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. 7 July 2017

Antibiotic use in pregnancy and spontaneous abortion

The safety of antibiotics during pregnancy has been assessed in a nested case-control study conducted in Canada. The authors conclude that some antibiotics were associated with an increased risk of spontaneous abortion, notably with azithromycin (differed from a previous study), clarithromycin, metronidazole, sulphonamides, tetracyclines and quinolones.

***DTB comment**: Public Health England's guidance on antibiotic use in primary care was updated to include the results of this study. The section on pregnancy now states, "Penicillins, cephalosporins and erythromycin are not associated with increased risks. If possible, avoid tetracyclines, quinolones, aminoglycosides, azithromycin, clarithromycin, high dose metronidazole (2g stat) unless the benefits outweigh the risks. Short-term use of nitrofurantoin is not expected to cause foetal problems (theoretical risk of neonatal haemolysis). Trimethoprim is also unlikely to cause problems unless poor dietary folate intake, or taking another folate antagonist." Further advice is available for healthcare professionals from the UK Teratology Information Service website and for members of the public from the Best Use of Medicines in Pregnancy website.*

The local antimicrobial treatment guideline will be updated to reflect PHE advice in due course.

Single-inhaler triple therapy for prevention of COPD exacerbations

A randomised controlled trial has tested the efficacy of triple therapy with a single inhaler containing a long-acting beta2 agonist (LABA), a long-acting muscarinic antagonist (LAMA) and an inhaled corticosteroid (ICS) (extrafine beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide,(fixed triple therapy using a single inhaler) versus tiotropium alone (monotherapy) and beclomethasone/formoetrol plus tiotropium (open triple therapy using two inhalers). After 52 weeks of treatment, moderate-to-severe exacerbation rates were 0.46 per patient per year (95% CI 0.41 to 0.51) for fixed triple, 0.57 (95% CI 0.52 to 0.63) for tiotropium and 0.45 (95% CI 0.39 to 0.52) for open triple therapy.

***DTB comment**: Although it might be anticipated that triple therapy would be more effective than LAMA monotherapy, the reduction in the rate of moderate-to-severe exacerbations was relatively small (0.1 exacerbation per patient per year over LAMA monotherapy). A comparison of triple therapy with LABA/LAMA dual therapy would have been more useful. Concerns remain over the increase in the incidence of pneumonia in people with COPD treated with high-dose ICS. This study does not provide evidence to promote a strategy of triple therapy ahead of LABA/LAMA dual therapy.*

Local COPD guidance limits the use of triple therapy for exceptional use only and further states that 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

Repeat warning on valproate in pregnancy as message fails to raise awareness.

The MHRA advice for healthcare professionals (issued 2017) is as follows:

- do not prescribe valproate medicines for epilepsy or bipolar disorder in women and girls unless other treatments are ineffective or not tolerated; migraine is not a licensed indication;
- ensure women and girls taking valproate medicines understand the 30-40% risk of neurodevelopmental disorders and 10% risk of birth defects and are using effective contraception;
- valproate use in women and girls of childbearing potential must be initiated and supervised by specialists in the treatment of epilepsy or bipolar disorder.

However, evidence from the Clinical Practice Research Datalink suggests that, although prescription rates for valproate have been declining gradually in recent years, the measures put in place have not had a significant effect

***DTB comment**: It is of concern that such a simple message around such a major risk is proving difficult to implement. This highlights the need for all prescribers to systematically review their records to identify all girls and women of child-bearing potential who are currently taking valproate and related medicines. Given the limited success of previous initiatives, a new approach may be required to highlight and manage the risks associated with valproate products.*

Prescribers are reminded to identify systematically and review all women and girls taking valproate medicines and arrange a review of medication and contraception advice. Links to valproate resources can be found in section 2 – Drug safety update (p3).

