Evidence-based Management of Neurological Disease (2012)

CPLD reviews its distance learning programmes every twelve months to ensure currency. This update has been produced by an expert and should be read in conjunction with the Evidence-based Management of Neurological Disease (2012) distance learning course. Where updated information has been provided, we have indicated the relevant section and page number in Evidence-based Management of Neurological Disease (2012) for your reference. All updated information is available to download from www.nicpld.org

Pharmacists are reminded that information contained in this addendum is correct at the time of publication (November 2015) but it is their responsibility to keep up-to-date with any changes in practice.

Section 1: Epilepsy

Page 14. A new practical clinical definition of epilepsy has now been published: Fisher RS, Acevedo C, Arzimanoglou A et al. A practical clinical definition of epilepsy. Epilepsia 2014; 55(4): 475-482 available at http://www.ilae.org/visitors/centre/documents/Definition2014-RFisher.pdf
Epilepsy is a disease of the brain defined by any of the following conditions
1. At least two unprovoked (or reflex) seizures occurring >24 hours apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
3. Diagnosis of an epilepsy syndrome
Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

Page 24. The address for the ILAE classification proposals has changed:
http://www.ilae.org/visitors/centre/definition_class.cfm

Page 30. Antiepileptic Medicines - in 2013 the MHRA published a statement regarding switching formulations of antiepileptic drugs (AEDs), in response to ongoing debate about the need for individuals with epilepsy to remain on a consistent manufacturer's product. The report places each AED in one of 3 categories depending on pharmacokinetic characteristics. For category 1 drugs a consistent brand is recommended, for category 2 it is individual choice, and for category 3 consistent supply is thought to be unnecessary for most people. This report has been controversial and practice still varies in different parts of the UK.

Pages 33, 40, 46-48, 54 and **64**. New warnings and restrictions have been issued by the MHRA regarding use of medicines related to valproate in women. This is based on data showing that children exposed to valproate during pregnancy may have delays in their early development such as talking, walking and low intellectual abilities. Further details including patient and healthcare professional information booklets are available at https://www.gov.uk/drug-safety-update/medicines-related-to-valproate-risk-of-abnormal-pregnancy-outcomes
In summary:

- children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and/or congenital malformations (in approximately 10% of cases)
- valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated
- valproate must be started and supervised by a specialist
- female patients prescribed valproate must be given and understand comprehensive information regarding risks and measures to avoid them
- If a woman taking valproate is considering or becomes pregnant, alternative treatments should be considered. If valproate treatment is continued during pregnancy, strategies for risk reduction and monitoring are suggested

Page 35. Buccal midazolam is now licensed for acute treatment of prolonged seizures in children.

Page 36 and **42**. In December 2012 the MHRA published an update about risks of skin related adverse reactions to carbamazepine. A new allele, HLA-A*3101, may increase the risk in patients of European descent or Japanese origin. There is insufficient data currently to support genetic screening before treatment. The MHRA recommends that for people in these groups who are known to be positive for this allele, a careful risk/benefit assessment should be undertaken before starting carbamazepine or the related drugs oxcarbazepine and eslicarbazepine. For further information see:
http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con214991.pdf

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Page 37. Gabapentin is now licensed as monotherapy; levetiracetam is licensed as add on therapy only.

Page 38. Paraldehyde is an unlicensed medicine.

Page 39. Retigabine's license now restricts it to use only where other appropriate drug combinations have failed. This is due to reports of blue-grey discolouration of nails, lips, skin and ocular tissue and visual impairment. Comprehensive ophthalmological examinations are required before treatment and at 6 month intervals.

Page 39 and **50**. A new antiepileptic drug, perampanel, is now available in the UK, licensed as add on therapy for focal seizures. See BNF (section 4.8.1) for further details including interactions.

Page 40. Stiripentol is licensed for add on therapy.

Page 41. Zonisamide is now licensed for monotherapy of focal seizures.

Page 50. Interactions advice has changed slightly; see the latest BNF for up to date advice.

Page 56. Driving - regulations about driving and epilepsy have been updated and are more complex. For full information see
http://www.gov.uk/current-medical-guidelines-dvla-guidance-for-professionals-conditions-d-to-f

Page 62. Regarding phenytoin formulations and conversions: BNF comment has changed and now states phenytoin base 92mg (liquid or chewable tabs) is equivalent to phenytoin sodium 100mg (capsules). Previously this stated 90mg instead of 92mg. However, in practice dose conversions are still based on the 90mg figure.

In February 2013, NICE published a new Quality Standard for the Epilepsies.
Available at: http://publications.nice.org.uk/quality-standard-for-the-epilepsies-in-adults-qs26

Section 2 – Parkinson's disease

Pages 82, 97 and **108**. In 2014 the MHRA restricted the use of domperidone to nausea and vomiting, introduced new contra-indications and reduced the recommended doses and duration of use. This was due to concerns over risk of QT prolongation, especially in the elderly, those with other risk factors and those on other medicines which may cause QT prolongation. Parkinson's disease however was specifically highlighted as an example where there may be a clinical need for higher doses or durations of domperidone than those authorised. Domperidone is still commonly used in Parkinson's disease, but with more caution than previously. For example, some centres have amended their regimens for domperidone before and during treatment with apomorphine, using lower doses and shorter durations before considering whether it is feasible to discontinue domperidone.

