

Online Quiz

Test Your Knowledge: Ten Questions about Multiple Sclerosis

This quiz is related to a Perspective in the February issue of *PLoS Medicine* (DOI: 10.1371/journal.pmed.0020033).

Gavin Yamey

Question 1. Which is the most common form of multiple sclerosis (MS) at the onset of the disease?

- Primary progressive
- Secondary progressive
- Relapsing, remitting

Question 2. In Europe and North America, what is the approximate prevalence of MS?

- One in 100
- One in 400
- One in 800
- One in 1,500

Question 3. Which of the following is true about the epidemiology of MS?

- There is a gradient of increasing prevalence with increasing latitude
- There is a gradient of increasing prevalence with decreasing latitude
- There is a gradient of increasing prevalence with increasing longitude
- There is a gradient of increasing prevalence with decreasing longitude

Question 4. Based on clinical trial evidence, which of the following treatments is most effective for an acute relapse?

- Corticosteroids
- Plasma exchange
- Interferon beta

Question 5. Which of the following best reflects the evidence on using corticosteroids for treating an acute relapse of MS?

- The optimal dose, duration of treatment, and route of administration are unclear
- There is good evidence that 15 days of treatment is more effective than five days
- There is good evidence that giving corticosteroids for an acute relapse can help prevent further relapses

Question 6. Which of the following best reflects the evidence on interferon beta for treating MS?

- There is good evidence that it prevents disease progression in people with secondary progressive MS
- There is no value in giving it after a first demyelinating event
- There is some evidence that interferon beta can reduce exacerbations and disease progression in people with relapsing, remitting disease

Question 7. Which of the following treatments for fatigue in MS is well supported by high-quality evidence?

- Exercise
- Behavior modification
- Pemoline
- None of the above

Question 8. Which of the following best reflects our current knowledge of the relationship between stressful life events and acute exacerbations of MS?

- A meta-analysis found a consistent association between stressful life events and subsequent exacerbations
- Although some individual studies have suggested an association between the two, a meta-analysis of all of these studies found no consistent association
- While some studies have suggested an association between the two, they were retrospective case-control studies, and the association has not been shown in a prospective study

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Gavin Yamey is a senior editor at *PLoS Medicine*. E-mail: gyamey@plos.org

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Question 9. Which of the following best reflects the evidence on physiotherapy (physical therapy) as a treatment for spasticity in MS?

- There is good evidence that physiotherapy improves mobility and activities of daily living in people with progressive MS
- There is good evidence that physiotherapy improves mobility and activities of daily living in people with relapsing, remitting MS
- Although physiotherapy is a very common treatment for spasticity in MS, there is insufficient evidence from RCTs to be sure of its effectiveness

Question 10. Which of the following interventions for MS is best supported by clinical trial evidence?

- Hyperbaric oxygen to slow the progress of the disease
- Intravenous immunoglobulins to reduce the relapse rate and disease progression in relapsing, remitting disease
- Amantadine to reduce the fatigue of MS

Answer 1: Relapsing, remitting

In 90% of people, early disease is relapsing, remitting, characterized by episodes of neurological dysfunction interspersed with periods of stability. The other 10% have primary progressive disease, in which progressive neurological disability occurs from the outset. Most people with relapsing, remitting MS at presentation will go on to develop secondary progressive disease, usually about 6–10 years after onset [1].

In one study of the natural history of primary progressive MS (216 patients), the mean age of onset was 38.5 years, and the female:male ratio was 1.3:1 [2]. Relapsing, remitting MS typically begins in the second or third decade of life, and the female:male ratio is about 2:1 [3].

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3. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG (2000) Multiple sclerosis. *N Engl J Med* 343: 938–952.

Answer 2: One in 800

The prevalence of MS in Europe and North America is one in 800 people, with an annual incidence of two to ten cases per 100,000 people, making MS the most common cause of neurological disability in young adults [1,2].

Regions with the highest prevalence of MS are Europe, Israel, Canada, northern United States, southeastern Australia, New Zealand, and easternmost Russia [3]. Medium frequency areas include southern United States, most of Australia, South Africa, the southern Mediterranean basin, Russia into Siberia, the Ukraine, and parts of Latin America. Prevalence rates under five per 100,000 are found in the rest of Asia, Africa, and northern South America.

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3. Kurtzke JF (2000) Multiple sclerosis in time and space—Geographic clues to cause. *J Neurovirol* 6(Suppl 2): S134–S140.

Answer 3: There is a gradient of increasing prevalence with increasing latitude

One of the most striking epidemiological features of MS is a gradient of increasing prevalence with increasing latitude [1]. For example, in Australia, the risk of developing MS in temperate Tasmania is 5-fold that in subtropical Queensland [2].

A recent case-control study found that higher levels of sun exposure during childhood and early adolescence, and greater actinic damage (skin damage from sun exposure), are associated with a *reduced* risk of MS; this association persisted after adjustment for fair skin and exposure after onset of disease [3]. These findings suggest that ultraviolet radiation may be beneficial against MS, possibly through increasing vitamin D levels [3].

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2. McLeod JG, Hammond SR, Hallpike JF (1994) Epidemiology of multiple sclerosis in Australia. With NSW and SA survey results. *Med J Aust* 160: 117–122.
3. van der Mei IAF, Ponsonby AL, Dwyer T, Blizzard L, Simmons R, et al. (2003) Past exposure to sun, skin phenotype, and risk of multiple sclerosis: Case-control study. *BMJ* 327: 316.

