Derbyshire Medicines Management Newsletter

www.derbyshiremedicinesmanagement.nhs.uk

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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.

1. What's in the news

DTB Vol 55 no. 6 June 2017

Turning the tide of high-dose inhaled corticosteroids.

In the late 1990s, attention turned to the role that ICS might play in the management of COPD. In recent years, there has been concern expressed at the extent of high-dose ICS use, in part because of the cost to the NHS but also because of adverse effects. These include an increase in the incidence of pneumonia in people with COPD treated with high-dose ICS.

The new British asthma guideline has veered away from using 'stepping up' terminology and instead discusses options for 'trials of treatment' with assessment of response. In addition the asthma guideline proposes the option of adding a leukotriene antagonist prior to increasing the dose of ICS from low to medium. In COPD, a long-acting muscarinic antagonist (LAMA) in combination with a LABA is now preferred to LABA+ICS in terms of reduction in exacerbation rate. Furthermore, there is research supporting a strategy of withdrawal of the ICS component from some patients with COPD on 'triple therapy' (LABA+ICS+LAMA).

Locally the asthma guidance is under review, with a view to bringing the guidance in line with NICE national guidance, once this is published. The local COPD guidance has recently been updated with inclusion of LABA/LAMAs as a preferred option over LABA/ICS, with Ultibro (indacaterol & glycopyrronium inhaler) being the LABA/LAMA of choice (GREEN 1st line option, based on the emerging evidence)

More on gastric acid suppression and C. difficile risk

A large systematic review and meta-analysis of observational studies has attempted to clarify whether medicines that suppress gastric acid increase the risk of recurrence of Clostridium difficile infection (CDI).

The review included 16 observational studies with a total of 7,703 patients with CDI. The rate of recurrent CDI in patients with gastric acid suppression was 22.1% (892/4,038 patients) compared with 17.3% (633/3,665) in patients without gastric acid suppression (odds ratio [OR] 1.52, 95% CI 1.20 to 1.94; p<0.001). There was substantial heterogeneity among studies (I2=64%). Subgroup analyses of studies adjusted for age and potential confounders confirmed an increased risk of recurrent CDI with use of gastric acid suppression (OR 1.38, 95% CI 1.08 to 1.76; p=0.02).

When PPIs and H2RAs were assessed separately, meta-analyses revealed an increased risk of CDI recurrence with PPIs (OR 1.66, 95% CI 1.18 to 2.34; p=0.04).

Comment: This study adds some weight to a possible association between PPIs and recurrence of CDI. However, the results have to be viewed with caution as data from observational studies may be affected by confounding factors. There were variations in the studies included in this systematic review, such as differences in design, definition of recurrence of CDI, drugs used for gastric suppression and other features of the populations studied, which could all be confounding factors. Despite the lack of firm evidence for causality, Public Health England guidelines recommend that consideration be given to stopping or reviewing the need for PPIs in patients with or at high risk of CDI. The Health Protection Network, NHS Scotland also recommends stopping any antimotility agents and gastric acid suppressant agents (including PPIs), if possible, following a first episode of CDI.

Local PPI guidance states:

"The risk of acquiring Clostridium difficile (C. difficile) associated diarrhoea is approximately 2–3 times higher in PPI users than in non-users and there is a 42% increased risk of recurrent C. difficile due to PPI use. It has therefore been suggested that all PPIs are discontinued in patients diagnosed with C. difficile, as they may also increase the risk of recurrence. Alternatively, it may be appropriate to withhold the PPI for the duration of any future courses of broad spectrum antibiotics."

The role of contraindications in prescribing anticoagulants to patients with atrial fibrillation: a cross-sectional analysis of primary care data in the UK

Adderley N, Ryan R and Marshall T.Br J Gen Pract. 19 June 2017; bjgp17X691685.

DOI: https://doi.org/10.3399/bjgp17X691685

Analysis (2004-2012) found presence/absence of recorded contraindications (CIs) has little influence on decision to prescribe anticoagulants (ACs) for prevention of stroke in AF patients. Nationally, 38,000 with AF and CIs were treated with ACs, which has safety implications.
The researchers note that based on the recorded prevalence of AF in recent data there are 1.03 million UK patients diagnosed with AF, of which 59,000 (5.8%) have contraindications to anticoagulants, and 57,000 (96%) of those with contraindications have a CHADS2 score ≥1, and 38,000 (67.2%) are treated. They warn that this represents a significant concern for patient safety and call for further work to determine whether outcomes are worse among contraindicated patients with AF who are treated with anticoagulants than among those who are not, and whether the reduced stroke risk offsets any other potential adverse events.
Prescribers are reminded to check the patient's contra-indication to anti-coagulants carefully before commencing their patients on appropriate treatment for AF. This will reduce the potential for adverse events and exposure to contra-indicated treatment.

