Derbyshire Medicines Management Newsletter

www.derbyshiremedicinesmanagement.nhs.uk

Volume 7 Issue 6 September 2017

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. 8 August 2017

Eluxadoline for IBS-D http://dtb.bmj.com/content/55/8

Review of eluxadoline used in the treatment of IBS-D. In the published trials, eluxadoline resulted in a small increase in the number of people who achieved the composite primary outcome (improved stool consistency and decreased abdominal pain) compared with placebo. However, this change was deemed to be of borderline clinical relevance. Although eluxadoline improved stool consistency, it did not result in a statistically significant improvement in abdominal pain (the key measure in the Rome IV criteria for IBS-D) compared with placebo, whereas the much cheaper antispasmodics, loperamide and antidepressants have been shown to produce statistically significant differences from placebo on this outcome.

NICE TA 471, recommends eluxadoline as an option for treating irritable bowel syndrome with diarrhoea in adults, only if:

- the condition has not responded to other pharmacological treatments (for example, antimotility agents, antispasmodics, tricyclic antidepressants) or
- pharmacological treatments are contraindicated or not tolerated, and
- it is started in secondary care.

JAPC has classified eluxadoline as RED – for use by secondary care specialist, to establish its place in the treatment of IBS-D.

Glycopyrronium for severe drooling in children http://dtb.bmj.com/content/55/8

Glycopyrronium bromide oral solution is a newly licensed product for the symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children ≥ 3 years. The licence specifies that it is only for short-term intermittent use. Evidence of its efficacy in this setting comes from two small 8-week RCTs in children, mainly with cerebral palsy, in which it was shown to reduce drooling. The efficacy in children with other neurological conditions is not known. In addition to the two 8-week studies, evidence on its harms also comes from a 24-week open study.

DTB state, the availability of this product does not make it the automatic first choice for treatment of severe drooling. However, if glycopyrronium is the drug treatment of choice, the licensed product should be used in preference to off-label or unlicensed glycopyrronium-containing products.

Based on the evidence JAPC has classified glycopyrronium as BROWN after consultant/specialist initiation: for hypersalivation(sialorrhoea) or drooling after a trial or consideration of hyoscine (oral and patches):

- For children: Glycopyrronium (Sialanar) is the preferred product (licenced for children). For short term intermittent use, but may be continued for long term use after assessment from the specialist.
- For adults: off-licence use of 1mg/5ml strength is the preferred option over tablets

Limited treatment options for molluscum contagiosum http://dtb.bmj.com/content/55/8

Treatment options for cutaneous molluscum contagiosum have been re-examined in an updated Cochrane review. The review (22 studies, 1,650 participants) assessed treatments aimed at eradicating molluscum contagiosum lesions, including physical interventions, systemic treatments and topical agents, as well as the effect of awaiting natural resolution.

The Cochrane review noted that no single intervention has been shown to be convincingly effective in the treatment of molluscum contagiosum. In 2014, DTB assessed potassium hydroxide for this indication and concluded that they could not recommend it. Given that the condition is self-limiting and usually mild, a strategy of no treatment is reasonable for most people, unless symptoms or complications occur.

Locally both Potassium hydroxide 5% solution (Molludab) and imiquimod 5% (included in the Cochrane review) have RED classification – restricted for use by the specialists.

Delayed antibiotic prescription for lower respiratory tract infections http://dtb.bmj.com/content/55/8

The impact of different antibiotic prescribing strategies for lower respiratory tract infections (RTIs) in people aged over 16 years has been assessed in a new prospective cohort study – includes reviewing no antibiotics, immediate antibiotics and delayed prescription for antibiotics for primary care patients with RTIs.

Analysis showed no significant reductions in hospital admission or death with immediate antibiotics or with delayed antibiotics). Reconsultation for new, worsening or non-resolving symptoms was significantly reduced by delayed antibiotics (but not by immediate antibiotics.

This study supports the national initiative to promote use of delayed prescriptions as part of antibiotic stewardship.