Liraglutide for weight management

***DTB comment**: Liraglutide, an injectable GLP-1 agonist originally licensed for glycaemic control in diabetes, is now also licensed as a separate product (Saxenda) for weight control in adults, as an adjunct to a calorie controlled diet and physical exercise.*

Placebo controlled trials of liraglutide included dietary and exercise counselling with participants advised to increase physical activity to 150 minutes/week and to reduce daily energy intake to 500kcal below their individualised energy requirement. Liraglutide resulted in additional weight loss of approximately 5% over placebo. Indirect comparisons suggest that it produces greater weight loss than orlistat.
It is not clear whether any benefit is maintained without continued treatment, as an average of 2-3% body weight was regained within 12 weeks of stopping liraglutide therapy in the studies that measured this outcome.
Up to 10% of patients taking liraglutide dropped out of clinical trials because of adverse effects. Gastrointestinal adverse effects such as nausea and vomiting were very common with liraglutide and occurred in approximately 40% and 15% of patients, respectively. Some patients experienced more serious adverse effects, including pancreatitis.
Given the modest weight loss, concerns over adverse effects, the inconvenience of a daily subcutaneous injection and the high cost of liraglutide (at nearly £2,400 per year) we do not recommend it for routine use for weight management.
Locally liraglutide has been classified as BLACK (not commissioned) as an adjunct for to diet and exercise for weight loss management.

Prophylactic drug management for febrile seizures in children
Offringa M,Newton R,Cozijnsen MA, Nevitt, SJ. Cochrane Database Syst Rev Volume 2 , 2017
https://discover.dc.nihr.ac.uk/portal/article/4000735/prescribing-regular-drugs-to-prevent-febrile-convulsions-risks-more-harm-than-benefit
Febrile seizures occurring in a child older than one month during an episode of fever affect 2% to 4% of children in Great Britain and the United States and recur in 30%. Rapid-acting antiepileptics and antipyretics given during subsequent fever episodes have been used to avoid the adverse effects of continuous antiepileptic drugs. The objective of this study was to evaluate primarily the effectiveness and safety of antiepileptic and antipyretic drugs used prophylactically to treat children with febrile seizures.
This systematic review suggests that intermittent diazepam or continuous phenobarbitone may have some effect in preventing further febrile convulsions. However, this benefit was not large enough to outweigh the potential harms associated with these drugs. Other anticonvulsants are ineffective yet still carry potential harms.
Parents and carers may feel concerned about not receiving specific preventive treatment for these worrying, but predominantly harmless, convulsions. Clinicians should therefore make more effort to explain to families the benign nature of these convulsions and provide information on how to act when a fever or febrile convulsion occurs.
NICE CG160:
Drug interventions to reduce body temperature
- Consider using either paracetamol or ibuprofen in children with fever who appear distressed.
- Do not use antipyretic agents with the sole aim of reducing body temperature in children with fever.
- When using paracetamol or ibuprofen in children with fever:
  - continue only as long as the child appears distressed
  - consider changing to the other agent if the child's distress is not alleviated
  - do not give both agents simultaneously
  - only consider alternating these agents if the distress persists or recurs before the next dose is due.

Optimal Systolic Blood Pressure Target after SPRINT Insights from a Network Meta-Analysis of Randomized Trials
Bangalore S, Toklu B, Gianos E, et al. Am J Med, 2017
https://discover.dc.nihr.ac.uk/portal/article/4000692/new-evidence-for-lower-blood-pressure-targets
More than one in four UK adults has high blood pressure (hypertension). Hypertension is estimated to account for 12% of all visits to GPs in England. Associated diseases, like heart disease and stroke, are estimated to cost the NHS over £2 billion every year.
There is uncertainty over the blood pressure target which gives the best balance between benefits and side effects. Most national guidelines recommend an upper (systolic) target of <140mmHg but results from several recent trials have been conflicting. The SPRINT trial found a lower target of 120mmHg improved overall cardiovascular risk in people without diabetes, while the ACCORD BP trial found this lower target gave little benefit for people with diabetes.
This study aimed to combine the results of trials to shed light on the optimal systolic blood pressure target. A lower systolic blood pressure target of 130mmHg may benefit cardiovascular health. A survey by NICE in 2015 shows how hypertension is being managed nationally. More than 85% of patients aged 80 years or over with treated hypertension had their previous blood pressure reading at 150/90 mmHg or below. These findings may inform discussion of whether a lower systolic blood pressure target could further reduce cardiovascular events and NHS costs.
However, the balance of benefits against harms of lower blood pressure targets is likely to be an important determinant. This balance should be discussed with patients. Commissioners will also be interested in the health system cost and cost-effectiveness of lowering the targets.
National guidance on blood pressure target levels remains. See local formulary for further details.

