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 January 2016,Volume 54 Number 1 reports on:

- MHRA advice from October 2015. Mirabegron is contraindicated in patients with severe uncontrolled hypertension; advice about regular blood pressure monitoring is being introduced because of cases of severe hypertension.
  Their recommendation includes reviewing patients with hypertension who are currently taking mirabegron.
- **OTC analgesics for acute pain:** An overview of Cochrane review cites that several OTC analgesics are effective for acute pain, with simple combinations and fast acting formulations at low doses. This overview demonstrates that there is a reliable body of evidence to show that simple, inexpensive, readily available painkillers give good pain relief with acute pain such as toothache, sprains and strains. Ibuprofen/paracetamol combinations and fast-acting ibuprofen formulations are particularly good and are often effective in their lower dosage range. The findings do not apply to chronic pain such as in osteoarthritis and data on tension headache, migraine and period pain.
- **Interventions have lasting effect on preventing or delaying diabetes:** Intensive lifestyle intervention or metformin can significantly reduce diabetes development over 15 years for people at high risk of developing the disease, reports the long-term follow-up to the Diabetes Prevention Program (DPP) trial. After a mean follow-up of 15 years, diabetes incidence was reduced by 27% in the lifestyle intervention group and by 18% in the metformin group, compared to placebo. The differences between groups lessened over time. By year 15 the cumulative incidences of diabetes were 55% in the lifestyle group, 56% in the metformin group and 62% in the placebo group. The prevalence of microvascular disease was not significantly different among the treatment groups at the end of the study but participants across all treatment groups who did not develop diabetes had a 28% lower prevalence of microvascular complications than those who did develop diabetes.
- **The management of dry eye:** Dry eyes are a common condition. The prevalence of dry eye syndrome increases with age especially in the elderly with reported prevalence rates range from 15–33%. There are two main types of dry eye: aqueous insufficiency (due to reduced aqueous secretion from lacrimal glands) and evaporative (due to a deficient lipid layer). Management of dry eye includes practical measures (such as increasing humidity in the environment) and symptomatic treatment with artificial tears and ocular lubricants. In the absence of comparative evidence of safety or efficacy it makes sense to start with the lowest cost preparations. In the absence of UK national guidelines. NICE CKS recommends the following treatment where practical advice alone is insufficient:
  - For mild or moderate symptoms: artificial tears.
  - For severe symptoms: preservative-free artificial tears, perhaps with an ocular lubricant ointment to use at night.
  - For people with visible strands of mucus: consider acetylcysteine drops (limited evidence).
    In general first-line treatment with a generic or low-cost brand of hypromellose is recommended. Preservative intolerance should be diagnosed by an ophthalmologist as preservative free (PF) products are more expensive. If PF formulation is warranted, proprietary preservative-free formulations (often available as unit dose preparations) should be prescribed if at all possible. Manufactured "specials" are unlicensed and almost invariably cost significantly more.

PF formulations are appropriate for example when a patient wears soft contact lenses or daily disposable contact lenses and wearing glasses instead is not a viable option such as for long courses OR where patient shows signs of preservative toxicity sometimes seen with multiple daily administrations. See local formulary choices in eye chapter

Risks and benefits of nalmefene for alcohol dependence

Nalmefene is an option in alcohol dependence treatment. Its approval was controversial.

In alcohol-dependant adults, nalmefene use does not affect mortality rates (at six months and one year) or quality of life (at six months) compared to placebo, and after sensitivity analyses there is no difference in alcohol consumption outcomes between groups, according to results of this meta-analysis. NICE recommended it as a 'possible' treatment for alcohol dependence. The French National Authority for Health Transparency Committee (NAHTC) was also cautious and considered that nalmefene provided a minor improvement in actual benefit compared to psychosocial support alone in the treatment of alcohol dependence . In contrast, the German IQEHC concluded that studies of nalmefene showed no additional benefits for alcohol dependence compared to naltrexone another opioid antagonist that was an earlier and less costly comparator therapy. Furthermore, the Swedish DPBA concluded that the lack of advantage of nalmefene compared to existing treatments suggested that it did not warrant recommendation for reimbursement.

Researchers' opinions are more divided, with some arguing that nalmefene is a 'paradigm shift' and others claiming that it is a perfect example of 'bad medicine'. This meta-analysis aimed to objectively reappraise the efficacy of nalmefene for relevant health outcomes, not solely restricted to alcohol consumption endpoints. Primary outcomes were mortality, accidents (including motor vehicle crashes) or injuries, quality of life or functioning, and somatic complications of alcoholism. Secondary outcomes included alcohol consumption outcomes, biological outcomes, and treatment safety outcomes.

