PostScript

NHS Greater Glasgow and Clyde

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This edition contains articles on:

Novel Oral Anticoagulants (NOACs): update

Inclusion of the NOACs (dabigatran, rivaroxaban, apixaban) on the NHSGGC Formulary is established for existing patients with non-valvular atrial fibrillation (AF) who are intolerant of, or poorly controlled on, warfarin. To date there has been cautious uptake of these new agents.

Supporting guidance is on GGC Prescribing which includes information to guide choice of NOAC and how to manage the transition period. Potentially suitable patients, with poor INR control (time in target range <60%), will be identified and highlighted to general practice by the Glasgow & Clyde Anticoagulation Service (GCAS).

The role of NOACs in the management of new patients has been under consideration and the Heart Managed Clinical Network (MCN) is undertaking a review of the NHSGGC AF guideline. This will include a change which will support the option of prescribing a NOAC as a first-line alternative to warfarin where anticoagulation is indicated in patients newly diagnosed with non-valvular AF. The Formulary status of dabigatran and apixaban has been updated to reflect this change. The position for rivaroxaban is unchanged and is in line with SMC advice.

Patients are at high risk of a stroke before they are fully anticoagulated and the NOACs have the advantage of a quicker onset of action compared to warfarin, and can be immediately prescribed by the GP rather than awaiting referral to GCAS. The significant financial implications of introducing NOACs for new diagnoses of AF have been included in the Board's financial plan for medicines for 2014/15. The updated guideline will be communicated in due course through PostScript and the Heart MCN.

Patients who are well controlled on warfarin should remain on warfarin; a switch to NOAC in these patients is discouraged and remains non-Formulary.

New oral therapies for Multiple Sclerosis

It is exciting times in the treatment of Multiple Sclerosis (MS) with the approval of two new oral therapies for the treatment of the relapsing remitting form of the disease; dimethyl fumarate and teriflunomide. There has been significant media attention and interest from patient groups and clinicians who welcome these new oral therapies.

Dimethyl fumarate and teriflunomide have both been added to the *Total Formulary* after being accepted by the SMC for the treatment of adults with relapsing remitting multiple sclerosis (RRMS). These will offer an alternative to existing first line therapies, beta-interferon and glatiramer acetate, which are given by injection. The assessment, prescribing and monitoring of these treatments will continue to be undertaken by the specialist regional centre at the Neurological Institute, Southern General Hospital.

Dimethyl fumarate (Tecfidera®)

Dimethyl fumarate is accepted for use within NHS Scotland for the treatment of adult patients with RRMS. Two phase 3 clinical trials of dimethyl fumarate have been completed for RRMS, which included more than 2,000 people worldwide. Both studies evaluated the effect of on relapse rate, the progression of disability, and the damage to the brain caused by MS.

Dimethyl fumarate is administered orally twice daily and reduces relapse rate by approximately 50%. Beta-interferon and glatiramer acetate, existing first line therapies, reduce relapse rates by around one-third. Although no direct comparison has been undertaken in a clinical trial setting, this suggests dimethyl fumarate may offer improved efficacy. Clinically relevant effects on disability worsening were also seen, though the trials were only of two years' duration. The main side effects with dimethyl fumarate are flushing (approximately one third of

patients) and gastrointestinal (GI) disturbance (diarrhoea, nausea, upper abdominal pain) which are most common in the first month. GI side effects can be minimised by taking dimethyl fumarate with food.

Teriflunomide (Aubagio®)

Teriflunomide is accepted for restricted use in RRMS. Teriflunomide is not expected to be used for the treatment of patients with highly active disease.

The clinical trial programme for teriflunomide was similar to that for dimethyl fumarate. Teriflunomide is administered orally once daily and reduces relapse rate by approximately 30%. This suggests a similar effect to beta-interferon or glatiramer acetate, although again direct comparisons have not been made. Clinically relevant effects on disability worsening were also seen, though the trials were only of 2 - 2.5 years' duration. The main side effects with teriflunomide are nausea, headaches, diarrhoea and hair thinning/loss. Teriflunomide requires fortnightly blood monitoring for the first six months of treatment and a washout procedure is recommended if patients need to discontinue therapy.

Tramadol to be a Schedule 3 Controlled Drug

The Home Office has announced changes to CD classification for a number of drugs which should be implemented from 10th June 2014. More detailed information on the practical implications will follow when the date of the change is confirmed.

