All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Polypharmacy: Guidance for Prescribing

Supplementary Guidance – BNF Sections to Target

July 2014

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1.0 GASTRO-INTESTINAL SYSTEM

1.1 Proton pump inhibitors

Proton pump inhibitors (PPIs) have been associated with *Clostridium difficile*, pneumonia, bone fractures and hypomagnesaemia. Consider reducing the dose or stopping, especially if antibiotics are required due to increased risk of *C. difficile*.

Points for consideration:

- Use lowest possible dose to achieve desired therapeutic effect.
- Consider 'when required' use.
- Step patients down and stop where possible (with the exception of long-term indications for treatment such as Barrett's oesophagus/on specialist advice)[1].
- Co-prescribed clopidogrel?
  - Medicines and Healthcare products Regulatory Agency (MHRA) Drug Safety Update (2010) advises that the use of either omeprazole or esomeprazole with clopidogrel should be discouraged due to reduced antiplatelet effect. Current evidence does not support extending this advice to other PPIs.
- Patients at risk of gastro-intestinal (GI) adverse effects co-prescribed a non-steroidal anti-inflammatory drug (NSAID) should be co-prescribed a PPI. Risk factors for GI adverse effects include[2];
  - Use of maximum dose NSAIDs
  - Aged ≥ 65 years
  - History of gastroduodenal ulcer, GI bleeding, or gastroduodenal perforation
  - Concomitant use of medicines known to increase upper GI adverse events (e.g. anticoagulants, aspirin [including low dose], corticosteroids, selective serotonin reuptake inhibitors [SSRIs], venlafaxine, duloxetine – see current British National Formulary [BNF] for full list)
  - Serious co-morbidity (e.g. cardiovascular disease [CVD], hepatic/renal impairment, diabetes)
  - Prolonged NSAID use (including patients with osteoarthritis or rheumatoid arthritis at any age and chronic low back pain in patients ≥ 45 years).

The following AWMSG educational pack aims to support the appropriate prescribing of PPIs by providing a practical approach for the initiation and review of PPI prescribing: www.awmsg.org/docs/awmsg/medman/All%20Wales%20Proton%20Pump%20Inhibitor%20and%20Dyspepsia%20Resource%20Pack.pdf

1.2 Laxatives

Avoid long-term prescriptions where possible and review regularly.

Points for consideration:

- Check dose and choice of laxative. Treatments should be selected from available options and reflect patient preference, severity, type and duration of symptoms (see AWMSG Common Ailment Service Formulary).
  - Start with an osmotic laxative e.g. macrogol (Laxido®) or a bulk-forming laxative e.g. ispaghula husk (Fybogel®) (ensure adequate fluid intake with both).
  - Bulking agents, e.g. ispaghula husk, are less suitable in patients with limited mobility, e.g. bedbound, and can take up to two weeks to be effective; therefore, stimulant laxatives e.g. senna should be considered first-line in this group[3].
  - Consider adding a stimulant laxative if stools are soft but difficult to pass or emptying is inadequate.

- Prescribed two laxatives from the same class, e.g. lactulose and macrogol are both osmotic laxatives – consider review.
- Reduce overuse of laxatives if possible.
  - If more than one laxative is used, reduce and stop one at a time. Reduce stimulant laxative first, increasing the dose of osmotic laxative if necessary.
- Consider discontinuation of laxatives if:
  - Previous opioid use has reduced/stopped
  - Regular bowel movements occur without difficulty
  - Patient is eating/drinking with an adequate fluid intake
- Review medicines that commonly cause constipation e.g. opioids, verapamil (also other calcium channel blockers (CCBs) to a lesser extent), tricyclic antidepressants (TCAs), iron, diuretics, aluminium antacids, calcium, anticholinergics, sedating antihistamines etc.
- Advice regarding the non-pharmacological management of constipation can be found at: http://cks.nice.org.uk/constipation#!scenariorecommendation:4
- Use of dantron (as co-danthramer or co-danthrusate) is limited by potential carcinogenicity and evidence of genotoxicity. Dantron should ONLY be used to manage constipation in terminally ill patients[1].
- Liquid paraffin should not be used long term; associated with anal seepage of paraffin and consequent anal irritation with prolonged use[2].

1.3 Antimotility medicines

Consider potential for antimuscarinic side effects with co-phenotrope (medicine considered less suitable for prescribing by BNF)[2]. Loperamide may be a more appropriate alternative.

2.0 CARDIOVASCULAR SYSTEM

2.1 Anti-anginal medication

Points for consideration:

- Consider reducing anti-anginal medication particularly if mobility has decreased with less need for medication[4].
- Is glyceryl trinitrate (GTN) spray being used too frequently? – Marker of poorly controlled angina.

2.2 Antiplatelets

Consult relevant National Institute for Health and Care Excellence (NICE) guidance and local guidance on the use of antiplatelets.

