Derbyshire Medicines Management Newsletter

www.derbyshiremedicinesmanagement.nhs.uk

Volume 5 Issue 2 May 2015

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 April 2015, Volume 53, Number 4
Articles relevant to primary care
For full access to the DTB articles login via Open Athens. Those without accounts: https://openathens.nice.org.uk/

The impact of molluscum contagiosum

The DTB reports results from a large prospective cohort study of children in the UK investigating the time to resolution of molluscum contagiosum, a common presenting condition in primary care and its impact on quality of life.

1. The study found no association between time to resolution and gender, having an affected family member, treatment, and increased number of lesions
2. For most children the effect on quality of life was small; but in 11% of cases it was reported as very severe (female sex, longer duration of lesions at baseline, and lesion number more associated)

The authors of the study suggest where quality of life is severely affected an active treatment should be an option. In October 2013 debated whether the medical device Molludab (potassium hydroxide solution 5%) should be made available across Derbyshire. JAPC classified the product as RED allowing its restricted use in secondary care and by dermatology champions.

Reassessing treatments for neuropathic pain

The DTB reports on a systematic review highlighting inconsistencies in methods used to assess quality of evidence in previous reviews; it suggested that publication bias led to a 10% over-estimation of treatment effect.
In the absence of overwhelming evidence of superiority of one drug over another it would seem sensible to use the lowest cost agents first. Prescribers should follow our local neuropathic pain guideline where amitriptyline is recommended as a first line cost effective treatment option.

Sick day rules in kidney disease

Acute Kidney Injury is extremely common in hospitalised patients, occurring in 10-20% of emergency hospital admissions and is associated with extremely poor outcomes. Recognising that primary care has a role in prevention some organisations are starting to think about sick day rules' that recommend the temporary cessation of potentially nephrotoxic drugs including ACE inhibitors, angiotensin-II receptor antagonists, diuretics and NSAIDs. The DTB highlights unintended consequences associated with sick day rules such as clinicians being reluctant to restart or initiate medication after an episode of acute kidney injury, focusing on short-term change in kidney function at the expense of the drugs' long-term benefits. Southern Derbyshire Erewash are with DHFT are part of a pathfinder project for AKI and have produce guidance on its management for primary care for use across SDCCG and Erewash CCG.

Olodaterol

JAPC undertook a new drug review of olodaterol a new once daily LABA in the management of COPD classifying it as BLACK (not routinely recommended or commissioned). This view is reflected by the DTB "… there is insufficient evidence to recommend olodaterol over existing LABAs".

Managing back pain and osteoarthritis without paracetamol

BMJ 2015;350:h1352 doi: 10.1136/bmj.h1352 (Published 1 April 2015)
A systematic review and meta-analysis by Machado et al questions the efficacy and safety of paracetamol for spinal pain and osteoarthritis. A similar suggestion was put forward by NICE in their draft management of osteoarthritis guidance, a decision later reversed following feedback from a range of stakeholders citing that more toxic drugs may be widely used. Prescribers should be made aware of this evidence but should continue to follow the Derbyshire guidelines for the management of non-malignant chronic pain. They should also consider non-pharmacological options, which form the cornerstone of self-management of spinal pain and osteoarthritis.

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Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials

Elainon Pio Navarese et al. BMJ 2015;350:h1618 | doi: 10.1136/bmj.h1618

A meta-analysis of ten RCTs (n=32,287) compared short term (<12months) to extended (>12months) dual antiplatelet (DAPT) regimens following percutaneous coronary intervention with drug eluting stents.

The authors concluded that compared with a standard 12 month duration, short term DAPT (<12 months) after drug eluting stent implementation yields reduced bleeding with no apparent increase in ischaemic complications, and could be considered for most patients. In selected patients with low bleeding risk and very high ischaemic risk, extended DAPT (>12 months) could be considered. The increase in all cause but not cardiovascular death with extended DAPT requires further investigation.

Prescribers in Derbyshire should continue to follow local guidelines. It should be noted that the North and South Derbyshire pathways differ in choice of DAPT. Discharges should contain clear communication on duration of DAPT (usually up to 12 months) between the consultant and GP and should be documented in patient notes.