Answer 4: Corticosteroids

One systematic review identified four randomized, controlled trials (RCTs) of methylprednisolone against placebo, and two of corticotrophin against placebo, in people with an acute exacerbation of MS (377 patients in total) [1]. Corticosteroids improved symptoms compared with placebo within the first five weeks of treatment.

One small, double-blind crossover RCT (22 people) provided insufficient evidence to assess the effects of plasma exchange in people with acute relapses of MS [2].

Interferon beta is used to prevent relapses and disability, not as a treatment for an acute relapse.

References

1. Filippini G, Brusaferrri F, Sibley WA, Citterio A, Ciucci G, et al. (2004) Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. *Cochrane Database Syst Rev* 2004: CD001331.
2. Weinshenker BG, O'Brien PC, Petterson TM, Noseworthy JH, Lucchinetti CF, et al. (1999) A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. *Ann Neurol* 46: 878–886.

Answer 5: The optimal dose, duration of treatment, and route of administration are unclear

While a systematic review did show that corticosteroids are effective at reducing symptoms of an acute relapse [1], there was insufficient evidence from the trials to determine the optimal dose, duration, and route of administration [1,2].

A small subgroup analysis using an indirect comparison suggested no difference between five days and 15 days of treatment with methylprednisolone.

One of the RCTs included in the systematic review [1] found no significant difference between oral methylprednisolone and placebo in the prevention of new relapses after one year.

References

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2. Boggild M, Ford H (2003) Multiple sclerosis. *Clin Evid* 2003: 1566–1581.

Answer 6: There is some evidence that interferon beta can reduce exacerbations and disease progression in people with relapsing, remitting disease

One systematic review identified seven RCTs comparing interferon beta with placebo in people with active relapsing, remitting MS (two relapses in the previous two or three years) [1]. The review found that, over two years, interferon significantly reduced the risk of exacerbations and disease progression compared with placebo.

Two RCTs found that interferon beta given to patients after a first demyelinating event significantly reduced the risk of a second clinical event and, therefore, of conversion to a definite diagnosis of MS [2,3].

Three RCTs provided insufficient evidence to assess the effects of interferon beta on disease progression in people with secondary progressive MS [4,5,6].

References

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3. Comi G, Fillipi M, Barkhof F, Durelli L, Edan G, et al. (2001) Effect of early interferon treatment on conversion to definite multiple sclerosis: A randomised study. *Lancet* 357: 1576–1582.
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6. Cohen JA, Cutter GR, Fischer JS, Goodman AD, Heidenreich FR, et al. (2002) Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. *Neurology* 59: 679–687.

Answer 7: None of the above

A systematic review of the RCTs of treatments for fatigue in MS found that exercise, behavior modification, and pemoline were all of “unknown effectiveness” [1].

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1. Boggild M, Ford H (2003) Multiple sclerosis. *Clin Evid* 2003: 1566–1581.

Answer 8: A meta-analysis found a consistent association between stressful life events and subsequent exacerbations

A recent meta-analysis, which included 14 individual studies, showed a significant increase in risk of exacerbation of MS after stressful life events [1]. Seven of the studies in the meta-analysis were prospective longitudinal studies.

References

1. Mohr DC, Hart SL, Julian L, Cox D, Pelletier D (2004) Association between stressful life events and exacerbation in multiple sclerosis: A meta-analysis. *BMJ* 328: 731.

Answer 9: Although physiotherapy is a very common treatment for spasticity in MS, there is insufficient evidence from RCTs to be sure of its effectiveness

There have been two small RCTs, which provided insufficient evidence to assess the effects of physiotherapy in people with spasticity due to MS [1,2]. The first RCT (40 patients) found limited evidence that twice-weekly hospital- or home-based physiotherapy for eight weeks briefly improved mobility compared with no physiotherapy. The second RCT, involving 45 people with progressive MS, found no significant difference between early (week 5) and delayed (week 13)

physiotherapy (two weeks of inpatient sessions) in mobility or activities of daily living.

References

1. Wiles CM, Newcombe RG, Fuller KJ, Shaw S, Furnival-Doran, et al. (2001) Controlled randomised crossover trial of the effects of physiotherapy on mobility in chronic multiple sclerosis. *J Neurol Neurosurg Psychiatry* 70: 174–179.
2. Fuller KJ, Dawson K, Wiles CM (1996) Physiotherapy in chronic multiple sclerosis: A controlled trial. *Clin Rehabil* 10: 195–204.

Answer 10: Intravenous immunoglobulins to reduce the relapse rate and disease progression in relapsing, remitting disease

In a Cochrane systematic review of RCTs of intravenous immunoglobulins for the secondary prevention of relapses and disease progression in MS, two trials met the inclusion criteria (involving a total of 168 patients) [1]. These found a reduction in relapse rate and increased time to first relapse during treatment with intravenous immunoglobulins.

Another Cochrane systematic review included nine RCTs of hyperbaric oxygen versus a sham therapy in patients with MS [2]. Two trials produced generally positive results, but the remaining seven reported generally no evidence of a treatment effect. The reviewers concluded, “We found no consistent evidence to confirm a beneficial effect of hyperbaric oxygen therapy for the treatment of multiple sclerosis and do not believe routine use is justified.”

A third Cochrane systematic review included four RCTs of amantadine in patients with MS-related fatigue [3]. The reviewers concluded that the quality of the studies was poor and that all trials were open to bias. All of the studies reported small and inconsistent improvements in fatigue, but the clinical relevance of these findings and the impact on patients’ functioning and health-related quality of life remained undetermined. The reviewers concluded, “Amantadine treatment is generally well tolerated, however its efficacy in reducing fatigue in people with MS is poorly documented.”

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