

Drugs used to treat joint and muscle disease

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Abstract

Joint disease: Arthritis can be simply broken into osteoarthritis and rheumatoid arthritis (RA). Osteoarthritis is treated with symptomatic pain relief and surgery. RA is a chronic autoimmune disease that causes inflammation of joints (leading to their destruction), tissues around joints and other organ systems. Treatment (for pain) of RA in the first instance is with non-steroidal anti-inflammatory drugs, with second-line treatment using disease-modifying antirheumatic drugs (DMARDs). DMARDs are a disparate group and include methotrexate, D-penicillamine, sulphasalazine, gold salts, antimalarial drugs and immunosuppressant drugs. The newer class of 'biological' DMARDs includes etanercept (tumour necrosis factor α (TNF- α) receptor-immunoglobulin G chimera), infliximab (monoclonal anti-TNF- α antibody), anakinra (interleukin 1 receptor antagonist) and rituximab (an anti-CD20 antibody that depletes B cells).

Muscle disease: Myasthenia gravis is an autoimmune disease targeted to muscle type nicotinic receptors. Treatment is based on improving neuromuscular function by: (i) increasing acetylcholine concentrations with neostigmine and pyridostigmine, (ii) immunosuppression, (iii) thymectomy and (iv) plasmapheresis. General muscle spasticity can be caused by a wide range of conditions including multiple sclerosis, cerebral palsy, Parkinson's disease and secondary to stroke. This can be treated centrally with baclofen, tizanidine and benzodiazepines or peripherally with dantrolene. Botulinum toxin inhibits the exocytosis of acetylcholine-containing vesicles and can be used for cervical dystonia, strabismus, blepharospasm, severe axillary hyperhidrosis and cosmetic procedures.

Keywords Arthritis; disease-modifying antirheumatics; gout; immunosuppressants; joint disease; muscle disease; myasthenia gravis; NSAIDs

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Joint disease

There are several classification systems available for joint disease (Figure 1). The simplest is inflammatory and non-inflammatory. Arthritis is a general term used to describe painful conditions of joints and bones. There are many types of arthritis, including osteoarthritis, rheumatoid, spondylitis, gout and psoriatic arthritis, Reiter's syndrome and lupus. Arthritis is the most common long-term condition in the UK, affecting 20% of adults (approximately 387,000 with rheumatoid). A similar pattern is seen in Europe as a whole (100 million with one form of arthritis) and in the USA (~70 million with arthritis, ~2 million with rheumatoid).

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Learning objectives

After reading this article, you should be able to:

- list the main joint and muscle diseases and their treatments
- describe the treatment options for arthritic disease, myasthenia gravis and muscle spasticity

1. Osteoarthritis: this is the most common joint disease and is often described as a disease of wear and tear. This disease affects around 8.5 million people in the UK alone, is more common in women and those who are overweight and affects a range of joints (knees, hips, hands and neck). There are important anaesthetic consequences relating to a reduced range of movement when the neck is affected. Typical degenerative changes include a thinning of joint cartilage, growth of osteophytes and increased synovial fluid production. Typical presenting symptoms are pain, joint stiffness, swelling and a reduced range of joint movement. Treatment options include pain control with non-steroidal anti-inflammatory drugs (NSAIDs) and surgery of the affected joint(s).

2. Rheumatoid arthritis (RA): RA is autoimmune in origin, more frequent in women, has a peak incidence in the 40–60-year age group and causes chronic inflammation of joints (leading to their destruction), tissues around joints and other organ systems. Multiple joints are involved and the symptoms can relapse and remit. Approximately 80% of patients are seropositive for rheumatoid factor (RF). Other blood results are consistent with an immune cause and include increased erythrocyte sedimentation rate, C-reactive protein and antinuclear antibodies. There are guidelines for the management of RA from the British Society for Rheumatology and British Health Professionals in Rheumatology.¹ These guidelines contain a comprehensive disease management algorithm for the first 2 years.