The following results were reported:

- Mortality at six months (risk ratio 0.39 [95% CI 0.08 to 2.01]) and one year (0.98 [0.04 to 23.95]) and quality of life at six were not different across groups. Other health outcomes were not reported.
- There were differences in alcohol consumption outcomes such as monthly number of heavy drinking days at six months (Mean difference -1.65 [-2.41 to -0.89]) and at one year (MD -1.60 [-2.85 to -0.35]) and total alcohol consumption at six months (standardised MD -0.20 [-0.30 to -0.10]).
- An attrition bias could not be excluded, with more withdrawals for nalmefene than for placebo, including more withdrawals for safety reasons at both six months (RR 3.65 [2.02 to 6.63]) and one year (RR 7.01 [1.72 to 28.63]).

The authors conclude that the value of nalmefene for treatment of alcohol addiction is not established. At best, nalmefene has limited efficacy in reducing alcohol consumption.

PLOS Medicine; published online 22 December 2015

Deleted products 2016 | MIMS online for January 2016

Acupan (nefopam)	Amlostin (amlodipine)	Cilguard Border
Cilguard Overlap	Cilguard Standard	Climaval (estradiol valerate)
Colomycin tablets (colistimethate sodium)	De-Noltab (tri-potassium di-citrato bismuthate)	Dermablend
Ditropan Elixir (oxybutynin)	Hormonin (estradiol/estriol/estrone)	Hospicrepe 229
Losec Infusion (omeprazole)	Nivemycin (neomycin)	Norcuron (vecuronium)
Pripsen Mebendazole (mebendazole)	Sorbsan Silver Plus SA	Stiemycin (erythromycin)

2. Drug safety update relating to primary care prescribing

(For more information see Drug Safety Update) Volume 9, Issue 6, January 2016

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

Headlines:

- Updated advice on use of nicorandil as second-line treatment for stable angina; nicorandil can cause serious skin, mucosal, and eye ulceration, including gastrointestinal ulcers. Some ulcers may progress to complications unless treatment is stopped. Prescribers should follow the Derbyshire pharmacological angina pathway (appendix 6) in the cardiovascular chapter of the BNF.
- Levonorgestrel-releasing intrauterine systems: prescribe by brand name because products have different indications, durations of use, and introducers.

NHS England Patient Safety Alert

(For more information see NHSE Patient Safety Alert; NHS/PSA/W/2016/001)

NHS England has produced a Stage one (Warning) Patient Safety Alert to highlight the *'Risk of severe harm or death when desmopressin is omitted or delayed in patients with cranial diabetes insipidus'*.

Cranial diabetes insipidus is a rare disorder of the pituitary gland characterised by an inability to produce antidiuretic hormone (ADH). This results in the production of large volumes of dilute urine. Cranial diabetes insipidus is the most common type of diabetes insipidus, which can be caused by damage to the hypothalamus or pituitary gland. Left untreated, patients with cranial diabetes insipidus will develop life-threatening dehydration and hypernatraema. In the treatment of cranial diabetes insipidus, desmopressin is most commonly administered as an intranasal spray or oral tablets, but may also be given as an injection in the treatment of acutely unwell or fasting patients. Desmopressin treatment should never be omitted or delayed in patients with cranial diabetes insipidus.

Local safety message

1. Potential diversion & known misuse of clozapine

It has been reported that a small number of patients have been buying and taking clozapine tablets which may be being diverted from other patient(s). The misuse of clozapine is associated with a number of risks, particularly if the person has never taken clozapine before, or takes it sporadically. The product literature lists the following signs and symptoms of clozapine toxicity:

Drowsiness, lethargy, areflexia, coma, confusion, hallucinations, agitation, delirium, extrapyramidal symptoms, hyperreflexia, convulsions; hypersalivation, mydriasis, blurred vision, thermolability; hypotension, collapse, tachycardia, cardiac arrhythmias; aspiration pneumonia, dyspnoea, respiratory depression or failure1.

Clozapine is potentially very dangerous in overdose; the ingestion of as little as 400mg has led to life-threatening comatose conditions, and in one case, death. Children are at risk at significantly lower doses.

Clinicians working in mental health services are asked to have a higher index of suspicion regarding the potential for diversion of clozapine tablets by patients.

Clinicians working in other areas of the health service are asked to be aware of this recent trend and be vigilant towards potential cases of clozapine toxicity that may present, particularly to urgent care settings. Advice on the management of suspected clozapine toxicity can be found in the product literature or from TOXBASE®, which can be accessed at any time.