UK rated first in report on international healthcare systems
http://www.commonwealthfund.org/interactives/2017/july/mirror-mirror/
Using data available from Commonwealth Fund international surveys of the public and physicians and other sources of standardized data on quality and health care outcomes, the report identified 72 measures relevant to health care system performance, organizing them into five performance domains: Care Process, Access, Administrative Efficiency, Equity, and Health Care Outcomes.
The report finds that in general, the UK achieves superior performance compared to other countries in all areas except Health Care Outcomes, a category that measures how successful treatment has been. This is despite experiencing the fastest reduction in deaths amenable to health care in the past decade.
The guardian comment: https://www.theguardian.com/society/2017/jul/14/nhs-holds-on-to-top-spot-in-healthcare-survey

Systematic meta-review of supported self-management for asthma: a healthcare perspective
Pinnock,H, Parke HL, Panagioti M, et al. BMC Medicine, 2017
https://discover.dc.nihr.ac.uk/portal/article/4000670/asthma-self-management-programmes-can-reduce-unscheduled-care
Current guidelines recommend self-management programmes for people with asthma, which centre on education and written personalised asthma action plans. This is most effective when it's supported through regular reviews with a professional. Self-management programmes aren't always delivered effectively. The 2014 UK National Review of asthma deaths found that self-management training was only reported for 23%.

This large systematic overview aimed to gather the available evidence on supported self-management for asthma, from systematic reviews and recent trials. The reviewers focused on how self-management might affect asthma control and the use of healthcare resources. This is a meta-review (systematic overview) of systematic reviews updated with randomised controlled trials (RCTs) published since the review search dates, and health economic meta-analysis of RCTs. Twelve electronic databases were searched in 2012 (updated in 2015; pre-publication update January 2017) for systematic reviews reporting RCTs (and update RCTs) evaluating supported asthma self-management. The authors assessed the quality of included studies and undertook a meta-analysis and narrative synthesis.
Asthma self-management support is already recommended in the UK. This comprehensive body of evidence reinforces current guidance to prioritise the provision of programmes supported by regular professional review. People with asthma, as with other long-term conditions, can be empowered by learning to manage their condition confidently. This can ease the burden on the NHS by reducing the number of unplanned visits to healthcare services. Further clarity on the optimal components of self-management support for different population groups would be beneficial. Studies with longer follow up might confirm long-term sustainability of self-management interventions in asthma.

Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis
Birkeland, Kåre I et al. The Lancet Diabetes & Endocrinology, Volume 5 , Issue 9 , 709 – 717, September 2017.
http://dx.doi.org/10.1016/S2213-8587(17)30258-9
In patients with type 2 diabetes and a high cardiovascular risk profile, the sodium-glucose co-transporter-2 (SGLT2) inhibitors empagliflozin and canagliflozin have been shown to lower cardiovascular morbidity and mortality. Using real-world data from clinical practice, the authors aimed to compare cardiovascular mortality and morbidity in new users of SGLT2 inhibitors versus new users of other glucose-lowering drugs, in a population with a broad cardiovascular risk profile.
In a population of patients with type 2 diabetes and a broad cardiovascular risk profile, SGLT2 inhibitor use was associated with reduced cardiovascular disease and cardiovascular mortality compared with use of other glucose-lowering drugs—a finding consistent with the results of clinical trials in patients at high cardiovascular risk.
This study adds to the growing volume of evidence for the cardiovascular outcomes with empagliflozin and canagliflozin.

Deleted products 2017 | MIMS online for July 2017

Elave Intensive Cream	Exjade Dispersible Tablets (deferasirox)
Haemate P (factor VIII)	Mononine (factor IX)
Solu-Medrone 2G (methylprednisolone)	

2. Drug safety update primarily relating to primary care prescribing
(For more information see Drug Safety Update) Volume 10 Issue 12 July 2017

