

The purpose of the Medicines Management newsletter is to deliver succinct, evidence-based advice and information on primary care prescribing issues. Aimed at busy prescribers wanting to know key messages from the many publications in the previous month.

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1. Round up of what's in the news

Triple therapy in the management of chronic obstructive pulmonary disease: systematic review and meta-analysis.

Zheng Y, Zhu J, Liu Y, Lai W et al. BMJ 2018;363:k4388. <http://dx.doi.org/10.1136/bmj.k4388>

Triple therapy with long acting muscarinic antagonists (LAMA), long acting β 2 agonists (LABA), and inhaled corticosteroids (ICS) are commonly used in patients with chronic obstructive pulmonary disease (COPD). Meta-analyses have previously shown that triple therapy using multiple inhalers can improve forced expiratory volume in 1 second (FEV1) and health status, but evidence of triple therapy versus dual therapy for preventing exacerbations is not well documented.

In this meta-analysis of 21 trials, moderate to high quality evidence indicated that use of triple therapy significantly decreased the risk of moderate or severe COPD exacerbations compared with dual therapy (of ICS and LABA, or LAMA and LABA) or LAMA monotherapy, together with improvements in lung function, and in a range of other clinically relevant measures. Triple therapy should be limited to patients with more severe COPD symptoms that cannot be adequately managed by dual therapy. Results suggested that triple therapy delivered in a single inhaler is non-inferior to the use of multiple inhaler in terms of clinical efficacy, but this needs further examination

Local COPD guidance states

- Triple therapy is reserved for exceptional use only.
- It remains unclear whether there is a benefit from using the triple combination. Use only in severe disease in the presence of persistent exacerbations despite other treatment.
- The quality adjusted life years for triple therapy ranges from £35,000 to £130,000, rendering triple therapy as the least cost effective intervention.

(Triple therapy is currently under review by NICE)

Deleted products 2018 | MIMS online November 2018

Benzoyl peroxide (Brevoxyl)
Lofexidine (Britlofex)
Naltrexone (Nalorex)
Probiotic (VSL#3)
Levetiracetam (Desitrend Oral Solution)

2. Drug safety update primarily relating to primary care prescribing

(For more information see [Drug Safety Update](#))

Hydrochlorothiazide: risk of non-melanoma skin cancer, particularly in long-term use

Advise patients taking hydrochlorothiazide-containing products of the cumulative, dose-dependent risk of non-melanoma skin cancer, particularly in long-term use, and the need to regularly check for (and report) any suspicious skin lesions or moles. Counsel patients to limit exposure to sunlight and UV rays and to use adequate sun protection.

Systemic and inhaled fluoroquinolones – there is a small increased risk of aortic aneurysm and dissection.

Advice for healthcare professionals:

- systemic (by mouth or injection) and inhaled fluoroquinolones may be associated with a small increased risk of aortic aneurysm and dissection, particularly in older patients
- fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients at risk for aortic aneurysm and dissection
- conditions predisposing to aortic aneurysm and dissection include:
 - a family history of aneurysm disease

- o diagnosis with pre-existing aortic aneurysm and/or aortic dissection
- o other risk factors or conditions predisposing for aortic aneurysm and dissection (for example, Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, and known atherosclerosis)
- advise patients, particularly elderly people and those at risk, about rare events of aortic aneurysm and dissection and of the importance of seeking immediate medical attention in case of sudden-onset severe abdominal, chest or back pain

3. Local news and GP/pharmacist queries

GP Query

Question:

My patient has been prescribed ondansetron for nausea/vomiting in pregnancy. Is there any local information about this use?