Page 91. The PD MED trial has been completed and the results have been published in The Lancet (27 September 2014; Vol. 384, Issue 9949, Pages 1196-1205). Based on patient-rated mobility scores, levodopa had very small but persistent benefits compared to dopamine agonists and MAO B inhibitors. MAO B inhibitors as initial therapy were at least as effective as dopamine agonists. A cost utility analysis is to be reported separately.

Page 98. A new NICE guideline was published in August 2012: Urinary incontinence in neurological disease: management of lower urinary tract dysfunction in neurological disease (CG148). Text in course is still appropriate but for further information see: www.nice.org.uk

Page 98. A licensed formulation of midodrine is now available in the UK. NICE has published an evidence summary for midodrine for orthostatic hypotension (ESNM61). Text in course is still appropriate but for further information see: https://www.nice.org.uk/advice/esnm61/chapter/Full-evidence-summary

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Section 3 – Multiple Sclerosis

Page 125. Disease Management – NICE clinical guideline 186 'Multiple sclerosis: management of multiple sclerosis in primary and secondary care' was issued in October 2014. This recommends oral methylprednisolone 500mg daily for 5 days for relapses. IV methylprednisolone 1g daily for 3-5 days can be considered as an alternative if the relapse is severe, oral steroids have failed/not been tolerated, or if people need admitting to monitor eg diabetes or depression.

Page 126. The MHRA released a warning in December 2013 regarding a possible risk of thrombotic microangiopathy with interferon beta.
A pegylated version of interferon beta-1a is now available, peginterferon beta-1a, which allows subcutaneous injections every two weeks.
A new formulation of glatiramer is now available with a dose regimen of 40mg three times weekly as an alternative to the original formulation given 20mg daily.

Page 128. Comments regarding fingolimod are ambiguous.
1) Text on page 128 says 'fingolimod is licenced for adults with highly active relapsing-remitting MS who have high disease activity despite treatment with interferon beta'. It is also licensed for rapidly evolving severe relapsing remitting MS, but text implies there is only the 1 licensed indication.
2) Text on page 130 says 'it is not licensed for first line treatment'. This is correct in that it is not a first line option for any/every patient with RRMS. However for the subgroup of RRMS patients with rapidly evolving MS (which is strictly defined in the SPC) it would be a first line option. The current statement is therefore potentially misleading.

Page 128. Further warnings regarding cardiac risks of fingolimod have been issued, with contraindications in certain patients groups, and extra monitoring advised.
For further information see the MHRA Drug Safety Bulletin January 2013
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON228738 and the product SPC:
http://www.medicines.org.uk/emc/medicine/24443/SPC/Gilenya+0.5mg+hard+capsules/

Page 128. NICE guidance for fingolimod was issued in April 2012. Fingolimod is recommended as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults, only if:
• they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon, and
• the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme.
NICE Technology Appraisal Guidance (TA254) Fingolimod for the treatment of highly active relapsing remitting multiple sclerosis is available at: http://publications.nice.org.uk/fingolimod-for-the-treatmentof-highly-active-relapsingremitting-multiple-sclerosis-ta254

Page 128. Alemtuzumab is now licensed for MS (for two courses only) and not for B cell lymphocytic lymphoma – see NICE technology appraisal guidance 312 'Alemtuzumab for treating relapsing-remitting multiple sclerosis' issued in May 2014 for up to date information. Two additional oral disease modifying therapies have been licensed for RRMS: teriflunomide and dimethyl fumarate. See NICE technology appraisal guidance 303 'Teriflunomide for treating relapsing–remitting multiple sclerosis' issued in January 2014 and modified in June 2014, and NICE technology appraisal guidance 320 'Dimethyl fumarate for treating relapsing-remitting multiple sclerosis' issued in August 2014 for further information.

Page 129. Choice of Disease Modifying Therapy – The ABN have published revised guidance on disease modifying treatments: Scolding N, Barnes D, Cader S et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. These guidelines are published online at http://pn.bmj.com/content/early/2015/06/20/practneurol-2015-001139 and are to be used in conjuction with the NICE technology appraisals for individual medicines. The ABN guidelines give an overview of the available diseases modifying treatments, subdividing them categories of moderate and high efficacy. They include revised recommendations for starting and stopping disease modifying treatments. First line options (as approved by NICE or via the Risk Sharing Scheme) for anyone with active RRMS are now beta interferon, glatiramer, teriflunomide, dimethyl fumarate and alemtuzumab (although in practice alemtuzumab would usually be confined to those with higher disease activity). Natalizumab is available first line for those with higher disease activity only.

Page 132. Fatigue - NICE clinical guideline 186 recommends offering amantadine for MS-related fatigue. It also recommends a supervised exercise programme to treat fatigue.