Tramadol is a synthetic analogue of codeine and, like other opioids, can be liable to misuse. The Advisory Council on the Misuse of Drugs recommended that tramadol should be re-classified as a Class C Schedule 3 drug; prompted by increasing reports of misuse and harm. Of the 581 drug related deaths in Scotland in 2012, tramadol was present or implicated as a contributory factor to the death in 48 cases.

Although safe storage and register keeping will not be required, tramadol will need the full CD prescription writing requirements including the quantity in both words and figures. Prescriptions will only be valid for 28 days. Work is ongoing in the acute service to understand changes required to ordering procedures.

Tramadol has a unique dual-action, pharmacological profile. Its analgesic action results mainly from its agonist effects at opioid receptors with an added influence from its inhibition of the re-uptake of serotonin and noradrenaline. This dual mechanism increases the potential for adverse effects, especially in overdose.

Tramadol overdose results in drowsiness, constricted pupils, agitation, tachycardia, hypertension and nausea, vomiting and sweating. Seizures occur in up to 15% of cases; this is more common than with other opioids. In severe poisoning coma, seizures and hypotension can occur. Overdose can also cause serotonin syndrome which is potentially fatal.

Other changes to CD legislation include:

- Lisdexamfetamine is being classed as schedule 2 (requiring safe storage and register keeping).
- Temazepam prescription writing exemptions to be removed. This means the quantity must be in words and figures, prescriptions will only be valid for 28 days. Temazepam will continue to require safe storage.
- Zopiclone and zaleplon to be classed as schedule 4 CDs with the benzodiazepines.
- A consultation will follow on a proposal to classify ketamine as schedule 2.

Nitrofurantoin in renal impairment

The MHRA has intimated plans to amend the contraindication against use of nitrofurantoin in renal impairment from CrCl <60 mL/min to eGFR < 30mL/min. There will be additional advice that nitrofurantoin may be used with caution in eGFR 30-44mL/min for short term treatment of lower UTI involving resistant pathogens, when the benefits outweigh the risks of undesirable effects. Nitrofurantoin should not be used alongside alkalinising agents, eg potassium citrate.

Each of the UK Marketing Authorisation Holders of nitrofurantoin products will be asked to submit applications to MHRA to update their respective Summary of Product Characteristics which is likely to take a few months. The NHSGGC Therapeutics Handbook and antibiotic guidelines will be updated in light of this change.

Safety Update: Contraceptive Interaction

St John's wort (*Hypericum perforatum* L.) is a herbal medicine used to relieve slightly low mood and mild anxiety. The MHRA advise that St John's wort interacts with all hormonal contraceptives and reduces the effectiveness so increasing the risk of unplanned pregnancy. This applies to all hormonal contraceptives except intrauterine devices, for which there are currently no data. Women taking hormonal contraceptives should be advised not to take herbal products containing St John's wort and encouraged to read the Patient Information Leaflet with their hormonal contraceptive.

Kid's Corner: Specials

Specials may be required if a particular preparation is required but not available; for example a liquid for an unusual dose, or to overcome swallowing difficulties; or where a patient has an allergy, intolerance or be unsuitable for an ingredient, eg alcohol as an ingredient for an infant.

Specials are made to varying formulations by different companies (the exact contents can differ every time) and may have very limited safety, stability or efficacy testing. As these are not licensed products, there are liability implications for those involved in prescribing and dispensing. NHSGGC has issued detailed guidance.

Paediatric "special" prescriptions

It is important to ensure continuity of supply when children have been started on specials in Yorkhill Hospital. Continuing on the same strength reduces the potential for dose errors. Yorkhill try to limit the range of different strengths used to one per product where possible. This allows staff, parents and carers to become familiar with a single product. Yorkhill pharmacy issue a letter to parents to give to their community pharmacy with information on strength and supplier for the special required for their child. Other paediatric units have similar policies.

Calcium carbonate case study

Calcium carbonate preparations are used as phosphate binders in patients with chronic kidney disease. There are several licensed preparations available but not all are suitable for children. The first choice for young children is dispersible calcium carbonate 250mg tablet. Although unlicensed, this is a more suitable strength and form for children who can be as young as six months old.

A three year old boy was discharged on dispersible calcium carbonate 250mg tablets, one tablet three times a day; and a month's supply was given on discharge. At clinic follow up, his mum said that they were struggling to give the medication. It was no longer a small dispersible tablet, but a large pink tablet which they had to half and he had to chew. It transpired that the GP had prescribed Calcium 500®; half a tablet with each meal. The GP has inadvertently prescribed two and a half times the intended dose. This was resolved by discussion with the GP and the child was prescribed the correct dose and formulation.

