies; eight studies (18%) (Bornstein 1987; Bornstein 1991; BPSM 1995; Goodkin 1995; INCOMIN 2002; Lewanska 2002; Likosky 1991; Miller 1961) were supported by public institutions or had no funding; and five studies (11%) (Edan 1997; Etemadifar 2006; Ghezzi 1989; Koch-Henriksen 2006; Millefiorini 1997) did not provide enough information to understand if any sponsor had a role in the trial (see Characteristics of included studies). As the number of studies and treatments evaluated in publicly sponsored studies were very small, we did not undertake a sensitivity analysis as planned.

2. Acceptability of the interventions

See: Table 7

The network meta-analysis showed that there was no difference among treatments in the number of participants who dropped out (withdrawals or lost to follow-up) due to adverse events throughout the studies, up to 24 months. The heterogeneity standard deviation was 0.16 (95% CrI 0.01 to 0.46). No sensitivity to prior for heterogeneity was observed.

Secondary outcomes

Results of pairwise meta-analyses are summarized below.

1. *Participants with at least one AE*: most of the trials reported only the number of events; the number of participants was reported rarely. Moreover, definitions and reporting of AEs were so different among the included studies that it was impossible to extract quantitative data (Table 2).

2. *Serious adverse events (SAEs)*: there was no statistically significant effect of the treatments compared to the placebo groups (Analysis 6.1). In one study (Hartung 2002) mitoxantrone (12 mg/m²) was associated with increased odds of participants who had SAEs compared with placebo (OR 2.58, 95% CI 0.48 to 13.81); in another two trials with this agent (Edan 1997; Millefiorini 1997) no SAEs were reported. Trials of azathioprine reported the occurrence of AEs, although severity was not detailed. The number of deaths (related or unrelated to the agent) or number of participants who committed or attempted suicide were not significantly more frequent (P = 0.91; P = 0.86) in the active treatment arms compared to placebo (data not shown).

3. *Withdrawals due to AEs*: overall, there was a statistically significant effect of the treatments as a group compared to placebo (OR 2.41, 95% CI 1.92 to 3.03; P = 0.001) (Analysis 6.2). Agents associated with significantly increased odds of participants who were withdrawn due to AEs compared with placebo were interferons (OR 3.08, 95% CI 2.23 to 4.26; P < 0.001), glatiramer acetate (OR 3.48, 95% CI 1.55 to 7.84; P = 0.003), natalizumab (OR 1.36, 95% CI 0.99 to 1.85; P = 0.06), azathioprine (OR 6.35, 95% CI 2.50 to 16.11; P < 0.001), and intravenous immunoglobulins (OR 1.99, 95% CI 1.07 to 3.71; P = 0.03). No difference in withdrawals due to AEs was found for mitoxantrone, however only one study was included, which was likely to lead to type-II error. There were no significant differences in withdrawals in direct comparison trials of the interferons compared to each other or to glatiramer acetate (data not shown).

4. *Serious infections*: two cases of progressive multifocal leukoencephalopathy, one of which was fatal, were reported in natalizumab-treated participants (SENTINEL 2006). Overall, there was not a statistically significant effect of the treatments as a group compared with the placebo groups (data not showed).

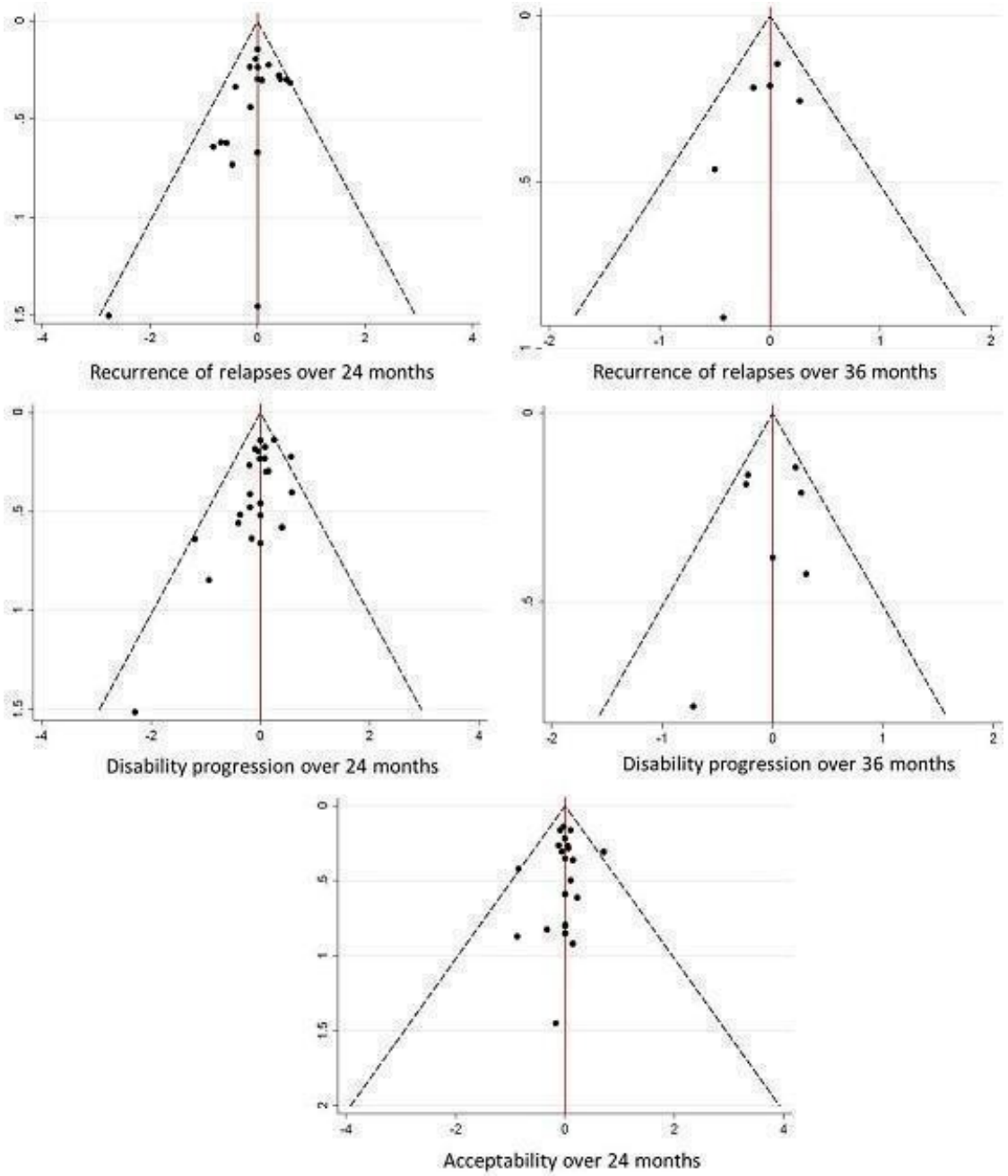
5. *Leukaemia, lymphoma, or any other type of cancer*: no increased odds for active treatments compared with placebo were reported in the included trials (data not showed).

6. *Other AEs* are reported in the Cochrane reviews on interferons (La Mantia 2012; Rice 2001; Rojas 2010), glatiramer acetate (La Mantia 2010), natalizumab (Pucci 2011), azathioprine (Casetta 2007), mitoxantrone (Martinelli 2005), intravenous immunoglobulins (Gray 2003), cyclophosphamide (La Mantia 2007), methotrexate (Gray 2004), and long-term corticosteroids (Ciccone 2008).

Reporting bias

The funnel plots for recurrence of relapses and disability progression over 24 and 36 months and acceptability over 24 months are showed in Figure 7. For outcomes at 36 months there are not enough data to judge the reporting bias; for recurrence of relapses over 24 months there is an indication of small study effects where asymmetry in the plot is present due to 'missing' studies on the right side. For the other outcomes, the plots suggested that there was no association between the study size and its effect.

Figure 7. 'Comparison-adjusted' funnel plots. In the horizontal axis the differences between the observed log-odds ratios of each active treatment versus placebo and their summary effect obtained from the pairwise meta-analysis are presented; in the vertical axis the standard errors of the log-odds ratios are presented. Differences on the left of null represent studies with estimates larger than the comparison-specific mean.



DISCUSSION

Summary of main results

This review of the effects of treatments for MS included 44 RCTs with 17,401 randomised participants. The majority of studies were short-term trials, with the median RCT duration being 24 months, therefore the effects of these treatments beyond two years remain uncertain.

In terms of a protective effect against recurrence of relapses in RRMS during the first two years of treatment, natalizumab, IFNß-1a (Rebif), IFNß-1b (Betaseron), glatiramer acetate, and mitoxantrone outperformed other drugs, being statistically significantly more effective than IFNß-1a (Avonex), azathioprine, methotrexate, cyclophosphamide, intravenous immunoglobulins, and long-term corticosteroids. The relapse outcome at three years' follow-up was not reported by any of the included trials for RRMS.

There were few studies providing data for the risk of clinical relapses in patients with progressive MS. Direct comparisons suggested that azathioprine decreased and IFNß-1b (Betaseron) decreased slightly the odds of participants with progressive MS having relapses over three years.

Disability progression was based on surrogate markers in the majority (55%) of included studies that used serial in-trial upward changes of 0.5 or 1.0 point on the EDSS scale, confirmed at three months' follow-up or unconfirmed, reflecting an effect on relapse-related disability. Beyond two to three years, disability outcome data were unavailable or dropouts compromised the interpretation. From the network meta-analysis, mitoxantrone appeared to be the most effective agent at two years' follow-up, but our confidence in this result was graded as 'very low' using the GRADE approach. The direct comparison analysis suggested that natalizumab and IFNß-1a (Rebif) probably decreased the odds of participants with RRMS having disability progression at two years' follow-up, with an absolute reduction of 14% and 10%, respectively. However, these findings also should be interpreted with caution because only one study was available for each of the two agents and both studies used a surrogate outcome to measure disability progression.

Both direct and indirect comparison revealed that none of the nine agents (IFNß-1b (Betaseron), IFNß-1a (Avonex or Rebif), glatiramer acetate, mitoxantrone, methotrexate, cyclophosphamide, intravenous immunoglobulins, and long-term corticosteroids) that were evaluated in included studies were effective in preventing disability worsening over two or three years in patients with progressive MS.

We found that there was not an important dose-effect relationship for any of the included treatments except for mitoxantrone, which appeared to be the most effective drug in delaying disability progression when administered intravenously at 12 mg/m²/body surface area every three months.

All the agents included in this review were associated with a statistically significant higher rate of total withdrawals due to adverse events (AEs) compared to placebo, even if the network meta-analysis revealed that these agents did not differ from each other with regards to total withdrawals due to AEs. Information on serious adverse events (SAE) was available only for interferons, glatiramer acetate, natalizumab, mitoxantrone, and intravenous immunoglobulins. All of them, except interferons, were associated with a non-significantly higher rate of total SAEs compared with the control treatment during a median two years' follow-up period. Lack of statistical significance in our analyses was likely to have been caused by low quality, that is no active monitoring, an overall poor reporting of SAEs, and short follow-up in the included studies, as described in the limitations section.

Safety data from observational and registry studies need to be considered for medium and long-term SAEs associated with these treatments. Cutaneous necrosis (Nakamura 2008), thyroiditis (Nonchev 2010), ophthalmological complications (Fragoso 2011), grade 3 or higher hepatotoxicity (Byrnes 2006), severe depression (Fragoso 2010), and haematological side effects (Nabavi 2011) were reported as significantly related to interferon ß treatment.

Glatiramer acetate is associated with a number of SAEs including immediate post-injection reaction, anaphylaxis or hypersensitivity requiring emergency medical care, dyspnea, chest pain, lipoatrophy and skin necrosis, immunosuppression and infections, and decrease in pulmonary function. The most common adverse reactions ($\geq$ 10% and $\geq$ 1.5 times higher than placebo) reported in controlled studies were injection site reactions, vasodilatation, rash, dyspnea, and chest pain (FDA 2011).

Treatment with natalizumab is associated with an increased risk of progressive multifocal leukoencephalopathy (PML). A risk of PML of 11/1,000 users has been estimated for patients with all the following risk factors: the presence of anti-JC virus antibodies; longer duration of treatment, especially beyond two years; and prior treatment with an immunosuppressant medication (for example mitoxantrone, azathioprine, methotrexate, cyclophosphamide, or mycophenolate mofetil) (Bloomgren 2012).

A French cohort of 5354 MS patient-years was prospectively followed from 2001 to at least five years after initiation of mitoxantrone therapy (Le Page 2011). One out of 802 patients (0.1%) presented with acute congestive heart failure and 39 out of 794 patients (4.9%) presented with asymptomatic left ventricular ejection fraction reduction under 50% (persistent in 11 patients (28%), transient in 27 patients (69%), on the last scan at

year five in one patient). Two cases of therapy-related leukaemia (0.25%) were detected 20 months after the start of mitoxantrone (one death and one with eight years confirmed remission). Of the 317 women treated before the age of 45 years, 17.3% developed a persistent age-dependant amenorrhoea.

A possible long-term risk of cancer from azathioprine may be related to a treatment duration above 10 years and cumulative doses above 600 g (Casetta 2007).

Severe AEs leading to discontinuation of the treatment with intravenous immunoglobulins were noted in 4% of 84 treatment courses with a total 341 infusions under routine clinical conditions. They included thrombosis of the jugular vein, allergic reaction, and retrosternal pressure. However, based on the available literature, intravenous immunoglobulins can generally be regarded as a relatively safe treatment (Elovaara 2008).

Overall completeness and applicability of evidence

All eligible trials (up to November 2010) of agents that are currently used for treatment of MS were included in the review with the exception of fingolimod, for which trials had been not published when we were planning our review.

The findings presented in this review originated mostly from trials on the interferon ß family, glatiramer acetate, and natalizumab, which overall contributed outcome data for 9881 participants (66%) included in 33 trials (75%). The majority of the studies included RRMS participants, who represented 60% of those included in the review. Due to the few studies and data for participants with SPMS, PRMS, and PPMS, we decided to combine data for these phenotypes considering also that natural history studies show a similar disease course once onset of progression has manifested, independent of the prior history (Ebers 2006), and certainly over the two to three year time frame of the included trials.

Our review was not intended to be a comprehensive review of all effects of these treatments. We focused on three main clinical outcomes (relapses, disability progression, acceptability of treatment) that we considered clinically meaningful. Patient reported outcomes such as behavioural functions or quality of life were not included. They are certainly important outcomes for participants but are reported rarely in clinical trials, often without adequate monitoring and availability of appropriate published results. Different scales used and at different assessment time points do not allow comparisons to be made. Moreover, these measures may be susceptible to bias in trials in which many, if not most, treated participants have become aware of the treatment they are receiving owing to the well documented side effects of the treatments included in our review. Short duration trials and poor reporting of AEs were other major limitations in determining the overall completeness and the most favourable balance between benefits and risks of the included treatments.

Although magnetic resonance imaging (MRI) measures are widely used in trials of MS, we did not include them in this review since MRI alone adds little if anything to the clinical outcomes (Daumer 2009). Moreover, it was not possible to compare MRI outcomes adequately across trials from the published results since MRI criteria, measures, and the timing of the scans differed between trials.

Quality of the evidence

Five (11%) out of 44 trials were judged to be at low risk of bias, when allocation concealment, blinding of outcome assessors and complete outcome data were met. In more than 50% of studies allocation concealment was judged to be 'unclear' due to the lack of details provided in the articles. Only two RCTs were judged at a 'high' risk of bias for allocation concealment. Blinding of outcome assessment was reported in the majority of the included studies; however side effects of each treatment make it likely that treated participants had become aware of the treatment they were receiving during the course of the trial, and most of these trials should be regarded as single-blind.

In our review a primary outcome was disability progression and its definition was taken from the original articles. All studies defined progression as a sustained (three month or six month) increase in EDSS (Kurtzke 1983) score by at least one point recorded outside of exacerbations throughout the follow-up. This is a validated measure of unremitting disability in MS, provided it is confirmed after a sufficient period of time (at least six months is necessary and one year would be better) (Ebers 2008). Twenty-four (54.5%) of the 44 included trials required only three months of confirmation to assess sustained disability progression. Although we had to accept the definition given in the original papers, we considered the three month criterion to be at high risk of bias because this definition meant that participants who recovered slowly from exacerbations were regarded as having unremitting disability progression.

There were greater than 85% of participants followed-up in more than 50% of the included studies. Six trials were stopped early, two for benefit, three for futility, and one for lack of funding. Although protocols of the included studies were not available, the majority of them reported the number of participants who had relapses or disability progression, which were the primary efficacy outcomes in this review. However, in most trials these outcomes were reported at only two years' follow-up, that is a too short period to establish valid treatment efficacy in MS.

Only 20 RCTs reported that AEs were actively monitored, and only one study provided sufficient information on how a SAE was defined. More than 50% of studies did not report SAEs. Moreover, due to the short duration of follow-up in the majority of the trials, rare and long-term adverse events were not available. Therefore caution is needed in interpreting the apparent safety reported for most of the agents ("treatments appeared not statistically significantly different from placebo in terms of the number of participants with SAEs"). Given the low quality of monitoring adverse

events and overall poor reporting in the included studies, it is difficult to understand whether an event actually did not happen or it happened but was not detected or was selectively not reported.

Potential biases in the review process

The studies were deemed sufficiently similar across comparisons and we believe that the consistency assumption is reasonable in this type of data. The models fit the data well, no loops were found to be inconsistent and model parsimony was always higher for the consistency model; this provided support for our assumption of consistency. However the power of these tests and approaches to detect inconsistency are low, particularly for networks with a small number of included studies. The possible presence of publication bias, partially supported by the contour-enhanced funnel plot, can never be totally excluded.

A small number of studies with few comparisons were recognised as having low risk of bias and in many cases results came from a single study. We couldn't predict the impact of industry sponsorship as most of the presented studies were sponsored by industry or the information was not reported.

In this review pairwise meta-analyses were performed in a frequentist approach while network meta-analyses were performed in a Bayesian context. Implementation of the models in the Bayesian framework yielded wider confidence intervals than frequentist implementation in STATA because the framework accounted for the uncertainty in the estimation of the heterogeneity. For some comparisons the estimate of network meta-analysis was less precise that the estimate from the pairwise meta-analysis. This happened when there was no heterogeneity in the pairwise comparison but there was heterogeneity overall in the network and random-effects models were used. This was because the network meta-analysis assumes a common 'average' heterogeneity parameter τ for all pairwise comparisons.

Agreements and disagreements with other studies or reviews

Our findings agree with and extend the findings of a previous review (Smith 2010) that examined all available RCTs (up to December 2009) of glatiramer acetate, IFNß-1a, IFNß-1b, mitoxantrone, and natalizumab. They also reported that there was fair evidence that IFNß-1a (Avonex) was less effective than IFNß-1a (Rebif) and IFNß-1b for preventing relapse in patients with RRMS. They found no difference between the interferons on changes in disability but did find IFNß-1b to be superior to IFNß-1a (Avonex) on disease progression (relative risk 0.48, 95% CI 0.27 to 0.86) in RRMS. They confirmed our findings that evidence was insufficient to make any judgments regarding effectiveness in primary progressive or secondary progressive MS. They did not find any difference in withdrawal rates among the interferon ß family in head-to-head trials.

Zintzaras 2012 performed a network meta-analysis of 109 trials and compared different therapies commonly used for MS, but also many agents that are not currently in clinical use, such as bovine myelin, or that were rejected by the FDA and the EMA because they were found to cause toxicity, such as cladribine. The meta-analysis considered 145 arms as different treatments (that is one for each dose of each treatment) compared to IFNß-1b (250 μg) (that is the chosen reference treatment for analysis) and provided about 90 estimates based on eight direct comparisons with IFNß-1b. Thus, the remaining estimates were obtained through the use of indirect analysis. The authors reported that their results needed to be interpreted with caution because the network was dominated by indirect comparisons, but they claimed that combination therapies could be more promising than monotherapies. Important facts invalidate this conclusion in our opinion. First, this claim came only from indirect comparisons. Second, combined treatments did not affect clinical outcomes any more than the comparison treatment alone or resulted in a worst outcome. For example, methylprednisolone in combination with IFNß-1a did not affect disability progression any more than IFNß-1a alone (Ravnborg 2010), or atorvastatin combined with IFNß-1a resulted in increased MRI and clinical disease activity (Birnbaum 2008). Third, some of the primary studies included in the indirect analysis were phase two small trials (Birnbaum 2008; Goodman 2009; Weiner 1993) or used no validated clinical outcomes to assess treatment effects (Khoury 2010). Fourth, combination therapies increased the frequency of SAEs.

In a retrospective cohort study (Shirani 2012) based on prospectively collected data (1985 to 2008) from British Columbia, Canada, patients with RRMS treated with interferon ß (n = 868) were compared with untreated contemporary (n = 829) and historical (n = 959) cohorts. The median active follow-up times (first to last EDSS measurement) were 5.1, 4.0, and 10.8 years, respectively. The authors concluded that among patients with RRMS, administration of interferon ß was not associated with a reduction in progression of disability.

AUTHORS' CONCLUSIONS

Implications for practice

Our review includes direct and indirect comparisons of immunotherapies for MS and should provide some guidance to clinicians and patients on their efficacy. On the basis of high quality evidence, natalizumab and IFNß-1a (Rebif) are superior to all other treatments for preventing clinical relapses and disability progression in the short-term (24 months) in patients with RRMS. Natalizumab can induce progressive multifocal leukoencephalopathy, especially with more than two years of treatment.

Moderate quality data support the efficacy of IFNß-1b (Betaseron), glatiramer acetate, and mitoxantrone for preventing relapse and disability progression in RRMS in the short-term. All

these treatments are associated with medium and long term serious adverse events and the benefit-risk balance might be unfavourable.

There are insufficient high quality data for a definitive conclusion on whether there is a favourable benefit-risk balance with azathioprine, however this agent might be effective in decreasing the odds of participants with RRMS having clinical relapses and disability progression over 24 to 36 months.

The lack of convincing efficacy data from both direct and indirect comparisons shows that IFNß-1a (Avonex), intravenous immunoglobulins, cyclophosphamide, and long-term corticosteroids have an unfavourable benefit-risk balance in RRMS.

Few randomised studies are available for patients with progressive MS. In comparison with placebo, IFNß-1b (Betaseron) and azathioprine decrease slightly the odds of these patients having clinical relapses over three years. IFNß-1a (Avonex or Rebif), glatiramer acetate, mitoxantrone, methotrexate, cyclophosphamide, intravenous immunoglobulins, and long-term corticosteroids are not effective in decreasing disability progression in patients with progressive MS.

There is a dose-effect associated with mitoxantrone administered intravenously at 12 mg/m²/body surface area every three months, but the risk of serious adverse events (cardiotoxicity and therapy-related leukaemia) unfavourably influences the benefit-risk balance. There is not a dose-effect associated with the use of all the other treatments included in our review.

It is important to consider that the clinical effects of all these treatments beyond two years are uncertain, and this is a relevant point for a disease of 30 to 40 years duration.

More than 70% of included studies were sponsored by pharmaceutical companies and this could have influenced the results of our review.

Implications for research

We believe that there are two urgent needs that the research agenda should address. First, large randomised trials of direct comparisons are needed and follow-up of the original trial cohorts should be mandatory. Direct head-to-head comparison(s) between natalizumab and IFNß-1a (Rebif) or between azathioprine and IFNß-1a (Rebif) should be top priority on the research agenda.