Pathogenesis – a basic understanding of the pathogenesis of RA is required to appreciate the current treatment strategies.² The initial stimulus for the production of RA is largely unknown, although an infectious 'trigger' may be present. The presence of this 'trigger' recruits a population of T cells, which interact with B cells and macrophages. Interaction with B cells results in the production of several antibodies; one of the more important is RF, which is involved in the diagnosis of RA. Via a range of cytokines and cell–cell contact, activated T cells interact with macrophages that go on to produce interleukin 1 (IL-1) and tumour necrosis factor α (TNF- α). Activation of macrophages and the production of these two cytokines is one of the main events that lead to a chronic inflammatory condition. IL-1 and TNF- α then interact with synovial fibroblasts, and chondrocytes in joint cartilage and osteoclasts in joint bone tissue. This ultimately leads to joint erosion and destruction. The linkage of these events to joint erosion/destruction is unclear, but the matrix metalloproteinases (MMPs) and aggrecanases are involved. These are enzymes capable of degrading extracellular matrix proteins. A schematic representation of the basic pathology and sites of current clinical intervention are shown in Figure 2.

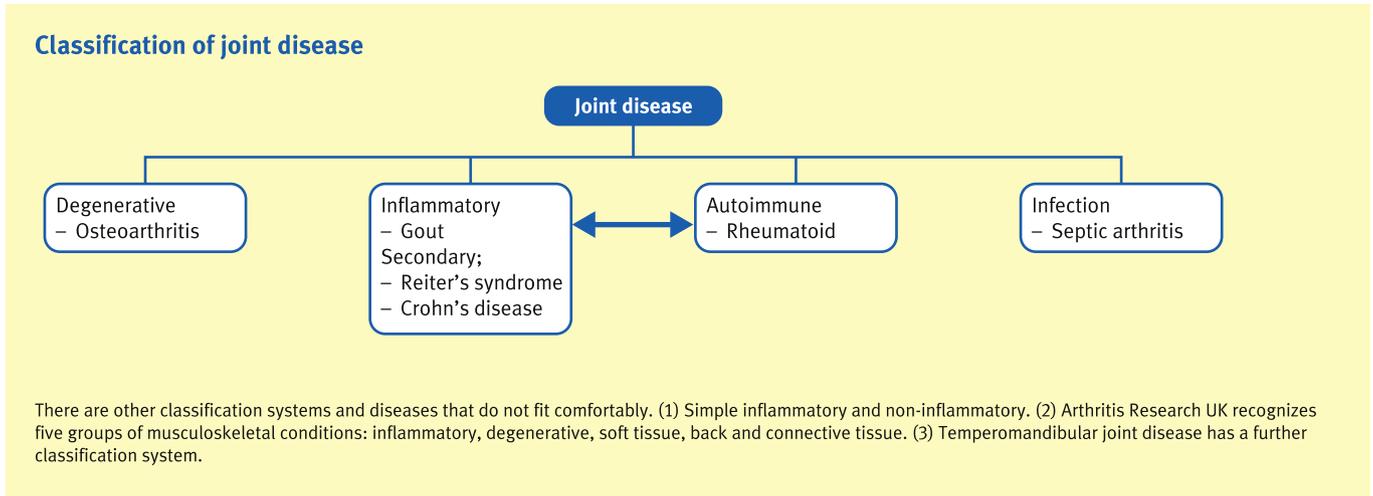


Figure 1

Treatment – this can be broken down into first-line use of NSAIDs for symptomatic (pain) control, second-line use of disease-modifying antirheumatic drugs (DMARDs), and newer ‘biological’ therapy. This last class could be considered as biological DMARDs.

First line: NSAIDs are the current first-line treatment. These variably block cyclo-oxygenase (COX) 1 or 2 and reduce

prostaglandin synthesis. This reduces pain, but has little effect on the immunological basis of the disease itself.

Side effects: all NSAIDs are associated with gastrointestinal (GI) toxicity. The Committee on Safety of Medicines classifies upper GI toxicity as highest for azapropazone and lowest for ibuprofen (piroxicam, ketoprofen, indometacin, naproxen and diclofenac are intermediate). Therefore, ibuprofen (as a non-selective COX inhibitor) should be used where appropriate. Although the risk of GI toxicity is reduced for COX-2-selective NSAIDs (e.g. the ‘COXIBs’), there is an increased risk of thrombotic events. For this and subsequent side-effect descriptions, the reader is advised to consult the *British National Formulary* and product information sheets.

Second line (DMARDs): As the name suggests, this group of pharmaceuticals modifies the inflammatory and destructive progress of the disease. It is a highly disparate group of compounds with complex (and often unproven) modes of action. This group includes methotrexate, D-penicillamine, sulphasalazine, gold salts, antimalarial drugs and immunosuppressant drugs. The evidence for DMARD use is to treat early and in combination. The current gold standard with which all other DMARDs are compared is methotrexate. The presumed site(s) of action and an estimate of clinical efficacy of the major DMARDs are illustrated in Table 1.