Strontium ranalate discontinued http://dtb.bmj.com/content/55/8/86.1

Strontium ranalate was used for the treatment of severe osteoporosis in postmenopausal women and adult men who are at high risk of fracture and for whom other medicinal products approved for the treatment of osteoporosis are not possible. Prescribers are reminded that the company (Les Laboratoires Servier) have ceased distribution of the drug as of August 2017.

For patients receiving treatment, local advice is for a clinical review and fracture risk assessment in primary care. Stopping treatment may be appropriate in some patients e.g. if the fragility fractures were from long ago or the mechanism of the fracture dubious. The concept of fracture risk and tools to assess fracture risk is a recent development and some people may have been started on strontium years ago and newer treatments (other than bisphosphonates) such as denosumab and zoledronic acid are now available.

Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration (AMD)

Evans JR; Lawrenson JG. Cochrane Database Syst Rev. 2017 Jul 31; 7:CD000254. doi: 10.1002/14651858.CD000254.pub4. (Review) PMID: 28756618

The objective of this Cochrane review was to assess the effects of antioxidant vitamin or mineral supplementation on the progression of AMD in people with AMD. People with AMD may experience some delay in progression of the disease with multivitamin antioxidant vitamin and mineral supplementation. This finding was largely drawn from one large trial, conducted in a relatively well-nourished American population. We do not know the generalisability of these findings to other populations. Although generally regarded as safe, vitamin supplements may have harmful effects. A systematic review of the evidence on harms of vitamin supplements is needed. Supplements containing lutein and zeaxanthin are heavily marketed for people with age-related macular degeneration but our review shows they may have little or no effect on the progression of AMD.

Locally all antioxidants for ocular health have been classified as BLACK – not routinely commissioned or recommended.

Deleted products 2017 | MIMS online for August 2017

Aureocort (triamcinolone/chlortetracycline)	Dyazide (co-triamterzide)
Elastolabo	Intanza (influenza vaccine)
Maxolon High Dose (metoclopramide)	Maxolon Injection (metoclopramide)
Protelos (strontium ranelate) (see section 1 above)	Resource Dessert Energy

2. Drug safety update primarily relating to primary care prescribing

(For more information see Drug Safety Update) Volume 11 Issue 1 August 2017

A. Corticosteroids: rare risk of central serous chorioretinopathy with local as well as systemic administration

Central serous chorioretinopathy is a retinal disorder that has been linked to the systemic use of corticosteroids. Recently, it has also been reported after local administration of corticosteroids via inhaled and intranasal, epidural, intra-articular, topical dermal, and periocular routes.

Advice for healthcare professionals:

- advise patients to report any blurred vision or other visual disturbances during corticosteroid treatment
- consider referral to an ophthalmologist for evaluation of possible causes if a patient presents with vision problems
- report suspected adverse reactions to us on a Yellow Card

B. Adrenaline auto-injectors: updated advice after European review

It is recommended that 2 adrenaline auto-injectors are prescribed, which patients should carry at all times.

Advice for healthcare professionals:

- it is recommended that 2 adrenaline auto-injectors are prescribed, which patients should carry at all times

Advice to give to people with allergies and their carers:

- it is recommended that you carry 2 adrenaline auto-injectors at all times; this is particularly important for people who also have allergic asthma because they are at increased risk of a severe anaphylactic reaction .
- check the expiry date of the adrenaline auto-injectors and obtain replacements before they expire; expired injectors will be less effective

C. Important: dosage adjustment advice in the BNF

Clinical laboratories routinely report renal function in adults based on estimated glomerular filtration rate (eGFR) normalised to a body surface area of 1.73m2—this is derived from either the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula or the Modification of Diet in Renal disease (MDRD) formula. However, in product literature, the effects of renal impairment on drug elimination are usually stated in terms of creatinine clearance as a surrogate for GFR.

The information on dosage adjustment in the BNF is usually expressed in terms of eGFR. Exceptions to the use of eGFR include **toxic drugs, in elderly patients and in patients at extremes of muscle mass** (see Estimating renal function in patients at extremes of muscle mass and Estimating renal function in elderly patients, below) where calculation of CrCl is recommended. Although these two measures of renal function are not interchangeable, for most drugs and for most adult patients of average build and height, eGFR (rather than CrCl) can be used to determine dosage adjustments

Prescribing in renal impairment

Issues encountered in renal impairment

The use of drugs in patients with reduced renal function can give rise to problems for several reasons:

- reduced renal excretion of a drug or its metabolites may cause toxicity;
- sensitivity to some drugs is increased even if elimination is unimpaired;
- many side-effects are tolerated poorly by patients with renal impairment;
- some drugs are not effective when renal function is reduced.