Proton pump inhibitors and the risk of acute kidney injury in older patients: a population-based cohort study

A Canadian population-based study (290,592 individuals) observed an increase in the short-term risk for hospital admission with acute kidney injury in older patients starting treatment with a PPI compared to matched controls not prescribed PPIs. The authors say that their findings are in agreement with those from three previous case-control studies and advise clinicians to maintain a high index of suspicion for acute interstitial nephritis among patients taking PPIs who present with a decline in renal function, particularly at the outset of treatment. They also recommend against the indiscriminate use of PPIs; those taking these medicines should be monitored appropriately.

http://www.cmajopen.ca/content/3/2/E166.full.pdf+html

Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study

Neena S Abraham et al BMJ 2015;350:h1857 doi: 10.1136/bmj.h1857

The BMJ reports on a large real world retrospective cohort study (n-92,816) from the US with the use of warfarin, dabigatran and rivaroxaban in patients with and without atrial fibrillation (AF). They conclude that the risk of gastrointestinal (GI) bleeding related to new oral anticoagulants was similar to that of warfarin, but that the risk of GI bleeding increased after the age of 65. By the age of 76 the risk exceeded that with warfarin amongst patients with AF taking dabigatran and patients with rivaroxaban (with and without AF). This prompted the authors to advise caution when prescribing new oral anticoagulants to older people, particularly those over 75 years old.

Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study

Hsien-Yen Chang et al BMJ 2015;350:h1585 doi:10.1136/bmj.h1585

The BMJ reports on another retrospective cohort study comparing dabigatran and rivaroxaban with warfarin with gastrointestinal bleeding using patient data from a large US insurance database over a different period to that in the study above. They conclude that there are similar rates of GI bleeding but cannot rule out as much as 50% increase in the risk of GI bleeding with dabigatran or more than twofold higher bleeding risk with rivaroxaban compared to warfarin.

NICE Medicines Evidence Commentary

Asthma: tiotropium as add-on therapy to inhaled corticosteroids in moderate asthma

NICE reports and comments on a two large trials conducted in non UK patients with moderate asthma already treated with an inhaled corticosteroid. Compared with placebo, tiotropium improved lung function but did not produce a clinically meaningful improvement in asthma control score or any other patient-oriented outcomes. Tiotropium is currently licensed in the UK for use at step 4 of the SIGN/BTS guidance but not in combination with an ICS without a LABA, as it was used in these 2 trials.

Commentary provided by the Medicines and Prescribing Centre

Previous large studies for tiotropium in asthma have been limited to people with severe asthma with persistent airflow obstruction, already treated with ICS and LABA. These new studies add to the emerging evidence base for tiotropium in asthma, specifically as add-on therapy to ICS in adults with moderate asthma. However, although salmeterol was included as an active comparator, the studies were not designed to compare efficacy of tiotropium and salmeterol. The benefits or harms of using tiotropium as add-on therapy (at step 3) instead of the more established bronchodilators are not known. Also, although tiotropium was more effective than placebo at improving lung function, this is a disease-oriented outcome. No clinically meaningful difference was seen when patient-oriented outcomes were measured such as the mean asthma control score or measures of quality of life.

These results may not be generalisable to UK clinical practice as the studies did not include any participants from the UK. In particular, prescribers are reminded that tiotropium is currently licensed in the UK only for use at step 4 of the SIGN/BTS guidance and not in combination with an ICS without a LABA, as it was used in these 2 trials.

In December 2014 JAPC recognized the limited benefit of tiotropium for asthma and classified this as a BROWN drug with specialist/consultant assessment and initiation. Other cheaper options are available at step 4of the BTS asthma guidance but tiotripium may be better suited where there is evidence of airflow obstruction.

Deleted products 2015 | MIMS online for April 2015

Brochlor Drops (chloramphenicol)	HumaPen Memoir
Lumecare Sodium Hyaluronate	Mucodyne Paediatric (carbocisteine)
Novasource GI Control	Piportil Depot (pipotiazine palmitate)
Resource Dessert Fruit	Rupafin (rupatadine)
Ursogal (ursodeoxycholic acid)	

2. Drug safety update relating to primary care prescribing

(For more information see Drug Safety Update) Volume 8, Issue 9, April 2015

The website that hosts the Drug Safety Update has now been moved. You can subscribe to alerts by using the following sign up link

Hydroxyzine (Atarax, Ucerax): risk of QT interval prolongation and Torsade de Pointes

The MHRA advises that hydroxyzine should not be prescribed to people with a prolonged QT interval or risk factors for QT interval prolongation stating also maximal doses when it is used

- 100 mg for adults
- 50 mg for the elderly (if use cannot be avoided)
- 2 mg per kg body weight for children up to 40 kg in weight

Codeine for cough and cold: restricted use in children

When prescribing or dispensing codeine-containing medicines for cough and cold, Do not use codeine-containing medicines in children under 12 as it is associated with a risk of respiratory side effects related to opiate toxicity. Codeine is not recommended for adolescents (12 to 18) who have problems with breathing.