Communications links with GPs and community pharmacists have been improved to minimise the risk of mis-selection of calcium carbonate preparations.

ADTC decisions summary

See the website for full list of medicines and details of indications and restrictions.

The following medicines were added to the *Adult Total Formulary*:

- Teriflunomide for relapsing remitting multiple sclerosis. Restricted to specialist use as an alternative to interferon beta or glatiramer acetate.
- Dimethyl fumarate for relapsing remitting multiple sclerosis. Oral treatment restricted to specialist use in accordance with local guidelines.
- Fluticasone furoate and vilanterol. Restricted to use in patients with severe COPD (FEV1 <50% predicted normal) in accordance with NHSGGC COPD Guidelines.
- Trospium chloride for symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder. Moved to Preferred List.
- Diclofenac moved out of Preferred List into Total Formulary following MHRA safety alerts.

The following medicine was added to the *Paediatric Formulary*

- Zonisamide as adjunctive therapy in treatment of partial seizures, with or without secondary generalisation, in adolescents, and children aged ≥ 6 years. Restricted to specialist initiation.

Fluticasone furoate and vilanterol (Relvar Ellipta®)

This product has been launched for both COPD and asthma, although SMC advice has been issued for COPD only at this stage. A more detailed article will appear in a future edition but prescribers should be aware of the following points:

- This contains high potency inhaled corticosteroid (92 micrograms of fluticasone furoate once daily is approximately equivalent to fluticasone propionate 250 micrograms twice daily according to SPC for the asthma indication).
- The name and / or colour of this device may inadvertently lead patients to confuse it as a 'reliever'. Careful counselling to avoid overuse is advised.
- The device has a six week expiry once removed from the foil pouch packaging.
- Only 92 / 22 microgram strength licensed for COPD.
- See NHSGGC Formulary, COPD guideline and COPD Inhaler Device Guide for preferred options.

Guidelines

- Corrected NHSGGC guideline on management of hypertension from the Heart Disease MCN.
- The Prescribing Management Group for Primary Care have approved a Question and Answer document and Patient Information Leaflet to support the Vitamin D insufficiency guideline.
- The updated NHSGGC Chronic Non Malignant Pain Opioid Guideline is available. It contains information on:
    - Assessing for appropriateness of a trial of opioid treatment
    - Need for regular assessment and review
    - Choice of opioid and maximum recommended doses
    - When to consider referral to the pain clinic
    - It also links to opioid treatment plan, patient information leaflets, pain assessment tool and an opioid equivalence conversion calculator

Valsartan Supply Problem

There are problems with supply of valsartan. April's PostScript Primary Care has information on switching to alternative AIIRAs.

Clomipramine Capsules Supply Problem

Clomipramine is a tricyclic antidepressant most often used in the treatment of severe obsessional compulsive disorder (OCD). It is generally a second line option after SSRIs prove ineffective or are not tolerated. Consequently there is a small but important group of patients who rely on this drug. There is a supply problem with all versions of clomipramine 25mg and 50mg capsules. The Prescribing Management Group – Mental Health, recommend clinicians review ongoing need for treatment and take the following action for patients affected.

Clomipramine dose modification

1. Where ongoing clomipramine treatment is required, change to an equivalent dose using clomipramine 75mg MR tablets.
2. If an exact equivalent dose is not possible, consider switching to the nearest equivalent dose that can be given using 75mg MR tablets:
    - total daily dose 50mg or 100mg: switch to 75mg daily
    - total daily dose 125mg or 175mg: switch to 150mg daily
    - total daily dose 200mg: switch to 225mg daily
    - Once the stock situation resolves, patients may return to their original dose and preparation where clinically appropriate.

Switching from clomipramine

The following drugs are licensed alternatives to clomipramine in OCD & panic disorder.

Drug	OCD dose	Panic Disorder dose
Fluoxetine	20mg initially increased gradually to 60mg daily	n/a
Paroxetine	20mg increased gradually in 10mg steps to 40mg daily	10mg increased gradually in 10mg steps to 40mg daily
Sertraline	50mg increased if necessary in weekly steps of 50mg to 200mg daily	25mg increased to 50mg after one week then if necessary in weekly steps of 50mg to 200mg daily

1. Stop the clomipramine
2. 24 hours later add fluoxetine, paroxetine or sertraline, taking care to increase dose gradually.
3. Be aware of the risk of serotonin syndrome, cholinergic rebound and tricyclic withdrawal.

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