Early non-persistence with dabigatran and rivaroxaban in patients with atrial fibrillation.
http://heart.bmj.com/content/early/2017/03/08/heartjnl-2016-310672/
Cynthia A Jackevicius CA, Tsadok MA et al. Heart Published Online First: 12 March 2017
doi: 10.1136/heartjnl-2016-310672
Dabigatran and rivaroxaban are novel oral anticoagulants (NOACs) approved for stroke prevention in atrial fibrillation (AF). Although NOACs are more convenient than warfarin, their lack of monitoring may predispose patients to non-persistence. Limited information is available on NOAC non-persistence rates and related clinical outcomes in clinical practice.
A retrospective cohort study was conducted, using administrative data from Ontario, Canada, from January 1998 to March 2014 of patients with AF who were dispensed dabigatran or rivaroxaban. Non-persistence was defined as a gap in dabigatran or rivaroxaban prescriptions ≥14 days.
The authors concluded that NOAC non-persistence rates are high in clinical practice, with approximately one in three patients becoming non-persistent to dabigatran or rivaroxaban within 6 months after drug initiation. Non-persistence with either dabigatran or rivaroxaban is significantly associated with worse clinical outcomes of stroke/TIA/death.
Local AF guidance recommends assessing compliance and reinforcing advice regarding the importance of a regular dosing schedule every 3 months. Compliance with warfarin is easily monitored through regular review of the INR.

Effect of adherence to antihypertensive medication on stroke incidence in patients with hypertension: a population-based retrospective cohort study
Lee HJ, Jang S, Park E. BMJ Open 2017; 7:e014486.
doi: 10.1136/bmjopen-2016-014486
High blood pressure is a modifiable risk factor for stroke, but non-adherence to antihypertensive medication is a growing concern for healthcare providers in controlling blood pressure. This study aimed to investigate the effect of adherence to antihypertensive medication on stroke incidence. This was a retrospective cohort study, which analysed National Health Insurance claim data and check-up data from 2009 to 2013. Among 38 520 patients with hypertension, 957 (2.5%) strokes occurred during the study period. Non-adherence to medication was significantly associated with a higher risk of stroke (intermediate adherence: adjusted relative risk (aRR) =1.13, 95% CI=1.06 to 1.21; poor adherence: aRR=1.27, 95% CI=1.17 to 1.38). Non-adherence to antihypertensive medication in patients with hypertension was associated with an increased risk of stroke. Therefore, healthcare providers need to focus on interventional strategies to ensure that these patients adhere to medication therapy and to provide continuing support to achieve long-term adherence, ultimately minimising negative health outcomes.

Hepatitis A and B vaccine – shortage
As you may be aware, there are current issues affecting the supplies of hepatitis A and B vaccines. Department of Health (DH) and Public Health England (PHE) are working very closely with manufacturers of these vaccines to understand their supply situations. In light of the current supply issues, PHE have published clinical guidance to manage need for vaccination with availability of vaccine.

Below is a summary of stock situation for Hepatitis A and B vaccines:

Hepatitis A
Clinical Guidance
In light of an on-going hepatitis A outbreak primarily affecting men who have sex with men (MSM) and global supply constraints of the Hepatitis A vaccine, PHE has issued guidance for public health management of hepatitis A infection as well as temporary vaccination recommendations for different patient groups, including travellers.
This can be found at the following link https://www.gov.uk/government/publications/hepatitis-a-infection-prevention-and-control-guidance

Hepatitis A Vaccine Supply to MSM community:
To manage the outbreak in the MSM community, PHE have procured vaccines through a tender process to enable this patient group to be vaccinated.
GUM clinics should order vaccines for this group through ImmForm via the following link:
https://portal.immform.dh.gov.uk/Logon.aspx?returnurl=%2f

Current stock availability of Hepatitis A vaccine for non MSM community:

Adult		
Manufacturer	**Product**	**Current supply situation**
GSK	Havrix Pre filled syringes	Both single packs and packs of 10 are unavailable until 2018
Sanofi Pasteur	Avaxim	Limited supplies available for 2017. Likely to be order restrictions in place.
MSD	VAQTA	Limited supplies available for 2017. Likely to be order restrictions in place.
Paediatric		
Manufacturer	**Product**	**Current supply situation**
GSK	Havrix Junior Monodose	Singles packs are unavailable until late 2017. Likely to be order restrictions in place There are limited supplies of packs of 10 available for 2017. Likely to be order restrictions in place
MSD	VAQTA Paedatric	Unavailable until September 2017

Hepatitis B

Clinical Guidance

In light of global supply issues with the Hepatitis B vaccine, PHE has issued guidance on temporary vaccination recommendations for different patient groups, including prioritisation of patient groups requiring vaccination.
This guidance can be found at the following link: https://www.gov.uk/government/publications/hepatitis-b-vaccine-recommendations-during-supply-constraints

Current Stock Availability of Hepatitis B Vaccine:

Adult		
Manufacturer	**Product**	**Current supply situation**
GSK	Engerix B Pre filled Syringes	Limited supplies of single packs available until September 2017 and then unavailable until 2018 Packs of 10 are unavailable until late 2017
GSK	Engerix B vials	Limited supplies are available.
GSK	Fendrix	Available
MSD	HBVAXPRO 10µg	Unavailable until the end of August
MSD	HBVAXPRO 40µg	Unavailable until the early August
Paediatric		
Manufacturer	**Product**	**Current supply situation**
GSK	Engerix B Paediatric	Unavailable from August until September. Limited supplies available for the rest of 2017
MSD	HBVAXPRO 5µg	Unavailable until mid-August

Combination Vaccines Availability.

In addition to Hepatitis A and Hepatitis B monovalent vaccines, there are a number of combination vaccines on the market. Please see stock availability of these vaccines below:

Adult			
Manufacturer	**Combination**	**Product**	**Current supply situation**
GSK	Hepatitis A Hepatitis B	Twinrix	Limited supplies available for 2017 for both single packs and packs of 10. Likely to be order restrictions in place.
GSK	Hepatitis A Typhoid	Hepatyrix	Unavailable until at least 2019
Sanofi Pasteur	Hepatitis A Typhoid	ViATim	Unavailable until October 2017
Paediatric			
Manufacturer	**Combination**	**Product**	**Current supply situation**
GSK	Hepatitis A Hepatitis B	Twinrix Paedatric	Limited supplies available for 2017. Likely to be order restrictions in place.
GSK	Hepatitis A Hepatitis B	Ambirix	Supplies are unavailable in August with limited supplies available for the rest of 2017

Further information:

All vaccine orders are being monitored and any excessive ordering will be investigated which may lead to a delay in the process. If you require any further information, please see below:

Query	Contact Details
*General Vaccine Supply Queries, including stock availability and ordering	Contact your regular wholesaler. If unable to obtain supplies, try an alternative wholesaler and if still unable to obtain vaccine, contact the manufacturer directly through their customer services.
Hepatitis A vaccine procurement queries	hepatitisA@phe.gov.uk
Clinical or Public Health Hepatitis A and B queries	Local Health Protection Team or immunisation.lead@phe.gov.uk
Hepatitis A and B Queries from the public	Local Health Protection Team or Screening and Immunisation team
Hepatitis A travel queries	NATHNAC in England via www.travelhealthpro.org.uk Travax in Scotland via www.travax.nhs.uk

*please note, there may be processes that have been put into place by manufacturers to allow exceptional requests for additional doses if there is a clear clinical and public health need on an individual patient basis or as part of an outbreak response e.g. transmission event in a renal dialysis unit.