High strength, fixed combination and biosimilar insulin products: minimising the risk of medication error

Several new insulin products have come to market recently; three high strength insulins which have concentrations greater than 100 units/mL (Tresiba▼, Humalog, Toujeo▼), a fixed combination of insulin degludec and liraglutide (Xultophy▼) and a biosimilar of insulin glargine (Abasaglar▼).

Healthcare professionals and patients need to understand the insulin strength of these products and how to use them correctly to minimise the risk of medication errors such as the wrong insulin dose being administered.

3. Local news and GP/pharmacist queries

GP query

Is nitrofurantoin the first line drug choice in urinary tract infections or are there circumstances when trimethoprim is preferable?

Our nurses have been using trimethoprim if patients haven't had recent treatment because of the cost difference (3 day course of nitrofurantoin 100mg MR twice daily £4.07, trimethoprim 200mg twice daily £0.44)

Answer (from the primary care antimicrobial specialist pharmacist):

The latest advice from Public Health England Primary Care guidance (November 14)
https://www.gov.uk/government/publications/managing-common-infections-guidance-for-primary-care

Focusing on non-pregnant females, please look at p6, this has lots of guidance on Lower UTIs and it also states:
Use nitrofurantoin first line, as general resistance and community multi-resistant Extended-spectrum Betalactamase E. coli are increasing.
Trimethoprim (if low risk of resistance) and pivmecillinam are alternative first line agents.

Risk factors for increased resistance include: care home resident, recurrent UTI, hospitalisation >7d in the last 6 months, un resolving urinary symptoms, recent travel to a country with increased antimicrobial resistance (outside Northern Europe and Australasia) especially health related, previous known UTI resistant to trimethoprim, cephalosporins or quinolones

Anecdotally we are hearing reports that there is an increasing resistance to trimethoprim (and lower resistance with nitrofurantoin) locally.
It is worth noting also from the front of PHE guidance – it now states this (for mild UTI symptoms) under point 5:
"Consider a NO, or back-up / delayed, antibiotic strategy for acute self-limiting upper respiratory tract infections, and mild UTI symptoms"

Further details can be found on page 6
Treat women with severe/or ≥ 3 symptoms for women mild/or ≤ 2 symptoms AND

a) Urine NOT cloudy 97% negative predictive value, do not treat unless other risk factors for infection.
b) If cloudy urine use dipstick to guide treatment. Nitrite plus blood or leucocytes has 92% positive predictive value; nitrite, leucocytes, blood all negative 76% NPV4A
c) Consider a back-up / delayed antibiotic option

Finally see the references section on p 26
20.http://www.scottishmedicines.org.uk/files/sapg/Alternative_management_of_lower_UTI_in_non-pregnant_women.pdf

Accessed 23.09.14.
RATIONALE: This evidence based guidance has been reviewed, and now recommends that clinicians consider the use of delayed / back-up antibiotics for the management of women with less severe or limited urinary symptoms. The guidance is based on two randomised controlled trials in English and Dutch general practice. 51 of 137 (37%) of Dutch women were willing to delay their antibiotics, 55% (28/51) did not use the antibiotics and 71% of these patients (20/28) reported clinical cure

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

Think! Why A&E?
Developed in partnership with NHS Blackpool Clinical Commissioning Group (CCG) and Blackpool Teaching Hospitals NHS Foundation Trust, it encourages people to choose the right NHS service for them and their families according to their symptoms.
This may be a useful resource for general practices to link on their websites and perhaps use on practice television systems with due regard for the copyright. Practices wishing to use this resource should contact Colette Cassin at Blackpool CCG

Medicines Optimisation (NICE March 2015)
NICE has published this document to support organisations in medicines optimisation. Principles applying equally to GP practices. Medicines optimisation is defined as 'a person-centred approach to safe and effective medicines use, to ensure people obtain the best possible outcomes from their medicines. Medicines optimisation applies to people who may or may not take their medicines effectively. Shared decision-making is an essential part of evidence-based medicine, seeking to use the best available evidence to guide decisions about the care of the individual patient, taking into account their needs, preferences and values.