Second, more studies regarding the medium and long-term efficacy and safety of immunotherapies and the comparative safety of different agents are needed. As the number of drugs, including biologics, that are available for treatment of MS increases, more options will become available to participants and clinicians. In the absence of comparative trials, national and international registries and other types of large non-randomised studies might be relevant sources for providing complementary data regarding the long-term effectiveness and safety of immunotherapies for MS.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Achiron 1998

Methods	RCT
Participants	Age: 19-60 years; definite RRMS; mean disease duration 4 years; mean EDSS 3.0
Interventions	Loading dose of intravenous immunoglobulins 0.4 g/kg/body weight per day for 5 consecutive days followed by additional booster doses of intravenous immunoglobulins 0.4 g/kg/body weight once daily every 2 months for 2 years (n 20) placebo consisting of 0.9% saline administered with the same schedule as the active treatment (n 20)
Outcomes	Relapses at 12 and 24 months. Progression at 24 months
Notes	Funding: Miles Inc. Cutter Biological, Bayer and Promedico

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were assigned to receive immunoglobulin or placebo by a block-stratified randomisation procedure, performed at the pharmacy
Allocation concealment (selection bias)	Low risk	Allocation made in pharmacy. Bottle of immunoglobulin or placebo were wrapped in sealed opaque bags and brought to the patients' rooms. Use also of an opaque plastic bag for fluid
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*All patients and evaluators were blinded to treatment...the bottles of immunoglobulin or placebo were wrapped in sealed opaque bags and brought to the patients' rooms. The entire IV set was covered by an opaque plastic bag to ensure that any possible fluid turbidity or frothing would not be evident to the investigators or patients*". Page 399
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*All patients and evaluators were blinded to treatment*". Page 399
Incomplete outcome data (attrition bias) All outcomes	Low risk	"*Two patients discontinued treatment after the first year (one in each group).*" Page 400. The intention-to-treat analysis was performed including the 2 withdrawals
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes

Achiron 1998 (*Continued*)

Other bias	High risk	Sustained disability progression confirmed at 3 months' follow-up

AFFIRM 2006

Methods	RCT
Participants	Age: 18-50 years; clinical definite RRMS; disease duration 0-33 years; EDSS 0-5.0; ≥ 1 relapses in the year before randomisation
Interventions	Natalizumab 300 mg by intravenous infusion every 4 weeks for up to 116 weeks (n. 627) Placebo (unspecified) (n. 315)
Outcomes	Relapses at 12 and 24 months. Progression at 24 months.
Notes	Funding: Biogen Idec, Inc. and Elan Pharmaceutical.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Patients were randomly assigned to treatment that was stratified according to study site in blocks of three (two active, one placebo) with the use of a computer-generated block randomization schedule.* " Page 900
Allocation concealment (selection bias)	Low risk	"*A multidigit identification number, implemented by an interactive voice-response system was used*." Page 900
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*All study personnel, patients, sponsor personnel involved in the conduct of the study, and the investigator advisory committee were unaware of treatment assignments throughout the study* (Page 900) *... Treating neurologists were responsible for all aspects of patient care, including the management of adverse events and the treatment of relapsing disease*." Page 901
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*Examining neurologists performed objective evaluation with use of the EDSS and neurologic examination during all study visits; they were not in contact with patients in any other capacity, so as to reduce the possibility of being unblinded by side effects or laboratory assessments.*" Page 901
Incomplete outcome data (attrition bias) All outcomes	Low risk	"*8% of patients in the* natalizumab*group and 10% of those in the placebo group withdrew from the study*". Pages 902-903

AFFIRM 2006 (*Continued*)

Selective reporting (reporting bias)	High risk	The number of patients who progressed at 2 years were not available
Other bias	High risk	Data analysis performed by Biogen Idec and Elan Pharmaceuticals. Sustained disability progression confirmed at 3 months' follow-up. Relapses assessed also as adverse events. The number of lost to follow-up at 1 year were not available

Andersen 2004

Methods	RCT
Participants	Age: 18-65 years; clinical definite SPMS defined as $\geq$ 1 EDSS point increase in 4 years before randomisation, with or without superimposed exacerbations; EDSS < 7.0
Interventions	IFNß-1a (Rebif) 22 μg subcutaneously weekly for 36 months (n.188) Placebo (unspecified) (n. 183)
Outcomes	Relapses at 36 months. Progression at 36 months
Notes	Funding: Serono International, Geneva, Switzerland

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	"*equal allocation.*" Page 707
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*Patients were instructed to cover injection sites*." Page 707
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*Neurologists blinded to dose assignment were responsible for neurological assessments*". Page 707
Incomplete outcome data (attrition bias) All outcomes	High risk	The study had ended prematurely due to negative results from SPECTRIMS study. Only 83% of randomised patients completed about 3 years. Losses to follow-up not included in analysis: treatment 21%; placebo 16%. More AE and patients' decision in the treated group. The median time on treatment was 35.2 months (mean 32.0) for placebo and 35.0 months (mean 31.1) for IFNß-1a
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes

Other bias	Low risk	The study appears to be free of other sources of bias

BEYOND 2009

Methods	RCT
Participants	Age: 18-55 years; clinical or laboratory-supported definite RRMS; EDSS 0-5; disease duration 3-8 years; ≥ 1 relapses in the year before randomisation
Interventions	IFNß-1b 250 μg subcutaneous every other day (n. 897) IFNß-1b 500 μg subcutaneous every other day (n. 899) glatiramer acetate 20 mg subcutaneous every day (n. 448)
Outcomes	Relapses at 24 months. Progression at 24 months
Notes	Funding: Bayer HealthCare Pharmaceuticals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Use of SAS-based block randomisation with regional stratification*". Page 890
Allocation concealment (selection bias)	Low risk	"*Patients were randomly assigned in a 2:2:1 ratio ... by the central randomisation group...*" Page 890
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*Physicians and patients were double-blind to comparisons between the two doses of IFNß-1b... Ibuprofen or acetaminophen were given at the same time as random assignment to IFNß-1b, at least during the first 3 months, to reduce flu-like symptoms. The treating physicians and the patients were therefore aware of treatment assignments*". Page 891
Blinding of outcome assessment (detection bias) All outcomes	Low risk	" *The masked evaluating physicians did all neurological assessments and ascertained functional system and EDSS scores... The evaluating physicians were not involved in the care of patients and had no access to patient files or previous assessments. ... Patients covered their injection sites during neurological examination and did not discuss any adverse events with the evaluating physician*". Page 891-2
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up not included in analysis: 500 μg IFNß-1b 13%; 250 μg IFNß-1b 20%; glatiramer acetate 16%
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes

Other bias	High risk	Sustained disability progression confirmed at 3 months' follow-up

Bornstein 1987

Methods	RCT
Participants	Age: 20-35 years; definite RRMS; EDSS 0-6.0; disease duration ≥ 1 year; at least 2 relapses in the 2 years before randomisation
Interventions	Glatiramer acetate 20 mg subcutaneous every day (n. 25) Placebo bacteriostatic saline subcutaneous every day (n. 25)
Outcomes	Relapses at 12 and 24 months. Progression at 24 months
Notes	Funding: Grants from the NINCDS and the NIH, Bethesda, Md.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"*The random assignment of the first patient of a pair determined the assignment of both*". Page 409
Allocation concealment (selection bias)	High risk	An open allocation schedule was used: "*Treatment assignments were made known to the clinical assistant responsible for the production, labelling and distribution of medication*". Page 409
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*The patient's self evaluation of ... side effects were reported to the clinical assistant, how was not blinded to the treatment*". Page 409
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*A neurologist unaware of the patient's treatment group completed a neurologic examination and status evaluation*". Page 409
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up excluded from the study analysis: 2 of 25 placebo patients
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes and those outcomes that were pre-specified in the methods section
Other bias	High risk	Sustained disability progression was confirmed at 3 months' follow-up

Bornstein 1991

Methods	RCT
Participants	Age: 20-60 years; progressive MS; EDSS 2-6.5; progression ≥ 18 months; ≤ 2 relapses in the 2 years before randomisation
Interventions	glatiramer acetate 30 mg subcutaneous twice a day (n. 51) placebo, saline alone, subcutaneous twice a day (n. 55)
Outcomes	Progression at 24 months
Notes	Funding: Grants from the NINCDS and the NIH, Bethesda, Md.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*... by randomized block design with two baseline EDSS strata < 5.0 and 5.0 or greater*" Page 534
Allocation concealment (selection bias)	Unclear risk	"*The investigator notified the statistical center, which assigned a randomization code number. Shipment of* glatiramer acetate*to the patients at their individual centers were totally at random and were dictated by the patients' date of entry into the trial. Only the statistician and the clinical assistant at Albert Einstein College of Medicine, who distributed medication, were aware of patients assignments*". Page 534
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*Side effects were reported to a clinical assistant*". Page 534
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*The blinded neurologist performed a complete neurological examination... Side effects were not discussed with the study neurologist... Another blinded neurologist was available to examine patients with severe or unusual side effects*." Page 534
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up and 20 withdrawals were included in the data analyses. Page 536
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes and those outcomes that were pre-specified in the methods section
Other bias	High risk	Sustained disability progression was confirmed at 3 months' follow-up

BPSM 1995

Methods	RCT
Participants	Mean age: 35 years; clinical definite RRMS; EDSS < 5.5; disease duration: not reported; no relapses in the previous 45 days before randomisation
Interventions	Intravenous methylprednisolone 2 g in saline solution for 12 hours, every 45-60 days for two years or until relapse (n. 17) Placebo i.v. saline solution at the same schedule (n. 19)
Outcomes	Relapses at 12 and 24 months
Notes	Funding: None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"*The method of randomisation was centralised*" (Cochrane review)
Allocation concealment (selection bias)	Low risk	"*Allocation were generated by computer by personnel not involved in patients management*" (Cochrane review)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*the study was double blind*" (Cochrane review)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*the study was double blind*" (Cochrane review)
Incomplete outcome data (attrition bias) All outcomes	High risk	"*There were 10 patients (7 treated) lost to follow-up (28% overall). Moreover, patients experiencing an exacerbation were not followed up although a two year follow-up was planned*". (Cochrane review)
Selective reporting (reporting bias)	High risk	*"Patients were not followed-up after the first exacerbation, contrary to what was planned. Since patients not experiencing a relapse in the two years of the study were just 2, we did not have any data on disability progression for the majority of the patients".* (Cochrane review)
Other bias	High risk	"*Prematurely interrupted at 36 out of 72 planned patients for organisational reasons and lack of funding*". (Cochrane review)

British and Dutch 1988

Methods	RCT
Participants	Age: 30-65 years; definite RRMS, SPMS or PPMS; disease duration 5-15 years; EDSS 2.5-6.5; ≤ 1 relapses in the 2 years before randomisation
Interventions	Azathioprine 2.5 mg/Kg body weight oral daily (n. 174) Placebo (n. 180)
Outcomes	Relapses at 12, 24 and 36 months
Notes	Funding: Wellcome Company

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation sequence was generated for each centre by the trial statistician "*by randomized block design*". Page 534
Allocation concealment (selection bias)	Low risk	"*The investigator notified the statistical center, which assigned a randomization code number*" Page 534. The packs of trial tablets were issued to individual pharmacies labelled with a code. The treatment and placebo tablets were identical
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were blind to treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A masked assessor recorded the number of relapses, the ambulatory index and the Kurtzke scale
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up not included in the study analysis (at the end of the study): Treatment arm 8%; placebo 6%
Selective reporting (reporting bias)	High risk	Proportion of participants who progressed at 2 years was not available
Other bias	High risk	Sustained disability progression confirmed at 3 months' follow-up

CCMSSG 1991

Methods	RCT
Participants	Mean age: 32 years; clinically or laboratory-supported SPMS, PPMS or PRMS; ≥ 1.0 EDSS in the year before randomisation; mean disease duration 10 years; mean EDSS 5.8 (0.6)

CCMSSG 1991 (*Continued*)

Interventions	Cyclophosphamide 1 g intravenous three times weekly + 40 mg prednisone tapered for 16 days (total dose ≤ 9 gm) (n. 55) Placebo (n. 56)
Outcomes	Progression at 36 months
Notes	Funding: BRISTOL Myers; Upjohn

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"*A randomisation sequence was generated separately for each centre. Patients were stratified by centre and EDSS score.*" Page 442
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*Patients with exacerbation or progression were seen by the monitoring neurologist... who was aware of the treatment allocation*". Pages 442, 444
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*The evaluating neurologist (not involved with the patients' ongoing care) was blinded*". Page 444
Incomplete outcome data (attrition bias) All outcomes	Low risk	"*Subjects who did not complete the allocated treatment were followed and their outcome was assigned to the group to which they were randomised (intention to treat analysis)*". Page 443
Selective reporting (reporting bias)	Low risk	The published reports included patients who progressed at 36 months
Other bias	High risk	Sustained disability progression confirmed at 3 months' follow-up

Comi 2001

Methods	RCT
Participants	Age: 18-50 years; clinical or laboratory-supported definite RRMS; EDSS 0-5.0; disease duration ≥ 1years; ≥ 1 relapses in the 2 years before randomisation
Interventions	Glatiramer acetate 20 mg subcutaneous every day (n. 119) Placebo (not described) (n. 120)
Outcomes	Relapses at 9 months

Comi 2001 (*Continued*)

Notes	Funding: Teva Pharmaceutical

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*The randomization list, stratified by centers, was computer-generated by the TEVA Statistical Data Management Department. Equal allocation of the two treatment groups was used*". Page 291
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	*"A treating neurologist was responsible for the overall medical management of the patient including safety monitoring... All personnel were unaware of treatment allocation... both the treating neurologist and the patient were informed on the importance of not discussing safety issue with the examining neurologist*" . Page 291
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	" *An examining neurologist was responsible for all scheduled neurological examinations and exacerbation follow-up*". Page 291
Incomplete outcome data (attrition bias) All outcomes	Low risk	"*Analyses were based on an intention to treat dataset. The last observation carried forward (LOCF) method was implemented to account for early discontinuation and missing data." 7 (6%) patients dropped out in each arm*". Page 292
Selective reporting (reporting bias)	High risk	Progression was not measured in the trial.
Other bias	High risk	Teva Pharmaceutical was involved in the trial.

Edan 1997

Methods	RCT
Participants	Age: 18-45 years; definite SPMS or PRMS; disease duration < 10 years; $\geq$ 2 relapses or $\geq$ 2 EDSS points increase in the year before randomisation; EDSS $\leq$ 6.0
Interventions	20 mg intravenously/month and methylprednisolone (1 g intravenously/month) (n. 21) methylprednisolone alone (1 g intravenously/month) (n. 21)
Outcomes	Relapses at 6 months.
Notes	Funding: not reported

Risk of bias

Edan 1997 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	"*The allocation of the treatment was done after inclusion by a central randomisation service by fax*". Page 113
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*In the present study, ... neither the patients nor the clinical investigators were blinded during the study. Blinding of patients was not possible in this trial, as obvious side effects of mitoxantrone were experienced in almost all cases. Blinding of the physician was made difficult by the fall in white cell count that always accompanies mitoxantrone treatment*". Page 116
Blinding of outcome assessment (detection bias) All outcomes	High risk	"*Blind clinical observers might have been appointed, but this could not be done for economic reasons*". Page 116
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 withdrawals "*due to pronounced clinical worsening*" (all in the methylprednisolone group) were included in analysis
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes
Other bias	High risk	Sustained disability progression confirmed at 2 months' follow-up. It's unclear if this study was sponsored

Ellison 1989

Methods	RCT
Participants	Mean age: 32 years; definite SPMS or PPMS; disease duration 5-15 years; EDSS 2.5-6.5; $\leq$ 1 relapses in the 2 years before randomisation
Interventions	Azathioprine 3 mg/kg body weight oral daily (n. 31) Azathioprine 3 mg/kg body weight oral daily and methylprednisolone for 36 weeks (n. 34) Placebo (n. 34)
Outcomes	Relapses at 12, 24 and 36 months. Progression at 36 months
Notes	Funding: Wellcome Company and Upjohn Company

Risk of bias

Bias	Authors' judgement	Support for judgement

Ellison 1989 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"*Patient sequence was the order of presenting the initial prescription to the pharmacy*". Page 1019
Allocation concealment (selection bias)	Unclear risk	"*The statistician told the examining neurologists that the treatments would be allocated by a randomisation process to blocks of 4 successive patients, but the assignment rules were not revealed*". Page 1019
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*Monitoring neurologist, study nurse, clinic coordinator, technician and patients were masked to the treatment assigned*". Page 1019
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*Observer neurologist was masked to the treatment assigned*". Page 1019
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up at 1 year; 2 placebo and 1 methylprednisolone+ azathioprine arm at 2 years; 6 placebo, 5 azathioprine and 6 methylprednisolone+ azathioprine at 3 years
Selective reporting (reporting bias)	Low risk	Primary outcomes of interest were reported completely.
Other bias	High risk	Sustained disability progression confirmed at 3 months' follow-up

Etemadifar 2006

Methods	RCT
Participants	Age: 15-50 years; clinical or laboratory-supported definite RRMS; mean disease duration 3 years; EDSS $\leq$ 5.0; $\geq$ 2 relapses in the 2 years before randomisation
Interventions	IFNß-1b 250 μg subcutaneous every other day for 24 months (n. 30) IFNß-1a (Avonex) 30 μg intramuscular once a week for 24 months (n. 30) IFNß-1a (Rebif) 44 μg subcutaneous three times a week for 24 months (n. 30)
Outcomes	Relapses at 24 months
Notes	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Patients "*were assigned randomly and equally to one of the three treatment groups*". Page 284
Allocation concealment (selection bias)	Unclear risk	Not described.

Etemadifar 2006 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	"*The trial was single-blinded in that patients were aware*". Page 284
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*Physicians who assessed the outcome were unaware of the treatment type that the patient had received*". Page 284
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients were included in the study analysis.
Selective reporting (reporting bias)	High risk	Progression at 2 years was not reported.
Other bias	Unclear risk	It's unclear if this study was sponsored.

European Study Group 1998

Methods	
Participants	Age: 18-55 years; clinical definite SPMS; $\geq$ 2 relapses or $\geq$ 1.0 EDSS points in the 2 years before randomisation; EDSS 3.0-6.5; mean disease duration 13 years
Interventions	Subcutaneous injection every other day of IFN-1b 250 ug (8.0 million international units [MIU]), for 36 months (n. 360) Placebo (unspecified) for 36 months (n. 358).
Outcomes	Relapses at 36 months. Progression at 36 months
Notes	Funding: Schering AG, Berlin

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Central randomisation schedule assigned placebo or IFNß-1b to blocks of six patients in a 1/1 ratio*". Page 1492
Allocation concealment (selection bias)	Low risk	"*Access to the code was strictly limited according to study protocol*". Page 1492
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*Separate treating and examining physicians were employed... IFNß-1b was indistinguishable from placebo*". Page 1492
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*Evaluating physicians received no potentially unmasking information from the treating physicians, and were allowed to speak to patients only as necessary to carry out neurological tests*". Page 1492

European Study Group 1998 (*Continued*)

		It is unclear if the 3 years evaluation was double blind or open for the early study termination
Incomplete outcome data (attrition bias) All outcomes	High risk	90 (25%) of 360 patients in the treatment group and 97 (27%) of 358 controls had not completed the scheduled 3 years' follow-up because the study had ended prematurely for benefit
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes
Other bias	High risk	Schering AG, Berlin performed the statistical analysis.

EVIDENCE 2007

Methods	RCT
Participants	Age: 18-55 years; clinical or laboratory-supported definite RRMS; EDSS 0-5.5; median disease duration 4 years; $\geq$ 2 relapses in the 2 years before randomisation
Interventions	IFNß-1a (Rebif) 44 μg subcutaneous three times a week (n. 339) IFNß-1a (Avonex) 30 μg intramuscular once a week (n. 338)
Outcomes	Relapses at 12 months
Notes	Funding: Serono Inc.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer-generated scheme with block size of 6 followed by block size of 4". Page 2033
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*Patients and a treating physician who was not involved in end point assessment were aware of treatment assignments*". Page 2033
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*Evaluating physicians who were blinded to the patients' treatment and symptoms performed all clinical exams*". Page 2033
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up not included in analysis: IFN-β1a (Avonex) 9.5%; IFN-β1a (rebif) 12%
Selective reporting (reporting bias)	High risk	Only relapses at 12 months were reported.

Other bias	High risk	Data management and study analysis were done by Serono. Sustained disability progression confirmed at 3 months' follow-up

Fazekas 1997

Methods	
Participants	Age: 15-64 years; clinical definite RRMS; EDSS, range 1.0-6.0; disease duration, range: 5.7-8.6 years; ≥ 2 relapses in the 2 years before randomisation
Interventions	Immunoglobulins 0.15-0.20 gm/kg body weight intravenously monthly (n. 75) Placebo (n. 73).
Outcomes	Relapses at 24 months.
Notes	Funding: Sero-Merieux (Vienna, Austria)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Centralised computer-generated randomisation schedule with stratification by centre, age, sex, and deterioration rate*." Page 590
Allocation concealment (selection bias)	Low risk	"*Randomly and centrally allocated*". Page 590
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*Infusions of* intravenous immunoglobulins*and placebo were identical in appearance and were stored in plastic bags for concealment during administration*". Page 590 The treating physician was aware of treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*The assessing physician was unaware of treatment assignment*". Page 590
Incomplete outcome data (attrition bias) All outcomes	High risk	64 (85%) patients in the intravenous immunoglobulins group and 56 (75%) in the placebo group completed the trial
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes
Other bias	Unclear risk	Definition of sustained disability progression was not clearly reported

Fazekas 2008

Methods	RCT
Participants	Age: 15-64 years; clinical definite RRMS; mean EDSS 2.0; disease duration 1.3-1.6 years; ≥ 2 relapses in the 2 years before randomisation
Interventions	Immunoglobulins 0.2 gm/kg body weight intravenously monthly (n. 45) Immunoglobulins 0.4 gm/kg body weight intravenously monthly (n. 42) Placebo (n. 41).
Outcomes	Relapses at 12 months.
Notes	Funding: Bayer HealthCare AG.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"*The random code number was computer generated by the Statistics and Data System Department of Bayer.*" Page 266
Allocation concealment (selection bias)	Low risk	"*Randomisation performed by an unblinded pharmacist who assigned code numbers from sealed envelopes in a sequential manner*". Page 266
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clearly reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Endpoints "*assessed by an evaluating physician who was otherwise not involved in patient care*"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts: intravenous immunoglobulins 0.2 g: 7/45 (15%); intravenous immunoglobulins 0.4 g: 4/42 (9%); placebo 4/41 (10%)
Selective reporting (reporting bias)	High risk	Only relapses at 12 months were reported.
Other bias	High risk	Bayer HealthCare AG supported the study.

Ghezzi 1989

Methods	RCT
Participants	Age not reported; definite RRMS or SPMS; disease duration 5-15 years; EDSS 2.5-6.5; ≤ 1 relapses in the 2 years before randomisation

Ghezzi 1989 (*Continued*)

Interventions	Azathioprine 2.5 mg/Kg/body weight oral daily (n. 93) Placebo (n. 92)
Outcomes	Relapses 24 months. Progression at 24 months
Notes	Funding: Not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Examining neurologist blinded to treatment arm.
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up not included in the study analysis: treatment 26%; placebo 28%
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes and those outcomes that were pre-specified in the methods section
Other bias	Unclear risk	Definition of sustained disability progression not clearly reported. It is unclear if the study was sponsored

Goodkin 1991

Methods	RCT
Participants	Mean age: 30 years; definite RRMS; disease duration 5-15 years; EDSS 2.5-6.5; $\leq$ 1 relapses in the 2 years before randomisation
Interventions	Azathioprine 3.0 mg/Kg/body weight oral daily for 24 moths (n. 30) Placebo for 24 months (n. 29)
Outcomes	Relapses 12 and 24 months. Progression at 24 months
Notes	Funding: Wellcome Company

Goodkin 1991 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomised by the statistician using random number tables". Page 21
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The examining neurologist was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 (12%) people were lost to 2 years follow-up (3 azathioprine, 4 placebo)
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes
Other bias	Unclear risk	Definition of sustained disbility progression not clearly reported

Goodkin 1995

Methods	RCT
Participants	Age: 21-60 years; definite PPMS or SPMS ; disease duration >1 years; EDSS 3.0-6.5; $\leq$ 1 relapses in the 2 years before randomisation
Interventions	Methotrexate 7.5 mg oral weekly for 24 months (n. 31) Placebo for 24 months (n. 29)
Outcomes	Relapses at 12 and 24 months. Progression at 24 months
Notes	Funding: none

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"*The randomisation scheme was developed prior to the initiation of the study and was blocked in groups of 10*". Page 32

Goodkin 1995 (*Continued*)

Allocation concealment (selection bias)	High risk	"*Treatment assignments were made by the unblinded study coordinator who appeared to be not responsible for patients' recruitment*". Page 32
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not clearly reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*The examining neurologist performed all neurological examinations without reference to earlier examinations and was not permitted to talk to the patient or treating physician about the general progress of the study, clinical events, or therapy provided to any study participants*." Page 32
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up not included in the study analysis: treatment 2/31; placebo 0/29
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes and those outcomes that were pre-specified in the methods section
Other bias	High risk	"Sustained" disability progression was confirmed at ≥ 2 months of follow-up

Hartung 2002

Methods	RCT
Participants	Age: 18-65 years; definite SPMS or PRMS; mean disease duration 10 years; ≥ 1.0 EDSS n the 18 months before randomisation; no clinical relapses or treatment with steroids for at least 8 weeks before enrolment; EDSS 3.0-6.0
Interventions	Mitoxantrone 5 mg/m² body surface area intravenously every 3 months (n. 66) Mitoxantrone 12 mg/m² body surface area intravenously every 3 months (n. 63) Placebo (n. 65).
Outcomes	Relapses at 24 months. Progression at 24 months.
Notes	Funding: Wyeth-Lederle Benelux and Germany

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Randomisation by a computer-generated schedule, block size of three*". Page 2019

Hartung 2002 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*A separate treating physician was aware of treatment assignment.* " Page 2019
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*Neurologist who assessed outcome measures was unaware of treatment assignment (assessing physician).*" Page 2019
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up not included in the study analysis: treatment arms 3/63 (5%) and 2/66 (3%); placebo 1/65 (1.5%)
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes
Other bias	High risk	Wyeth-Lederle Benelux and Germany sponsored the trial and financially supported statistical analysis

Hommes 2004

Methods	RCT
Participants	Age: 18-55 years; clinical definite SPMS; progression $\geq$ 1.0 EDSS points in the 2 years before randomisation; EDSS 3.0-6.5; disease duration $\geq$ 3 years
Interventions	Immunoglobulins 1 gm/kg body weight intravenously monthly (n. 159) Placebo (n. 159).
Outcomes	Relapses at 12 and 24 months. Progression at 24 months.
Notes	Funding: Bayer Corporation.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"*The randomisation was done centrally as block randomisation with stratification by centre.*" Page 1150
Allocation concealment (selection bias)	Unclear risk	"*Concealment of treatment was guaranteed by use of an albumin solution identical in appearance to the study medication, with identical labelling and opaque plastic wrapping.*" Page 1150
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*Concealment of treatment was guaranteed by use of an albumin solution* *identical in appearance to the study medication, with identical labelling and opaque plastic wrapping...a treating neurologist or*

Hommes 2004 (*Continued*)

		a study nurse administered the study drug.. Physicians and study nurses were unaware of treatment allocation." Page 1150
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*The clinical assessment of the patients was made by an evaluating neurologist, who was not allowed to discuss therapy or adverse effects with the patients.*" Page 1150
Incomplete outcome data (attrition bias) All outcomes	Low risk	"32 patients (10%) withdrew from the study.Thus, complete data for 27 months were available for 280 (90%) patients." Page 1152
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes
Other bias	High risk	Bayer Corporation was involved in every phase of the trial. Sustained disability progression confirmed at 3 months' follow-up

IFNB MS Group 1993

Methods	RCT
Participants	Age: 18-50 years; clinical or laboratory-supported definite RRMS; EDSS $\leq$ 5.5; disease duration > 1 year; $\geq$ 2 relapses in the 2 years before randomisation; no relapses for at least 1 month before randomisation
Interventions	IFNß -1b (Betaseron) 50 μg subcutaneously every other day (n. 125) IFNß -1b (Betaseron) 250 μg subcutaneously every other day (n. 124) Placebo (n. 123).
Outcomes	Relapses at 24 months. Progression at 24 months.
Notes	Funding: Triton Biosciences, Inc., Alameda, CA and Berlex Laboratories Inc

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*One treating neurologist who knew about side effects, reviewed laboratory findings for toxicity, and was responsible for overall care*". Page S4
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoints were measured by "*One examining neurologist who was not aware of drug side effects*". Page S4

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals and losses to follow-up were difficult to find, and different data were given in different articles about the same trial. Specifically, 2 years after randomisation, withdrawals plus losses to follow-up in the treated group were described as either 18 or 20 in the 1.6 million IU interferon group and as 24 or 25 in the 8 million IU group. Patients included into analysis in the treated group were described as either 184 or 205 in the 1.6 million IU interferon group and as 244 or 255 in the 8 million IU group
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes and those outcomes that were pre-specified in the methods section
Other bias	High risk	"Sustained" disability progression was confirmed at 3 months' follow-up. The role of the study sponsor was unclear

IMPACT 2002

Methods	RCT
Participants	Age: 18-55 years; clinical definite SPMS; progression not reported; EDSS 3.5-6.5; mean disease duration 16 years
Interventions	IFNß -1a (Avonex) 60 μg intramuscular injections weekly (n. 217) Placebo (n. 219)
Outcomes	Relapses at 24 months. Progression at 24 months.
Notes	Funding: BIOGEN INC.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"*The contract research organization computer generated two minimization schemes, one for North America and one for Europe and Israel*". Page 680
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*A treating nurse and neurologist were responsible for clinical management of the subjects*". Page 680
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"T*he examining neurologist was not involved with any other aspect of subject care, and neither had access to the results of prior examinations or to clinical information that might compromise blinding*".