None for primary care
Sodium Valproate resources
Letters sent to Healthcare Professionals in July 2017 – Prescribing of valproate medicine in girls, women of childbearing potential, and women who are pregnant or planning pregnancy. Despite previous communications, valproate continues to be used frequently in this patient group. General Practitioners caring for girls or women of childbearing age taking valproate, MUST ENSURE that patients are seen by the specialist responsible for prescribing valproate at least annually, and as a matter of urgency if planning a pregnancy or becomes pregnant. Community Pharmacists have also been contacted and requested to CHECK with this group of patients that their prescriber has discussed the risks of in utero exposure with them. If the prescriber HAS NOT DISCUSSED the risk with the patient, pharmacists are advised to CONTACT THE PRESCRIBER and REMIND them of their responsibility to do so and ask for an urgent follow-up action with patient.
Resources to support the safety of girls and women who are being treated with valproate, all resources can be found on the EMC website http://www.medicines.org.uk/emc/medicine/23020#rmm and
https://assets.publishing.service.gov.uk/media/598dbe6440f0b679518fb4c2/Valproate_DHPC_-_all_providers.pdf

Medication Safety Article:
Promazine prescribed for a child instead of Promethazine – 'look alike, sound alike' drugs
An incident has been reported locally whereby a 10 year old patient was prescribed promazine 25mg at night instead of the intended promethazine 25mg at night for sedation. This error was identified by a medicines management team technician during the course of routine checks for patients being switched from alimemazine to promethazine. In this case, a GP was carrying out this switch as advised by a consultant paediatrician and information about switching to promethazine was clear in the letter received by the GP practice. The patient received 7 days' worth of promazine at a dose of 25mg at night, as this error was not identified by the community pharmacy at the point of dispensing/checking. Prescribing clinical systems, clearly state that the use of promazine is contraindicated in children and this should have alerted the prescriber at the point of prescribing.
A mix-up between promazine and promethazine is a well-known 'look alike, sound alike' drug error and it is likely to occur when selecting drugs with a similar name at the point of prescribing within electronic prescribing systems – especially when they have similar doses and/or strengths. These medicines may also appear next to each other on shelves within community pharmacies or dispensing doctor's premises.
Other common 'look alike, sound alike' drugs we all should be aware of include the following:

Aminophylline	Amitriptyline
Amoxicillin	Ampicillin
Amiloride	Amlodipine
Amiloride	Amiodarone
Amitriptyline	Nortriptyline
Anafranil	Enalapril
Atenolol	Timolol
Azithromycin	Erythromycin
Baclofen	Bactroban®
Beclometasone	Betamethasone
Beconase®	Becotide®
Betnovate®	Dermovate®
Bisacodyl	Bisoprolol
Carbamazepine	Carbimazole
Carbimazole	Chlorpromazine
Ciclosporin	Cycloserine
Clobazam	Clonazepam
Clomiphene	Clomipramine
Clotrimazole	Co-trimoxazole
Co-codamol	Co- proxamol
Co-dydramol	Co- proxamol
DepoMedrone	DepoProvera
Dermovate	Betnovate
Dothiepin	Doxepin
Epinephrine(Adrenaline)	Ephedrine

Fluoxetine	Fluvoxamine
FolicAcid	FolinicAcid
Gliclazide	Glipizide
Humalog®	Humulin®
Hydroxyurea	Hydroxyzine
Hydroxyzine	Hydralazine
Imipramine	Trimipramine
IsosorbideDinitrate	IsosorbideMononitrate
Lamivudine	Lamotrigine
Levothyroxine	Liothyronine
Lisinopril	Fosinopril
Lofepramine	Loperamide
Maxidex	Maxitrol
Mebendazole	Metronidazole
Metformin	Methyldopa
Methylprednisolone	Medroxyprogesterone
Metolazone	Metoprolol
Olsalazine	Olanzapine
Penicillamine	Penicillin
Promazine	Promethazine
Sandocal	Sando-K
Selegiline	Stelazine
Senokot	Seroxat
Sinemet	Cimetidine
Tamoxifen	Temazepam
Tramadol	Trazodone

3. Local news/selfcare and GP/pharmacist queries

Educational Risk Minimisation Materials to help reduce the risk associated with using valproate.
http://www.medicines.org.uk/emc/medicine/23020#rmm

GP QUERY
Question:
I've been asked to prescribe Gonapeptyl (Triptorelin) 3.75mg IM to a 14 year female transitioning to a male. The patient has been seen by the endocrinology department at the Specialist Centre and the practice have been asked to initiate Gonapeptyl (Triptorelin) 3.75mg IM 4 weekly (GP information sheet has been provided, but not a specific shared care).
The advice on our website clearly relates to adults. What is the CCG policy?