Many of these problems can be avoided by reducing the dose or by using alternative drugs. If even mild renal impairment is considered likely on clinical grounds, renal function should be checked before prescribing any drug which requires dose modification.

General guidance

Where care is needed when prescribing in renal impairment, this is indicated under the relevant drug monograph in the BNF.

When both efficacy and toxicity are closely related to plasma-drug concentration, recommended regimens should be regarded only as a guide to initial treatment; subsequent doses must be adjusted according to clinical response and plasma-drug concentration. Dose recommendations are based on the severity of renal impairment. The total daily maintenance dose of a drug can be reduced either by reducing the size of the individual doses or by increasing the interval between doses. For some drugs, although the size of the maintenance dose is reduced it is important to give a loading dose if an immediate effect is required. This is because it takes about five times the half-life of the drug to achieve steady-state plasma concentrations. Because the plasma half-life of drugs excreted by the kidney is prolonged in renal impairment it can take many doses for the reduced dosage to achieve a therapeutic plasma concentration.

Important: dosage adjustment advice in the BNF

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Nephrotoxic drugs

Nephrotoxic drugs should, if possible, be avoided in patients with renal disease because the consequences of nephrotoxicity are likely to be more serious when renal reserve is already reduced. During intercurrent illness the risk of acute kidney injury is increased in patients with an eGFR of less than 60 mL/min/1.73 m^2; potentially nephrotoxic or renally excreted drugs may require dose reduction or temporary discontinuation.

Renal replacement therapy and transplantation

For prescribing in patients who have received a renal transplant or who are on renal replacement therapy (peritoneal dialysis or haemodialysis), consult specialist literature.

Estimating renal function

Direct measure of Glomerular filtration rate (GFR) using plasma or urinary clearance is considered the best overall index of renal function. However, this is difficult to do in practice. As an alternative, the *estimated* Glomerular filtration rate (eGFR) based on serum creatinine is used to assess renal function. Creatinine clearance (CrCl) is also used as an estimate of GFR.

Various equations for estimating glomerular filtration rate exist, however there is no compelling evidence to support the superiority of any given method for drug dosing in *all* patient populations or clinical situations. There is also insufficient evidence to provide *definitive* guidance about dosage adjustment of all drugs in patients with reduced renal function. Therefore, an understanding of drug pharmacokinetics is necessary in order to make appropriate dosing decisions.

Using serum creatinine to derive eGFR has a number of limitations; serum creatinine levels are dependent on muscle mass and diet, therefore estimates should be interpreted with caution in certain individuals (such as the elderly, body builders, amputees, in muscle-wasting disorders and vegans)—estimates will be higher or lower than the true value. Creatinine-derived measurements are also **not** useful in periods of rapidly changing renal function or in patients with AKI.

Estimated glomerular filtration rate

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula

The CKD-EPI formula is the recommended method for estimating GFR and calculating drug doses in **most** patients with renal impairment.

CKD-EPI is adjusted for body surface area (BSA) and utilises serum creatinine, age, sex and race as variables. Clinical laboratories should use the CKD-EPI formula to routinely report eGFR.

CKD-EPI equation

eGFR (ml/min/1.73 m^2) = 141 x $\min(S_{Cr}/K, 1)^{\alpha}$ x $\max(S_{Cr}/K, 1)^{-1.209}$ x 0.993^{Age} [x 1.018 if female] [x 1.159 if black]

Where:

- S_{Cr} = serum creatinine in mg/dL;
- K = 0.7 for females and 0.9 for males;
- α = -0.329 for females and -0.411 for males;
- $\min(S_{Cr}/K, 1)$ indicates the minimum of S_{Cr}/K or 1;
- $\max(S_{Cr}/K, 1)$ indicates the maximum of S_{Cr}/K or 1.