IMPACT 2002 (*Continued*)

		Page 680
Incomplete outcome data (attrition bias) All outcomes	High risk	*"Twenty-three (11%) subjects in the placebo group and 29 (13%) subjects in the IFN-1a group failed to complete 24 months of follow-up. The between-group difference in reason for study discontinuation was subject request (six placebo subjects vs 16 IFN-1a subjects, $p < 0.05$)"* Page 682
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes
Other bias	High risk	Sustained disability progression confirmed at 3 months' follow-up. Unclear the role of Biogen Inc. The FDA letters of July 23, 1998, December 6, 1999, and March 8, 2000 informed Biogen that the primary study endpoint, the Multiple Sclerosis Functional Composite (MSFC), is not a validated efficacy outcome measure and therefore is not appropriate as a primary efficacy endpoint in this Phase 3 study (FDA 2001)

INCOMIN 2002

Methods	RCT
Participants	Age: 18-50 years; clinical definite RRMS; mean disease duration 6 years; EDSS 1.0-3.5; $\geq$ 2 relapses in the 2 years before randomisation; in remission at randomisation
Interventions	IFNß -1b 250 μg subcutaneously every other day for 24 months (n. 96) IFNß -1a (Avonex) 30 μg by weekly intramuscular injections for 24 months (n. 92)
Outcomes	Relapses at 12 and 24 months. Progression at 24 months
Notes	Funding: The Italian Ministry of Health and the Italian MS Society

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Randomisation followed computer-generated random sequences of digits that were different for each centre and for each sex, to achieve centre and sex stratification*". Page 1454
Allocation concealment (selection bias)	Low risk	"*The codes were randomly assigned to treatments by an independent team of statisticians unaware of the patient's clinical characteristics*". Page 1454
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*All clinical outcomes were assessed in an open-label manner*". Page 1454

Blinding of outcome assessment (detection bias) All outcomes	High risk	"*All clinical outcomes were assessed in an open-label manner*". Page 1454
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up not included in analysis: IFNß -1a 4/92 (4%); IFNß -1b 2/96 (2%)
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes
Other bias	Low risk	The study appears to be free of other sources of bias.

Johnson 1995

Methods	RCT
Participants	Age: 18-45 years; clinical or laboratory-supported definite RRMS; EDSS 0-5.0; ≥ 2 relapses in the 2 years before randomisation
Interventions	Glatiramer acetate 20 mg subcutaneously every day (n. 125). Placebo (n. 126)
Outcomes	Relapses at 24 months. Progression at 24 months.
Notes	Funding: Teva Pharmaceutical.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	"*A centralized randomization scheme was used*". Page 1270
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*Treating neurologists were blinded*". Page 1270
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*Examining neurologists were blinded*". Page 1270
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals: glatiramer acetate = 19 (15%); placebo = 17 (13%) .They were included in the analyses
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes

Johnson 1995 (*Continued*)

Other bias	High risk	"Sustained" disability progression confirmed at 3 months' follow-up

Knobler 1993

Methods	RCT
Participants	Age: 18-50 years; clinical definite RRMS; EDSS $\leq$ 5.5; disease duration $\geq$ 1 and $\leq$ 15 years; $\geq$ 2 relapses in the 2 years before randomisation; in remission at randomisation
Interventions	IFNß -1b 25 μg subcutaneous three times weekly for three years (n. 6) IFNß -1b 125 μg subcutaneous three times weekly for three years (n. 6) IFNß -1b 250 μg subcutaneous three times weekly for three years (n. 6) IFNß -1b 500 μg subcutaneous three times weekly for three years (n. 6) Placebo for three years (n. 7)
Outcomes	Relapses at 12 months
Notes	Funding: Triton Biosciences, Inc., Alameda, CA and Berlex Laboratories Inc

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	"One treating neurologist not blinded". Page 335
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"An examining neurologist blinded to treatment arms". Page 335
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals and losses to follow-up not described
Selective reporting (reporting bias)	High risk	Progression was not reported.
Other bias	Unclear risk	The role of the study sponsor was unclear.

Koch-Henriksen 2006

Methods	RCT
Participants	Age: 18-55 years; clinical definite RRMS; disease duration 0-35; ≥ 2 relapses within 2 years before randomisation; EDSS ≤ 5.5
Interventions	IFNß -1b 250 μg subcutaneous every other day for 24 months. (n. 158) IFNß -1a (Rebif) 22 μg subcutaneous weekly for 24 months (n. 143)
Outcomes	Progression at 24 months
Notes	Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	"*A central computerized randomization schedule assigned patients to treatment*". Page 1057
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label trial. "*Blinding was abandoned because it could not be maintained owing to the different administration schemes of the two study drugs*". Page 1057
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label trial. Page 1057
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up not included in analysis: IFNß -1b 28%; IFNß -1a 23%
Selective reporting (reporting bias)	High risk	Relapses were not reported.
Other bias	High risk	Sustained disability progression confirmed at 3 months' follow-up. Is is unclear if the study was sponsored

Leary 2003

Methods	RCT
Participants	Age: 25-59 years; definite PPMS; disease duration 2-21 years; EDSS 2.0-7.0
Interventions	IFNß-1a (Avonex) 30 μg intramuscular weekly for 24 months (n. 15) IFNß-1a (Avonex) 60 μg intramuscular weekly for 24 months (n. 15) Placebo for 24 months (n. 20)

Leary 2003 (*Continued*)

Outcomes	Progression at 24 months	
Notes	Funding: BIOGEN	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"*The randomization was carried out off-site by Biogen using a randomization block method*."Page 44
Allocation concealment (selection bias)	Low risk	"*The study drug was blinded off-site by Biogen and delivered to the study centre with the study numbers already allocated. Subjects were allocated by study number consecutively as they were entered into the study. A copy of the randomization codes was kept in pharmacy and by Biogen, but no codes were broken until the study and analysis was completed*".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*All personnel at the study site (dispensing pharmacists, treating physicians and EDSS physicians) were blinded to the study drug*." Page 44
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*EDSS and clinical assessments were performed by an independent evaluating physician blinded to all clinical information*." Page 44
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one patient (arm IFN 60µg) was lost to follow-up.
Selective reporting (reporting bias)	High risk	Relapses were not reported.
Other bias	High risk	"Sustained" disability progression was confirmed at 3 months' follow-up. Funding: Biogen, Multiple Sclerosis Society of Great Britain and Northern Ireland

Lewanska 2002

Methods	RCT
Participants	Age: 18-55 years; clinical definite RRMS; EDSS 0-6.5; mean disease duration >2 years; $\geq$ 2 relapses in the 2 years before randomisation
Interventions	Intravenous immunoglobulins 0.2 g/kg/body weight intravenous monthly for 12 months.(n. 17) Intravenous immunoglobulins 0.4 g/kg/body weight intravenous monthly for 12 months (n. 16) Placebo (saline) for 12 months (n. 18)

Lewanska 2002 (*Continued*)

Outcomes	Relapses at 12 months
Notes	Funding: Supported by the KBN (State Research Committee)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*The generation of allocation sequence was based on random-number table*." Page 566
Allocation concealment (selection bias)	Unclear risk	Infusions of intravenous immunoglobulins and placebo were stored in identical opaque plastic bags for concealment during administration. No more information about treatment allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*Infusions of* intravenous immunoglobulins*and placebo were stored in identical opaque plastic bags for concealment*." Page 566
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*Evaluating physician was unaware of the actual treatment allocation...Monitoring and recording of relapses, concomitant treatment, side-effects or other medical events were documented throughout the study."* Page 566
Incomplete outcome data (attrition bias) All outcomes	Low risk	49 patients completed the trial: 15/16 in the intravenous immunoglobulins 0.4 g/kg arm; 17/17 in the intravenous immunoglobulins 0.2 g/kg arm; 17/18 in the placebo arm
Selective reporting (reporting bias)	High risk	Progression was not reported.
Other bias	High risk	Sustained disability progression confirmed at 3 months' follow-up. Supported by the KBN (State Research Committee).

Likosky 1991

Methods	RCT
Participants	Age: 18-60 years; SPMS, PPMS or PRMS; progression $\geq$ 1.0 EDSS in the year before randomisation; disease duration 1-29 years; EDSS 2.0-7.0
Interventions	"*short course*" of cyclophosphamide 500 mg administered intravenously five days per week; (n. 22) Folic acid (1 mg) administered intravenously five days per week (n. 21)
Outcomes	Progression at 24 months

Likosky 1991 (*Continued*)

Notes	Funding: The Community Service Program of Kaiser Foundation Hospitals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*Evaluating physicians were unaware of the treatment status of the patients they evaluated*". Page 1056
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up not included in the study analysis: treatment 3/22 (15%); placebo 3/21 (14%). Losses appear to be balanced between the groups
Selective reporting (reporting bias)	Low risk	The published report included expected efficacy outcome.
Other bias	Unclear risk	Definition of sustained disability progression not clearly reported *"The research was supported in part by the Community Service Program of Kaiser Foundation Hospitals. Evansville, Indiana, provided cyclophosphamide as Cytoxan."* Page 1060

Milanese 1993

Methods	RCT
Participants	Mean age: 30 years; definite RRMS, SPMS or PPMS; disease duration 5-15 years; EDSS 2.5-6.5; $\leq$ 1 relapses in the 2 years before randomisation
Interventions	Azathioprine 2.5 mg/Kg/body weight oral daily for 3 years (n. 19) Placebo (lactose) in identical form (50 mg tablets) for three years (n. 21)
Outcomes	Relapses at 12, 24 and 36 months. Progression at 24 and 36 months
Notes	Funding: Wellcome Company.

Risk of bias

Milanese 1993 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"*Wellcome Italia provided the randomisation code*". Page 295
Allocation concealment (selection bias)	Unclear risk	"*Patients were allocated to* azathioprine*or placebo groups according to a list of random code numbers*". Page 295
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"azathioprine*and placebo tablets in identical form were supplied by Wellcome Company*". Page 295
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*EDSS and relapses evaluated by the same blinded neurologist*". Page 295
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up not included in the study analysis: azathioprine 26%; placebo 14%
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes
Other bias	High risk	Sustained disability progression confirmed at 3 months' follow-up. Funding: Wellcome Company

Millefiorini 1997

Methods	RCT
Participants	Age: 18-45 years; clinical or laboratory-supported definite RRMS; disease duration 1-10 years; EDSS 2.0-5.0; $\geq$ 1 relapses in the 2 years before randomisation
Interventions	12 pulses of mitoxantrone 8 mg/m²/body surface every month for 1 year (total dosage of 96 mg/m^2 of body surface over 1 year) (n. 27) Placebo (n. 24)
Outcomes	Relapses at 12 and 24 months, Progression at 24 months
Notes	Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described

Millefiorini 1997 (*Continued*)

Allocation concealment (selection bias)	Low risk	"*Central allocation and the intravenous bag and tubing were black to ensure no differences between the treatment groups.*" Page 154.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treating physicians were not blinded. Unclear blinding of patients
Blinding of outcome assessment (detection bias) All outcomes	High risk	"*The interaction of the EDSS physicians with the patient was strictly restricted to the neurological examination. The neurologist was not allowed to talk with the patient about adverse events, or any other issue which could potentially disclose the patient's treatment...The assessment of exacerbations was monitored by treating physicians not blinded to study treatment.*" Page 154, 157
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients were included in the analysis.
Selective reporting (reporting bias)	Low risk	The published reports included all expected efficacy outcomes
Other bias	High risk	Sustained disability progression confirmed at 3 months' follow-up. It's unclear if this study was sponsored

Miller 1961

Methods	RCT
Participants	Mean age: 33 years; SPMS, or PRMS; mean disease duration 10-13 years; EDSS not reported
Interventions	Prednisolone tablets 15 mg oral daily for 8 months then 10 mg/day for 10 months (n. 29) Calcium aspirin 9 tablets (54 g) oral daily (n. 27) Placebo corresponding number of "dummy" tablets (n. 30)
Outcomes	Progression at 24 months
Notes	No funding.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Miller 1961 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clearly described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up: prednisolone 3/29 (10%); "dummy" tablets 1/30 (3%); calcium aspirin 3/27 (11%)
Selective reporting (reporting bias)	Low risk	The published report included the expected efficacy outcome.
Other bias	Unclear risk	Definition of sustained disability progression not clearly reported

Montalban 2009

Methods	RCT
Participants	Age: 18-65 years; definite PPMS or "transitional" MS; mean disease duration 11 years; EDSS 3.0-7.0
Interventions	IFNß -1b 250 μg subcutaneously every other day for 2 years (n. 36) Placebo for 2 years (n. 37)
Outcomes	Progression at 24 months
Notes	Funding: SCHERING ESPANA S.A

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*...Using a randomisation list. This randomization was performed in blocks of 6 and for each treatment was assigned in a 1:1 ratio*". Page 1196
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*All personnel at the study site (dispensing pharmacists, treating physicians and participants) were blinded to the outcome assessment and study drug.*" Page 1197
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*EDSS physicians were blinded to the outcome assessment and study drug.*" Page 1197

Incomplete outcome data (attrition bias) All outcomes	Low risk	3 patients dropped out the study: 1 in the IFNß -1b arm; 2 in the placebo arm
Selective reporting (reporting bias)	Low risk	The published report included the expected efficacy outcome.
Other bias	High risk	"*An external company (MDS Pharma Services Espana) named and funded by the study sponsor produced the statistical analyses under supervision from the principal investigator*".

MSCRG 1996

Methods	RCT
Participants	Age: 18-55 years; definite RRMS; EDSS 1-3.5; disease duration $\geq$ 1 year; $\geq$ 2 relapses in the 3 years before randomisation; no relapses for at least 2 months before randomisation
Interventions	IFNß-1a (Avonex) 30 μg intramuscular weekly (n. 158). Placebo (n. 143).
Outcomes	Relapses at 12 and 24 months. Progression at 24 months.
Notes	Funding: Biogen, Inc, Cambridge, MA

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"*Randomisation performed at statistical centre of Buffalo General Hospital, one of the participating centres (biased coin assignment used for sequence generation*". Page 286
Allocation concealment (selection bias)	Unclear risk	"*schedule sent to each clinical centre, included patients were sequentially assigned the next ID number from the schedule."* Page 286
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*Personnel and participants were blinded to treatment status.*" Page 286
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*Evaluating physicians were blinded to treatment status*." Page 286
Incomplete outcome data (attrition bias) All outcomes	High risk	The study stopped early for benefit without a formal-stopping rule. 73 (46%) of 158 patients in the treatment group and 56 (39%) of 143 controls had not completed the scheduled 2 years of follow-up. At 2 years' follow-up primary outcomes were available for only 57% of randomised participants

MSCRG 1996 (*Continued*)

Selective reporting (reporting bias)	Low risk	Expected efficacy outcomes were reported.
Other bias	High risk	*"Supported by National Institutes of Health, National Institute of Neurological Disorders and Stroke (NINDS) and Biogen, Inc, Cambridge, MA. Personnel of the study sponsor (Biogen) were involved in the conduct and data analysis".* Page 293

NASP 2004

Methods	RCT
Participants	Age 18-65 years, clinically definite SPMS of at least 2 years' duration; ≥ 1.0 EDSS increase in the 2 years before randomisation; ≥ 1.0 relapses followed by progressive deterioration sustained for at least 6 months; EDSS 3.0-6.5
Interventions	IFNß -1b (Betaseron) 250 μg subcutaneously every other day (n. 317) INFß -1b (Betaseron) 160 μg/m² body surface area (mean administered dose 220 μg) every other day (n. 314) Placebo (n. 308)
Outcomes	Relapses at 36 months. Progression at 36 months.
Notes	Funding: Berlex Laboratories (Richmond, CA)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*The randomisation schedule was generated by the Biostatistics and Data Management Group of Berlex Laboratories (Richmond, CA) using an SAS program (Cary, NC)... Each block allocated 2 subjects to fixed-dose Betaseron, 2 to Body Surface Area (BSA)-adjusted Betaseron, 1 to fixed placebo, and 1 to BSA-adjusted placebo. Each site received an adequate number of blocks, based on projected subject recruitment, to ensure sequential subject numbering within each site*." Page 1789
Allocation concealment (selection bias)	Low risk	"*The biostatistician and supporting programmers were the only individuals with access to the randomisation codes" (FDA page 9). "The active study drug was indistinguishable from placebo in appearance, smell and color, and labels and packages for active study agent and placebo were indistinguishable*" (FDA page 9)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*All sponsor personnel directly involved in the conduct of the study, investigators, and subjects remained blinded to subject treatment assignment throughout the study*". (FDA page 9)

NASP 2004 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*Investigators remained blinded to subject treatment assignment throughout the study*". (FDA page 9)
Incomplete outcome data (attrition bias) All outcomes	High risk	*"The study had ended prematurely based on the results of a planned interim analysis indicating that "continuing the trial was unlikely to change the results". The study initiated in August 2, 1995, interrupted November 22, 1999. The last patient enrolled on April 1, 1997. The final patient visit occurred on November 15, 1999".* (FDA report page 21). "*Only 72% of randomised patients completed 33 months or more on study and could be included in analysis*" (FDA 2001 page 26).
Selective reporting (reporting bias)	Unclear risk	The published reports included relapses and progression at 36 months (no data at 24 months)
Other bias	High risk	Funding: Berlex Laboratories (Richmond, CA).

OWIMS 1999

Methods	RCT
Participants	Age: 18-50 years; clinical or laboratory-supported definite RRMS; EDSS 0-5.0; disease duration $\geq$ 1 year; $\geq$ 1 relapses in the 2 years before randomisation; no relapses for at least 2 months before randomisation
Interventions	IFNß -1a (Rebif) 22 μg subcutaneous three times/week for 48 weeks (n. 95) IFNß -1a (Rebif) 44 μg subcutaneous three times/week for 48 weeks (n. 98) Placebo (human albumin and mannitol) for 48 weeks (n. 100)
Outcomes	Relapses at 12 months
Notes	Funding: Ares-Serono International SA, Geneva, Switzerland

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Randomisation performed at Corporate Biometrics Department of Ares-Serono (computer-generated list).*" Page 680
Allocation concealment (selection bias)	Unclear risk	"*Sealed envelopes were used but it was unclear whether envelopes were sequentailly numbered and opaque.*" Page 680
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*Participants were blinded to treatment*" Page 681

OWIMS 1999 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*The evaluating physician was responsible for neurologic assessments and remained unaware of adverse event profiles and any changes in safety assessments.*" Page 681
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up: treatment arms 13% and 8%; placebo arm 3%. Reason for missing data was likely related to outcome with imbalance in numbers across intervention groups
Selective reporting (reporting bias)	High risk	Only relapses at 12 months were reported.
Other bias	High risk	Sponsored by Ares-Serono International SA, Geneva, Switzerland

Pohlau 2007

Methods	
Participants	Age: 18-65 years; SPMS, or PPMS; progression $\geq$ 0.5 EDSS point in the year before randomisation; disease duration > 2 years; EDSS 3.0-7.0
Interventions	IVIg 0.4 gm/kg body weight intravenous monthly (n. 116). Placebo (n. 115).
Outcomes	Progression at 24 months.
Notes	Fundings: Novartis Pharma GmbH and ZLB Behring.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Randomisation was performed by the Biometric Department Novartis Germany using a scheme, which provided balanced blocks of patient numbers for both treatment groups and the two diagnostic layers.*" Page 1109
Allocation concealment (selection bias)	Unclear risk	Not clearly described. Only "*randomly assigned*" Page 1109
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clearly described. Only "intravenous immunoglobulins*and placebo could not visually be distinguished.*" Page 1109
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"*113 patients (49%) completed the 112 weeks of the study, and 118 (51%) discontinued their participation prematurely.*" Page 1110 . Follow-up of the participants who discontinued participation was not reported
Selective reporting (reporting bias)	Low risk	Progression at 24 months is the expected efficacy outcome.
Other bias	High risk	Sustained disability progression confirmed at 16 weeks' follow-up. Supported by Novartis Pharma GmbH, Nürnberg, Germany and ZLB Behring, Bern Switzerland

PRISMS 1998

Methods	RCT
Participants	Age: 28-41 years; clinical or laboratory-supported definite RRMS; EDSS 0-5.0; disease duration $\geq$ 1 year; at least 2 relapses in the 2 years before randomisation
Interventions	IFNß -1a (Rebif) 22 μg subcutaneous three times/week for 2 years (n. 189) IFNß -1a (Rebif) 44 μg subcutaneous three times/week for 2 years (n. 184) Placebo (unspecified) for 2 years (n. 187)
Outcomes	Relapses at 12 and 24 months. Progression at 24 months
Notes	Fundng: Ares-Serono International SA, Geneva, Switzerland

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Randomisation at Corporate Biometrics Department of Ares-Serono (computer-generated list, stratified by centre, equal allocation of the treatment groups by a block size of 6).*" Page 1499
Allocation concealment (selection bias)	Low risk	"*The study drug was packed accordingly to the randomisation list and delivered to the centres so that treatment allocation remained concealed*". Page 1499
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*All personnel involved in the study were unaware of treatment allocation*". Page 1499
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*All personnel involved in the study were unaware of treatment allocation. All injection sites were covered up at neurological examinations to ensure that masking was not compromised because of local reactions*". Page 1499

PRISMS 1998 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up excluded from study analysis: treatment arms 6% and 3%; placebo arm 5%
Selective reporting (reporting bias)	Low risk	The published report included all expected efficacy outcomes
Other bias	High risk	"Sustained" disability progression was confirmed at 3 months' follow-up. Ares-Serono was involved in the trial

REGARD 2008

Methods	RCT
Participants	Mean age: 37 years; clinical or laboratory-supported definite RRMS; EDSS 0-5.5; mean disease duration 6 years; ≥ 1 relapses in the year before randomisation
Interventions	IFNß -1a (Rebif) 44 μg subcutaneous three times/week for 96 weeks (n. 386) Glatiramer acetate 20 mg subcutaneous every day for 96 weeks (n. 378)
Outcomes	Relapses at 24 months. Progression at 24 months
Notes	Funding: EMD Serono and Pfizer

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Computer-generated randomisation list stratified by centre*". Page 904
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	"*Neither the patients nor the treating physicians were blinded to treatment*." Page 904
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*The physicians who assessed patients ...were blinded to treatment and communicated with the patients only as needed to complete the EDSS, Kurtzke functional scale (KFS), and relapse assessments. Patients were asked not to discuss their treatment with the assessing physician and they covered their injection sites*." Page 904
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: IFNß -1a 20/386 (5%); glatiramer acetate 5/378 (1%)
Selective reporting (reporting bias)	Low risk	The published report included all expected efficacy outcomes

REGARD 2008 (*Continued*)

Other bias	High risk	"The study protocol was drafted and developed by the study sponsors, EMD Serono and Pfi zer, in conjunction with the investigator steering committee. Data management and analysis were done by the study sponsors." Page 907

SENTINEL 2006

Methods	RCT
Participants	Age: 18-55 years; clinical definite RRMS; disease duration 1-34 years; EDSS 0-5.0; ≥ 1 relapses in the year before randomisation
Interventions	Natalizumab 300 mg intravenous monthly and IFNß-1a (Avonex) 30 μg intramuscular weekly for 116 weeks.(n. 589) Placebo and IFNß-1a (Avonex) 30 μg intramuscular weekly for 116 weeks.(n. 582)
Outcomes	Relapses at 12 and 24 months. Progression at 24 months
Notes	Funding: Biogen Idec, Inc. and Elan Pharmaceutical

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Randomization was stratified according to study site in blocks of four (two active and two placebo) with the use of a computer-generated schedule and a multidigit identification number*". Page 912
Allocation concealment (selection bias)	Low risk	"*An interactive voice-response system was used*". Page 912
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"*All study personnel, patients, sponsor personnel involved in the conduct of the study, and members of the investigator advisory committee were blinded to the treatment assignments throughout the study.*" Page 912 "*The treating neurologists were responsible for all patient care, including the management of adverse events and relapses of multiple sclerosis*". Page 913
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"*Examining neurologists performed the EDSS and neurologic examinations but were otherwise not involved in the patients' medical care.*" Page 913
Incomplete outcome data (attrition bias) All outcomes	Low risk	516/589 (88%) in the natalizumab + IFNß-1a group and 487/582 (84%) in the placebo+ IFNß-1a group completed the 120-week study
Selective reporting (reporting bias)	Low risk	The published report included all expected efficacy outcomes