National Travel Health Network and Centre (NaTHNaC) in consultation with PHE, is updating its country-specific travel guidance. As a consequence, hepatitis A immunisation will no longer be recommended for most travellers visiting a number of countries. Please visit the NaTHNaC website for a full list of countries for which hepatitis A vaccine is recommended. (https://travelhealthpro.org.uk/countries)

Deleted products 2017 | MIMS online for June 2017

Cleosensa (ethinylestradiol/drospirenone)	Daylette (ethinylestradiol/drospirenone)
Luvinsta XL (fluvastatin)	Trobalt (retigabine)
Orgaran (Danaparoid sodium)	Panoxyl Aquagel (Benzoyl peroxide)

2. Drug safety update primarily relating to primary care prescribing

(For more information see Drug Safety Update) Volume 10 Issue 11 June 2017

Denosumab (Prolia, Xgeva): Osteonecrosis of the external auditory canal

The safety update reports of the risk of osteonecrosis of the external auditory canal associated with denosumab. Prescribers are reminded to be aware of the risk of osteonecrosis of the external auditory canal as well as the jaw in patients receiving denosumab who present with ear symptoms including chronic ear infections or in those with suspected cholesteatoma or oral symptoms such as dental mobility, pain, or swelling.

Novo Nordisk: Novopen® devices - Field safety medical device alert.

The MHRA have issued a Field Safety Notice (FSN) Medical Device Alert for Novo Nordisk NovoPen® Echo® and NovoPen® 5 – please see web link (scroll down to 'Novo Nordisk' & click on the MHRA weblink) for further information regarding this, with affected batch numbers, in case of any patient or prescriber queries. Information within the web link also contains all the different letters sent out from Novo Nordisk® to patients, pharmacies, wholesalers & healthcare professionals. The batch recall is to be actioned by pharmacies & wholesalers (or anyone else who may stock these pens e.g. Diabetes nurses, clinics).

3. Local news/selfcare and GP/pharmacist queries

Self-care

Re-classification of Nasonex Allergy Control Nasal Spray

The MHRA has agreed to reclassify Nasonex Allergy Control 0.05% (mometasone) Nasal Spray from a POM to a P medicine for symptoms of seasonal allergic rhinitis and perennial allergic rhinitis in those 18 years and over, for a period of not more than 3 months.

Vitamin D recommendation

In a change to previous advice, Scientific Advisory Committee on Nutrition (SACN) is now recommending:

- a reference nutrient intake (RNI) of 10 micrograms (400units) of vitamin D per day, **throughout the year**, for everyone in the general population aged 4 years and older
- an RNI of 10 micrograms of vitamin D per day for pregnant and lactating women and population groups at increased risk of vitamin D deficiency
- a 'safe intake' of 8.5 to 10 micrograms per day for all infants from birth to 1 year of age
- a 'safe intake' of 10 micrograms per day for children aged 1 to 4 years.

These recommendations are reflected in the local guidance. Prescribers are reminded to encourage patients to purchase Vitamin D supplements over the counter for maintenance therapy following deficiency treatment and those with insufficiency. See the Vitamin D – position statement for self-care.

A new BNF and BNF for Children app is now available

The BNF is proud to announce the launch of a new app, providing NHS health care professionals with the latest content from the British National Formulary (BNF) and the BNF for Children (BNFC). Created for prescribers, pharmacists, and other health & social care professionals who provide NHS commissioned care in the UK, the BNF & BNFC app delivers practical, evidence-based medicines information when and where you need it.

The new app will replace the NICE BNF app. To begin with, both apps will be available in order to allow users time to download and familiarise themselves with the new

The new BNF & BNFC App can be downloaded from the AppStore for iOS devices, and the Google Play for Android devices. To learn more please visit https://www.bnf.org/products/bnfbnfcapp/

GP QUERY

Question: Restless legs syndrome (RLS) – what are the options for treatment in primary care?

Answer: For patients with mild symptoms, explanation, reassurance and self-help measures should be sufficient. To reduce the severity, good sleep, reduced caffeine/alcohol, stopping smoking and exercise should help. To relieve an episode patients are recommended to try walking/stretching/massaging the limb/s, heat pads/hot bath, relaxation and distraction e.g. games/reading. CKS recommend to tackle the underlying cause that may have precipitated or exacerbated restless legs syndrome (e.g. iron deficiency)

JAPC only recommend pramipexole, ropinirole and rotigotine - all classified as **BROWN** (based on the level of evidence) for severe RLS that has a significant impact on quality of life **after self-help measures have been tried**. Gabapentin and pregabalin are alternative first line agents according to CKS. JAPC has not classified them for RLS and their use would be off-label.