Answer:

SPS Q&A (Dec 2017):

- Most cases of nausea and vomiting in pregnancy (NVP) resolve within 16-20 weeks with no harm to the pregnancy.
- Prescribing treatment in the first trimester is usually not indicated unless the symptoms are debilitating.
- The choice of drug will be based on its adverse effect profile as well as its efficacy and safety in pregnancy. Availability of suitable preparations and patient preference are also relevant.
- NICE recommend that non pharmacological treatments should be tried first, such as changes in diet, use of ginger or wrist acupressure.
- No drug is specifically licensed for the treatment of NVP though some anti-emetics are considered useful for NVP and compatible with pregnancy.
- First line recommended treatment, by the Royal College of Obstetricians and Gynaecologists (RCOG), is currently an antihistamine such as promethazine or cyclizine, both of which can cause sedation. It is suggested that prochlorperazine be used with caution due to the risk of dystonic reactions in young pregnant women.
- Second line treatments, as recommended by RCOG, are domperidone and metoclopramide due to concerns about maternal side effects.
- There is a growing body of evidence on the use of ondansetron in pregnancy, which generally shows no increased incidence in the risk of major malformations and other pregnancy outcomes. There are some concerns about cardiac and kidney malformations in neonates born to women using ondansetron during pregnancy but overall, data are reassuring. The RCOG advise that other anti-emetics, such as anti-histamines, should therefore be tried first.
- Doses of antiemetic drugs used for NVP correspond with doses used for their licensed indications.
- This Medicines Q&A does not discuss treatment of **severe NVP, or hyperemesis gravidarum**, which affects around 1% of pregnant women. These cases should be managed in hospital by specialists.

The Derbyshire traffic light classification for ondansetron is BROWN after consultant/specialist initiation: for off-licence use in hyperemesis gravidarum (the specialist to specify the dose and length of treatment for the patient).

The University hospital of Derby and Burton have a [management guideline](#) which details the use of ondansetron as a 2nd line treatment option.

Local news

GREATIX- learning from excellence

Portal for POSITIVE news -

'We have fairly recently introduced something called Greatix (learning from excellence) <https://www.derbyhospitals.nhs.uk/greatix-learning-from-excellence/submit-a-greatix/>

Unlike most systems that normally focus on avoiding harm, learning from errors etc., this is an opportunity to highlight and share good practice. The 'Greatix' team will contact a person or team you have nominated to tell them their good work has been celebrated.'

4. Medicines safety issues

Extended use beyond labelled expiry date for selected lots of Jext® 150 mcg and 300 mcg

Adrenaline Auto-Injectors

This letter is sent in agreement with the MHRA to inform you of the following:

"To ease the current shortage of adrenaline auto injectors, ALK has obtained acceptance from the MHRA to extend the use of specific lot (batch) numbers of Jext® 150 mcg and Jext® 300 mcg autoinjectors, beyond the labelled expiry date by four months. The affected lot numbers are available on www.jext.co.uk."

Important: the extended use only applies to the lots of Jext® 150 mcg and Jext® 300 mcg autoinjectors listed on jext website. Patients can continue to use the Jext® auto-injectors of these specified lots safely until the extended use by date as stated. This extended use does not apply to any other lot number of Jext® auto injectors not specified. Patients must continue to adhere to the labelled expiry date on any Jext® auto injector not covered by the lot numbers above.

Actions for GP practices - Valproate medicines (Epilim®, Depakote®): Contraindicated in women and girls of childbearing potential unless conditions of Pregnancy Prevention Programme (PPP) are met.

You will be aware that the MHRA have recently issued warnings regarding Valproate medicines and that these medicines must no longer be used in women or girls of childbearing potential unless a Pregnancy Prevention Programme (PPP) is in place.

As a sub group of the Joint Area Prescribing Committee (JAPC), the Derbyshire Medicines Safety Network have been tasked with ensuring effective communication and implementation of the requirements of the MHRA Drug Safety Update for Valproate medicines and ensuring compliance with the alert across all providers in Derbyshire.

All women and girls (and their parent, caregiver, or responsible person, if necessary) must be fully informed of the risks and the need to avoid exposure to Valproate medicines in pregnancy.