SENTINEL 2006 (*Continued*)

Other bias	High risk	Sustained disability progression confirmed at 3 months' follow-up The study protocol was developed by the investigator advisory committee and the sponsors (Biogen Idec and Elan Pharmaceuticals). Data were analyzed by the sponsor. Relapses were assessed also as adverse events

SPECTRIMS 2001

Methods	RCT
Participants	Age: 18-55 years; clinical definite SPMS; progression $\geq$ 1 EDSS over the previous 2 years, with or without superimposed relapses before randomisation; EDSS 3.0-6.5; mean disease duration 14 years
Interventions	IFNß -1a (Rebif) 22 μg subcutaneous three times/week for 3 years (n. 209) IFNß -1a (Rebif) 44 μg subcutaneous three times/week for 3 years (n. 204) Placebo (unspecified) for 3 years (n. 205)
Outcomes	Progression at 24 and 36 months
Notes	Funding: Serono International, Geneva, Switzerland

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"*Computer generated randomisation list provided by Serono, stratified by center; treatments were equally allocated with a block size of six*". Page 1497
Allocation concealment (selection bias)	Unclear risk	*"The block size was not revealed to the investigators.* T*he manufacturer labelled containers of study medication with patient identification numbers based on the randomisation list, and patients received the medication labelled with their numbers.*" Page 1497
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*A treating physician supervised drug administration, monitored safety, and managed adverse events*". Page 1497
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"*A separate evaluating physician conducted neurologic assessments and followed-up exacerbations. Patients were instructed to cover injection sites and to discuss only neurologic matters during neurologic evaluations. Clinical and neurologic data were recorded in separate binders.*" Page 1497

SPECTRIMS 2001 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	195/209 (93%) in the IFNß -1a 22 μg group, 190/204 (93%) in the IFNß -1a 44 μg group and 186/205 (91%) in the placebo group completed 3 years' follow-up
Selective reporting (reporting bias)	Low risk	The published report included all expected efficacy outcomes
Other bias	High risk	Sustained disability progression confirmed at 3 months' follow-up. Serono Biometrics (Geneva) performed statistical analysis

Wolinsky 2007

Methods	RCT
Participants	Age: 30-65 years; definite chronic progressive MS; EDSS 3.0-6.5; progression $\geq$ 6 months; $\leq$ 2 relapses in the 2 years before randomisation
Interventions	Glatiramer acetate 20 mg subcutaneous every day for 3 years (n. 627) Placebo (unspecified) for 3 years (n. 316)
Outcomes	Progression at 24 months
Notes	Funding: Teva Pharmaceutical

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"*All patients were attended by a treating neurologist and an examining neurologist who were blinded to treatment. The treating neurologist supervised drug administration, recorded and treated adverse events, and coordinated MRI testing*." Page 16
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"... examining neurologist was blinded to treatment." Page 16
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study stopped early for futility. 376/627 (60%) of participants in the glatiramer acetate group and 186/315 (59%) in the placebo group had received study drugs for 24 months. Insufficient information to judge whether withdrawals and lost to follow-up were included in data analysis

Selective reporting (reporting bias)	Unclear risk	Progression at 24 months was reported.
Other bias	High risk	Sustained disability progression confirmed at 3 months' follow-up. Funding: Teva Pharmaceutical

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arnason 1999	Study on TNF neutralization (Lenercept).
Barkhof 2003	ETOMS trial MRI subgroup analysis.
Baum 2006	Study evaluating two formulations of interferon b (IFNbeta-1b-G or the refrigeration-free formulation (IFNbeta-1b-M) without a control group
BENEFIT 2006	Study on interferon beta 1b for clinically isolated syndromes (CIS)
Boiko 2001	Trial on short course of antibodies to IFN gamma or antibodies to tumour necrosis factor alpha
Burton 2009	A Cochrane review on oral versus Intravenous steroids for treatment of relapses in multiple sclerosis
CHAMPS 2000	Study on interferon beta 1a for clinically isolated syndromes (CIS)
Christodoulou 2006	Study on donepezil.
Clanet 2002	A dose-comparison study of interferon beta-1a without a control group
Durelli 1994	Study on interferon alfa for multiple sclerosis.
ETOMS 2001	Study on interferon beta 1a for clinically isolated syndromes (CIS)
Fernandez 2002	Prospective study evaluating combination therapy with interferon beta 1b and azathioprine in MS
Filippi 2004	ETOMS trial MRI subgroup analysis.
Filippi 2006	Study on oral glatiramer acetate for multiple sclerosis.
GLANCE 2009	Active treatment with natalizumab was confounded by glatiramer acetate
Goodkin 2000	Study on complex of human leukocyte antigen-DR2 with myelin basic protein84-102
Hauser 1983	Active treatment with cyclophosphamide was confounded by other treatments

(*Continued*)

Hoogervorst 2002	A phase II study evaluating the safety, tolerability and MRI effects of oral interferon beta-1a
Labetouelle 2001	Review about CHAMPS study.
Liu 2010	A Cochrane review on daclizumab for multiple sclerosis.
Myhr 1999	Study on interferon alfa for multiple sclerosis.
Patti 1999	Study on natural interferon beta derived from human fibroblasts (Ares-Serono@)
Rio 2007	Open label, non-randomised, observational study.
Skurkovich 2001	A trial comparing antibodies to TNF-a, to IFN-γ and placebo.
Steultjens 2003	A Cochrane review on occupational therapy for multiple sclerosis
Tejani 2010	A Cochrane review on carnitine for fatigue in multiple sclerosis
Tubridy 1999	Study on natalizumab with a dosage of 3 mg/kg.
Van de Wyngaert 2001	Study on mitoxantrone in which participants' inclusion criteria were not described
Wender 1988	Active treatment with cyclophosphamide was confounded by other treatments
Zavalishin 2003	Multicentre non-randomised study evaluating the effect of interferon alfa
Zivadinov 2001	A dose-comparison trial of long-term corticosteroids without a control group

DATA AND ANALYSES

Comparison 1. Comparisons for relapse over 12 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse over 12 months in MS of all types	21		Odds Ratio (IV, Random, 95% CI)	Subtotals only
1.1 IFNß-1b (Betaseron) versus placebo	1	25	Odds Ratio (IV, Random, 95% CI)	0.6 [0.10, 3.49]
1.2 IFNß-1a (Avonex) versus placebo	1	301	Odds Ratio (IV, Random, 95% CI)	0.72 [0.45, 1.14]
1.3 IFNß-1a (Rebif) versus placebo	2	853	Odds Ratio (IV, Random, 95% CI)	0.66 [0.25, 1.78]
1.4 Glatiramer acetate versus placebo	2	289	Odds Ratio (IV, Random, 95% CI)	0.34 [0.06, 2.05]
1.5 Natalizumab versus placebo	1	942	Odds Ratio (IV, Random, 95% CI)	0.38 [0.28, 0.51]
1.6 Mitoxantrone versus placebo	1	51	Odds Ratio (IV, Random, 95% CI)	0.14 [0.04, 0.48]
1.7 Azathioprine versus placebo	4	547	Odds Ratio (IV, Random, 95% CI)	0.63 [0.44, 0.89]
1.8 Immunoglobulins versus placebo	4	537	Odds Ratio (IV, Random, 95% CI)	0.56 [0.20, 1.60]
1.9 Corticosteroids versus placebo	1	36	Odds Ratio (IV, Random, 95% CI)	0.46 [0.12, 1.84]
1.10 IFNß-1a (Avonex) versus IFNß-1b (Betaseron)	1	188	Odds Ratio (IV, Random, 95% CI)	1.53 [0.86, 2.72]
1.11 IFNß-1a (Rebif) versus IFNß-1a (Avonex)	1	677	Odds Ratio (IV, Random, 95% CI)	0.79 [0.58, 1.07]
1.12 Natalizumab versus IFNß-1a (Avonex)	1	1171	Odds Ratio (IV, Random, 95% CI)	0.40 [0.32, 0.51]
1.13 Corticosteroids versus Mitoxantrone	1	42	Odds Ratio (IV, Random, 95% CI)	4.0 [1.11, 14.43]
2 Relapse over 12 months in relapsing-remitting MS	16	4806	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.49, 0.62]
2.1 IFNß-1b (Betaseron) versus placebo	1	25	Odds Ratio (M-H, Fixed, 95% CI)	0.6 [0.10, 3.49]
2.2 IFNß-1a (Avonex) versus placebo	1	301	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.45, 1.14]
2.3 IFNß-1a (Rebif) versus placebo	2	853	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.43, 0.81]
2.4 Glatiramer acetate versus placebo	2	289	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.37, 0.93]
2.5 Natalizumab versus placebo	1	942	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.28, 0.51]
2.6 Mitoxantrone versus placebo	1	51	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.04, 0.48]

2.7 Azathioprine versus placebo	1	54	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.25, 2.38]
2.8 Immunoglobulins versus placebo	3	219	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.38, 1.21]
2.9 Corticosteroids versus placebo	1	36	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.12, 1.84]
2.10 IFNß-1a (Avonex) versus IFNß-1b (Betaseron)	1	188	Odds Ratio (M-H, Fixed, 95% CI)	1.53 [0.86, 2.72]
2.11 IFNß-1a (Rebif) versus IFNß-1a (Avonex)	1	677	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.58, 1.07]
2.12 Natalizumab versus IFNß-1a (Avonex)	1	1171	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.32, 0.51]
3 Relapse over 12 months in progressive MS	3	459	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.70, 1.54]
3.1 Azathioprine versus placebo	1	99	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.16, 1.12]
3.2 Immunoglobulins versus placebo	1	318	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.66, 1.68]
3.3 Corticosteroids versus Mitoxantrone	1	42	Odds Ratio (M-H, Fixed, 95% CI)	4.0 [1.11, 14.43]

Comparison 2. Comparisons for relapse over 24 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse over 24 months in MS of all types	25		Odds Ratio (IV, Random, 95% CI)	Subtotals only
1.1 IFNß-1b (Betaseron) versus placebo	1	372	Odds Ratio (IV, Random, 95% CI)	0.55 [0.31, 0.99]
1.2 IFNß-1a (Avonex) versus placebo	2	737	Odds Ratio (IV, Random, 95% CI)	0.76 [0.56, 1.05]
1.3 IFNß-1a (Rebif) versus placebo	1	560	Odds Ratio (IV, Random, 95% CI)	0.45 [0.28, 0.71]
1.4 Glatiramer acetate versus placebo	2	301	Odds Ratio (IV, Random, 95% CI)	0.49 [0.18, 1.36]
1.5 Natalizumab versus placebo	1	942	Odds Ratio (IV, Random, 95% CI)	0.32 [0.24, 0.43]
1.6 Mitoxantrone versus placebo	2	245	Odds Ratio (IV, Random, 95% CI)	0.35 [0.09, 1.42]
1.7 Azathioprine versus placebo	5	737	Odds Ratio (IV, Random, 95% CI)	0.64 [0.44, 0.94]
1.8 Immunoglobulins versus placebo	4	705	Odds Ratio (IV, Random, 95% CI)	0.70 [0.40, 1.22]
1.9 Corticosteroids versus placebo	1	36	Odds Ratio (IV, Random, 95% CI)	1.13 [0.06, 19.50]
1.10 Methotrexate versus placebo	1	60	Odds Ratio (IV, Random, 95% CI)	1.15 [0.31, 4.28]

1.11 IFNß-1a (Avonex) versus IFNß-1b (Betaseron)	2	248	Odds Ratio (IV, Random, 95% CI)	2.26 [1.33, 3.83]
1.12 IFNß-1a (Rebif) versus IFNß-1a (Avonex)	1	60	Odds Ratio (IV, Random, 95% CI)	0.19 [0.06, 0.60]
1.13 Natalizumab versus IFNß-1a (Avonex)	1	1171	Odds Ratio (IV, Random, 95% CI)	0.28 [0.22, 0.36]
1.14 IFNß-1a (Rebif) versus Interferon beta 1b	1	60	Odds Ratio (IV, Random, 95% CI)	0.58 [0.21, 1.62]
1.15 Glatiramer acetate versus IFNß-1b (Betaseron)	1	2244	Odds Ratio (IV, Random, 95% CI)	1.05 [0.85, 1.29]
1.16 Glatiramer acetate versus IFNß-1a (Rebif)	1	764	Odds Ratio (IV, Random, 95% CI)	0.93 [0.69, 1.25]
2 Relapse over 24 months in relapsing-remitting MS	16		Odds Ratio (IV, Random, 95% CI)	Subtotals only
2.1 IFNß-1b (Betaseron) versus placebo	1	372	Odds Ratio (IV, Random, 95% CI)	0.55 [0.31, 0.99]
2.2 IFNß-1a (Avonex) versus placebo	1	301	Odds Ratio (IV, Random, 95% CI)	0.83 [0.46, 1.49]
2.3 IFNß-1a (Rebif) versus placebo	1	560	Odds Ratio (IV, Random, 95% CI)	0.45 [0.28, 0.71]
2.4 Glatiramer acetate versus placebo	2	301	Odds Ratio (IV, Random, 95% CI)	0.49 [0.18, 1.36]
2.5 Natalizumab versus placebo	1	942	Odds Ratio (IV, Random, 95% CI)	0.32 [0.24, 0.43]
2.6 Mitoxantrone versus placebo	1	51	Odds Ratio (IV, Random, 95% CI)	0.15 [0.04, 0.54]
2.7 Azathioprine versus placebo	1	59	Odds Ratio (IV, Random, 95% CI)	0.36 [0.11, 1.21]
2.8 Immunoglobulins versus placebo	2	190	Odds Ratio (IV, Random, 95% CI)	0.22 [0.03, 1.90]
2.9 Corticosteroids versus placebo	1	36	Odds Ratio (IV, Random, 95% CI)	1.13 [0.06, 19.50]
2.10 IFNß-1a (Avonex) versus IFNß-1b (Betaseron)	2	248	Odds Ratio (IV, Random, 95% CI)	2.26 [1.33, 3.83]
2.11 IFNß-1a (Rebif) versus IFNß-1a (Avonex)	1	60	Odds Ratio (IV, Random, 95% CI)	0.19 [0.06, 0.60]
2.12 Natalizumab versus IFNß-1a (Avonex)	1	1171	Odds Ratio (IV, Random, 95% CI)	0.28 [0.22, 0.36]
2.13 IFNß-1a (Rebif) versus IFNß-1b (Betaseron)	1	60	Odds Ratio (IV, Random, 95% CI)	0.58 [0.21, 1.62]
2.14 Glatiramer acetate versus IFNß-1b (Betaseron)	1	2244	Odds Ratio (IV, Random, 95% CI)	1.05 [0.85, 1.29]
2.15 Glatiramer acetate versus IFNß-1a (Rebif)	1	764	Odds Ratio (IV, Random, 95% CI)	0.93 [0.69, 1.25]
3 Relapse over 24 months in progressive MS	6		Odds Ratio (IV, Random, 95% CI)	Subtotals only
3.1 IFNß-1a (Avonex) versus placebo	1	436	Odds Ratio (IV, Random, 95% CI)	0.74 [0.51, 1.08]
3.2 Mitoxantrone versus placebo	1	194	Odds Ratio (IV, Random, 95% CI)	0.65 [0.35, 1.20]

3.3 Azathioprine versus placebo	1	99	Odds Ratio (IV, Random, 95% CI)	0.56 [0.24, 1.33]
3.4 Immunoglobulins versus placebo	2	515	Odds Ratio (IV, Random, 95% CI)	0.93 [0.66, 1.32]
3.5 Methotrexate versus placebo	1	60	Odds Ratio (IV, Random, 95% CI)	1.15 [0.31, 4.28]

Comparison 3. Comparisons for relapse over 36 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse over 36 months in MS of all types	6		Odds Ratio (IV, Random, 95% CI)	Subtotals only
1.1 IFNß-1b (Betaseron) versus placebo	2	1657	Odds Ratio (IV, Random, 95% CI)	0.71 [0.56, 0.90]
1.2 IFNß-1a (Rebif) versus placebo	1	371	Odds Ratio (IV, Random, 95% CI)	1.28 [0.85, 1.93]
1.3 Azathioprine versus placebo	3	493	Odds Ratio (IV, Random, 95% CI)	0.45 [0.27, 0.76]

Comparison 4. Comparisons for disability progression over 24 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disability progression over 24 months in MS of all types	30		Odds Ratio (IV, Random, 95% CI)	Subtotals only
1.1 IFNß-1b (Betaseron) versus placebo	2	445	Odds Ratio (IV, Random, 95% CI)	0.89 [0.59, 1.36]
1.2 IFNß-1a (Avonex) versus placebo	3	787	Odds Ratio (IV, Random, 95% CI)	0.94 [0.71, 1.25]
1.3 IFNß-1a (Rebif) versus placebo	2	1178	Odds Ratio (IV, Random, 95% CI)	0.71 [0.56, 0.92]
1.4 Glatiramer acetate versus placebo	4	1350	Odds Ratio (IV, Random, 95% CI)	0.76 [0.49, 1.17]
1.5 Natalizumab versus placebo	1	942	Odds Ratio (IV, Random, 95% CI)	0.56 [0.42, 0.74]
1.6 Mitoxantrone versus placebo	2	245	Odds Ratio (IV, Random, 95% CI)	0.34 [0.08, 1.44]
1.7 Azathioprine versus placebo	3	284	Odds Ratio (IV, Random, 95% CI)	0.77 [0.48, 1.24]
1.8 Immunoglobulins versus placebo	4	739	Odds Ratio (IV, Random, 95% CI)	0.78 [0.48, 1.25]
1.9 Cyclophosphamide versus placebo	1	44	Odds Ratio (IV, Random, 95% CI)	0.80 [0.22, 2.94]

1.10 Corticosteroids versus placebo	1	86	Odds Ratio (IV, Random, 95% CI)	1.58 [0.64, 3.87]
1.11 Methotrexate versus placebo	1	60	Odds Ratio (IV, Random, 95% CI)	0.67 [0.24, 1.87]
1.12 IFNß-1a (Avonex) versus IFNß-1b (Betaseron)	1	188	Odds Ratio (IV, Random, 95% CI)	2.88 [1.43, 5.79]
1.13 IFNß-1a (Rebif) versus IFNß-1b (Betaseron)	1	301	Odds Ratio (IV, Random, 95% CI)	0.98 [0.62, 1.54]
1.14 Natalizumab versus IFNß-1a (Avonex)	1	1171	Odds Ratio (IV, Random, 95% CI)	0.62 [0.49, 0.78]
1.15 Glatiramer acetate versus IFNß-1b (Betaseron)	1	2244	Odds Ratio (IV, Random, 95% CI)	0.86 [0.69, 1.06]
1.16 Glatiramer acetate versus IFNß-1a (Rebif)	1	764	Odds Ratio (IV, Random, 95% CI)	0.53 [0.34, 0.83]
1.17 Corticosteroids versus Mitoxantrone	1	42	Odds Ratio (IV, Random, 95% CI)	8.00 [0.87, 73.68]
2 Disability progression over 24 months in relapse-remitting MS	15		Odds Ratio (IV, Random, 95% CI)	Subtotals only
2.1 IFNß-1b (Betaseron) versus placebo	1	372	Odds Ratio (IV, Random, 95% CI)	0.96 [0.61, 1.52]
2.2 IFNß-1a (Avonex) versus placebo	1	301	Odds Ratio (IV, Random, 95% CI)	0.93 [0.59, 1.47]
2.3 IFNß-1a (Rebif) versus placebo	1	560	Odds Ratio (IV, Random, 95% CI)	0.65 [0.45, 0.93]
2.4 Glatiramer acetate versus placebo	2	301	Odds Ratio (IV, Random, 95% CI)	0.50 [0.14, 1.74]
2.5 Natalizumab versus placebo	1	942	Odds Ratio (IV, Random, 95% CI)	0.56 [0.42, 0.74]
2.6 Mitoxantrone versus placebo	1	51	Odds Ratio (IV, Random, 95% CI)	0.13 [0.03, 0.70]
2.7 Azathioprine versus placebo	1	59	Odds Ratio (IV, Random, 95% CI)	0.52 [0.17, 1.54]
2.8 Immunoglobulins versus placebo	2	190	Odds Ratio (IV, Random, 95% CI)	0.62 [0.30, 1.29]
2.9 IFNß-1a (Avonex) versus IFNß-1b (Betaseron)	1	188	Odds Ratio (IV, Random, 95% CI)	2.88 [1.43, 5.79]
2.10 IFNß-1a (Rebif) versus IFNß-1b (Betaseron)	1	301	Odds Ratio (IV, Random, 95% CI)	0.98 [0.62, 1.54]
2.11 Natalizumab versus IFNß-1a (Avonex)	1	1171	Odds Ratio (IV, Random, 95% CI)	0.62 [0.49, 0.78]
2.12 Glatiramer acetate versus IFNß-1b (Betaseron)	1	2244	Odds Ratio (IV, Random, 95% CI)	0.86 [0.69, 1.06]
2.13 Glatiramer acetate versus IFNß-1a (Rebif)	1	764	Odds Ratio (IV, Random, 95% CI)	0.53 [0.34, 0.83]
3 Disability progression over 24 months in progressive MS	13		Odds Ratio (IV, Random, 95% CI)	Subtotals only
3.1 IFNß-1b (Betaseron) versus placebo	1	73	Odds Ratio (IV, Random, 95% CI)	0.62 [0.22, 1.69]
3.2 IFNß-1a (Avonex) versus placebo	2	486	Odds Ratio (IV, Random, 95% CI)	0.95 [0.66, 1.36]

3.3 IFNß-1a (Rebif) versus placebo	1	618	Odds Ratio (IV, Random, 95% CI)	0.78 [0.55, 1.10]
3.4 Glatiramer acetate versus placebo	2	1049	Odds Ratio (IV, Random, 95% CI)	0.94 [0.73, 1.23]
3.5 Mitoxantrone versus placebo	1	194	Odds Ratio (IV, Random, 95% CI)	0.61 [0.27, 1.34]
3.6 Immunoglobulins versus placebo	2	549	Odds Ratio (IV, Random, 95% CI)	0.83 [0.39, 1.74]
3.7 Cyclophosphamide versus placebo	1	44	Odds Ratio (IV, Random, 95% CI)	0.80 [0.22, 2.94]
3.8 Corticosteroids versus placebo	1	86	Odds Ratio (IV, Random, 95% CI)	1.58 [0.64, 3.87]
3.9 Methotrexate versus placebo	1	60	Odds Ratio (IV, Random, 95% CI)	0.67 [0.24, 1.87]
3.10 Corticosteroids versus Mitoxantrone	1	42	Odds Ratio (IV, Random, 95% CI)	8.00 [0.87, 73.68]

Comparison 5. Comparisons for disability progression over 36 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disability progression over 36 months in progressive MS	7		Odds Ratio (IV, Random, 95% CI)	Subtotals only
1.1 IFNß-1b (Betaseron) versus placebo	2	1657	Odds Ratio (IV, Random, 95% CI)	0.87 [0.57, 1.33]
1.2 IFNß-1a (Rebif) versus placebo	2	989	Odds Ratio (IV, Random, 95% CI)	1.10 [0.68, 1.80]
1.3 Azathioprine versus placebo	2	139	Odds Ratio (IV, Random, 95% CI)	0.47 [0.19, 1.17]
1.4 Cyclophosphamide versus placebo	1	111	Odds Ratio (IV, Random, 95% CI)	1.60 [0.76, 3.39]

Comparison 6. Comparison for adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events	14	5785	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.96, 1.35]
1.1 Interferons versus placebo	5	1866	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.80, 1.39]
1.2 Glatiramer acetate versus placebo	3	1046	Odds Ratio (M-H, Random, 95% CI)	1.71 [0.87, 3.39]
1.3 Natalizumab versus placebo	2	2110	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.87, 1.50]
1.4 Mitoxantrone versus placebo	1	131	Odds Ratio (M-H, Random, 95% CI)	2.58 [0.48, 13.81]

1.5 Intravenous immunoglobulins versus placebo	3	632	Odds Ratio (M-H, Random, 95% CI)	2.28 [0.54, 9.74]
2 Withdrawals due to adverse events	26	8332	Odds Ratio (M-H, Random, 95% CI)	2.41 [1.92, 3.03]
2.1 Interferons versus placebo	10	3711	Odds Ratio (M-H, Random, 95% CI)	3.08 [2.23, 4.26]
2.2 Glatiramer acetate versus placebo	4	1096	Odds Ratio (M-H, Random, 95% CI)	3.48 [1.55, 7.84]
2.3 Natalizumab versus placebo	2	2110	Odds Ratio (M-H, Random, 95% CI)	1.36 [0.99, 1.85]
2.4 Azathioprine versus placebo	4	513	Odds Ratio (M-H, Random, 95% CI)	6.35 [2.50, 16.11]
2.5 Mitoxantrone versus placebo	1	131	Odds Ratio (M-H, Random, 95% CI)	3.15 [0.61, 16.22]
2.6 Intravenous immunoglobulins versus placebo	5	771	Odds Ratio (M-H, Random, 95% CI)	1.99 [1.07, 3.71]

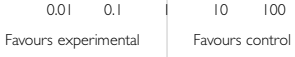
Analysis 1.1. Comparison 1 Comparisons for relapse over 12 months, Outcome 1 Relapse over 12 months in MS of all types.