Side effects: these are variable and agent specific. Methotrexate produces the fewest side effects, which include nausea and vomiting, skin rashes and a range of blood test abnormalities. D-Penicillamine produces nausea and vomiting, anorexia, skin rashes and a range of blood test abnormalities. Sulphasalazine is a combination of salicylate and a sulphonamide, so reactions typical of sulphonamides are present and include GI disturbance, headache and general malaise. Gold salts can produce serious toxic effects, including hepatitis, peripheral neuropathy and encephalopathy. In addition, skin rashes and mouth ulcers are reported. Antimalarial drugs produce nausea and diarrhoea. Immunosuppressant drugs produce a range of effects specific to the agent but include increased risk of infection, nephrotoxicity, hepatotoxicity, neurotoxicity, hypertension and GI disturbances.

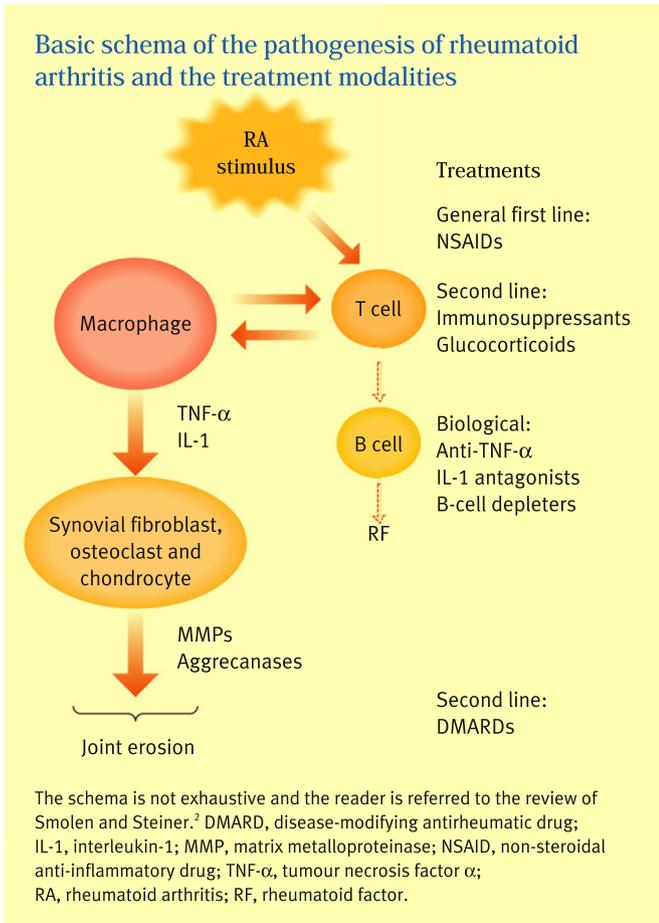


Figure 2

Some non-biological disease-modifying antirheumatic drugs and their main characteristics

	Site/mechanism of action ^a	Efficacy
Methotrexate	Inhibits dihydrofolate reductase, ↓ DNA synthesis	Most effective non-biological Onset in 4–6 weeks
D-Penicillamine	Anti-inflammatory via adenosine? Immune modulation via sulphhydryl exchange? Free radicals	Current 'gold standard' 30% improved pain at 6 months, but 36% dropout
Sulphasalazine	Eicosanoid formation? Chemokine activity? ↓ Transcription factor activity	31% improved pain at 6 months, but 39% dropout Onset 6 weeks to 3 months
Auranofin (gold)	Phospholipase C/A ₂ ? Lysosomes?	28% improved pain at 6 months, but 41% dropout Onset 4–6 months
Antimalarials	Lysosomes?	Moderate (low toxicity) Onset 2–4 months Consider failure if no effect after 4–6 months
Ciclosporin	Immunosuppressant	Decrease in the number of tender and swollen joints compared with placebo
Glucocorticoids	Immunosuppressant	Based on radiographs Reduce progression over 1–2 years
Leflunomide	Dihydroorotate dehydrogenase inhibitor (inhibits pyrimidine synthesis)	Similar to methotrexate Onset 4–8 weeks

Other gold salts include aurothiomalate Na⁺. Antimalarial drugs include chloroquine and hydroxychloroquine.