Modification of Diet in Renal disease (MDRD)

The MDRD formula, like CKD-EPI, is expressed in terms of body surface area. It is less accurate than the CKD-EPI formula when eGFR is greater than 60 mL/min/1.73 m^2. It also overestimates GFR in elderly patients.

Estimated creatinine clearance

Cockcroft and Gault

The Cockcroft and Gault formula is the preferred method for estimating renal function or calculating drug doses in patients with renal impairment who are elderly or at extremes of muscle mass (see below); it provides an estimate of CrCl (which is not equivalent to eGFR).

Formula

$$\text{Estimated Creatinine Clearance in mL/minute} = \frac{(140 - \text{Age}) \times \text{Weight} \times \text{Constant}}{\text{Serum creatinine}}$$

- Age in years
- Weight in kilograms (use ideal body weight where fat is likely to be the major contributor to body mass)
- Serum creatinine in micromol/litre
- Constant = 1.23 for men; 1.04 for women

Estimating renal function in patients at extremes of muscle mass

In patients at both extremes of muscle mass, eGFR should be interpreted with caution. Reduced muscle mass will lead to overestimation of GFR and increased muscle mass will lead to underestimation of the GFR. *Creatinine clearance* or *absolute glomerular filtration rate* should be used to adjust drug doses in patients with a BMI less than 18 kg/m^2 or greater than 40 kg/m^2.
Ideal body weight should be used to calculate the CrCl. Where the patient's actual body weight is less than their ideal body weight, actual body weight should be used instead.

The absolute glomerular filtration rate is determined by removing the normalisation for BSA from the eGFR using the following formula:
GFR (Absolute) = eGFR x (individual's body surface area / 1.73)

The ideal body weight is calculated as follows:
Ideal body weight (kilograms) = Constant + 0.91 (Height - 152.4)
Where:
- Constant = 50 for men; 45.5 for women
- Height in centimetres

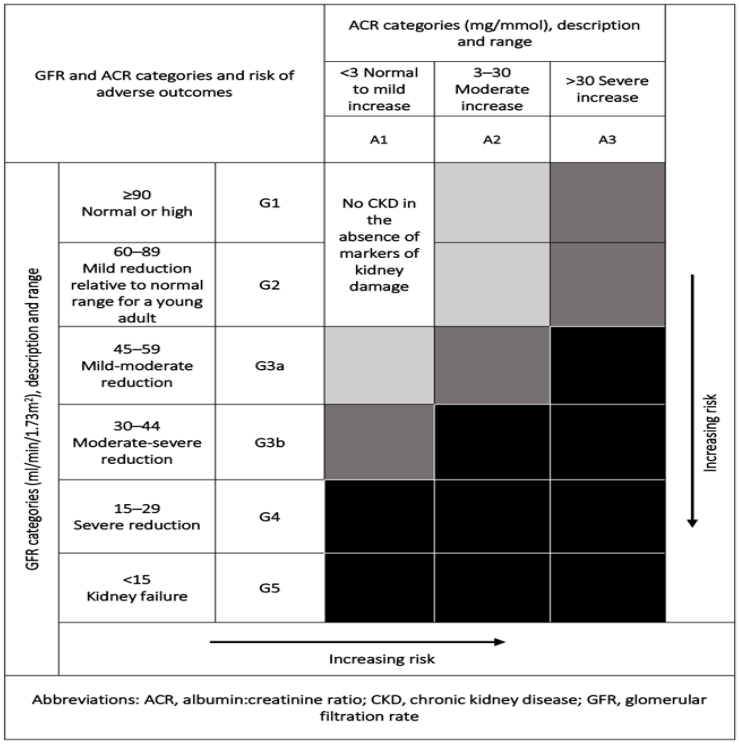
Estimating renal function in elderly patients

The Cockcroft and Gault formula is the preferred method for estimating renal function in elderly patients aged 75 years and over.