The following actions for GPs are required by the MHRA:

- identify and recall all women and girls on Valproate medicines who may be of childbearing potential
- provide the Patient Guide to the patient (or her parents or responsible person as necessary)
- check they have been reviewed by a specialist in the last year (i.e., they have an in-date Risk Acknowledgement Form) and are on highly effective contraception

Our Derbyshire secondary care providers have confirmed that they have not yet received many referrals to review relevant existing patients on Valproate medicines. We believe that a number of these patients are under primary care only, and hence will need specialist referral.

Derbyshire CCGs have sent out a letter to all Derbyshire GP practices outlining information on local progress with this important issue and asks for assurance that the MHRA requirements have been met.

GP practices are required to respond to this letter by 31st December 2018 to:

- acknowledge receipt of this letter and the MHRA Valproate medicines alerts
- confirm that your practice has completed the actions required in the MHRA Valproate medicines alerts
- confirm that your practice has implemented a robust process for the on-going annual review of women or girls of childbearing potential prescribed Valproate medicines (to also include any newly registered patients on valproate medicines).

5. Quality, Innovation, Productivity and Prevention (QIPP)

October 2018 – price concessions

Prescribers should note that the re-imburement price on FP10 may not necessarily reflect the Drug Tariff price as a result of a drug shortage. These concessionary prices are set by the Department of Health to reflect actual market prices.

A concession only lasts until the end of the month in which it was granted. If there is an on-going supply problem, it is possible that a new concession will be granted by the Department of Health the following month, however this is not guaranteed

| Drug | Pack size | Price concession | Drug tariff price |
|---|-----------|------------------|-------------------|
| Allopurinol 100mg tablets | 28 | £2.54 | £0.57 |
| Allopurinol 300mg tablets | 28 | £5.83 | £1.09 |
| Amisulpride 100mg tablets | 60 | £8.25 | £4.89 |
| Amisulpride 200mg tablets | 60 | £13.40 | £6.01 |
| Amisulpride 50mg tablets | 60 | £5.22 | £2.76 |
| Brimonidine 0.2% eye drops | 5ml | £3.17 | £1.50 |
| Buprenorphine 2mg sublingual tablets sugar free | 7 | £5.25 | £0.95 |
| Buprenorphine 8mg sublingual tablets sugar free | 7 | £15.40 | £2.14 |
| Diamorphine 10mg powder for solution for inj amps | 5 | £15.47 | £12.26 |
| Furosemide 40mg tablets | 28 | £2.49 | £0.57 |
| Hydroxocobalamin 1mg/1ml solution for inj amps | 5 | £9.50 | £7.35 |
| Lamotrigine 100mg tablets | 56 | £20.76 | £9.01 |
| Lamotrigine 200mg tablets | 56 | £24.17 | £12.09 |
| Lamotrigine 50mg tablets | 56 | £8.95 | £5.42 |
| Latanoprost 50micrograms/ml eye drops | 2.5ml | £9.50 | £1.69 |
| Lercanidipine 10mg tablets | 28 | £4.02 | £3.09 |
| Lercanidipine 20mg tablets | 28 | £7.87 | £3.24 |
| Levetiracetam 100mg/ml oral solution sugar free | 300ml | £27.30 | £7.55 |
| Losartan 50mg tablets | 28 | £1.40 | £0.84 |
| Metronidazole 400mg tablets | 21 | £7.00 | £2.73 |
| Naproxen 250mg tablets | 28 | £2.30 | £0.92 |
| Naproxen 500mg tablets | 28 | £5.00 | £1.31 |
| Nebivolol 5mg tablets | 28 | £6.54 | £1.15 |
| Nicorandil 10mg tablets | 60 | £3.39 | £2.00 |
| Ondansetron 4mg tablets | 10 | £16.59 | £0.85 |
| Orlistat 120mg capsules | 84 | £24.01 | £17.40 |
| Propranolol 10mg tablets | 28 | £3.07 | £0.88 |
| Propranolol 40mg tablets | 28 | £2.72 | £0.89 |
| Propranolol 80mg tablets | 56 | £5.00 | £1.36 |

