Derbyshire Medicines Management Newsletter

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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. Round up of what's in the news

Diclofenac use and cardiovascular risks: series of nationwide cohort studies

Schmidt M, Sørensen HT, Pedersen L. BMJ 2018; 362 doi: https://doi.org/10.1136/bmj.k3426.

This was a series of 252 Danish cohort studies undertaken to examine the cardiovascular risks of diclofenac initiation compared with initiation of other traditional non-steroidal anti-inflammatory drugs (NSAIDs), initiation of paracetamol, and no initiation.

Individuals eligible for inclusion were all adults without malignancy; schizophrenia; dementia; or cardiovascular, kidney, liver, or ulcer diseases (that is, with low baseline risk). The study included 1 370 832 diclofenac initiators, 3 878 454 ibuprofen initiators, 291 490 naproxen initiators, 764 781 healthcare seeking paracetamol initiators matched by propensity score, and 1 303 209 healthcare seeking non-initiators also matched by propensity score.

The relative risk of major adverse cardiovascular events was highest in individuals with low or moderate baseline risk (that is, diabetes mellitus), the absolute risk was highest in individuals with high baseline risk (that is, previous myocardial infarction or heart failure). Diclofenac initiation also increased the risk of upper gastrointestinal bleeding at 30 days, by approximately 4.5-fold compared with no initiation, 2.5-fold compared with initiation of ibuprofen or paracetamol, and to a similar extent as naproxen initiation. Diclofenac poses a cardiovascular health risk compared with non-use, paracetamol use, and use of other traditional non-steroidal anti-inflammatory drugs.

Locally ibuprofen and naproxen are 1st and 2nd line choice NSAIDs, and that treatment with NSAIDs should be continued for the shortest time and at the lowest dose necessary to control symptoms.

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group. August 26, 2018 DOI: 10.1056/NEJMoa1804988

Diabetes mellitus is associated with an increased risk of cardiovascular events. Aspirin use reduces the risk of occlusive vascular events but increases the risk of bleeding; the balance of benefits and hazards for the prevention of first cardiovascular events in patients with diabetes is unclear.

We randomly assigned adults who had diabetes but no evident cardiovascular disease to receive aspirin at a dose of 100 mg daily or matching placebo. The primary efficacy outcome was the first serious vascular event (i.e., myocardial infarction, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial haemorrhage). The primary safety outcome was the first major bleeding event (i.e., intracranial haemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding). Secondary outcomes included gastrointestinal tract cancer.

Aspirin use prevented serious vascular events in persons who had diabetes and no evident cardiovascular disease at trial entry, but it also caused major bleeding events. The absolute benefits were largely counterbalanced by the bleeding hazard.

The local type 2 diabetes guidance recommends not offering antiplatelet therapy (aspirin or clopidogrel) for adults with type 2 diabetes without cardiovascular disease.

Effects of n−3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group. August 26, 2018. DOI: 10.1056/NEJMoa1804989

Increased intake of n−3 fatty acids has been associated with a reduced risk of cardiovascular disease in observational studies, but this finding has not been confirmed in randomized trials. It remains unclear whether n−3 (also called omega-3) fatty acid supplementation has cardiovascular benefit in patients with diabetes mellitus

We randomly assigned 15,480 patients with diabetes but without evidence of atherosclerotic cardiovascular disease to receive 1-g capsules containing either n−3 fatty acids (fatty acid group) or matching placebo (olive oil) daily. The primary outcome was a first serious vascular event (i.e., nonfatal myocardial infarction or stroke, transient ischemic attack, or vascular death, excluding confirmed intracranial haemorrhage). The secondary outcome was a first serious vascular event or any arterial revascularization.

Among patients with diabetes without evidence of cardiovascular disease, there was no significant difference in the risk of serious vascular events between those who were assigned to receive n−3 fatty acid supplementation and those who were assigned to receive placebo.
The local lipid modification guidance recommends - Do not routinely offer omega-3 fatty acid compounds, alone or in combination with a statin, for the prevention of CVD for type 1 or type 2 diabetes.

Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders.
Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD007990. DOI:10.1002/14651858.CD007990.pub3.
Osland ST, Steeves TDL, Pringsheim T.
Cochrane review evaluated the available evidence for medications for ADHD used specifically in children with tic disorders. The review included eight studies with 510 participants (443 boys, 67 girls) with both ADHD and a chronic tic disorder. The included studies evaluated several different medications for ADHD, including stimulants (methylphenidate, dextroamphetamine) and non-stimulants (clonidine, guanfacine, desipramine, atomoxetine, and deprenyl). All studies took place in the USA and ranged from three to 22 weeks in duration.
Key results: the trials in this review suggested that several stimulant and non-stimulant medications may improve ADHD symptoms in children with ADHD and tics. At high doses, dextroamphetamine may initially worsen tics in some children, and dose increases of both dextroamphetamine and methylphenidate may be limited due to tic exacerbation. However, for most children, both tics and ADHD symptoms can improve with use of stimulant medications.
There is low-quality evidence for methylphenidate, atomoxetine, and clonidine, and very low-quality evidence for desipramine, dextroamphetamine, guanfacine, and deprenyl in the treatment of ADHD in children with tics. The evidence was limited by the small number of trials, small number of participants, and risk of bias of the included studies.

Releasing GP capacity with pharmacy prescribing support and new ways of working: a prospective observational cohort study.
Maskrey M, Johnson CF, Cormack J, Ryan M, Macdonald H. Br J Gen Pract 2018. 10.3399/bjgp18X699137.
This observational cohort study in 16 urban general practices (in Scotland) reviewed the impact prescribing support teams may have on freeing up GP capacity and time for clinical activities.
GPs recorded the time they spent dealing with special requests, immediate discharges, outpatient requests, and other prescribing issues for 2 weeks prior to the study and for two equivalent periods during the study. Specialist clinical pharmacists performed these key prescribing activities to release GP time and Read coded their activities. GP and practice staff were surveyed to assess their expectations at baseline and their experiences during the final data-collection period. Prescribing support staff were also surveyed during the study period. The study concluded that specialist clinical pharmacists are safe and effective in supporting GPs and practices with key prescribing activities in order to directly free GP capacity. The findings showed that the clinical pharmacists reduced GP time spent on these four key prescribing activities by 51% (79 hours, P<0.001) per week, saving 4.9 hours (95% confidence interval, 3.4 to 6.4) per week per practice.
Surveys of GPs and practice staff showed that the pharmacists were well received and appreciated, improved patient safety, had a positive impact on staff morale, and reduced staff stress levels. However, further work is required to assess the impact of such service developments on prescribing cost-efficiency and clinical pharmacist medication review work.

Deleted products 2018 | MIMS online September 2018
Nil

2. Drug safety update primarily relating to primary care prescribing

(For more information see Drug Safety Update)

Volume 12 Issue 2 September 2018 -relevant for primary care

Valproate Pregnancy Prevention Programme: actions required now from GPs, specialists, and dispensers
Valproate medicines must not be used in women of childbearing potential unless the Pregnancy Prevention Programme is in place.

Actions for GPs
- identify and recall all women and girls on valproate 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 (ie, they have an in-date Risk Acknowledgement Form) and are on highly effective contraception

Actions for specialists
- book in review appointments at least annually with women and girls under the Pregnancy Prevention Programme and re-evaluate treatment as necessary
- explain clearly the conditions as outlined in the supporting materials
- complete and sign with the patient or their responsible person the Risk Acknowledgement Form—copies of the form must be given to the patient or responsible person and sent to their

GP Actions for dispensers

- valproate medicines must always be dispensed with the accompanying patient information leaflet
- dispense whole packs whenever possible, and ensure there is a warning label either on the carton or added via a sticker
- discuss risks in pregnancy with female patients each time you dispense valproate medicines and ensure they have the Patient Guide and have seen their GP or specialist to discuss their treatment and the need for contraception
- ensure new packs of valproate information materials are placed in a designated place accessible to all dispensing staff and dispose of any old materials related to valproate medicines

3. Local news and GP/pharmacist queries

Frequently asked questions for GPs and pharmacies in North Midlands –

What if there are not enough vaccines at the time of a flu clinic?

If adjuvant trivalent vaccine (aTIV) is not available in the practice, patients are to be directed to local pharmacies or other providers that have stock of aTIV. Alternatively patients can be asked to rebook for a date when further delivery of aTIV has been received in the practice as part of the staged delivery.

Please ensure reception staff have current information about other providers who can offer the vaccination and/or when further stocks will arrive. It is important to reassure patients that there is an adequate supply of the vaccine available.

Can stock of aTIV be shared / transferred between practices if there is additional stock?

No, we do not have any national guidance that has been published on sharing Fluad vaccine between practices at present but wanted to highlight that the sharing of vaccines can only happen under strict guidance.

At the moment there are sufficient aTIV vaccines ordered in North Midlands. If you do not have sufficient vaccine it is recommended that you signpost the individuals to other local providers with the aTIV available. Otherwise provide the individual with a future appointment following the next scheduled Seqirus delivery.

Can patients 65 and over receive the quadrivalent vaccine?