Chronic kidney disease

Classification of chronic kidney disease using GFR and ACR categories

Chronic kidney disease is classified using a combination of GFR and albumin:creatinine ratio (ACR). A decreased GFR and an increased ACR is associated with an increased risk of adverse outcomes.
For example, a person with an eGFR of 25 ml/min/1.73 m^2 and an ACR of 15 mg/mmol has a CKD classification of G4A2.
Classification of chronic kidney disease using GFR and ACR categories



Adapted with the kind permission of the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013.

Highlighting Sodium valproate risk again – Educational Risk Minimisation Materials to help reduce the risk associated with using valproate can be found at the following link
http://www.medicines.org.uk/emc/medicine/23020#rmm

3. Local news/selfcare and GP/pharmacist queries

GP QUERY
Question:
Why is Duaklir (aclidinium/formoterol) a LABA/LAMA combination inhaler classified as Brown on the Derbyshire traffic lights? It is recommended in GOLD guidance,

Answer:
The local COPD guidance has been updated to include Ultibro (Indacaterol/glycopyrronium) as the LABA/LAMA of choice – GREEN 1st line. This is based on emerging evidence from the FLAME study (which compared ultibro vs salmeterol/fluticasone)[1] and the NICE surveillance report, 2016:

- the addition of a second long-acting bronchodilator is an effective strategy compared to monotherapy with LABA or LAMA in patients with moderate to severe COPD
- LABA/LAMA combinations are more effective than LABA/ICS in preventing COPD exacerbation in patients with a history of exacerbation during the previous year.
- Lower exacerbation rates were reported with indacaterol/glycopyrronium (ultibro Breezhaler) Vs salmeterol/fluticasone (Seretide Accuhaler) over 52 weeks[1].
- LABA/LAMA combination offers the advantage of steroid-sparing side-effects.

1. Wedzicha JA et al. (2016) Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD (FLAME study). New Eng J Med 374:2222-2234

The GOLD guidance states combination treatment with a LABA/LAMA increases FEV1 and reduces exacerbation rates compared to monotherapy or ICS/LABA. But the GOLD guidance does not advocate the use of one LABA/LAMA combination inhaler over another.

The local COPD guidance has classified LABA/LAMA combinations according to the table below:

LABA/LAMA combination inhaler (choice after 1st line should be driven by patient choice and device acceptability)						
Drug	**Brand name**	**Device**	**TLC**	**Dosage**	**30 day cost**	**Annual cost**
Indacaterol 110mcg /Glycopyrronium 50mcg	Ultibro Breezhaler and caps	DPI Breath actuated	**GREEN 1st line**	1 inhalation od	£32.50 (30 dose)	£390
Formoterol 12mcg /aclidinium 340mcg	Duaklir Genuair	DPI Breath actuated	**BROWN 2nd line**	1 inhalation bd	£32.50 (60 dose)	£390
Vilanterol 22mcg /umeclidinium 55mcg	Anoro Ellipta	DPI Breath actuated	**BROWN 2nd line**	1 inhalation od	£32.50 (30 dose)	£390
Olodaterol 2.5mcg /tiotropium 2.5 mcg	Spiolto Respimat	Multi-dose solution for inhalation.	**BROWN 2nd line**	2 inhalations od	£32.50 (60 dose)	£390

Promethazine: Mental Health Prescribing.
Promethazine is a drug derived from the phenothiazine group. In the UK it is licensed for use as a symptomatic treatment for allergic conditions, as an antiemetic, for short-term treatment of insomnia in adults and as a short-term paediatric sedative.
The Drugs & Therapeutics Committee of Derbyshire Healthcare NHS Foundation Trust have recently reviewed the formulary status of promethazine and have concluded that its use as an oral medication should remain within its licensed indications and that **we do not support its initiation for indications such as agitation, for which licensed treatment options are available.**
In accordance with NICE NG10 – Violence and aggression: short-term management in mental health, health and community settings (May 2015), promethazine injection can be prescribed as part of a combination with haloperidol injection for intramuscular administration as rapid tranquilisation. It is not approved for use as an injectable monotherapy for rapid tranquilisation.