Other immunosuppressant drugs include azathioprine, cyclophosphamide and tacrolimus.

^a The literature is extensive, often contradictory and as such precise site/mechanism of action data are lacking. ↓, decreases.

Table 1

A note on treatment termination: the wide range of (often major) side effects noted above and variable efficacy lead to problems with patient compliance and specialist withdrawal. Patients take methotrexate for longer than sulphasalazine or gold. Sulphasalazine is withdrawn more often for lack of efficacy and gold for an unacceptable side-effect profile.³

Biological therapy: the main thrust of current therapy is based on blocking either TNF- α or IL-1 activity or depleting B cells. Of the biological agents that are available, those on which there are the most data are etanercept (TNF- α receptor–immunoglobulin (Ig)G chimera), infliximab (monoclonal anti-TNF- α antibody) and anakinra (IL-1 receptor antagonist). Using the American College of Rheumatology (ACR) response criteria of ACR20 (20% improvement in tender and swollen joint count and 20% improvement in a further three out of five indices of disease), the numbers needed to treat of 2.3 (95% confidence interval (CI) 2.0–2.6), 2.9 (95% CI 2.4–3.6) and 7.0 (95% CI 5.0–11.0) are reported for etanercept, infliximab⁴ and anakinra⁵ respectively. The NHS Health Technology Assessment classifies anakinra as modestly effective.⁵ These biological agents can be combined with methotrexate.⁶ Rituximab is an anti-CD20 antibody that depletes B cells and may be of use in combination with methotrexate when TNF- α /IL-1 therapy fails. The mechanism(s) by which B-cell depletion reduces RA progress is unclear, but it may involve reduction in B-cell secretion of autoantibodies and cytokines and reduction of B-cell/T-cell interaction.

Side effects: in general these agents reduce immune function and therefore increase the risk of infection. Injection site

reactions and nausea are common. Other agent-specific side effects include increased incidence of lymphoma for etanercept.

3. Gout⁷: This is a disease associated with elevated plasma urate, secondary to impaired purine metabolism. The disease affects around 1 in 200 and is more common in men. First onset is typically in middle age and there is a familial link. Urate crystals are deposited in the joints leading to an inflammatory reaction which includes white cell infiltration into the affected joint. Typically there are intermittent attacks. The treatment strategy for gout (in addition to dietary advice to avoid purine-rich foods and symptomatic pain control with NSAIDs) is to: (i) increase uric acid excretion by the kidney (with sulfinpyrazone, probenecid and benzbromarone), (ii) reduce uric acid synthesis (with allopurinol and febuxostat; this preventative treatment takes a few months to become effective) and (iii) reduce immune cell migration (with colchicine).

Muscle disease

A classification of muscle disease is presented in Figure 3.

The neuromuscular junction: It is worth covering in brief the neuromuscular junction (NMJ) as the main diseases of anaesthetic relevance and their treatment options are best described on this background (Figure 4). The NMJ is a specialized synapse (or junction) between a motor nerve and muscle end plate. An action potential traveling along a motor neurone reaches the presynaptic end of the neurone which depolarizes via an influx of Na⁺ ions which in turn leads to opening of voltage dependent Ca²⁺ channels and an influx of Ca²⁺. This increased intracellular Ca²⁺ in turn leads to Ca²⁺-mediated exocytosis of vesicles containing