Individuals 65 years and over should be offered aTIV. QIV should only be offered in exceptional circumstances as it will likely still give important protection. Only if there is no accessible supply, and no further supplies are expected, would it be clinically appropriate to offer QIV to eligible patients, which would be after the delivery scheduled for November 2018. In the unlikely event of aTIV being unavailable the decision should be made on a case-by-case basis taking into account an individual's personal circumstances.

If individuals are requesting QIV (who would benefit from the more appropriate aTIV) when gaining consent for immunisation, practitioners should ensure that they inform the individual the vaccine is not one nationally recommended for them. Healthcare practitioners should ensure they explain to the individual the possible lower efficacy of the vaccine being offered to them and why it may still offer protection against seasonal flu, or attenuate the progression of the infection should they get it. The discussion should be documented in the individual's records.

What if an individual is inadvertently been given a flu vaccine that is not the one recommended for their age group?

If an individual has inadvertently received a flu vaccine different to the one recommended for their age group, the individual should be informed of the error and the potential implications of this error.

Although both the QIV and aTIV should provide some protection against flu in all age groups, individuals aged 65 years and over (particularly those more than 75 years of age) may not respond as well to the QIV as they would to the aTIV, and individuals aged under 65 years will not benefit from the opportunity to build protection against an additional flu strain if they have been given aTIV.

If the individual wishes to receive the vaccine that they should have been given, this can be offered following a discussion of the benefits and risks. The clear benefit is the additional protection that may be offered by the correct vaccine but they should be alerted to the potential increased risk of a local or systemic reaction.

If a decision is made to offer the vaccine the individual should have received, it is recommended that this is done as soon as possible after the first dose was given and ideally within a week. This will enable protection to be made as soon as possible. It can still be given if more than a week has elapsed however.

Administration of an inappropriate vaccine within a practice should be reported to the local screening and Immunisation team as an immunisations incident

4. Medicines safety issues

End of life care

Following a recent incident of incorrect dosage conversion of diamorphine to morphine for breakthrough pain relief, prescribers are reminded to follow the dose conversion chart for opioids and breakthrough pain relief doses available at the Derbyshire EOL website:

https://derbyshire.eolcare.uk/community/derbyshire-community-health-services/symptom-management/symptom-management-guidance-for-use-in-dchs-and-community-primary-care-staff

Learning points

1. Useful to have reference sources to refer to when calculating & deciding on doses for palliative care – however, it is important to also take into consideration patient factors & their wishes too, which appears to have driven prescribing factors in this case.

2. All healthcare professionals need to be aware of & ask questions about other pain relief the patient may be receiving/taking e.g. different formulations of opioids or other opioids etc.
3. Be careful when converting between different opioids and/or formulations and in particular check calculations to ensure correct doses have been prescribed.
4. Improve documentation in patient records to outline how a dose has been calculated; including number of 'when required' doses a patient has had/been given of different formulations or opioids, so that other healthcare professionals accessing patient records can determine how a decision has been made regarding doses prescribed.

EpiPen and EpiPen Junior (Adrenaline auto-injector devices) Supply disruption alert
Department of Health and Social Care. SDA/2018/001
Issued: 28th September 2018 valid until: 31st December 2018

EpiPen and EpiPen Junior will be subject to limited availability for the remainder of 2018. Mylan are now out of stock of EpiPen Junior and interruptions in the supply are anticipated to continue for the coming months.

For action by general practices, community pharmacies, acute trusts, community trusts, mental health trusts, ambulance trusts.

Action
All health care professionals in primary, secondary or specialist healthcare services who prescribe, dispense or administer adrenaline auto-injectors, or who advise patients and their carers, should ensure that:

1. Adult and child auto-injectors are only prescribed and dispensed to those who truly need them, as any additional issuing to patients who are worried about the shortages could exacerbate the overall supply situation.

2. Repeat prescriptions and supply are managed diligently and patients advised of the following:
   a) It is important to note that when validating the expiry date of an adrenaline auto-injector, the product expires on the last day of the month indicated e.g. a device labelled 'April 2019' does not expire until the end of April 2019.
   b) Certain batches of adult EpiPen can be safely used for four months after the expiry date has passed - please see further information about these batches below. Where possible, prescribers should not prescribe a replacement adult EpiPen whilst the original is within the extended use by date.
   c) Patients should be advised not to dispose of their expired devices until they have replaced them.

3. Due to ongoing constraints affecting EpiPen 300mcg and Epipen 150mcg devices, some adults and children may need to switch from their usual device to other alternative adrenaline auto-injector devices that may be more readily available. The different brands of adrenaline auto-injectors are not used in exactly the same way and therefore specific training and advice is required for each of the devices- please see information on these alternative devices below.