3. Local news and GP/pharmacist queries

Query from GP practice:

Tetanus Immunoglobulin

A young patient has been advised by a local ENT specialist that she will need to receive Human Tetanus Immunoglobulin (TIG) following a horse bite.

Upon investigation our practice pharmacist informed me that TIG can be difficult to obtain but could possibly be requested upon special order, however, the cost is likely to be over £90 per dose (2 doses are required).

Would the cost of a special order of TIG be covered in the same way as a standard tetanus vaccine, or would if fall to the practice/patient?

Answer:

There is a public health England document available at the link below on availability and ordering of TIG.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/441355/IMW165.02_Tetanus_Immunoglobulin_Handbook_v1.4.pdf

There are contact details in the link above and in the green book for how to order the TIG if needed.

Who should supply and administer the vaccine is subject to where the care of the patient lies. For example If seen at the hospital then the responsibility would lie with the provider.

NICE NG 23 Menopause: Diagnosis and management

On 12th November 2015 the National Institute for Health and Care Excellence (NICE) published gold standard evidence based guidelines on the support, information and treatments advised to manage the potentially debilitating symptoms that women can suffer through the menopause. The guideline is essential reading for GPs and practice nurses not only because of the high proportion of their patients for whom the guideline is relevant, but also because the information enclosed removes any doubt about what women should be offered, and supersedes the often conflicting evidence that has unfortunately found its way into medical textbooks over the past decade. To support this advice, a local statement is available with key take home messages

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

Opioids prescribing in chronic non-malignant pain

Last month we signposted prescribers to resources issued by the faculty of pain http://www.fpm.ac.uk/faculty-of-pain-medicine/opioids-aware In light of this our local pain guidelines (non-malignant and neuropathic) have been updated representing a significant change in the prescribing of long term strong opiates.

Thyroid function testing in primary care *(NICE- Eyes on Evidence January 2016)*

A cross-sectional study at a single UK general practice found that only 2% of people who underwent thyroid function tests in primary care had thyroid disease. The study identified specific clinical characteristics, such as hair loss or constipation that could possibly be used to target testing at people most likely to have hypothyroidism or hyperthyroidism.

Background: Thyroid disease can occur when the thyroid gland produces too little or too much of the hormone thyroxine. Both underactive thyroid (hypothyroidism) and overactive thyroid (hyperthyroidism) have non-specific symptoms, which can make the disorders hard to diagnose.

UK guidelines on the use of thyroid function tests can be accessed at:
http://www.british-thyroid-association.org/info-for-patients/Docs/TFT_guideline_final_version_July_2006.pdf
It should be noted that the NICE guideline on fertility problems advises that women with possible fertility problems are no more likely than the general population to have thyroid disease and the routine measurement of thyroid function should not be offered. Estimation of thyroid function should be confined to women with symptoms of thyroid disease.

Further analyses suggested that thyroid function tests could possibly be targeted at people with constipation, hair loss, palpitations and diarrhoea, particularly if pregnant. However, a normal test result may reassure the patient and the doctor in a person with any clinical symptoms associated with possible thyroid disease.

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

Inflammatory lesions of papulopustular rosacea: ivermectin 10 mg/g cream (ESNM68)

Background

Rosacea is a chronic relapsing disease of the facial skin, characterised by recurrent episodes of facial flushing, persistent erythema, telangiectasia (fine, dilated blood vessels), papules and pustules. Mild or moderate papulopustular rosacea (with a limited number of papules and pustules, and no plaques) is generally treated with a topical drug (metronidazole or azelaic acid). For moderate or severe papulopustular rosacea (with extensive papules, pustules, or plaques), oral tetracycline, erythromycin, doxycycline or lymecycline can be prescribed, although not all of these drugs are licensed for treating rosacea

Summary

In 2 randomised controlled trials (RCTs) ivermectin cream was statistically significantly more effective than vehicle cream (placebo) in improving rosacea severity score and reducing inflammatory lesion count. In another RCT, ivermectin was superior to metronidazole cream at reducing lesion count and improving rosacea severity score. Local adverse events, including skin burning sensation, skin irritation, pruritus and dry skin, are common, although these are mostly transient, mild to moderate in severity and usually decrease when treatment is continued.

JAPC has classified ivermectin cream as GREEN and another topical treatment option alongside topical metronidazole and azelaic acid. Licensed as a once daily application for up to 4 months. In case of no improvement after 3 months, the treatment should be discontinued.

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