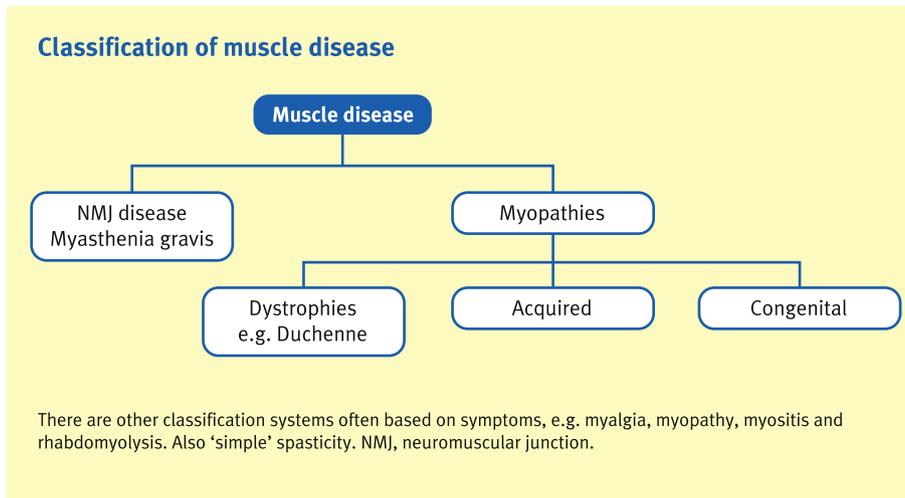


Figure 3

acetylcholine into the synaptic cleft or junctional space. Acetylcholine then interacts with muscle type nicotinic acetylcholine receptors to depolarize the muscle (producing an end plate potential). In the muscle the wave of depolarization uses the t-tubule system to release Ca^{2+} from the intracellular sarcolemmal store via the ryanodine receptor; this results in muscle contraction. Acetylcholine in the synapse is broken down by acetylcholinesterase enzymes with the resulting choline and acetate being recycled.

1. Myaesthesia gravis (Grave muscle weakness⁸): This disease affects around 1 in 10,000 in the UK alone and is more common in women under 40 years and men over 60 years of age. Myaesthesia gravis is an example of an autoimmune disease where the immunological target is the nicotinic acetylcholine receptor in the NMJ; the thymus is believed to be involved. Some of the initial distinguishing features are ptosis and diplopia, although fatiguability is important. Treatment options are based on improving any remaining neuromuscular