Answer:
The NHS England Service Specification for the Gender Identity Development Service for Children and Adolescents is provided in the link below:

https://www.england.nhs.uk/wp-content/uploads/2017/04/gender-development-service-children-adolescents.pdf

http://www.derbyshiremedicinesmanagement.nhs.uk/assets/Clinical_Guidelines/Formulary_by_BNF_chapter_prescribing_guidelines/BNF_chapter_6/Primary_Care_Responsibilities_for_Transgender_and_Non_Binary_Adults.pdf include this link

In a similar way to the Service Spec for adults, both the flow chart on page 18 and the text on page 26/27 clearly state that the expectation is that primary care will initiate and provide the medication, with appropriate support and guidance from the Specialist Centres in Leeds and London:

It is expected that all treatments will be prescribed and administered in primary care services. The Service will provide support to GP's with any queries regarding this. GPs are encouraged to discuss specific cases with the specialist centres so that the necessary support and information can be provided.

Further information
NHS England has launched a 12 week consultation on specialised gender identity services for adults (17 and above). The consultation is open until 16 October 2017. Further information can be found at the following link:
https://www.engage.england.nhs.uk/survey/gender-identity-services-for-adults/

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

Highlighting potential QIPP opportunities:

Generic prescribing of levetiracetam. Brand product - Keppra

Indication - Monotherapy in partial seizures with or without secondary generalisation in patients with newly diagnosed epilepsy. Adjunct in partial seizures with or without secondary generalisation. Adjunct in juvenile myoclonic epilepsy. Adjunct in primary generalised tonic-clonic seizures.

The MHRA recommends that antiepileptics are divided into three risk based-categories, with levetiracetam classed in category 3, where it is usually unnecessary to ensure a specific manufacturer.

Price comparison for generic and branded Keppra.

Strength	Keppra (MIMs price)	Generic* (DT price Aug 17)
250mg x 60	£28.01	£2.06
500mg x60	£49.23	£2.17
750mg x60	£84.02	£3.91
1g x 60	£95.34	£4.70

Over the previous 12 months (Jul 16-Jun 17) £191,180 has been spent across Derbyshire on Keppra prescribing.

- ECCG - £8,023
- HCCG - £18,012
- NDCCG - £50,689
- SDCCG - £114,456

If keppra had been prescribed as Levetiracetam, it would have generated a saving **£181,584** across Derbyshire.

Please note in August 2017 there is a price concession for Levetiracetam. This maybe short-lived or may continue. Please check PSNC website for on-going situation.

July

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	£1.51	£11.95
Betahistine 8mg tablets	84	£1.40	£5.85
Buspirone 10mg tablet	30	£5.88	£9.57
Dapsone 50mg tablets	28	£38.55	£46.19
Diamorpine 30mg powder for solution for injection ampoules	5	£13.54	£16.52
Mefenamic acid 500mg tablets	28	£5.96	£55.00
Nitrofurantoin 100mg tablets	28	£10.12	£15.00
Olanzapine 10mg tablets	28	£1.08	£69.82
Olanzapine 15mg tablets	28	£1.40	£85.00
Olanzapine 2.5mg tablets	28	£1.01	£16.00
Olanzapine 20mg tablets	28	£1.52	£110.00
Olanzapine 5mg tablets	28	£1.02	£32.00
Oxazepam 10mg tablets	28	£4.97	£19.97
Oxazepam 15mg tablets	28	£4.82	£19.97
Pramipexole 88 microgram tablets	30	£2.29	£12.00
Sumatriptan 50mg tablets	6	£1.43	£31.85
Tranexamic acid 500mg tablets	60	£4.22	£11.00
Valsartan 160mg capsules	28	£5.19	£12.00
Valsartan 40mg capsules	28	£5.98	£7.70
Valsartan 80mg capsules	28	£6.28	£9.99
Zolmitriptan 2.5mg tablets	6	£5.05	£17.45
Zolmitriptan 2.5mg orodispersible tablets SF	6	£9.55	£18.00

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

None for primary care

6. Useful resources

BMJ	www.thebmj.com
JAMA: The Journal of the American Medical Association	http://jama.ama-assn.org/
Drugs and Therapeutic Bulletin "Full access to articles available to SDCCG clinicians"	http://dtb.bmj.com/
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