Review: Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis

Comparison: 1 Comparisons for relapse over 12 months

Outcome: 1 Relapse over 12 months in MS of all types

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 IFN -1b (Betaseron) versus placebo					
Knobler 1993	8/18	4/7		100.0 %	0.60 [0.10, 3.49]
Subtotal (95% CI)	**18**	**7**		**100.0 %**	**0.60 [0.10, 3.49]**
Total events: 8 (Experimental), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.57 (P = 0.57)					
2 IFN -1a (Avonex) versus placebo					
MSCRG 1996	88/158	91/143		100.0 %	0.72 [0.45, 1.14]
Subtotal (95% CI)	**158**	**143**		**100.0 %**	**0.72 [0.45, 1.14]**
Total events: 88 (Experimental), 91 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.40 (P = 0.16)					
3 IFN -1a (Rebif) versus placebo					
OWIMS 1999	130/193	65/100		48.8 %	1.11 [0.67, 1.85]



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Study or subgroup	Experimental n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
PRISMS 1998	226/373	148/187		51.2 %	0.41 [0.27, 0.61]
Subtotal (95% CI)	**566**	**287**		**100.0 %**	**0.66 [0.25, 1.78]**
Total events: 356 (Experimental), 213 (Control)					
Heterogeneity: Tau² = 0.45; Chi² = 9.16, df = 1 (P = 0.002); I² =89%					
Test for overall effect: Z = 0.81 (P = 0.42)					
4 Glatiramer acetate versus placebo					
Bornstein 1987	7/25	19/25		44.9 %	0.12 [0.03, 0.44]
Comi 2001	53/119	61/120		55.1 %	0.78 [0.47, 1.29]
Subtotal (95% CI)	**144**	**145**		**100.0 %**	**0.34 [0.06, 2.05]**
Total events: 60 (Experimental), 80 (Control)					
Heterogeneity: Tau² = 1.46; Chi² = 7.01, df = 1 (P = 0.01); I² =86%					
Test for overall effect: Z = 1.18 (P = 0.24)					
5 Natalizumab versus placebo					
AFFIRM 2006	126/627	126/315		100.0 %	0.38 [0.28, 0.51]
Subtotal (95% CI)	**627**	**315**		**100.0 %**	**0.38 [0.28, 0.51]**
Total events: 126 (Experimental), 126 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.41 (P < 0.00001)					
6 Mitoxantrone versus placebo					
Millefiorini 1997	8/27	18/24		100.0 %	0.14 [0.04, 0.48]
Subtotal (95% CI)	**27**	**24**		**100.0 %**	**0.14 [0.04, 0.48]**
Total events: 8 (Experimental), 18 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.11 (P = 0.0019)					
7 Azathioprine versus placebo					
British and Dutch 1988	84/174	107/180		69.4 %	0.64 [0.42, 0.97]
Ellison 1989	11/65	11/34		13.1 %	0.43 [0.16, 1.12]
Goodkin 1991	18/29	17/25		9.7 %	0.77 [0.25, 2.38]
Milanese 1993	10/19	12/21		7.9 %	0.83 [0.24, 2.90]
Subtotal (95% CI)	**287**	**260**		**100.0 %**	**0.63 [0.44, 0.89]**
Total events: 123 (Experimental), 147 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 0.95, df = 3 (P = 0.81); I² =0.0%					
Test for overall effect: Z = 2.60 (P = 0.0094)					
8 Immunoglobulins versus placebo					
Achiron 1998	12/20	19/20		14.2 %	0.08 [0.01, 0.71]
Fazekas 2008	38/87	13/41		31.0 %	1.67 [0.76, 3.65]
Hommes 2004	55/159	53/159		34.9 %	1.06 [0.66, 1.68]
Lewanska 2002	17/33	16/18		19.8 %	0.13 [0.03, 0.67]
Subtotal (95% CI)	**299**	**238**		**100.0 %**	**0.56 [0.20, 1.60]**

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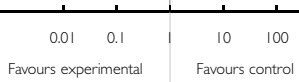
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
Total events: 122 (Experimental), 101 (Control)					
Heterogeneity: Tau² = 0.77; Chi² = 12.76, df = 3 (P = 0.01); I² =76%					
Test for overall effect: Z = 1.08 (P = 0.28)					
9 Corticosteroids versus placebo					
BPSM 1995	10/19	12/17		100.0 %	0.46 [0.12, 1.84]
Subtotal (95% CI)	**19**	**17**		**100.0 %**	**0.46 [0.12, 1.84]**
Total events: 10 (Experimental), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.10 (P = 0.27)					
10 IFN -1a (Avonex) versus IFN -1b (Betaseron)					
INCOMIN 2002	48/92	40/96		100.0 %	1.53 [0.86, 2.72]
Subtotal (95% CI)	**92**	**96**		**100.0 %**	**1.53 [0.86, 2.72]**
Total events: 48 (Experimental), 40 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.44 (P = 0.15)					
11 IFN -1a (Rebif) versus IFN -1a (Avonex)					
EVIDENCE 2007	188/339	207/338		100.0 %	0.79 [0.58, 1.07]
Subtotal (95% CI)	**339**	**338**		**100.0 %**	**0.79 [0.58, 1.07]**
Total events: 188 (Experimental), 207 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.53 (P = 0.13)					
12 Natalizumab versus IFN -1a (Avonex)					
SENTINEL 2006	165/589	286/582		100.0 %	0.40 [0.32, 0.51]
Subtotal (95% CI)	**589**	**582**		**100.0 %**	**0.40 [0.32, 0.51]**
Total events: 165 (Experimental), 286 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.35 (P < 0.00001)					
13 Corticosteroids versus Mitoxantrone					
Edan 1997	14/21	7/21		100.0 %	4.00 [1.11, 14.43]
Subtotal (95% CI)	**21**	**21**		**100.0 %**	**4.00 [1.11, 14.43]**
Total events: 14 (Experimental), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.12 (P = 0.034)					
Test for subgroup differences: Chi² = 46.02, df = 12 (P = 0.00), I² =74%					

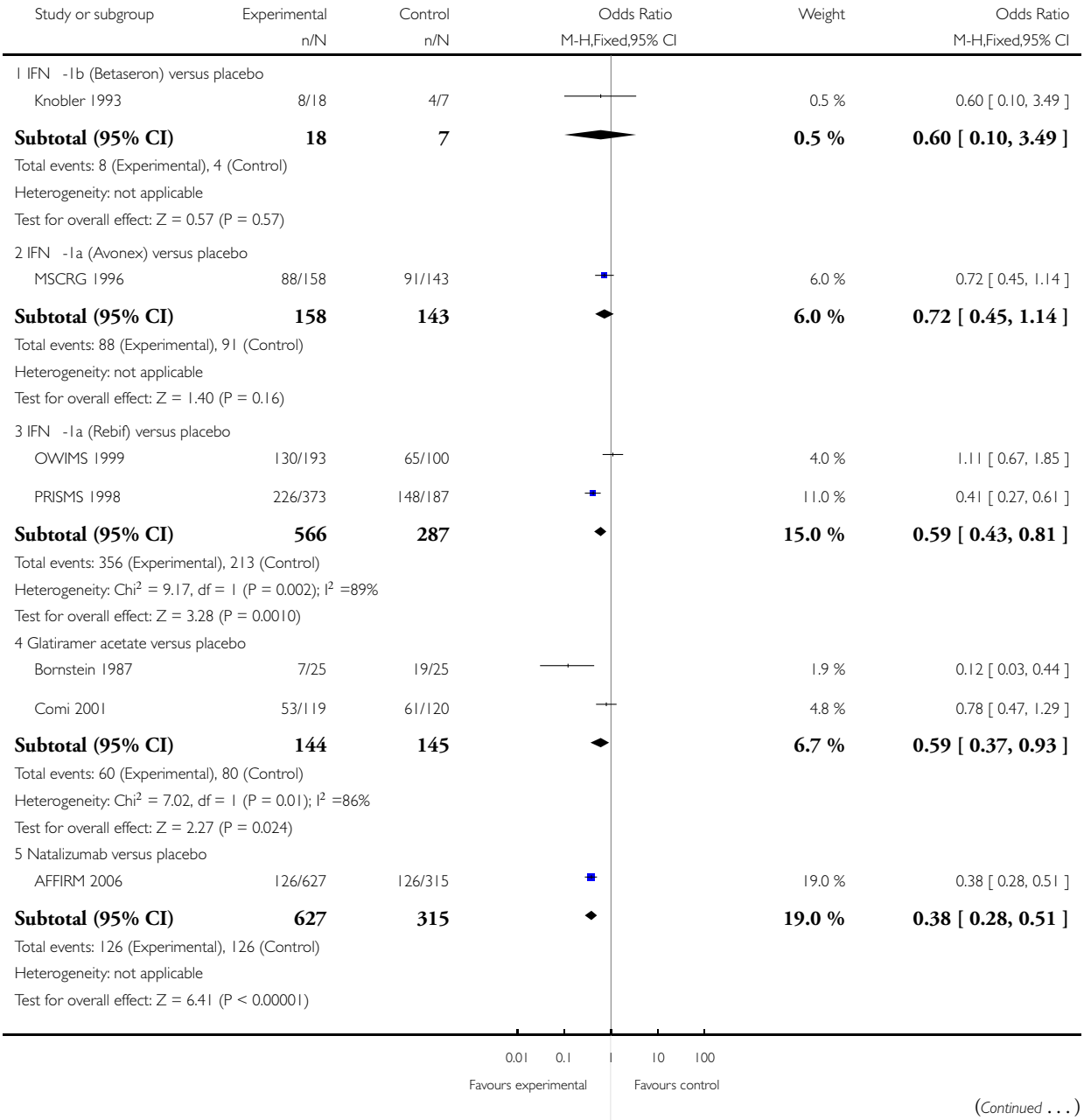


Analysis 1.2. Comparison 1 Comparisons for relapse over 12 months, Outcome 2 Relapse over 12 months in relapsing-remitting MS.

Review: Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis

Comparison: 1 Comparisons for relapse over 12 months

Outcome: 2 Relapse over 12 months in relapsing-remitting MS



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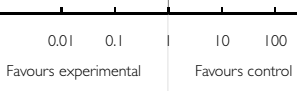
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
6 Mitoxantrone versus placebo					
Millefiorini 1997	8/27	18/24		1.9 %	0.14 [0.04, 0.48]
Subtotal (95% CI)	**27**	**24**		**1.9 %**	**0.14 [0.04, 0.48]**
Total events: 8 (Experimental), 18 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.11 (P = 0.0019)					
7 Azathioprine versus placebo					
Goodkin 1991	18/29	17/25		1.0 %	0.77 [0.25, 2.38]
Subtotal (95% CI)	**29**	**25**		**1.0 %**	**0.77 [0.25, 2.38]**
Total events: 18 (Experimental), 17 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.45 (P = 0.65)					
8 Immunoglobulins versus placebo					
Achiron 1998	12/20	19/20		1.1 %	0.08 [0.01, 0.71]
Fazekas 2008	38/87	13/41		1.4 %	1.67 [0.76, 3.65]
Lewanska 2002	17/33	16/18		1.4 %	0.13 [0.03, 0.67]
Subtotal (95% CI)	**140**	**79**		**3.9 %**	**0.67 [0.38, 1.21]**
Total events: 67 (Experimental), 48 (Control)					
Heterogeneity: Chi^2 = 12.68, df = 2 (P = 0.002); I^2 =84%					
Test for overall effect: Z = 1.33 (P = 0.18)					
9 Corticosteroids versus placebo					
BPSM 1995	10/19	12/17		0.9 %	0.46 [0.12, 1.84]
Subtotal (95% CI)	**19**	**17**		**0.9 %**	**0.46 [0.12, 1.84]**
Total events: 10 (Experimental), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.10 (P = 0.27)					
10 IFN -1a (Avonex) versus IFN -1b (Betaseron)					
INCOMIN 2002	48/92	40/96		2.7 %	1.53 [0.86, 2.72]
Subtotal (95% CI)	**92**	**96**		**2.7 %**	**1.53 [0.86, 2.72]**
Total events: 48 (Experimental), 40 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.44 (P = 0.15)					
11 IFN -1a (Rebif) versus IFN -1a (Avonex)					
EVIDENCE 2007	188/339	207/338		13.1 %	0.79 [0.58, 1.07]
Subtotal (95% CI)	**339**	**338**		**13.1 %**	**0.79 [0.58, 1.07]**
Total events: 188 (Experimental), 207 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.53 (P = 0.13)					
12 Natalizumab versus IFN -1a (Avonex)					



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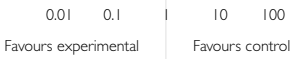
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
SENTINEL 2006	165/589	286/582		29.4 %	0.40 [0.32, 0.51]
Subtotal (95% CI)	**589**	**582**		**29.4 %**	**0.40 [0.32, 0.51]**
Total events: 165 (Experimental), 286 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.35 (P < 0.00001)					
Total (95% CI)	**2748**	**2058**		**100.0 %**	**0.55 [0.49, 0.62]**
Total events: 1142 (Experimental), 1142 (Control)					
Heterogeneity: Chi^2 = 66.51, df = 15 (P<0.00001); I^2 =77%					
Test for overall effect: Z = 9.68 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 36.94, df = 11 (P = 0.00), I^2 =70%					



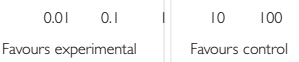
Analysis 1.3. Comparison 1 Comparisons for relapse over 12 months, Outcome 3 Relapse over 12 months in progressive MS.

Review: Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis

Comparison: 1 Comparisons for relapse over 12 months

Outcome: 3 Relapse over 12 months in progressive MS

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Azathioprine versus placebo					
Ellison 1989	11/65	11/34		24.5 %	0.43 [0.16, 1.12]
Subtotal (95% CI)	**65**	**34**		**24.5 %**	**0.43 [0.16, 1.12]**
Total events: 11 (Experimental), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.73 (P = 0.084)					
2 Immunoglobulins versus placebo					
Hommes 2004	55/159	53/159		70.7 %	1.06 [0.66, 1.68]
Subtotal (95% CI)	**159**	**159**		**70.7 %**	**1.06 [0.66, 1.68]**
Total events: 55 (Experimental), 53 (Control)					
Heterogeneity: not applicable					



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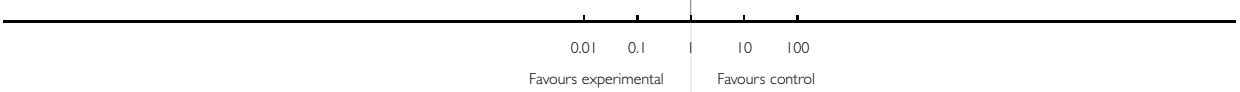
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.24 (P = 0.81)					
3 Corticosteroids versus Mitoxantrone					
Edan 1997	14/21	7/21		4.8 %	4.00 [1.11, 14.43]
Subtotal (95% CI)	**21**	**21**		**4.8 %**	**4.00 [1.11, 14.43]**
Total events: 14 (Experimental), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.12 (P = 0.034)					
Total (95% CI)	**245**	**214**		**100.0 %**	**1.04 [0.70, 1.54]**
Total events: 80 (Experimental), 71 (Control)					
Heterogeneity: Chi^2 = 7.51, df = 2 (P = 0.02); I^2 =73%					
Test for overall effect: Z = 0.21 (P = 0.83)					
Test for subgroup differences: Chi^2 = 7.51, df = 2 (P = 0.02), I^2 =73%					

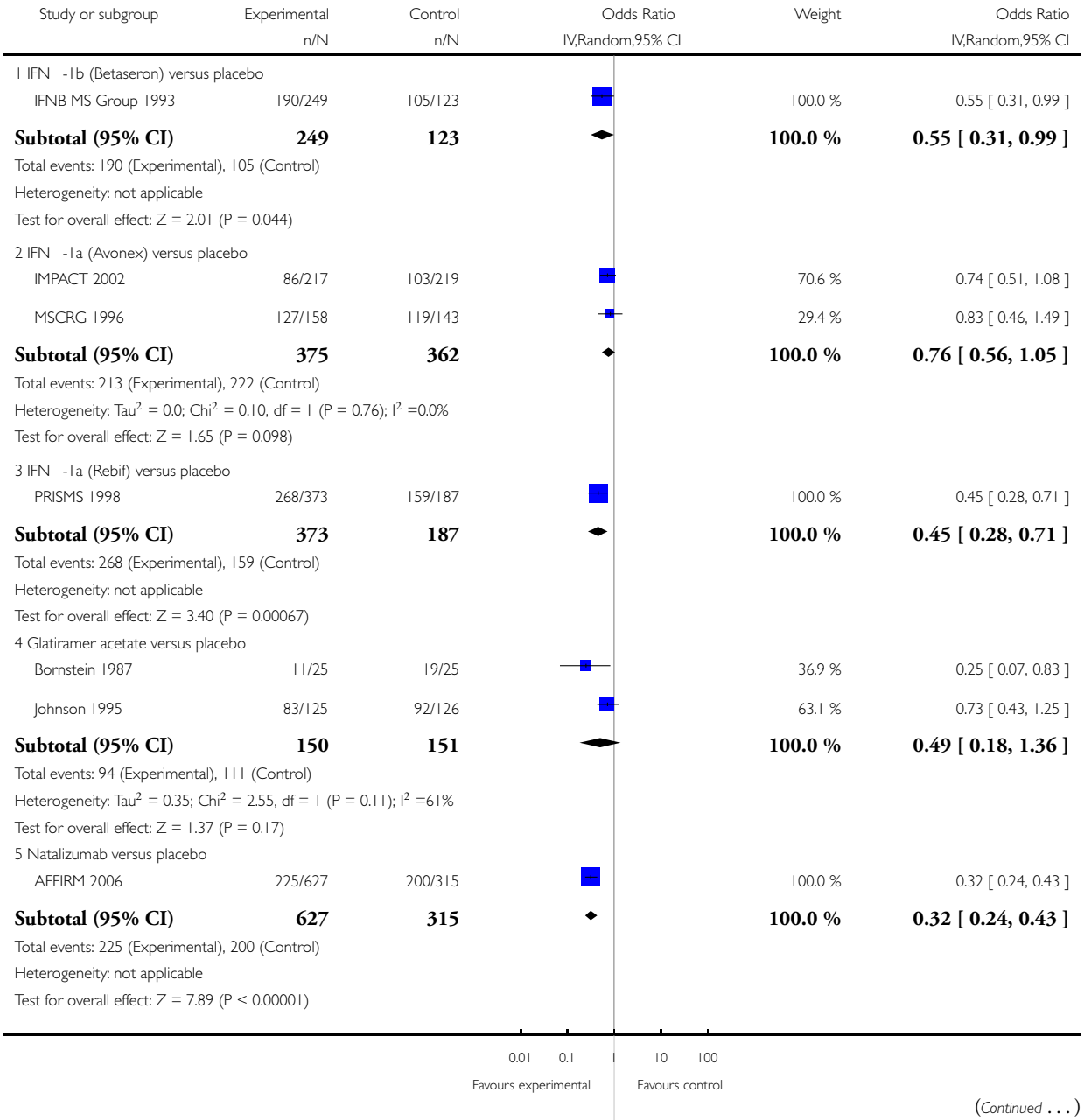


Analysis 2.1. Comparison 2 Comparisons for relapse over 24 months, Outcome 1 Relapse over 24 months in MS of all types.

Review: Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis

Comparison: 2 Comparisons for relapse over 24 months

Outcome: 1 Relapse over 24 months in MS of all types



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Study or subgroup	Experimental n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
6 Mitoxantrone versus placebo					
Hartung 2002	70/129	42/65		57.6 %	0.65 [0.35, 1.20]
Millefiorini 1997	10/27	19/24		42.4 %	0.15 [0.04, 0.54]
Subtotal (95% CI)	**156**	**89**		**100.0 %**	**0.35 [0.09, 1.42]**
Total events: 80 (Experimental), 61 (Control)					
Heterogeneity: Tau^2 = 0.77; Chi^2 = 4.03, df = 1 (P = 0.04); I^2 =75%					
Test for overall effect: Z = 1.47 (P = 0.14)					
7 Azathioprine versus placebo					
British and Dutch 1988	109/174	135/180		39.2 %	0.56 [0.35, 0.88]
Ellison 1989	20/65	15/34		16.2 %	0.56 [0.24, 1.33]
Ghezzi 1989	54/93	51/92		29.1 %	1.11 [0.62, 1.99]
Goodkin 1991	19/30	24/29		8.9 %	0.36 [0.11, 1.21]
Milanese 1993	12/19	17/21		6.6 %	0.40 [0.10, 1.69]
Subtotal (95% CI)	**381**	**356**		**100.0 %**	**0.64 [0.44, 0.94]**
Total events: 214 (Experimental), 242 (Control)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 5.14, df = 4 (P = 0.27); I^2 =22%					
Test for overall effect: Z = 2.26 (P = 0.024)					
8 Immunoglobulins versus placebo					
Achiron 1998	13/20	20/20		3.4 %	0.04 [0.00, 0.83]
Fazekas 2008	35/75	49/75		28.6 %	0.46 [0.24, 0.90]
Hommes 2004	77/159	83/159		36.6 %	0.86 [0.55, 1.34]
Pohlau 2007	37/99	35/98		31.4 %	1.07 [0.60, 1.92]
Subtotal (95% CI)	**353**	**352**		**100.0 %**	**0.70 [0.40, 1.22]**
Total events: 162 (Experimental), 187 (Control)					
Heterogeneity: Tau^2 = 0.17; Chi^2 = 7.42, df = 3 (P = 0.06); I^2 =60%					
Test for overall effect: Z = 1.25 (P = 0.21)					
9 Corticosteroids versus placebo					
BPSM 1995	18/19	16/17		100.0 %	1.13 [0.06, 19.50]
Subtotal (95% CI)	**19**	**17**		**100.0 %**	**1.13 [0.06, 19.50]**
Total events: 18 (Experimental), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.94)					
10 Methotrexate versus placebo					
Goodkin 1995	6/31	5/29		100.0 %	1.15 [0.31, 4.28]
Subtotal (95% CI)	**31**	**29**		**100.0 %**	**1.15 [0.31, 4.28]**
Total events: 6 (Experimental), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.21 (P = 0.83)					

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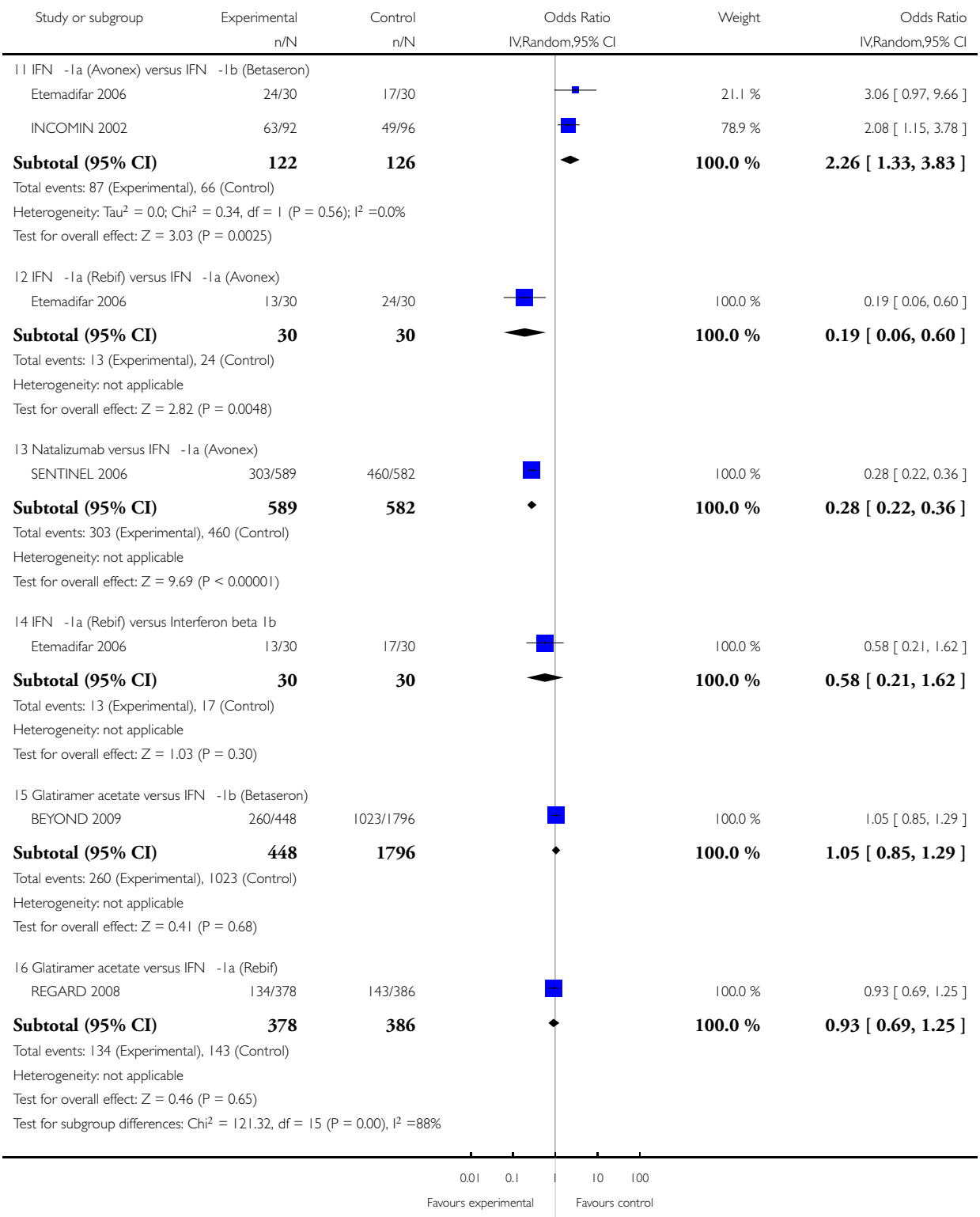
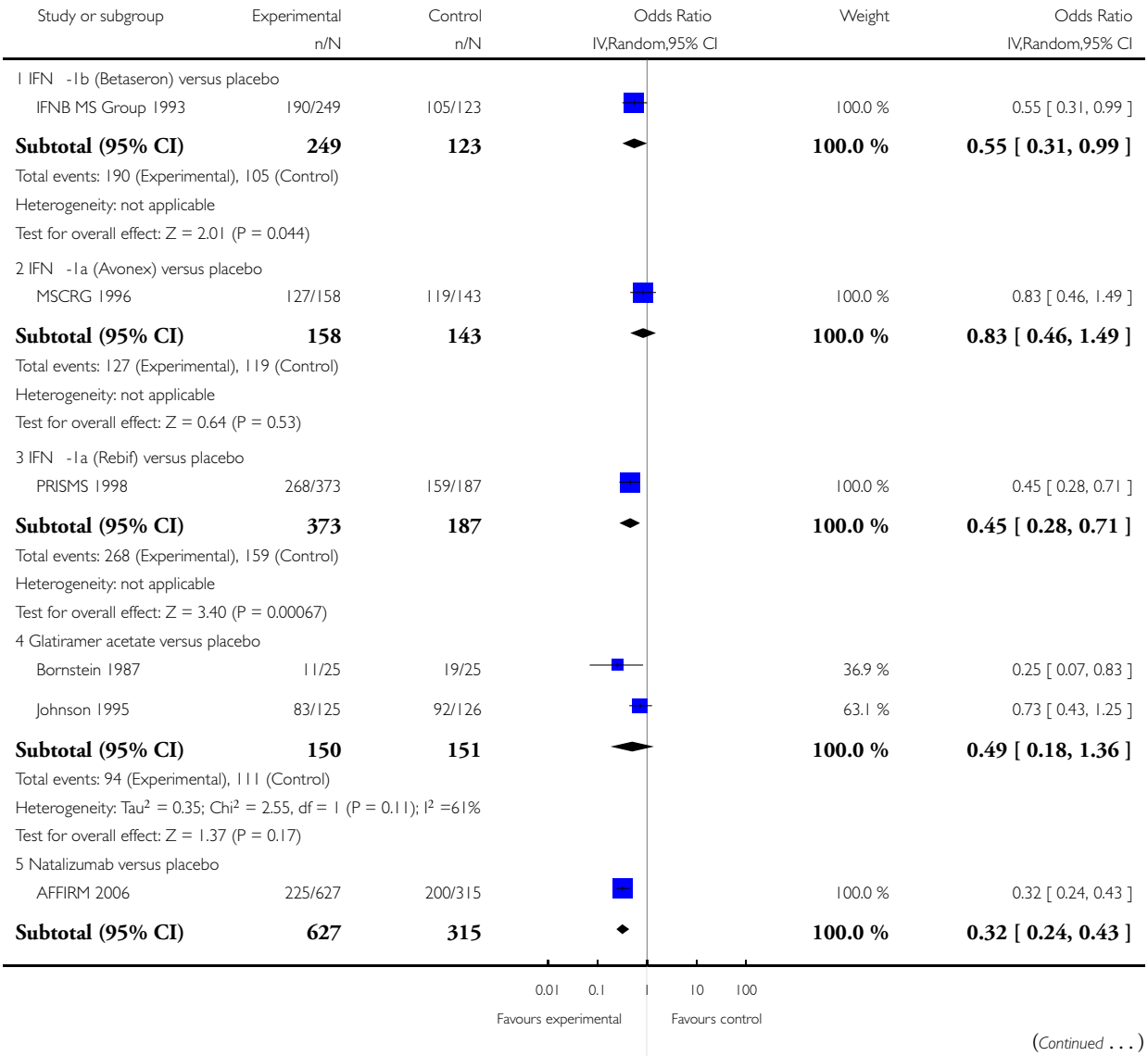


Analysis 2.2. Comparison 2 Comparisons for relapse over 24 months, Outcome 2 Relapse over 24 months in relapsing-remitting MS.

