



# Therapeutics Today

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**Update on Amyotrophic Lateral Sclerosis.** Amyotrophic Lateral Sclerosis (ALS) is an idiopathic fatal neurodegenerative disease of the human motor system. A recent paper summarised current concepts about ALS and its management (*Lancet 2011; 377: 942-55*). European population-based studies have established the incidence of ALS to be 2.16/100,000; the overall lifetime risk of ALS is 1:400 for women and 1:350 for men. Peak age at onset is 58-63 years for sporadic disease (=90%) and 47-52 years for familial disease. **The clinical hallmark of ALS is the presence of upper motor neuron (UMN) and lower motor neuron (LMN) features** involving brainstem

and multiple spinal cord regions of innervation.

**Presentation:** Patients can present with limb-onset disease (70%), bulbar-onset (25%) or respiratory or trunk involvement (5%) which spreads to other parts of the body. Atypical symptoms such as weight loss (indicator of poor prognosis) or muscle cramps / fasciculations in the absence of muscle weakness, emotional lability, or frontal lobe-type cognitive dysfunction may also occur. **Diagnosis:** there is no diagnostic test for ALS therefore clinicians mostly rely on identifying the combination of UMN and LMN signs in the same body region with subsequent evidence of disease progression to other regions. There is often a long delay in definitive diagnosis (median time to diagnosis of about 14 months) because of the insidious onset of symptoms, a low index of suspicion or unusual presentation. **Differential diagnoses** include other disorders of motor neurons or nerves (including polio, paraneoplastic syndromes, hereditary disorders), disorders of neuromuscular junction (such as myasthenia gravis), myopathies (e.g. polymyositis), endocrine (e.g. thyrotoxicosis, vitamin B12 deficiency).

**Investigations** include nerve conduction studies, electromyography, MRI (especially useful for excluding alternative pathological causes); muscle biopsy may also be undertaken.

**Management:** Symptomatic treatments remain the cornerstone of management for ALS. Optimum care is provided within a multidisciplinary environment (including physiotherapists, occupational and speech therapists, respiratory and GI physicians as well as neurologists, and social workers); the involvement of these teams has been shown to reduce the risk of death by 45% at 5 years as well as providing a better quality of life for the patient. Key care concerns include respiratory management, nutrition and palliative care. The development of malnutrition is due not only to reduced food intake, secondary to dysphagia, but also to hypermetabolism (present in 50-60% of patients). **Pharmacotherapy:** Riluzole, is a disease-modifying (neuroprotective) therapy for patients with ALS. It has been shown to extend survival by 3-6 months; benefits appear to be greater in patients with moderate functional impairment and when the drug is administered in a multidisciplinary setting. The authors conclude that recent developments in the understanding of the pathophysiology of ALS will hopefully lead to new treatment approaches in the future.

[**Editor's note:** the paper notes that ALS patients are often willing to try unproven therapies, given the terminal nature of their disease. **An internet-based initiative has been established recently, which enables the exchange of information about new alternative and off-label treatments between patients with ALS and clinicians.** The goal of this initiative is to consolidate and convey information about cost, scientific and ethical basis, and potential benefits and risks of, every so-called treatment for ALS. Check out the website (which also lists the expert contributors on each article) at: <http://www.alsuntangled.com/index.html>]



### ***Statin therapy protects the heart in patients with diabetes.***

Cardiovascular disease is the major cause of morbidity and mortality in patients with diabetes mellitus (DM); the risk of myocardial infarction (MI) in diabetic patients without prior coronary heart disease (CHD) is similar to the risk in non-diabetic patients with CHD. Large randomised trials have produced conflicting results about the value of statins in DM. In addition, trial results may not easily translate into real-life usage because of the selection and meticulous follow-up of patients in such trials. A recent study aimed to evaluate whether good statin adherence was associated with a reduced incidence of a major coronary event among community-dwelling patients with DM ( $n > 60,000$  patients), using linked national healthcare databases in Finland (*BJCP 2011; 71: 766-76*). The study identified cases ( $n = 3,513$ ) of major coronary events in DM patients and matched them to DM patients with no coronary events ( $n = 20,090$  controls) during a 12-year review period. Statin adherence was defined as  $\geq 80\%$  proportion of days covered (via prescription records). In addition, the cases were divided into those with known CHD at baseline and those with no prior CHD. **Results showed that those with good statin adherence had significantly lower rates of acute MI, angioplasty, stenting and coronary bypass surgery, compared with those with poor adherence. The rate of risk reduction (15-20%) was similar in patients with / without prior CHD.** The risk reduction was maintained even when the findings were adjusted for factors known to be associated with good adherence (advanced age, female gender, and presence of co-morbidities). The benefits of good statin adherence persisted beyond 5 years of follow-up. The authors comment that the lack of data on glycaemic control and lifestyle activities may have distorted the results. However, because of the large numbers involved and the consistency of the results, they conclude that **these findings provide further justification for maintenance statin therapy in patients with diabetes mellitus.**



### ***Risk of atypical fractures with use of bisphosphonates.***

The European Medicines Agency (EMA) recently concluded its safety review of the risk of atypical fractures of the femur with use of bisphosphonates as a class. Bisphosphonates have been licensed for the treatment of osteoporosis since the mid 1990s. In 2008, the EMA concluded that use of alendronic acid was associated with an increased (albeit rare) risk of atypical (stress) fracture of the femur that occurred with little or no trauma. Since that time, the possibility of this occurring with other bisphosphonates has been kept under review. The CHMP (the EU scientific Committee for Human Medicinal Products) recently reviewed all case reports of stress fracture, relevant published literature, observational study reports as well as information from the manufacturers of bisphosphonates. It noted that the number of reported atypical fractures of the femur had increased since the 2008 review. **Moreover, the reported fractures had a distinct pattern on X-rays and appeared to be related to bisphosphonate use, especially long-term use.** Although the exact mechanism is not known, it is possible that this could be related to the mode of action of bisphosphonates, which might lead to a delay in the repair of naturally occurring stress fractures. The CHMP has recommended the following:

- Prescribers should be aware that atypical fractures of the femur may occur rarely with use of bisphosphonate-containing medicines
- If an atypical fracture is suspected in one leg, the other leg should also be examined
- The need for continued treatment of a patient with bisphosphonates should be reviewed regularly, especially after  $\geq 5$  years' use
- Patients, taking bisphosphonate-containing medicines, should be made aware of this risk and should be advised to report any pain, weakness or discomfort in the thigh or groin area to their doctor or pharmacist

This updated safety advice will be added to the EU prescribing information for all bisphosphonate-containing medicines in the near future. Further background information and a Q & A document are available at the following address:

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2011/04/WC500105281.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/04/WC500105281.pdf)