How do you switch between pregabalin and gabapentin for neuropathic pain, and vice versa? (UKMi Q&A March 2015)
There is very limited evidence in the medical literature with regards to managing a switch between the two agents. The UKMI has produced an information sheet to try and answer this question.
The manufacturer of both pregabalin and gabapentin advises that if they are to be discontinued, or the dose reduced or substituted with an alternative medication, the dose should be tapered gradually over a minimum of a week. However, this withdrawal is to minimise the risk of increased seizure frequency where they are being used for patients with seizure disorders. The clinical importance of a slow withdrawal in patients with neuropathic pain remains unknown

UKMI does though report on an open label study that substituted gabapentin with pregabalin in patients with neuropathic pain due to peripheral neuropathy. The author describes an overnight switch from gabapentin to pregabalin, based on a conversion table which is described in the paper as “of the author’s creation” (table below).

Daily Dose of gabapentin pre-switch (mg/day)	Daily dose of pregabalin per day post switch (mg/day)	Dosing schedule of pregabalin
0-900	150	75mg twice daily
901-1500	225	75mg in the morning and 150mg in the evening*
1501-2100	300	150mg twice daily
2101-2700	450	150mg in the morning and 300mg in the evening
2700 or higher	600	300mg twice daily

Table 1: Dose conversion of gabapentin to pregabalin used in the Toth study
*the table in the published study actually reads 75mg in the morning and 225mg in the evening. This error has been corrected in the above table
Toth C. Substitution of gabapentin therapy with pregabalin therapy in neuropathic pain due to peripheral neuropathy. Pain Medicine 2010; 11: 456-465

Potential risk of error in selecting oxycodone strength (NPA April 2015)
Reports of incidents involving the selection of the wrong strength of oxycodone oral solution by the prescriber have been highlighted by a Controlled Drug Accountable Officer.

Oxycodone oral solution 10mg/ml appears as the first option on Egton Medical Information Systems (EMIS) used by GP surgeries, and has been picked instead of oxycodone oral solution 5mg/5ml. This error appears to have led to two patients needing hospital treatment.

Pharmacists should make sure they check all prescriptions for oxycodone oral solution 10mg/ml and confirm with the prescriber that it is the intended strength.
For further information on this or any other query, please contact the NPA Pharmacy Services Team on 01727 891 800 / 0844 736 4201 or email pharmacyservices@npa.co.uk

Prescribers using EMIS can speak to their medicines management pharmacist or pharmacy technician to advise on how to mitigate this risk

Topical ketoprofen: reminder on risk of photosensitivity reactions - MHRA august 2010

Healthcare professionals are reminded of the risk of photosensitivity reactions associated with topical ketoprofen

Advice for healthcare professionals:

- patients should ensure that treated areas are protected from sunlight during the whole period of topical ketoprofen treatment and for 2 weeks after stopping treatment; they should also carefully wash their hands after every application
- patients should stop treatment immediately if they develop any skin reaction after application of these medicines and seek their doctor's advice

patients should be informed of the appropriate use of topical ketoprofen as outlined in the product information

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

Chronic obstructive pulmonary disease: aclidinium/formoterol

Summary

Aclidinium/formoterol (Duaklir Genuair) is a combination inhaler containing a long-acting muscarinic antagonist (LAMA) and long-acting beta-2 agonist (LABA). It is licensed for treating chronic obstructive pulmonary disease (COPD).

Two randomised controlled trials (RCTs) found that aclidinium/formoterol statistically significantly improved lung function and breathlessness over 24 weeks compared with placebo and aclidinium and formoterol monotherapies. Not all of the improvements compared with aclidinium or formoterol monotherapy were considered to be clinically important using conventional criteria. Improvements in lung function and breathlessness were similar to those seen with the other recently licenced LAMA/LABA combinations, umeclidinium/vilanterol and indacaterol/glycopyrronium.

Regulatory status: Duaklir Genuair (aclidinium/formoterol) received a European marketing authorisation for maintenance bronchodilator treatment to relieve symptoms in adults with COPD in December 2014

Derbyshire's COPD guideline is currently under review and the place of combination inhalers is part of that. This NICE new evidence review adds to the lack of convincing evidence to support the routine use LABA/ LAMA combinations in COPD with patient orientated outcomes.

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/
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