Review: Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis

Comparison: 2 Comparisons for relapse over 24 months

Outcome: 2 Relapse over 24 months in relapsing-remitting MS



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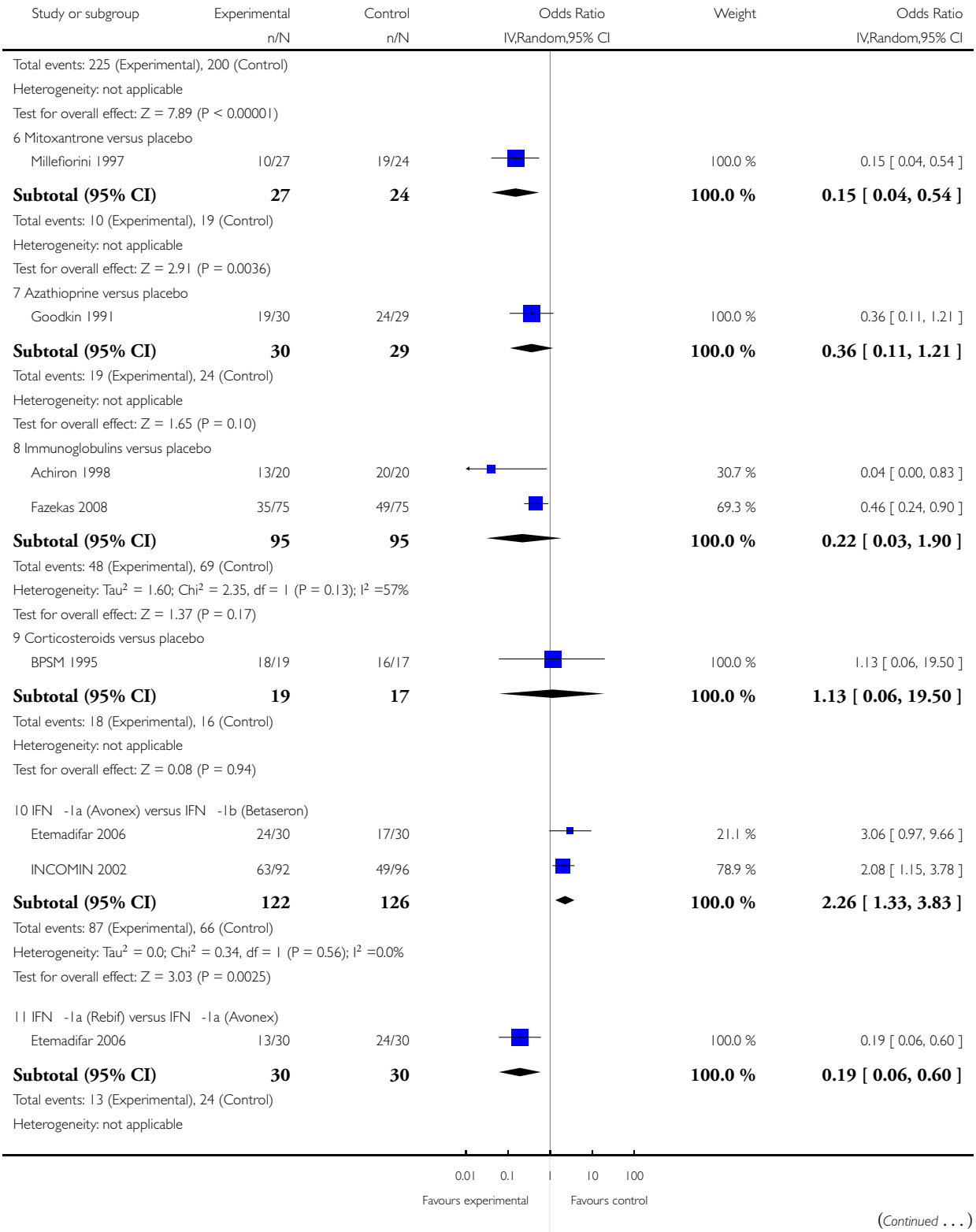

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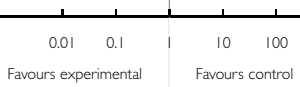
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
Test for overall effect: Z = 2.82 (P = 0.0048)					
12 Natalizumab versus IFN -1a (Avonex)					
SENTINEL 2006	303/589	460/582		100.0 %	0.28 [0.22, 0.36]
Subtotal (95% CI)	**589**	**582**		**100.0 %**	**0.28 [0.22, 0.36]**
Total events: 303 (Experimental), 460 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 9.69 (P < 0.00001)					
13 IFN -1a (Rebif) versus IFN -1b (Betaseron)					
Etemadifar 2006	13/30	17/30		100.0 %	0.58 [0.21, 1.62]
Subtotal (95% CI)	**30**	**30**		**100.0 %**	**0.58 [0.21, 1.62]**
Total events: 13 (Experimental), 17 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.03 (P = 0.30)					
14 Glatiramer acetate versus IFN -1b (Betaseron)					
BEYOND 2009	260/448	1023/1796		100.0 %	1.05 [0.85, 1.29]
Subtotal (95% CI)	**448**	**1796**		**100.0 %**	**1.05 [0.85, 1.29]**
Total events: 260 (Experimental), 1023 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.41 (P = 0.68)					
15 Glatiramer acetate versus IFN -1a (Rebif)					
REGARD 2008	134/378	143/386		100.0 %	0.93 [0.69, 1.25]
Subtotal (95% CI)	**378**	**386**		**100.0 %**	**0.93 [0.69, 1.25]**
Total events: 134 (Experimental), 143 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.46 (P = 0.65)					
Test for subgroup differences: Chi^2 = 124.89, df = 14 (P = 0.00), I^2 =89%					

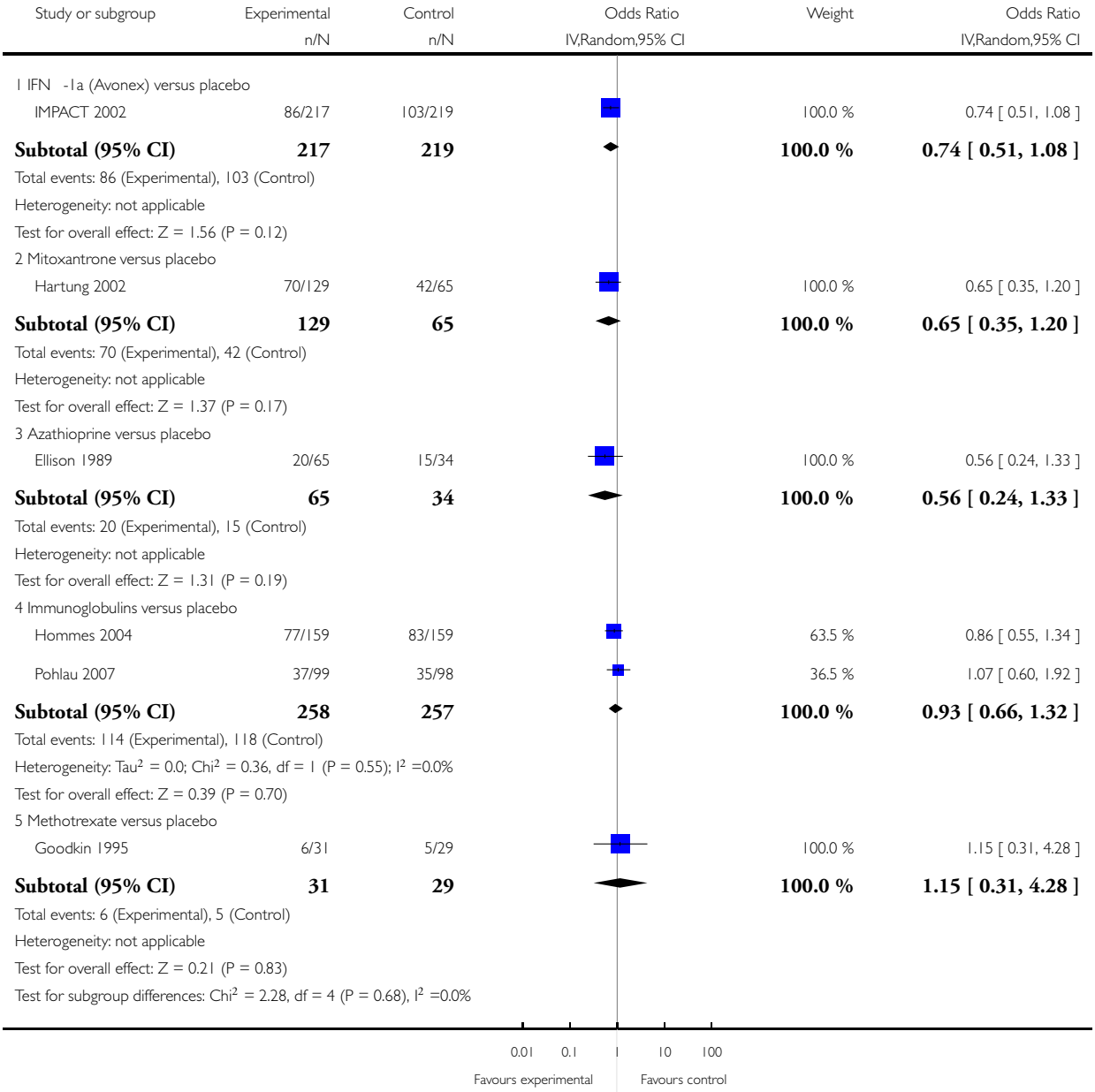


Analysis 2.3. Comparison 2 Comparisons for relapse over 24 months, Outcome 3 Relapse over 24 months in progressive MS.

Review: Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis

Comparison: 2 Comparisons for relapse over 24 months

Outcome: 3 Relapse over 24 months in progressive MS

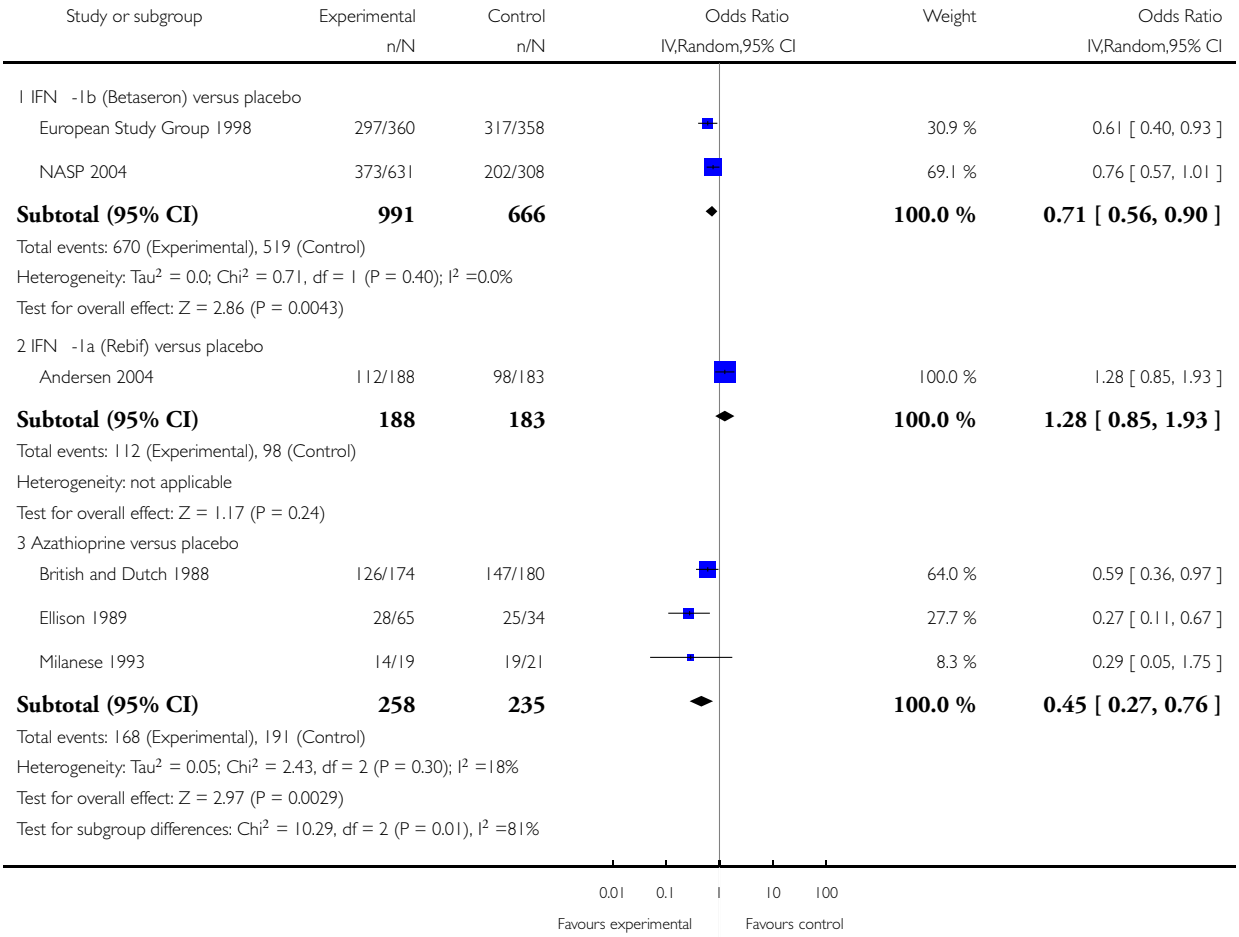


Analysis 3.1. Comparison 3 Comparisons for relapse over 36 months, Outcome 1 Relapse over 36 months in MS of all types.

Review: Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis

Comparison: 3 Comparisons for relapse over 36 months

Outcome: 1 Relapse over 36 months in MS of all types



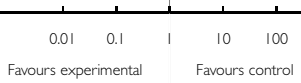
Analysis 4.1. Comparison 4 Comparisons for disability progression over 24 months, Outcome 1 Disability progression over 24 months in MS of all types.

Review: Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis

Comparison: 4 Comparisons for disability progression over 24 months

Outcome: 1 Disability progression over 24 months in MS of all types

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 IFN -1b (Betaseron) versus placebo					
IFNB MS Group 1993	83/249	42/123		83.1 %	0.96 [0.61, 1.52]
Montalban 2009	9/36	13/37		16.9 %	0.62 [0.22, 1.69]
Subtotal (95% CI)	**285**	**160**		**100.0 %**	**0.89 [0.59, 1.36]**
Total events: 92 (Experimental), 55 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.63$, df = 1 (P = 0.43); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.53 (P = 0.60)					
2 IFN -1a (Avonex) versus placebo					
IMPACT 2002	82/217	88/219		55.0 %	0.90 [0.62, 1.33]
Leary 2003	16/30	9/20		6.3 %	1.40 [0.45, 4.35]
MSCRG 1996	91/158	85/143		38.7 %	0.93 [0.59, 1.47]
Subtotal (95% CI)	**405**	**382**		**100.0 %**	**0.94 [0.71, 1.25]**
Total events: 189 (Experimental), 182 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.51$, df = 2 (P = 0.78); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.44 (P = 0.66)					
3 IFN -1a (Rebif) versus placebo					
PRISMS 1998	120/373	79/187		47.3 %	0.65 [0.45, 0.93]
SPECTRIMS 2001	233/413	128/205		52.7 %	0.78 [0.55, 1.10]
Subtotal (95% CI)	**786**	**392**		**100.0 %**	**0.71 [0.56, 0.92]**
Total events: 353 (Experimental), 207 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.52$, df = 1 (P = 0.47); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.65 (P = 0.0081)					
4 Glatiramer acetate versus placebo					
Bornstein 1987	5/25	13/25		9.8 %	0.23 [0.07, 0.81]
Bornstein 1991	9/51	14/55		15.4 %	0.63 [0.24, 1.61]
Johnson 1995	27/125	31/126		27.8 %	0.84 [0.47, 1.52]
Wolinsky 2007	290/627	148/316		46.9 %	0.98 [0.74, 1.28]
Subtotal (95% CI)	**828**	**522**		**100.0 %**	**0.76 [0.49, 1.17]**
Total events: 331 (Experimental), 206 (Control)					
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 5.45$, df = 3 (P = 0.14); $I^2 = 45\%$					



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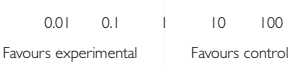
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
Test for overall effect: Z = 1.24 (P = 0.21)					
5 Natalizumab versus placebo					
AFFIRM 2006	206/627	147/315		100.0 %	0.56 [0.42, 0.74]
Subtotal (95% CI)	**627**	**315**		**100.0 %**	**0.56 [0.42, 0.74]**
Total events: 206 (Experimental), 147 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.11 (P = 0.000039)					
6 Mitoxantrone versus placebo					
Hartung 2002	17/129	13/65		62.1 %	0.61 [0.27, 1.34]
Millefiorini 1997	2/27	9/24		37.9 %	0.13 [0.03, 0.70]
Subtotal (95% CI)	**156**	**89**		**100.0 %**	**0.34 [0.08, 1.44]**
Total events: 19 (Experimental), 22 (Control)					
Heterogeneity: Tau^2 = 0.71; Chi^2 = 2.61, df = 1 (P = 0.11); I^2 =62%					
Test for overall effect: Z = 1.46 (P = 0.14)					
7 Azathioprine versus placebo					
Ghezzi 1989	51/93	53/92		66.8 %	0.89 [0.50, 1.60]
Goodkin 1991	8/30	12/29		18.8 %	0.52 [0.17, 1.54]
Milanese 1993	8/19	11/21		14.4 %	0.66 [0.19, 2.31]
Subtotal (95% CI)	**142**	**142**		**100.0 %**	**0.77 [0.48, 1.24]**
Total events: 67 (Experimental), 76 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.83, df = 2 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 1.07 (P = 0.28)					
8 Immunoglobulins versus placebo					
Achiron 1998	3/20	3/20		6.7 %	1.00 [0.18, 5.67]
Fazekas 1997	12/75	19/75		21.7 %	0.56 [0.25, 1.26]
Hommes 2004	77/159	70/159		38.0 %	1.19 [0.77, 1.86]
Pohlau 2007	56/116	72/115		33.6 %	0.56 [0.33, 0.94]
Subtotal (95% CI)	**370**	**369**		**100.0 %**	**0.78 [0.48, 1.25]**
Total events: 148 (Experimental), 164 (Control)					
Heterogeneity: Tau^2 = 0.11; Chi^2 = 5.76, df = 3 (P = 0.12); I^2 =48%					
Test for overall effect: Z = 1.04 (P = 0.30)					
9 Cyclophosphamide versus placebo					
Likosky 1991	15/22	16/22		100.0 %	0.80 [0.22, 2.94]
Subtotal (95% CI)	**22**	**22**		**100.0 %**	**0.80 [0.22, 2.94]**
Total events: 15 (Experimental), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					
10 Corticosteroids versus placebo					
Miller 1961	16/29	25/57		100.0 %	1.58 [0.64, 3.87]



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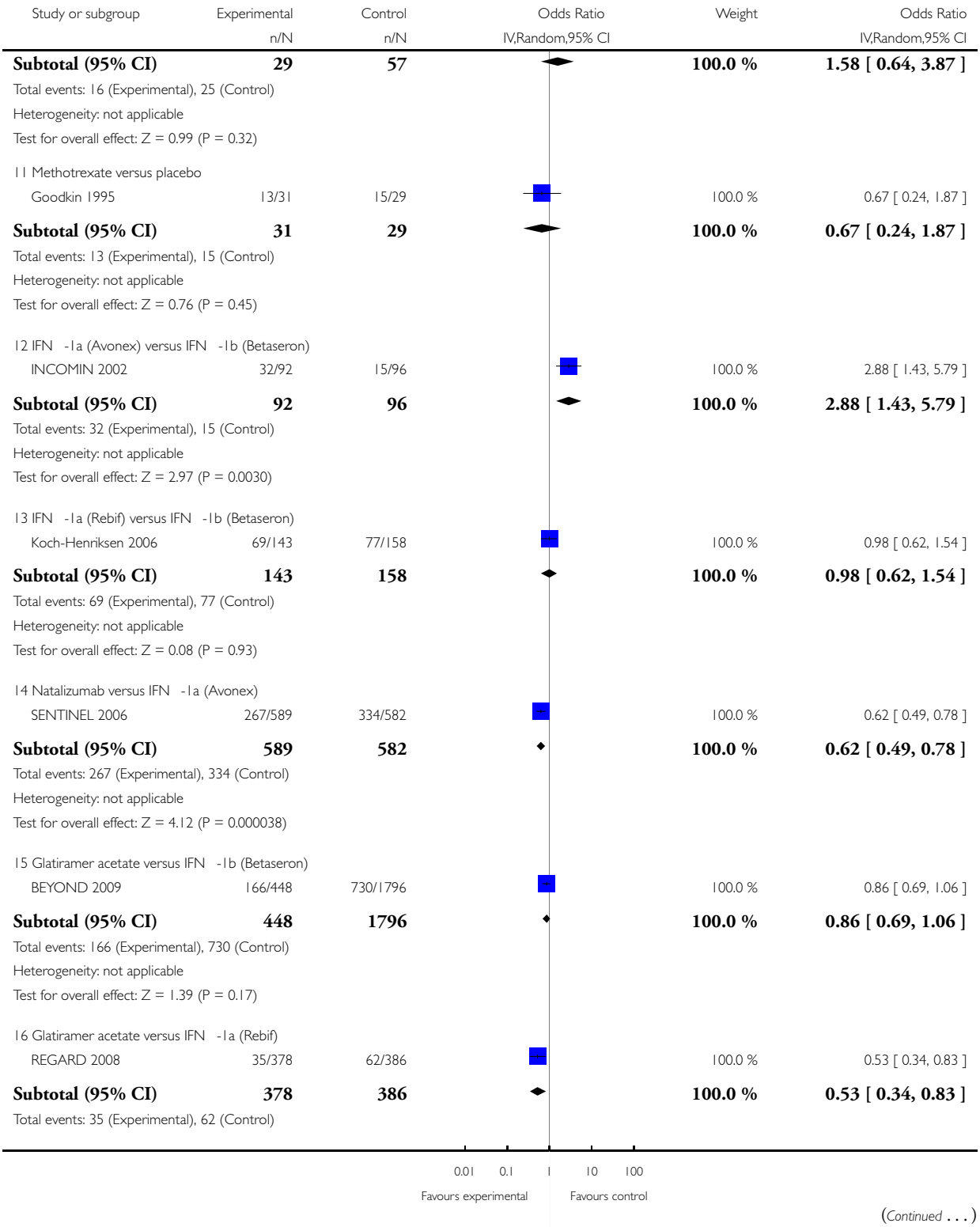