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Page 133. NICE has published an evidence summary (ESUOM9) for modafinil for fatigue. Information in course is still appropriate but further information available at: http://www.nice.org.uk/mpc/evidencesummariesunlicensedofflabelmedicines/ESUOM9.jsp

Page 133. Spasticity - NICE clinical guideline 186 recommends using baclofen or gabapentin first line for spasticity. The two can be combined if the individual drugs do not provide adequate relief or if side effects prevent the dose from being increased. Tizanidine or dantrolene are recommended second line, and benzodiazepines third line (NB benzodiazepines may be beneficial for nocturnal spasms). The oromucosal cannabinoid spray nabiximols (Sativex®) is not recommended to treat spasticity in people with MS because it is not a cost-effective treatment.

Page 136. A new NICE guideline was published in August 2012: Urinary incontinence in neurological disease: management of lower urinary tract dysfunction in neurological disease (CG148). Text in course is still appropriate but for further information see: www.nice.org.uk

Page 138. Pain - NICE clinical guideline 186 recommends treating neuropathic pain in people with MS according to NICE clinical guideline 173 'Neuropathic pain – pharmacological management'.

Page 139. Vision - NICE clinical guideline 186 recommends gabapentin first line for oscillopsia (moving images) and memantine second line.

Page 139. Walking Disability - fampridine is not recommended in NICE clinical guideline 186 to treat lack of mobility in people with MS because it is not a cost-effective treatment. A supervised exercise programme is recommended to treat mobility problems.

Page 139. Emotional lability (excessive emotional reactions and frequent mood changes) can also be experienced by people with MS. NICE clinical guideline 186 recommends considering amitriptyline to treat this symptom.

Page 141. Omega-3 or omega-6 fatty acid compounds (linoleic or linolenic acid) are not recommended in NICE clinical guideline 186 to treat MS as there is no evidence that they affect relapse frequency or progression of MS.

Page 146. Note that there are various alternative disease modifying treatments, including oral agents, that Jenny could potentially switch to if adverse effects are persistently troublesome.

Section 4 – Motor Neurone Disease

Page 153. Paragraph under Table 17: 'extramotorsystems' is a typo; this should read extramotor symptoms

Page 154. A new European guideline on ALS was published in 2012. The updated guideline states that the newer Awaji electrodiagnostic algorithm, used in conjunction with the El Escoria criteria, improve early diagnosis. (Anderson PM, Abrahams S, Borasio GD et al. EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) – revised report of an EFNS task force. Eur J Neurol 2012; 19 (3): 360-375).

Page 162. A new NICE guideline was published in August 2012: Urinary incontinence in neurological disease: management of lower urinary tract dysfunction in neurological disease (CG148). Text in course is still appropriate but for further information see: www.nice.org.uk

Section 5 – Myasthenia gravis

Page 178. New UK guidelines on MG have been published by the ABN, compiled from evidence-based practice where available and established best practice where evidence is unavailable: Sussman J, Farrugia ME, Maddison P et al. Myasthenia Gravis: Association of British Neurologists' management guidelines. Pract Neurol 2015; 15: 199-206. The 2015 ABN guidelines include a dosing protocol for starting and withdrawing pyridostigmine. The initial starting dose recommended is 30mg four times daily. The guidelines also suggest mebeverine as an alternative option to propantheline for muscarinic side effects.

Page 180. The 2015 ABN guidelines include dosing protocols for starting and withdrawing prednisolone. They recommend starting with a low dose and gradually increasing, including in inpatients, except for those patients in intensive care units who are ventilated and should be commenced on a high dose.

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Page 182. The 2015 ABN guidelines recommend that (steroid sparing) immunosuppressants are introduced only if a patient does not achieve remission on corticosteroid monotherapy. However they suggest that requiring more than prednisolone 15-20mg on alternate days maintenance, or presence of intolerable corticosteroid side effects, would be an indication for immunosuppression. Early immunosuppression should be considered in diabetes mellitus, osteoporosis, ischaemic heart disease or significant bulbar/respiratory weakness that does not respond rapidly to corticosteroids. Azathioprine is recommended as the first-line immunosuppressant and testing for thiopurine methyltransferase (TPMT) is recommended. The guidelines also recommend considering relevant vaccinations/update of vaccinations before starting immunosuppression where feasible.

Page 184. Ocular MG – for further information see new European guidelines (Kerty E, Elsais A, Argov Z et al. EFNS/ENS Guidelines for the treatment of ocular myasthenia. Eur J Neurol 2014; 21 (5): 687-693).

Page 187. See Table 23: comment box relating to oestrogens and progesterone should be blank. It should not read 'Exacerbations common when initiated, starting low and gradually increasing dose appears to reduce risk'. Information has been superimposed from the row above by mistake.

Page 187. Table 23 listing some medicines that may exacerbate MG is based on a key reference which has been updated. The table is not exhaustive so does not require updating but for further information see: Mehrizi M, Fontem RF, Pascuzzi RM. Medications and myasthenia gravis; a reference for healthcare professionals. Published 2012 by The Myasthenia Gravis Foundation of America Inc. http://www.myasthenia.org/HealthProfessionals/EducationalMaterials.aspx

Of note, there have been reports of bisphosphonates exacerbating MG.

Page 195. The Myasthenia Gravis Association is now called Myaware and has a new website www.myaware.org

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