4. Junior adrenaline auto-injectors (150mcg) must only be dispensed in line with the existing established guidance i.e. to children under 30kg. Other children weighing more than 30kg need to be given adult auto-injectors (300mcg).

5. Prescribers should work in close collaboration with their local pharmacies to understand which devices are available. Prescribers and pharmacists should work together to ensure patients who are switched to an alternative device are trained appropriately and understand how to use the new device.

6. Prescribers and pharmacies should regularly check the following Specialist Pharmacy Services website for additional updates to supply and clinical guidance.

Extended use beyond labelled expiry date
Mylan UK have obtained acceptance from the MHRA to extend the use of specific batch numbers of EpiPen 300mcg auto-injectors, beyond the labelled expiry date by four months. The affected lot numbers, which have labelled expiry dates between July 2018 and November 2018, are listed in the table below. EpiPen 300mcg auto-injectors within these batches will have likely already been dispensed by pharmacies and will therefore be in patients' possession. To the extent possible, clinicians should defer prescribing a replacement adult EpiPen for a pen in one of the lots in the table which is within the extended use by date.

LOT	Labelled Expiry Date (end of the month)	Extended Use by Date (end of the month)
6FA794J	07.2018	11.2018
6FA795Y	07.2018	11.2018
7FA112F	09.2018	01.2019
7FA106B	09.2018	01.2019
7FA283B	10.2018	02.2019
7FA251D	10.2018	02.2019
7FA250B	10.2018	02.2019
7FA265C	11.2018	03.2019
7FA265B	11.2018	03.2019

The extended use only applies to the lots of Epipen 300mcg auto-injectors listed above. Patients can continue to use the Epipen 300mcg auto-injectors of these specified lots safely until the extended use by date in the table above.
Important: This extended use **does not apply** to EpiPen 150mcg auto-injectors or any lot number of Epipen 300mcg auto-injectors not specified. Patients must continue to adhere to the labelled expiry date on any EpiPen not covered by the lot numbers above.
Further information about this can be found here: http://www.epipen.co.uk/

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

Sildenafil – reclassification from POM to P medicine
Key learning points Drug and therapeutics Bulletin Volume 56 issue 10, September 2018

- Sildenafil 50mg tablets (Viagra Connect) are available as a pharmacy medicine for use by men aged ≥18 years who have erectile dysfunction.
- In fixed-dose studies three times as many men reported that 50mg sildenafil improved their erections compared with placebo (74% vs. 25%).
- The market authorisation holder (Pfizer Consumer Healthcare Ltd.) has published training materials and a checklist to help pharmacists assess whether a patient is suitable for Viagra Connect.
- As part of the assessment process, pharmacists are advised to take into consideration a patient's cardiovascular health, other medical conditions and all medicines that the patient is taking.
- The market authorisation holder advises that men should make an appointment with their GP within 6 months of first purchasing Viagra Connect.
- Retail price: £19.99 (4 tablets), £34.99 (8 tablets).

Senna Vs Bisacodyl

Drug	Dose	Cost
Bisacodyl 5mg	1 - 2 ON	£6.19 x 60
Senna 7.5mg	2 - 4 ON	£1.89 x 60

Prices obtained from MIMs October 2018

Apr - Jun	Biscaodyl		Senna	
	Items	Cost	Items	Cost
ECCG	982	4,663	749	1,163.64
HCCG	2,379	8,386	1,180	1,334.66
NDCCG	3,366	13,406	2,881	3,699.45
SDCCG	3,976	18,649	4,983	7,336.91

Quarterly savings based on 100% switch from bisacodyl to senna = £41,985, therefore this equates to £167,940 annual saving if senna is prescribed.

Prescribers are reminded if a stimulant laxative is required then senna is the current cost effective choice.

September 2018 – price concessions
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 size	Price concession	Drug tariff price
Amisulpride 100mg tablets	60	£9.95	£3.46
Amisulpride 50mg tablets	60	£5.29	£1.81
Mometasone 0.1% cream	30g	£2.71	£1.78
Propranolol 10mg tablets	28	£2.84	£1.01
Propranolol 40mg tablets	28	£2.86	£1.02
Sodium valproate 200mg/5ml oral solution SF	300ml	£6.27	£5.31
Sodium valproate 500mg gastro-resistant tablets	100	£13.95	£8.93
Valsartan 40mg capsules	28	£3.99	£2.68

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

September 2018

Relevant for primary care: Chronic heart failure in adults: diagnosis and management. This guideline covers diagnosing and managing chronic heart failure in people aged 18 and over. It aims to improve diagnosis and treatment to increase the length and quality of life for people with heart failure.

Local heart failure guidance is currently under review to bring in line with NICE.

7. 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/
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&pageIdx=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