Useful resources for primary care:

- NHS England – North Midlands (Derbyshire & Nottinghamshire) Procedure for Lost, Stolen and Fraudulent Prescriptions
  This guidance establishs the principles that independent primary care contractors should follow (GPs, Independent Prescribers, Dentists and Community Pharmacists), for initiation of a local notification/alert process, and includes good practice guidance on the security and safe handling of prescriptions.
- Asthma UK has 11 non-English languages Action Plans available to download for use in practice.

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

Highlighting potential QIPP opportunities:

Cost of treatment options for bacterial conjunctivitis:
1st line - Chloramphenicol Eye drops 0.5% 10ml = £1.26
2nd line - Gentamicin Eye drops 0.3%, 10ml = £2.47
Preferred option for pregnant women - Azithromycin Eye drops 1.5% 6 x 0.25g=£6.99.

Prescribers are advised that fusidic acid eye drops have been classified as **BROWN** restricted for use in severe conjunctivitis and that the preparation is significantly more expensive than other treatment options for conjunctivitis. Fusidic acid 1% eye drops 5g=£29.06.

August
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
Betahistine 16mg tablets	84	£11.05	£1.36
Betahistine 8mg tablets	84	£6.33	£1.26
Buspirone 10mg tablets	30	£9.00	£5.28
Dapsone 50mg tablets	28	£44.50	£34.52
Diamorphine 30mg powder ampoules	5	£16.52	£12.13
Exemestane 25mg tablets	30	£63.50	£8.52
Levetiracetam 1g tablets	60	£95.34	£4.70
Levetiracetam 250mg tablets	60	£28.01	£2.06
Levetiracetam 500mg tablets	60	£49.32	£2.17
Levetiracetam 750mg tablets	60	£61.50	£3.91
Mefenamic acid 500mg tablets	28	£55.00	£5.35
Olanzapine 10mg tablets	28	£65.00	£0.98
Olanzapine 15mg tablets	28	£85.00	£1.27
Olanzapine 2.5mg tablets	28	£16.75	£0.92
Olanzapine 20mg tablets	28	£110.00	£1.38
Olanzapine 5mg tablets	28	£33.25	£0.92
Olanzapine 7.5mg tablets	28	£65.00	£1.00
Oxazepam 10mg tablets	28	£19.97	£4.46
Oxazepam 15mg tablets	28	£19.97	£4.33
Pramipexole 88mcg tablets	30	£13.50	£2.06
Quetiapine 100mg tablets	60	£90.48	£1.36
Quetiapine 200mg tablets	60	£90.48	£2.14
Quetiapine 25mg tablets	60	£27.06	£0.93
Rizatriptan 10mg tablets	3	£13.37	£1.44
Sodium cromoglicate 2% eye drops	13.5ml	£9.72	£2.08
Sumatriptan 100mg tablets	6	£32.00	£1.32
Sumatriptan 50mg tablets	6	£28.00	£1.29
Tranexamic acid 500mg tablets	60	£14.30	£3.79
Valsartan 160mg capsules	28	£12.00	£4.66
Valsartan 40mg capsules	28	£7.70	£5.37
Valsartan 80mg capsules	28	£9.99	£5.63
Zolmitriptan 2.5mg orodispersible tablets SF	6	£17.90	£4.53
Zolmitriptan 2.5mg tablets	6	£18.00	£8.56

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	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
Nathnac	http://www.nathnac.org/
NHS evidence	http://www.evidence.nhs.uk/
Electronic medicines compendium	http://www.medicines.org.uk/emc/
Clinical Knowledge Summaries	www.cks.nhs.uk.
Medicines Prescribing Centre (Formerly NPC)	http://www.nice.org.uk/mpc/
Medicines for children (patient information leaflets	http://www.medicinesforchildren.org.uk/
Drugs in lactation	http://www.midlandsmedicines.nhs.uk/content.asp?section=6&subsection=17&pageIdx=1
Medicines Compliance aids	https://www.sps.nhs.uk/?s=&cat%5B%5D=3008 https://www.sps.nhs.uk/?s=&cat%5B%5D=266&cat%5B%5D=3253
Fridge excursions	https://www.sps.nhs.uk/?s=&cat%5B%5D=3252
Patent expiries	https://www.sps.nhs.uk/?s=&cat%5B1%5D=3242
New Medicines	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