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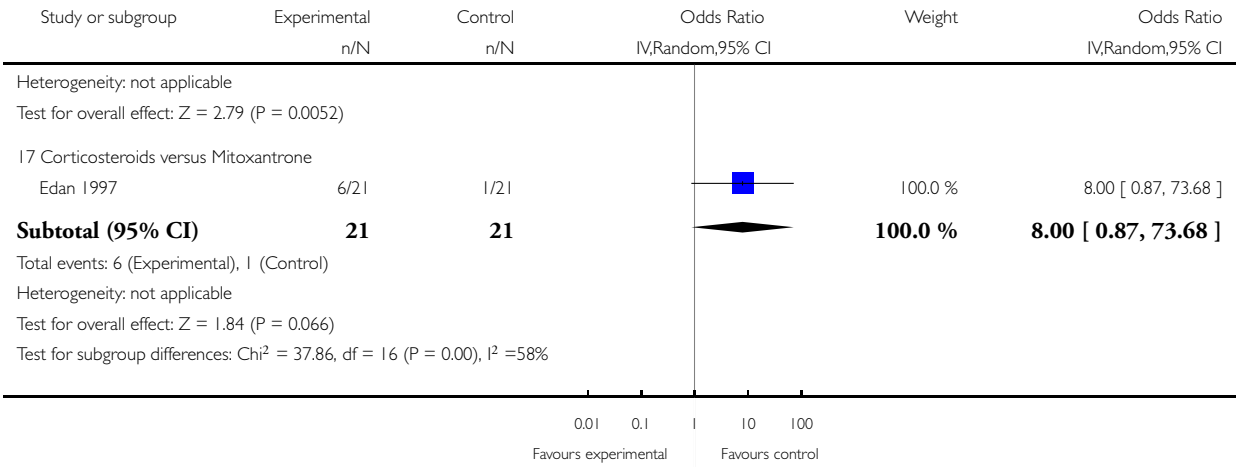
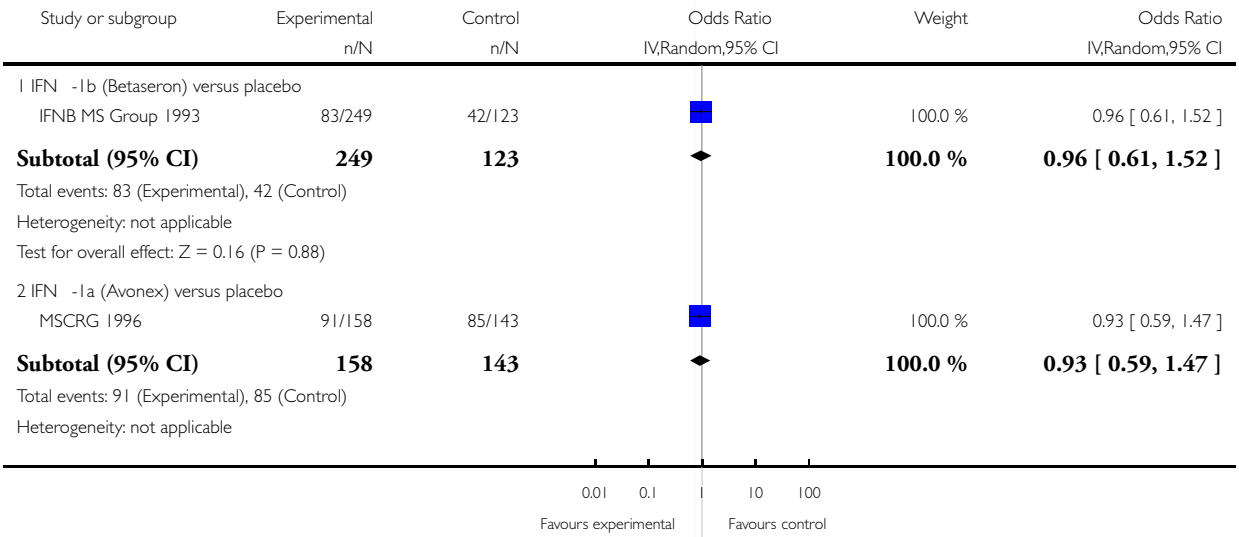


Analysis 4.2. Comparison 4 Comparisons for disability progression over 24 months, Outcome 2 Disability progression over 24 months in relapse-remitting MS.

Review: Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis

Comparison: 4 Comparisons for disability progression over 24 months

Outcome: 2 Disability progression over 24 months in relapse-remitting MS



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Study or subgroup	Experimental n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
Test for overall effect: Z = 0.32 (P = 0.75)					
3 IFN -1a (Rebif) versus placebo					
PRISMS 1998	120/373	79/187		100.0 %	0.65 [0.45, 0.93]
Subtotal (95% CI)	**373**	**187**		**100.0 %**	**0.65 [0.45, 0.93]**
Total events: 120 (Experimental), 79 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.34 (P = 0.019)					
4 Glatiramer acetate versus placebo					
Bornstein 1987	5/25	13/25		40.5 %	0.23 [0.07, 0.81]
Johnson 1995	27/125	31/126		59.5 %	0.84 [0.47, 1.52]
Subtotal (95% CI)	**150**	**151**		**100.0 %**	**0.50 [0.14, 1.74]**
Total events: 32 (Experimental), 44 (Control)					
Heterogeneity: Tau^2 = 0.59; Chi^2 = 3.36, df = 1 (P = 0.07); I^2 =70%					
Test for overall effect: Z = 1.09 (P = 0.28)					
5 Natalizumab versus placebo					
AFFIRM 2006	206/627	147/315		100.0 %	0.56 [0.42, 0.74]
Subtotal (95% CI)	**627**	**315**		**100.0 %**	**0.56 [0.42, 0.74]**
Total events: 206 (Experimental), 147 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.11 (P = 0.000039)					
6 Mitoxantrone versus placebo					
Millefiorini 1997	2/27	9/24		100.0 %	0.13 [0.03, 0.70]
Subtotal (95% CI)	**27**	**24**		**100.0 %**	**0.13 [0.03, 0.70]**
Total events: 2 (Experimental), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.38 (P = 0.017)					
7 Azathioprine versus placebo					
Goodkin 1991	8/30	12/29		100.0 %	0.52 [0.17, 1.54]
Subtotal (95% CI)	**30**	**29**		**100.0 %**	**0.52 [0.17, 1.54]**
Total events: 8 (Experimental), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.19 (P = 0.24)					
8 Immunoglobulins versus placebo					
Achiron 1998	3/20	3/20		17.8 %	1.00 [0.18, 5.67]
Fazekas 1997	12/75	19/75		82.2 %	0.56 [0.25, 1.26]
Subtotal (95% CI)	**95**	**95**		**100.0 %**	**0.62 [0.30, 1.29]**
Total events: 15 (Experimental), 22 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.35, df = 1 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 1.27 (P = 0.20)					
9 IFN -1a (Avonex) versus IFN -1b (Betaseron)					
INCOMIN 2002	32/92	15/96		100.0 %	2.88 [1.43, 5.79]

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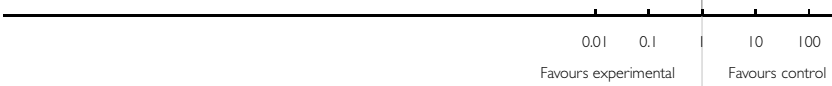
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
Subtotal (95% CI)	**92**	**96**		**100.0 %**	**2.88 [1.43, 5.79]**
Total events: 32 (Experimental), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.97 (P = 0.0030)					
10 IFN -1a (Rebif) versus IFN -1b (Betaseron)					
Koch-Henriksen 2006	69/143	77/158		100.0 %	0.98 [0.62, 1.54]
Subtotal (95% CI)	**143**	**158**		**100.0 %**	**0.98 [0.62, 1.54]**
Total events: 69 (Experimental), 77 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.93)					
11 Natalizumab versus IFN -1a (Avonex)					
SENTINEL 2006	267/589	334/582		100.0 %	0.62 [0.49, 0.78]
Subtotal (95% CI)	**589**	**582**		**100.0 %**	**0.62 [0.49, 0.78]**
Total events: 267 (Experimental), 334 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.12 (P = 0.000038)					
12 Glatiramer acetate versus IFN -1b (Betaseron)					
BEYOND 2009	166/448	730/1796		100.0 %	0.86 [0.69, 1.06]
Subtotal (95% CI)	**448**	**1796**		**100.0 %**	**0.86 [0.69, 1.06]**
Total events: 166 (Experimental), 730 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.39 (P = 0.17)					
13 Glatiramer acetate versus IFN -1a (Rebif)					
REGARD 2008	35/378	62/386		100.0 %	0.53 [0.34, 0.83]
Subtotal (95% CI)	**378**	**386**		**100.0 %**	**0.53 [0.34, 0.83]**
Total events: 35 (Experimental), 62 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.79 (P = 0.0052)					
Test for subgroup differences: Chi^2 = 34.14, df = 12 (P = 0.00), I^2 =65%					

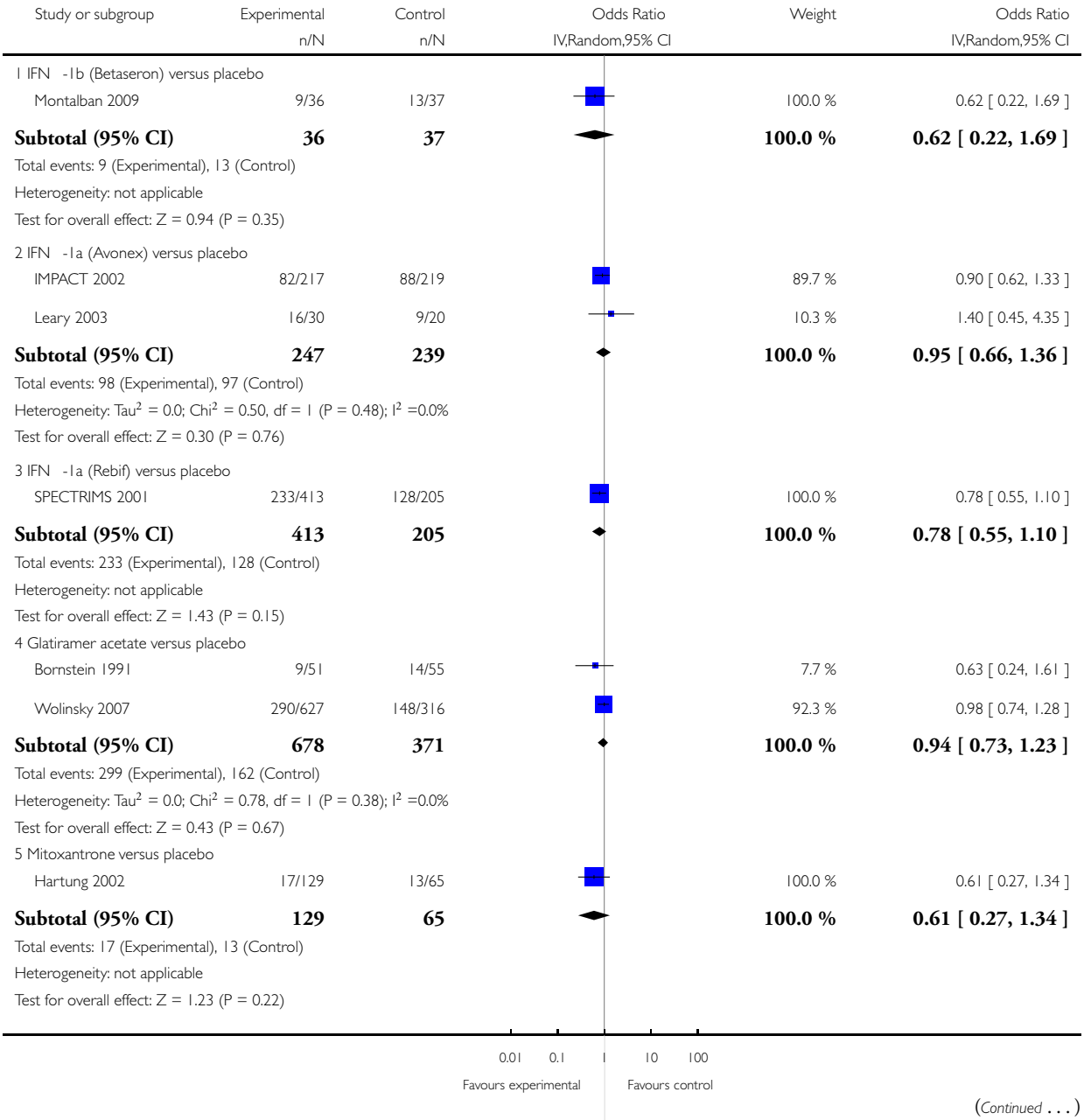


Analysis 4.3. Comparison 4 Comparisons for disability progression over 24 months, Outcome 3 Disability progression over 24 months in progressive MS.

Review: Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis

Comparison: 4 Comparisons for disability progression over 24 months

Outcome: 3 Disability progression over 24 months in progressive MS



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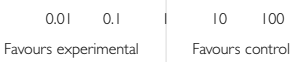
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
6 Immunoglobulins versus placebo					
Hommes 2004	77/159	70/159		51.8 %	1.19 [0.77, 1.86]
Pohlau 2007	56/116	72/115		48.2 %	0.56 [0.33, 0.94]
Subtotal (95% CI)	**275**	**274**		**100.0 %**	**0.83 [0.39, 1.74]**
Total events: 133 (Experimental), 142 (Control)					
Heterogeneity: Tau^2 = 0.23; Chi^2 = 4.74, df = 1 (P = 0.03); I^2 =79%					
Test for overall effect: Z = 0.50 (P = 0.62)					
7 Cyclophosphamide versus placebo					
Likosky 1991	15/22	16/22		100.0 %	0.80 [0.22, 2.94]
Subtotal (95% CI)	**22**	**22**		**100.0 %**	**0.80 [0.22, 2.94]**
Total events: 15 (Experimental), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					
8 Corticosteroids versus placebo					
Miller 1961	16/29	25/57		100.0 %	1.58 [0.64, 3.87]
Subtotal (95% CI)	**29**	**57**		**100.0 %**	**1.58 [0.64, 3.87]**
Total events: 16 (Experimental), 25 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.99 (P = 0.32)					
9 Methotrexate versus placebo					
Goodkin 1995	13/31	15/29		100.0 %	0.67 [0.24, 1.87]
Subtotal (95% CI)	**31**	**29**		**100.0 %**	**0.67 [0.24, 1.87]**
Total events: 13 (Experimental), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.76 (P = 0.45)					
10 Corticosteroids versus Mitoxantrone					
Edan 1997	6/21	1/21		100.0 %	8.00 [0.87, 73.68]
Subtotal (95% CI)	**21**	**21**		**100.0 %**	**8.00 [0.87, 73.68]**
Total events: 6 (Experimental), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.84 (P = 0.066)					
Test for subgroup differences: Chi^2 = 7.94, df = 9 (P = 0.54), I^2 =0.0%					

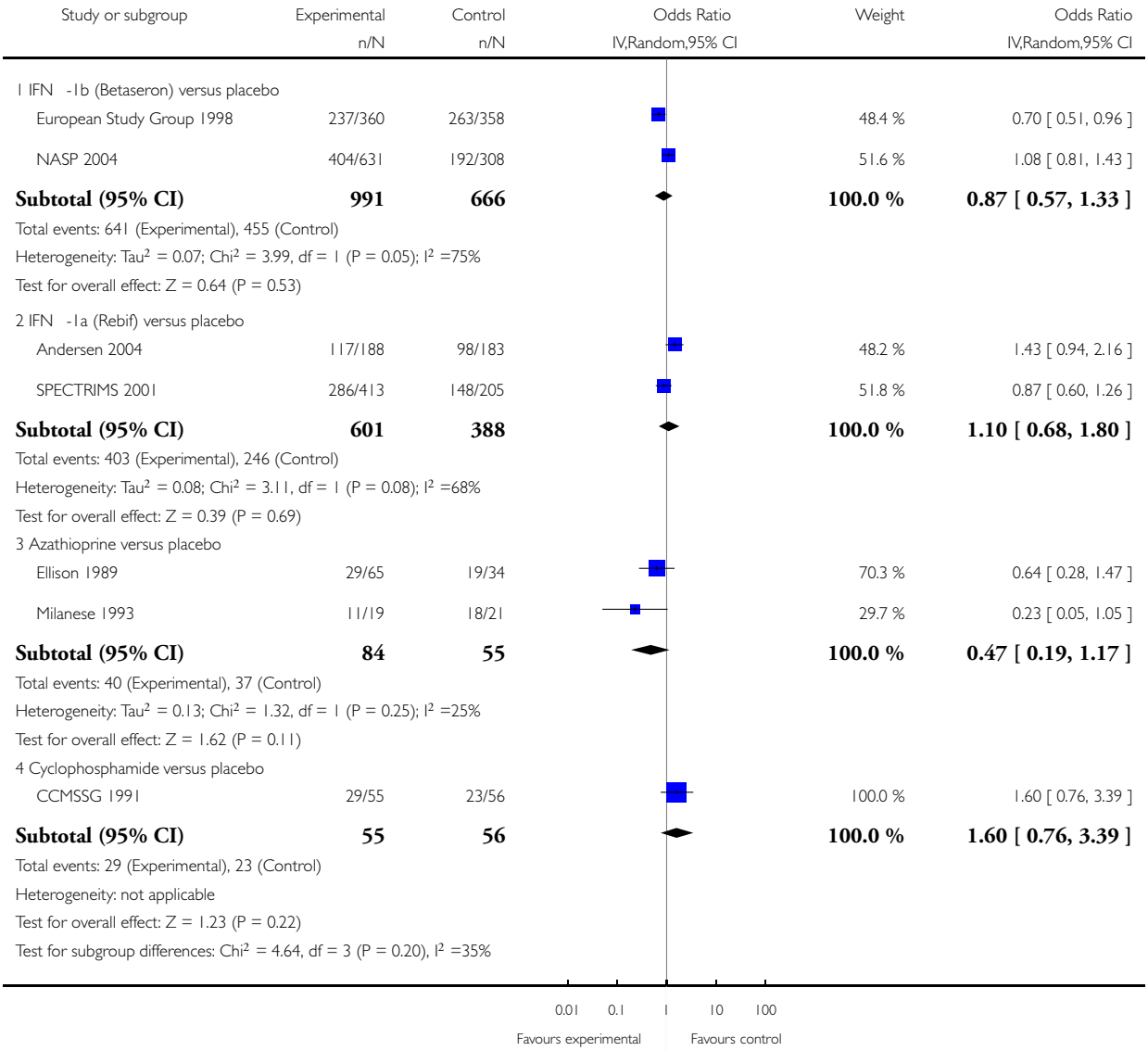


Analysis 5.1. Comparison 5 Comparisons for disability progression over 36 months, Outcome 1 Disability progression over 36 months in progressive MS.

Review: Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis

Comparison: 5 Comparisons for disability progression over 36 months

Outcome: 1 Disability progression over 36 months in progressive MS

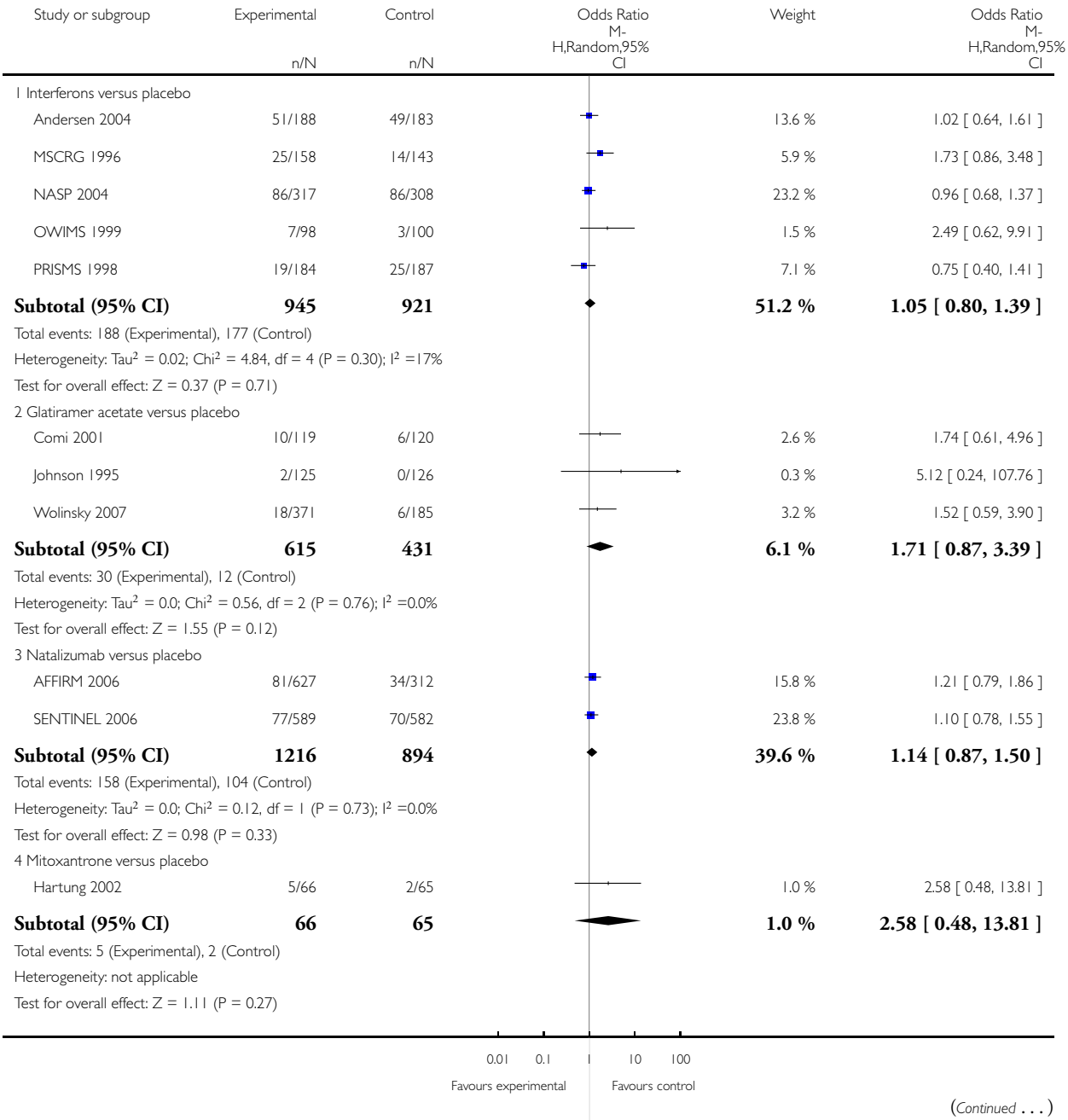


Analysis 6.1. Comparison 6 Comparison for adverse events, Outcome 1 Serious adverse events.

Review: Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis

Comparison: 6 Comparison for adverse events

Outcome: 1 Serious adverse events



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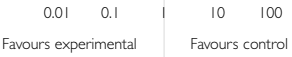
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
5 Intravenous immunoglobulins versus placebo					
Fazekas 2008	2/42	3/41		0.8 %	0.63 [0.10, 4.00]
Hommes 2004	6/159	1/159		0.6 %	6.20 [0.74, 52.07]
Pohlau 2007	4/116	1/115		0.6 %	4.07 [0.45, 36.99]
Subtotal (95% CI)	**317**	**315**		**2.1 %**	**2.28 [0.54, 9.74]**
Total events: 12 (Experimental), 5 (Control)					
Heterogeneity: $Tau^2 = 0.55$; $Chi^2 = 3.00$, df = 2 (P = 0.22); $I^2 = 33\%$					
Test for overall effect: Z = 1.12 (P = 0.26)					
Total (95% CI)	**3159**	**2626**		**100.0 %**	**1.14 [0.96, 1.35]**
Total events: 393 (Experimental), 300 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 12.55$, df = 13 (P = 0.48); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.51 (P = 0.13)					
Test for subgroup differences: $Chi^2 = 3.46$, df = 4 (P = 0.48), $I^2 = 0.0\%$					



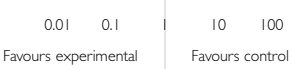
Analysis 6.2. Comparison 6 Comparison for adverse events, Outcome 2 Withdrawals due to adverse events.