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| Ramipril 2.5mg tablets | 28 | £3.93 | £1.28 |
| Ramipril 5mg tablets | 28 | £5.54 | £0.83 |
| Ramipril 10mg tablets | 28 | £5.00 | £1.03 |
| Risperidone 1mg tablets | 20 | £4.80 | £0.58 |
| Risperidone 2mg tablets | 60 | £20.00* | £1.51 |
| Risperidone 3mg tablets | 60 | £37.02 | £1.82 |
| Risperidone 4mg tablets | 60 | £25.70 | £1.96 |
| Risperidone 500microgram tablets | 20 | £3.03 | £0.63 |
| Sevelamer 800mg tablets | 180 | £60.02 | £31.52 |
| Tadalafil 5mg tablets | 28 | £28.50 | £6.87 |
| Telmisartan 40mg tablets | 28 | £9.31 | £1.17 |
| Topiramate 50mg tablets | 60 | £9.38 | £7.19 |
| Topiramate 100mg tablets | 60 | £18.68 | £14.64 |
| Valsartan 40mg capsules | 28 | £5.15 | £1.98 |
| Valsartan 160mg capsules | 28 | £11.95 | £3.32 |
| Valsartan 80mg capsules | 28 | £9.95 | £2.89 |

*The reimbursement price for Risperidone 2mg was previously £1.80, the reimbursement price for October has been increased following further negotiation with DHSC

6. NICE summaries: New medicines (relating to primary care prescribing)

- [NG109](#) - Urinary tract infection (lower): antimicrobial prescribing
- [NG110](#) - Prostatitis (acute): antimicrobial prescribing
- [NG111](#) - Pyelonephritis (acute): antimicrobial prescribing
- [NG112](#) - Urinary tract infection (recurrent): antimicrobial prescribing

7. Useful resources

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| BMJ | www.thebmj.com |
| JAMA: The Journal of the American Medical Association | http://jama.ama-assn.org/ |
| The Lancet | www.thelancet.com |
| The New England Journal of Medicine | http://content.nejm.org/ |
| BMJ, JAMA and NEJM can be accessed in full-text directly through your NHS Athens Account via: National Library for Health: search via My Journals MyAthens: Via National Library for Health Resources or Local Resources. Current Lancet articles are sometimes available with free registration from http://www.thelancet.com/content/register . Print copies of The Lancet are available at DCGH library. | www.library.nhs.uk or www.athens.ac.uk |
| If you have not already registered for an NHS Athens Account, please register at: NB: It is recommended that you register on a Trust (NHS) PC for speedy confirmation of your username a password. Once registered, your account can be accessed from any computer with online access. | https://register.athensams.net/nhs/nhseng/ |
| UKMI Nathnac NHS evidence Electronic medicines compendium Clinical Knowledge Summaries Medicines Prescribing Centre (Formerly NPC) Medicines for children (patient information leaflets Drugs in lactation | http://www.ukmi.nhs.uk/ https://www.evidence.nhs.uk/search?om=%5B%7B%22srn%22%3A%5B%22%20ukmi%20%22%5D%7D%5D http://www.nathnac.org/ http://www.evidence.nhs.uk/ http://www.medicines.org.uk/emc/ www.cks.nhs.uk http://www.nice.org.uk/mpc/ http://www.medicinesforchildren.org.uk/ http://www.midlandsmedicines.nhs.uk/content.asp?section=6&subsection=17&pageldx=1 |
| UK teratology services | http://www.uktis.org/index.html |
| Vaccine update- Vaccination newsletter for health professionals and immunisation practitioners | https://www.gov.uk/government/organisations/public-health-england/series/vaccine-update |