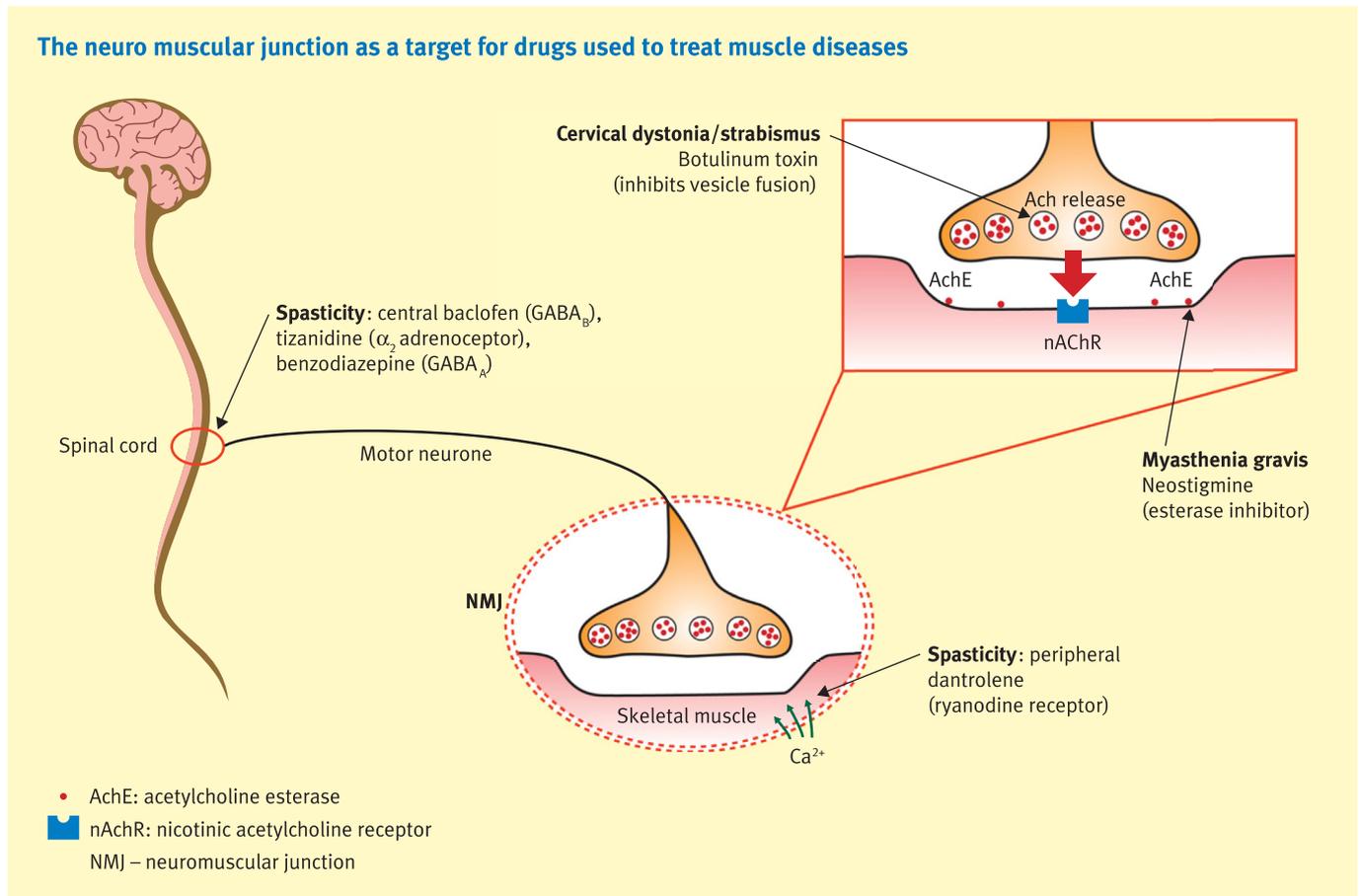


Figure 4

function by: (i) increasing acetylcholine concentrations with cholinesterase inhibitors (neostigmine and pyridostigmine) but these may increase muscarinic receptor activation with attendant side effect profiles, (ii) immunosuppression, (iii) thymectomy and (iv) plasmapheresis. Lambert-Eaton myasthenic syndrome is also an autoimmune disease but the target is the voltage-dependent Ca^{2+} channel. This condition can be treated with amifampridine (a K^+ channel inhibitor that enhances acetylcholine release).

Whilst discussing cholinesterase inhibitors it is also worth remembering the well-known pseudocholinesterase deficiency affecting the metabolism of suxamethonium (and also ester local anaesthetic agents and mivacurium).⁹ This can be acquired (e.g. pregnancy) or congenital.

2. Treatment of muscle spasticity:^{10,11} This is skeletal muscle hypertonia and can be caused by a wide range of conditions including multiple sclerosis, cerebral palsy, Parkinson's disease and secondary to stroke. From this description it is no surprise that the treatment options can be broken into those involving central and peripheral sites of action. Of the centrally active drugs used to treat spasticity baclofen (sometimes via implantable pump), targeting the γ -amino butyric acid (GABA) receptor is the best example. GABA receptors are classified into types A, B and C. The type A is well known as a target for most anaesthetic agents. The GABA_A–GABA receptor system is inhibitory and the GABA_B receptor (unlike A and C which are ligand gated ion channels) is a G-protein coupled receptor family member. Activation of this receptor with baclofen inhibits activation of spinal polysynaptic and monosynaptic motor neurones. Other centrally acting agents that reduce 'motor tone' include tizanidine which is an α_2 -adrenoceptor agonist that produces presynaptic inhibition of motor neurones. The anxiolytic benzodiazepines also have antispastic activity by facilitating the postsynaptic actions of GABA. The main peripherally acting agent is dantrolene which is a ryanodine receptor antagonist and inhibits the release of Ca^{2+} from intracellular stores in the sarcoplasmic reticulum. This agent is best known to anaesthetists as part of the treatment regimen for malignant hyperthermia (where there is unregulated sarcoplasmic reticulum Ca^{2+} release in response to a number of triggering agents¹²). There is some evidence (anecdotal and other) to suggest that cannabis-based medicines may have a role to play in the control of spasticity associated with multiple sclerosis.¹³

Botulinum toxin^{14,15} – this is an interesting poison associated with botulism (from *Clostridium botulinum*) and the cosmetic industry where local injection of a very low dose produces facial muscle paralysis and removal of 'wrinkles'. Botulinum toxin is comprised of seven neurotoxins (types A–G). These toxins are endopeptidases that attack vesicle fusion proteins involved in the exocytosis of acetylcholine-containing vesicles and hence muscle contraction. Botulinum toxin A and E target SNAP-25 (synaptosome-associated protein of 25 kDa); B, D, F and G target VAMP (vesicle-associated membrane proteins) 1 and 2; and C targets Syntaxin 1–3 and SNAP-25. The main botulinum toxin products available are Botox[®], Xeomin[®] and Dysport[®] (toxin type A) and Myobloc[®] (toxin type B). In addition to

cosmetic use these products are variably used for the treatment of cervical dystonia, strabismus, blepharospasm and severe axillary hyperhidrosis. ◆

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 Multiple Sclerosis Society: <http://www.mssociety.org.uk/>
 Muscular Dystrophy Campaign: <http://www.muscular-dystrophy.org/>