See https://cks.nice.org.uk/restless-legs-syndrome for more detail

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

Highlighting potential QIPP opportunities:

Dose optimisation of levothyroxine

Current drug tariff price for:

- Levothyroxine 25mcg = £2.91 x 28
- Levothyroxine 50mcg = £1.56 x 28
- Levothyroxine 75mcg = £3.14 x 28

One month supply of levothyroxine 75mcg prescribed as

- 75mcg od = £3.14
- 3x25mcg od = (3 x 2.91) = £8.73 - potential cost saving £5.59 per patient per month
- 1x25mcg + 1x50mcg od = (2.91 + 1.56) = £4.47 - potential cost saving £1.33 per patient per month

Prescriber are reminded to dose optimise for prescriptions for 75mcg Levothyroxine.

Kemadrin (Procyclidine) prescribing

Current MIMs price for

- Kemadrin 5mg £4.72 x 100 (therefore = £1.32 x 28)

Drug tariff price for

- Procyclidine 5mg £11.42 x 28

Epact data (Jun 16 – May 17) for procyclidine

CCG	Items	Cost
SDCCG	6,232	£114,321
ECCG	1,092	£18,311
NDCCG	3,921	£61,384
HCCG	1,752	£26,493
Total	12,997	£220,508

Prescribers are reminded to prescribe procyclidine as "Kemadrin" to achieve the potential cost saving of £10.10 per 28 tablets, resulting in approximately £193k savings based on Epact data for the previous 12 months.

June

Prescribers should note that the re-imbursement 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	Pack size	Current months Drug tariff price	Price concession
Betahistine 16mg tablets	84	£1.41	£11.95
Betahistine 8mg tablets	84	31.33	£6.33
Buspirone 5mg tablets (new)	30	£6.97	£9.57
Buspirone 10mg tablet	30	£3.81	£9.57
Dapsone 50mg tablets	28	£41.37	£45.20
Diamorpine 30mg powder for solution for injection ampoules	5	£13.93	£16.52
Ethosuximide 250mg/5ml oral solution	200ml	£4.22	£173.00
Exemestane 25mg tablets	30	£8.00	£12.00
Leflunomide 10mg tablets	30	£5.24	£8.35
Leflunomide 20mg tablets	30	£7.66	£8.16
Mefenamic acid 500mg tablets	28	£5.80	£55.00
Nitrofurantoin 100mg tablets	28	£9.85	£14.50
Nitrofurantoin 50mg tablets	28	£14.95	£20.50
Olanzapine 10mg tablets	28	£1.07	£69.82
Olanzapine 15mg tablets	28	£1.33	£88.95
Olanzapine 2.5mg tablets	28	£0.97	£16.95
Olanzapine 20mg tablets	28	£1.55	£127.12
Olanzapine 5mg tablets	28	£0.98	£33.00
Olanzapine 7.5mg tablets	28	£0.91	£52.44
Oxazepam 10mg tablets	28	£3.63	£18.95
Oxazepam 15mg tablets	28	£2.72	£6.50

Pramipexole 88 microgram tablets	30	£1.39	£12.00
Ropinirole 5mg tablets	84	£3.98	£165.00
Sodium cromoglicate 2% eye drops	13.5ml	£2.35	£6.99
Spironolactone 50mg tablets	28	£3.16	£5.20
Sumatriptan 100mg tablets	6	£1.51	£32.00
Sumatriptan 50mg tablets	6	£1.34	£31.85
Tranexamic acid 500mg tablets	60	£4.42	£11.45
Valsartan 160mg capsules	28	£4.78	£17.10
Valsartan 40mg capsules	28	£3.44	£8.80
Valsartan 80mg capsules	28	£3.63	£11.43
Zolmitriptan 2.5mg tablets	6	£5.06	£17.90
Zolmitriptan 2.5mg orodispersible tablets SF	6	£1.70	£17.90

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

None to note

6. Useful resources

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/
SPS/UKMI Nathnac NHS evidence Electronic medicines compendium Clinical Knowledge Summaries Medicines Prescribing Centre (Formerly NPC) Medicines for children (patient information leaflets Drugs in lactation Medicines Compliance aids Fridge excursions Patent expiries New Medicines	https://www.sps.nhs.uk/ 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&pageIdx=1 https://www.sps.nhs.uk/?s=&cat%5B%5D=3008 https://www.sps.nhs.uk/?s=&cat%5B%5D=266&cat%5B%5D=3253 https://www.sps.nhs.uk/?s=&cat%5B%5D=3252 https://www.sps.nhs.uk/?s=&cat%5B1%5D=3242 https://www.sps.nhs.uk/category/new-medicines/
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