Review: Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis

Comparison: 6 Comparison for adverse events

Outcome: 2 Withdrawals due to adverse events

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Interferons versus placebo					
Andersen 2004	16/188	6/183		5.0 %	2.74 [1.05, 7.18]
European Study Group 1998	45/360	15/358		10.6 %	3.27 [1.79, 5.98]
IFNB MS Group 1993	10/124	1/123		1.2 %	10.70 [1.35, 84.93]
IMPACT 2002	17/217	9/219		6.4 %	1.98 [0.86, 4.55]
Leary 2003	4/15	0/20		0.6 %	16.04 [0.79, 325.37]
MSCRG 1996	7/158	2/143		2.0 %	3.27 [0.67, 16.00]
NASP 2004	29/317	12/308		8.6 %	2.48 [1.24, 4.96]
OWIMS 1999	5/98	0/100		0.6 %	11.82 [0.64, 216.77]
PRISMS 1998	9/184	2/187		2.1 %	4.76 [1.01, 22.32]
SPECTRIMS 2001	18/204	5/205		4.6 %	3.87 [1.41, 10.64]
Subtotal (95% CI)	**1865**	**1846**		**41.7 %**	**3.08 [2.23, 4.26]**
Total events: 160 (Experimental), 52 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.49$, df = 9 (P = 0.79); $I^2 = 0.0\%$					
Test for overall effect: Z = 6.84 (P < 0.00001)					
2 Glatiramer acetate versus placebo					
Bornstein 1987	2/25	0/25		0.5 %	5.43 [0.25, 118.96]
Comi 2001	3/119	2/120		1.5 %	1.53 [0.25, 9.30]
Johnson 1995	5/125	1/126		1.1 %	5.21 [0.60, 45.23]
Wolinsky 2007	30/371	4/185		4.2 %	3.98 [1.38, 11.48]
Subtotal (95% CI)	**640**	**456**		**7.4 %**	**3.48 [1.55, 7.84]**
Total events: 40 (Experimental), 7 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.08$, df = 3 (P = 0.78); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.01 (P = 0.0026)					
3 Natalizumab versus placebo					
AFFIRM 2006	57/627	18/312		12.2 %	1.63 [0.94, 2.83]
SENTINEL 2006	65/589	53/582		19.0 %	1.24 [0.84, 1.81]
Subtotal (95% CI)	**1216**	**894**		**31.2 %**	**1.36 [0.99, 1.85]**
Total events: 122 (Experimental), 71 (Control)					



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Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.66, df = 1 (P = 0.42); I^2 =0.0%					
Test for overall effect: Z = 1.90 (P = 0.057)					
4 Azathioprine versus placebo					
British and Dutch 1988	17/174	3/180		3.1 %	6.39 [1.84, 22.21]
Ellison 1989	3/31	0/34		0.6 %	8.47 [0.42, 170.95]
Goodkin 1991	6/29	1/25		1.1 %	6.26 [0.70, 56.10]
Milanese 1993	4/19	1/21		1.0 %	5.33 [0.54, 52.73]
Subtotal (95% CI)	**253**	**260**		**5.7 %**	**6.35 [2.50, 16.11]**
Total events: 30 (Experimental), 5 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.06, df = 3 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 3.89 (P = 0.00010)					
5 Mitoxantrone versus placebo					
Hartung 2002	6/66	2/65		1.9 %	3.15 [0.61, 16.22]
Subtotal (95% CI)	**66**	**65**		**1.9 %**	**3.15 [0.61, 16.22]**
Total events: 6 (Experimental), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					
6 Intravenous immunoglobulins versus placebo					
Achiron 1998	1/20	1/20		0.6 %	1.00 [0.06, 17.18]
Fazekas 1997	3/75	1/73		1.0 %	3.00 [0.30, 29.52]
Hommes 2004	10/159	5/159		3.9 %	2.07 [0.69, 6.19]
Lewanska 2002	1/16	0/18		0.5 %	3.58 [0.14, 94.30]
Pohlau 2007	16/116	9/115		6.0 %	1.88 [0.80, 4.46]
Subtotal (95% CI)	**386**	**385**		**12.1 %**	**1.99 [1.07, 3.71]**
Total events: 31 (Experimental), 16 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.49, df = 4 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 2.18 (P = 0.029)					
Total (95% CI)	**4426**	**3906**		**100.0 %**	**2.41 [1.92, 3.03]**
Total events: 389 (Experimental), 153 (Control)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 27.90, df = 25 (P = 0.31); I^2 =10%					
Test for overall effect: Z = 7.52 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 19.85, df = 5 (P = 0.00), I^2 =75%					

ADDITIONAL TABLES

Table 1. Number of participants in each treatment group

Type of treatment	RCTs N	RRMS N = 9096	Progressive MS N = 7726	RRMS and progressive MS combined N = 579	All MS N = 17401
Azathioprine	5	30	65	286	381
Cyclophosphamide	2	0	77		77
Corticosteroids	3	19	50		69
Glatiramer acetate	7	1095	678		1773
IFNß-1b (Betaseron)	9	2347	1027		3374
IFNß-1a (Avonex)	7	1200	2647		3847
IFNß-1a (Rebif)	8	1464	601		2065
IV immunoglobulins	6	215	275		490
Methotrexate	1	0	31		31
Mitoxantrone	3	27	150		177
Natalizumab	2	1216	0		1216
placebo	36	1483	2125	293	3901

Table 2. Methods of adverse events monitoring

Study	Risk of bias	Did the researchers actively monitor for adverse events (AEs) (low risk of bias) or did they simply provide spontaneous reporting of AEs that arose (high risk of bias)?	Risk of bias	Did the authors define serious AEs (SAEs) according to an accepted international classification and report the number of SAEs?
Achiron 1998	Unclear	Not reported	High	SAEs not reported
AFFIRM 2006	Low	*"Treating neurologists were responsible for all aspects of patient care, including the man-*	Unclear	Insufficient information on SAEs definition

Table 2. Methods of adverse events monitoring (*Continued*)

		agement of adverse events". Participants *"visited the clinic every 12 weeks for ... blood chemical and hematologic analyses, evaluation of adverse events..."*		
Andersen 2004	Low	*"Adverse events and concomitant medications were recorded throughout the study, and clinical laboratory evaluation was performed at months 1, 3, and 6, and then at 6 monthly evaluation visits or as needed"*	Unclear	Insufficient information on SAEs definition
BEYOND 2009	Low	*"Clinic visits were scheduled every 3 months to assess ... safety, and tolerability. The occurrence of new neurological symptoms and adverse events was assessed by telephone, 6 weeks after each visit"*	Low	Categorisation of SAEs conformed to ICH guidelines (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use)
Bornstein 1987	High	*"Self-evaluation reported to a clinical assistant"*	High	SAEs not reported
Bornstein 1991	High	*"Self-reporting reported to a clinical assistant"*	High	SAEs not reported
BPSM 1995	Unclear	Not reported	Unclear	Insufficient information on SAEs definition
British and Dutch 1988	Unclear	*"The occurrence of side effects was notified to the trial centre every 3 months"*	High	SAEs not reported
CCMSSG 1991	Unclear	*"The external safety monitoring committee monitored the progress of the trial every 6 months (severe adverse experiences, deaths, clinical status)"*	High	SAEs not reported
Comi 2001	Unclear	*"The treating physician monitored safety..."*	Unclear	Insufficient information on SAEs definition
Edan 1997	Unclear	Not reported	Unclear	Insufficient information on SAEs definition

Table 2. Methods of adverse events monitoring (*Continued*)

Ellison 1989	Low	Participants*"were instructed to call the clinic anytime they suspected an adverse events and then actively monitored by neurologist"*	High	SAEs not reported
Etemadifar 2006	High	*"Given the lack of safety assessment of this trial, it is important to recall that the safety of IFN-b products in the treatment of RRMS had already been established for the three drugs in previous studies"*	High	SAEs not reported
European Study Group 1998	Low	*"Safety assessments included adverse events, vital signs, physical examinations, and concomitant medication. An independent advisory committee reviewed the results of regular interim safety analyses done after all* participants*had been in the study for at least 24 months"*	High	SAEs not reported
EVIDENCE 2007	High	*"Adverse events were determined by spontaneous reporting and monthly laboratory testing during the comparative phase"*	Unclear	Insufficient information on SAEs definition
Fazekas 1997	Low	Participants*"asked about safety monthly..."*	High	SAEs not reported
Fazekas 2008	Unclear	Not reported	Unclear	Insufficient information on SAEs definition
Ghezzi 1989	Unclear	Not reported	High	SAEs not reported
Goodkin 1991	High	*"Side effect were reported to the treating neurologist every 6 months"*	High	SAEs not reported
Goodkin 1995	Low	*"All* participants*maintained a daily diary of undesirable events… The adverse event diary was checked every 3 months by the study nurse during a clinical visit"*	High	SAEs not reported

Table 2. Methods of adverse events monitoring (*Continued*)

Hartung 2002	Unclear	Not reported	Unclear	Insufficient information on SAEs definition
Hommes 2004	Unclear	*"Several safety laboratory tests were done..."*	Unclear	Insufficient information on SAEs definition
IFNB MS Group 1993	Low	*"Treating neurologist reviewed side effects, laboratory findings for toxicity ..."*	High	SAEs not reported
IMPACT 2002	Unclear	*"An independent external Data and Safety Monitoring Committee reviewed safety data at three time points during the trial and performed a preplanned interim analysis after all subjects had been followed for 15 months"*	High	SAEs not reported
INCOMIN 2002	Low	*"Safety assessments included adverse events, vital signs, physical examination, and concomitant medications.* Participants*underwent haematology and biochemical tests, including liver-function tests, every 2 weeks for the first 8 weeks, and then every 3 months"*	High	SAEs not reported
Johnson 1995	Low	*"The evaluating physician monitored safety every 3 month..."*	Unclear	Insufficient information on SAEs definition
Knobler 1993	Unclear	Not reported	High	SAEs not reported
Koch-Henriksen 2006	Low	Participants*"were interviewed about side effects and had routine blood tests including hematology and liver function tests every 3 months and thyroid tests and neutralizing antibodies every 6 months"*	High	SAEs not reported

Table 2. Methods of adverse events monitoring (*Continued*)

Leary 2003	Low	*"AEs were monitored throughout the study..."*	High	SAEs not reported
Lewanska 2002	Unclear	*"Laboratory safety examinations were made at the beginning and at the end of the study period"*	Unclear	Insufficient information on SAEs definition
Likosky 1991	Unclear	Not reported	High	SAEs not reported
Milanese 1993	Unclear	Not reported	High	SAEs not reported
Millefiorini 1997	Low	*"The safety of the treatment was assessed on the basis of adverse events volunteered by the patient either spontaneously or on questioning and monitoring of the main laboratory parameters"*	Unclear	Insufficient information on SAEs definition
Miller 1961	Low	*"An independent observer unconnected with the trial, observed every 3 months the prednisolone* participants*to detect toxic effects"*	High	SAEs not reported
Montalban 2009	Low	*"Safety issues during the study were monitored by an independent Safety Committee.* Participants*were asked to report any adverse event,... the presence of adverse events and intercurrent illnesses was assessed at all visits"*	High	SAEs not reported
MSCRG 1996	Low	*"According to the FDA phase III requirements..."*	Unclear	Insufficient information on SAEs definition
NASP 2004	Unclear	*"As required by protocol, an Independent Data and Safety Monitoring Board (IDSMB) reviewed interim safety data every 6 months"*	Unclear	Insufficient information on SAEs definition
OWIMS 1999	Unclear	*"The treating physician recorded and treated AEs..."*	Unclear	Insufficient information on SAEs definition

Table 2. Methods of adverse events monitoring (*Continued*)

Pohlau 2007	Low	*"Safety and tolerability of the treatment were assessed by recording adverse events, vital signs and by laboratory findings. All adverse events and clinical symptoms related to the disease or the study medication were recorded every 4 weeks"*	Unclear	Insufficient information on SAEs definition
PRISMS 1998	Unclear	*"The treating physician treated AEs..."*	Unclear	Insufficient information on SAEs definition
REGARD 2008	Unclear	*"Adverse events (including pregnancy), withdrawals owing to adverse events, serious adverse events, and laboratory results were obtained for safety comparisons"*	Unclear	Insufficient information on SAEs definition
SENTINEL 2006	Low	*The treating neurologists were responsible for all patient care, including the management of adverse events and relapses of multiple sclerosis. Clinical visits every 12 weeks included (…) assessment of any adverse events.* Participants*were also seen by a treating neurologist during unscheduled visits within 72 hours after the development of new symptoms so that they could be assessed for possible relapses or adverse events"*	Unclear	Insufficient information on SAEs definition
SPECTRIMS 2001	Low	*"A treating physician supervised drug administration, monitored safety, and managed adverse events"*	High	SAEs not reported
Wolinsky 2007	Low	*"The treating neurologist supervised drug administration, recorded and treated adverse events"*	Unclear	Insufficient information on SAEs definition

Table 3. Model fit and parsimony measures for all the primary outcomes

	Posterior Residual Deviance (consistency model)	Data Points	DIC (consistency model)	DIC (inconsistency model)
Recurrence of relapses over 12 months	45	42	83	84
Recurrence of relapses over 24 months	60	51	104	106
Relapses over 36 months	12	12	22	22
Disability progression over 24 months	60	60	109	112
Disability progression over 36 months	14	14	28	28
Acceptability	54	57	85	86

Table 4. Network meta-analysis: summary results for recurrence of relapses at any time point, posterior ORs and their 95% credible intervals of all active interventions versus placebo and SUCRA values

	Recurrence of relapses over 12 months		Recurrence of relapses over 24 months		Recurrence of relapses over 36 months	
	Median OR (95%CrI)	SUCRA	Median OR (95%CrI)	SUCRA	Median OR (95%CrI)	SUCRA
Natalizumab	0.35 (0.12 to 1.06)	72%	0.29 (0.17 to 0.51)	92%	-	-
IFNß-1a (Rebif)	0.65 (0.27 to 1.59)	40%	0.44 (0.24 to 0.70)	73%	1.28 (0.40 to 4.05)	13%
Mitoxantrone	0.12 (0.03 to 0.55)	95%	0.43 (0.20 to 0.87)	71%	-	-
Glatiramer acetate	0.40 (0.11 to 1.15)	65%	0.48 (0.38 to 0.75)	66%	-	-
IFNß-1b (Betaseron)	0.54 (0.14 to 2.15)	50%	0.48 (0.29 to 0.78)	65%	0.69 (0.29 to 1.47)	64%
Azathioprine	0.63 (0.27 to 1.45)	42%	0.63 (0.39 to 0.97)	46%	0.43 (0.17 to 0.88)	94%

Table 4. Network meta-analysis: summary results for recurrence of relapses at any time point, posterior ORs and their 95% credible intervals of all active interventions versus placebo and SUCRA values (*Continued*)

Immunoglobulins	0.61 (0.22 to 1.31)	44%	0.69 (0.40 to 1.04)	41%	-	-
Corticosteroids	0.48 (0.10 to 2.29)	53%	1.13 (0.03 to 47.93)	36%	-	-
Methotrexate	-	-	1.16 (0.27 to 5.35)	23%	-	-
IFNß-1a (Avonex)	0.81 (0.33 to 1.99)	26%	0.96 (0.64 to 1.50)	19%	-	-

SUCRA: Surface below the Cumulative Ranking Curve. The larger the SUCRA value for a treatment, the higher its rank among the available treatment options.

Table 5. Network meta-analysis: summary results for disability progression at any time point, posterior ORs and their 95% credible intervals of all active intervnetions versus placebo and SUCRA values

	Disability progression over 24 months		**Disability progression over 36 months**	
	Median OR (95%CrI)	**SUCRA**	**Median OR (95%CrI)**	**SUCRA**
Mitoxantrone	0.42 (0.20 to 0.87)	89%	-	-
Natalizumab	0.61 (0.41 to 0.91)	74%	-	-
Glatiramer acetate	0.67 (0.49 to 0.88)	67%	-	-
Methotrexate	0.67 (0.22 to 2.04)	58%	-	-
Immunoglobulins	0.79 (0.53 to 1.17)	58%	-	-
IFNß-1b (Betaseron)	0.74 (0.54 to 1.00)	54%	0.87 (0.35 to 2.09)	59%
Azathioprine	0.75 (0.42 to 1.30)	54%	0.45 (0.13 to 1.31)	92%
Cyclophosphamide	0.79 (0.19 to 3.27)	49%	1.62 (0.40 to 6.56)	18%
IFNß-1a (Rebif)	0.79 (0.60 to 1.04)	47%	1.10 (0.45 to 2.79)	36%
IFNß-1a (Avonex)	1.06 (0.78 to 1.51)	18%	-	-
Corticosteroids	1.58 (0.58 to 4.35)	11%	-	-

SUCRA: Surface below the Cumulative Ranking Curve. The larger the SUCRA value for a treatment, the higher its rank among the available treatment options.

Table 6. Network meta-analysis: summary results for patients with RRMS for recurrence of relapses over 12 and 24 months and disability progression over 24 months, posterior ORs (95% credible intervals) of all active interventions versus placebo and SUCRA values

	Recurrence of relapses over 12 months		Recurrence of relapses over 24 months		Disability progression over 24 months	
	Median OR (95%CrI)	SUCRA	Median OR (95%CrI)	SUCRA	Median OR (95%CrI)	SUCRA
Mitoxantrone	0.13 (0.01 to 1.32)	85%	0.14 (0.03 to 0.55)	92%	0.11 (0.01 to 0.65)	96%
Natalizumab	0.35 (0.07 to 1.67)	65%	0.31 (0.19 to 0.55)	75%	0.62 (0.33 to 1.24)	55%
Immunoglobulins	0.36 (0.08 to 1.28)	63%	0.34 (0.13 to 0.69)	70%	0.63 (0.24 to 1.67)	52%
Azathioprine	0.76 (0.08 to 7.40)	36%	0.34 (0.08 to 1.30)	65%	0.51 (0.13 to 1.95)	61%
IFNß-1a (Rebif)	0.65 (0.19 to 2.29)	46%	0.46 (0.25 to 0.71)	53%	0.74 (0.40 to 1.32)	40%
Glatiramer acetate	0.36 (0.07 to 1.54)	63%	0.50 (0.29 to 0.71)	46%	0.52 (0.28 to 0.88)	70%
IFNß-1b (Betaseron)	0.54 (0.09 to 3.33)	47%	0.50 (0.31 to 0.82)	45%	0.67 (0.38 to 1.13)	50%
Corticosteroids	0.44 (0.04 to 4.86)	54%	1.17 (0.02 to 50.83)	31%	-	-
IFNß-1a (Avonex)	0.81 (0.23 to 2.90)	29%	1.10 (0.69 to 1.82)	10%	1.11 (0.64 to 2.16)	10%

SUCRA: Surface below the Cumulative Ranking Curve. The larger the SUCRA value for a treatment, the higher its rank among the available treatment options.

Table 7. Network meta-analysis: summary results for patients who dropped out (withdrawals or lost to follow-up) due to adverse events (posterior ORs and 95% credible intervals of all active interventions versus placebo and SUCRA values)

	Median OR (95%CrI)	SUCRA
Cyclophosphamide	0.51 (0.08 to 2.75)	82%
Mitoxantrone	0.70 (0.31 to 1.56)	81%

Table 7. Network meta-analysis: summary results for patients who dropped out (withdrawals or lost to follow-up) due to adverse events (posterior ORs and 95% credible intervals of all active interventions versus placebo and SUCRA values) (*Continued*)

Glatiramer acetate	0.93 (0.69 to 1.25)	70%
IFNß-1b (Betaseron)	0.94 (0.72 to 1.22)	69%
Natalizumab	1.04 (0.52 to 2.17)	57%
Azathioprine	1.34 (0.39 to 4.82)	43%
Immunoglobulins	1.23 (0.82 to 1.84)	40%
IFNß-1a (Rebif)	1.23 (0.85 to 1.74)	39%
IFNß-1a (Avonex)	1.37(0.86 to 2.25)	32%
Corticosteroids	2.95 (0.62 to 17.66)	17%
Methotrexate	4.37 (0.86 to 37.96)	8%

SUCRA: Surface below the Cumulative Ranking Curve. The larger the SUCRA value for a treatment, the higher its rank among the available treatment options.

APPENDICES

Appendix 1. Search Strategy for CDSR

#1MeSH descriptor Multiple Sclerosis, this term only
#2MeSH descriptor Multiple Sclerosis, Chronic Progressive, this term only
#3MeSH descriptor Multiple Sclerosis, Relapsing-Remitting, this term only
#4MeSH descriptor Myelitis, Transverse explode trees 3, 5 and 7
#5MeSH descriptor Optic Neuritis explode all trees
#6MeSH descriptor Encephalomyelitis, Acute Disseminated, this term only
#7MeSH descriptor Demyelinating Autoimmune Diseases, CNS, this term only
#8"multiple sclerosis":ti,ab,kw or "chronic progressive multiple sclerosis":ti,ab,kw or "progressive relapsing multiple sclerosis":ti,ab,kw or "secondary progressive multiple sclerosis":ti,ab,kw or "primary progressive multiple sclerosis":ti,ab,kw
#9"relapsing remitting multiple sclerosis":ti,ab,kw or "remitting-relapsing multiple sclerosis":ti,ab,kw or "acute relapsing multiple sclerosis":ti,ab,kw or "neuromyelitis optica":ti,ab,kw or "optic neuritis":ti,ab,kw
#10"devic disease":ti,ab,kw or "demyelinating disease":ti,ab,kw or (adem):ti,ab,kw or "demyelinating disorder":ti,ab,kw or "clinically isolated syndrome":ti,ab,kw
#11"transverse myelitis":ti,ab,kw or "acute disseminated encephalomyelitis":ti,ab,kw or (encephalomyelitis):ti,ab,kw
#12MeSH descriptor Demyelinating Diseases, this term only
#13(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
#14(#13) in Cochrane Reviews

Appendix 2. Keywords for searching for direct comparison studies

Interferon v Glatiramer Acetate

{interferon*} OR {interferon beta} OR {beta-1 interferon} OR {beta 1 interferon} OR {interferon beta-1*} OR {rebif} OR {avonex} OR {Betaseron} OR {beta-seron} OR {betaferon} OR {beta-IFN-1*} OR {interferon beta-1*} OR {Interferon-beta*} OR {interferon beta*} OR {recombinant interferon beta-1*}

AND

{copolymer-1} OR {cop-1} OR {copaxone} OR {glatiramer acetate} OR {cpx} OR {cop1} OR {copolymer} OR {glatiramer} OR {immunomodulation*} OR {immunomodulator*} OR {immunosuppression}

Interferon v Methotrexate

{interferon*} OR {interferon beta} OR {beta-1 interferon} OR {beta 1 interferon} OR {interferon beta-1*} OR {rebif} OR {avonex} OR {Betaseron} OR {beta-seron} OR {betaferon} OR {beta-IFN-1*} OR {interferon beta-1*} OR {Interferon-beta*} OR {interferon beta*} OR {recombinant interferon beta-1*}

AND

{methotrexate} OR {mexate} OR {dicesium salt methotrexate} OR {disodium salt methotrexate} OR {sodium salt methotrexate} OR {methotrexate hydrate} OR {(D)-isomer methotrexate} OR {(DL)-isomer methotrexate}

Interferon v Azathioprine

{interferon*} OR {interferon beta} OR {beta-1 interferon} OR {beta 1 interferon} OR {interferon beta-1*} OR {rebif} OR {avonex} OR {Betaseron} OR {beta-seron} OR {betaferon} OR {beta-IFN-1*} OR {interferon beta-1*} OR {Interferon-beta*} OR {interferon beta*} OR {recombinant interferon beta-1*}

AND

{azathioprine} OR {azathioprine} OR {immuran} OR {imuran} OR {imurel}

Interferon v Cyclophosphamide

{interferon*} OR {interferon beta} OR {beta-1 interferon} OR {beta 1 interferon} OR {interferon beta-1*} OR {rebif} OR {avonex} OR {Betaseron} OR {beta-seron} OR {betaferon} OR {beta-IFN-1*} OR {interferon beta-1*} OR {Interferon-beta*} OR {interferon beta*} OR {recombinant interferon beta-1*}

AND

{cyclophosphamide} OR {phosphoramide mustard*}

Interferon v Natalizumab

{interferon*} OR {interferon beta} OR {beta-1 interferon} OR {beta 1 interferon} OR {interferon beta-1*} OR {rebif} OR {avonex} OR {Betaseron} OR {beta-seron} OR {betaferon} OR {beta-IFN-1*} OR {interferon beta-1*} OR {Interferon-beta*} OR {interferon beta*} OR {recombinant interferon beta-1*}

AND

{antegren} OR {natalizumab} OR {tysabri}

Interferon v Mitoxantrone

{interferon*} OR {interferon beta} OR {beta-1 interferon} OR {beta 1 interferon} OR {interferon beta-1*} OR {rebif} OR {avonex} OR {Betaseron} OR {beta-seron} OR {betaferon} OR {beta-IFN-1*} OR {interferon beta-1*} OR {Interferon-beta*} OR {interferon beta*} OR {recombinant interferon beta-1*}

AND

{novantrone} OR {novantron} OR {onkotrone} OR {pralifan} OR {mitozantrone} OR {mitoxantrone}

Interferon v Corticosteroids

{interferon*} OR {interferon beta} OR {beta-1 interferon} OR {beta 1 interferon} OR {interferon beta-1*} OR {rebif} OR {avonex} OR {Betaseron} OR {beta-seron} OR {betaferon} OR {beta-IFN-1*} OR {interferon beta-1*} OR {Interferon-beta*} OR {interferon beta*} OR {recombinant interferon beta-1*}

AND

{adrenal cortex hormones} OR {steroid*} OR {methylprednisolone} OR {prednisolone} OR {dexamethasone} OR {corticosteroid*} OR {acth} OR {prednisone} OR {Adrenocorticotropic Hormone}

Interferon v Immunoglobulins
{interferon*} OR {interferon beta} OR {beta-1 interferon} OR {beta 1 interferon} OR {interferon beta-1*} OR {rebif} OR {avonex} OR {Betaseron} OR {beta-seron} OR {betaferon} OR {beta-IFN-1*} OR {interferon beta-1*} OR {Interferon-beta*} OR {interferon beta*} OR {recombinant interferon beta-1*}
AND
{immunoglobulin*} OR {intravenous immunoglobulin*} OR {iV immunoglobulin*}

Avonex v Rebif®
{beta-1a interferon} OR {beta 1a interferon} OR {interferon beta-1a} OR {rebif}
AND
{beta-1a interferon} OR {beta 1a interferon} OR {interferon beta-1a} OR {avonex}

Avonex v Betaseron
{beta-1a interferon} OR {beta 1a interferon} OR {interferon beta-1a} OR {avonex}
AND
{Betaseron} OR {beta-seron} OR {beta 1b interferon} OR {interferon beta1b } OR {IFNb-1b} OR {IFNbeta-1b} OR {interferon beta-1b}

HISTORY

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Date	Event	Description
17 January 2013	Amended	Converted to Intervention review format. Title changed accordingly

CONTRIBUTIONS OF AUTHORS

Concept - GF, GS

Title registration - GF

Protocol draft - GF, GS

Protocol editing - GF, GS, CDP, DB

Title and abstract review - GF, GS

Search strategy - DB

Data abstraction - GF, LV

Data entry - GF, LV

Data analysis - GS, CDG

Drafting the review - GF, GS, CDG, LV

Editing and revising the review - GF, GS, CDG, LV, RDA, CDP

DECLARATIONS OF INTEREST

GF - none

GS - none

CDG - none

DB - none

LV - none

RDA - none

CDP - None

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None