Aspirin

Aspirin is not licensed for the primary prevention of vascular events[5].

Points for consideration:

- Prescribed for primary prevention? – Balance of benefits and risks should be considered, particularly the presence of risk factors for vascular disease (e.g. diabetes) and the risk of GI bleeding[5].
- Do not offer aspirin monotherapy solely for stroke prevention in atrial fibrillation (AF) (as per NICE Clinical Guideline (CG) 180 published June 2014).
- Reduce aspirin to evidence-based doses[4]. Are side effects dose related?
- Ensure evidence-based interventions are initiated (in patients likely to obtain benefit) where indicated, e.g. statins, blood pressure (BP) management and lifestyle measures (smoking cessation, diet and exercise)[1].

Dipyridamole
Unlike modified-release preparations, standard-release tablets and oral suspensions are not licensed for secondary prevention of ischaemic stroke and transient ischaemic attacks[2].

Combination antiplatelet and anticoagulant therapy
The addition of clopidogrel increases the risk of a bleed by 13.9% compared with warfarin alone[4]. The use of aspirin, clopidogrel and warfarin in combination further increases the risk to 15.7% compared with warfarin as monotherapy[4]. In view of the significant increased risks (particularly in frail patients), these combinations should only be prescribed when clinically indicated and where benefits are thought to outweigh the risks[1]. **Patients should be regularly reviewed[1].**

Ticagrelor
At the time of writing, ticagrelor (Brilique®) is to be used in combination with low-dose aspirin for up to 12 months as a treatment option in acute coronary syndrome. Clinicians should ensure that it is discontinued after 12 months (aspirin to continue) and be aware that concomitant use with doses of simvastatin greater than 40 mg is not recommended[6].

2.3 Anticoagulants
Following the introduction of new oral anticoagulants (NOACs) as a treatment option, AWMSG have produced guidance to promote the safe, effective and equitable use of oral anticoagulant therapies, as well as a risk/benefit assessment tool. Both documents can be found in the 'Library' section of the AWMSG website.

Please check AWMSG, NICE and local guidance for further updates as this area of prescribing continues to evolve. **N.B.** NICE published their guidance CG180 in June 2014 (please see www.nice.org.uk/ for further information).

Points for consideration:

- Good practice to add intended stop date to the patient's repeat prescription (or lifelong if this is applicable). Ensure any changes to the stop date are communicated to the patient and/or community pharmacist and prescriptions updated accordingly[1].
- **Anticoagulant therapy should be discontinued if risk of bleeding outweighs risk of thrombosis during the course of treatment. In all cases, this risk/benefit analysis should be fully documented and reviewed in light of significant changes to relevant clinical or social circumstances[1].**
- The AWMSG risk/benefit assessment tool contains an assessment form to be completed prior to initiation and as an annual review for oral anticoagulation (both warfarin and NOACs) in AF. It includes details on $CHADS_2$ and CHA_2DS_2-VASc scoring systems as well as the HAS-BLED scoring system.
- HAS-BLED is a therapeutic bleeding risk stratification score for patients on oral anticoagulants in AF and identifies bleeding risk factors (e.g. systolic BP > 160 mmHg, abnormal renal/liver function, history of stroke/bleeding, unstable international normalised ratio (INR), ≥ 65 years of age, concomitant medication, alcohol use etc.).
- The assessment also highlights other relevant clinical/social factors which should be considered (e.g. evidence of trips/falls, Alzheimer's, sensory/visual/literacy deficits etc.).

Warfarin

See AWMSG Guidance on Warfarin Monitoring:
www.awmsg.org/docs/awmsg/medman/Warfarin%20Monitoring.pdf

Additional consideration:

- Are monitoring arrangements robust?
- Are processes in place to ensure patients receive and understand any changes in dose? Consider any additional requirements for patients with specific needs e.g. visually impaired, dementia.
- Is the INR within the recommended therapeutic range?
- Where possible, it is good practice to restrict the prescribing of warfarin to one or two strengths of tablet (1 mg and 3 mg), in order to minimise the risk of patient confusion/error.
- Please note: it is recommended that INR is measured 3–5 days after any changes in medication with the potential to affect the pharmacokinetics of warfarin[1] – see current BNF for full list of interactions.

Combination antiplatelet therapy with warfarin

Taking warfarin as baseline, i.e. one, risk of bleeding in a recent large study is as follows[7]:

Table 1. Bleeding risk for patients with AF[4].

Medicine(s)	Hazard ratio for bleed (warfarin = 1)*	% of Bleed/patient year
Aspirin	0.93 (0.88 to 0.98)	
Clopidogrel	1.06 (0.87 to 1.29)	
Aspirin + clopidogrel	1.66 (1.34 to 2.04)	
Warfarin + aspirin	1.83 (1.72 to 1.96)	
Warfarin + clopidogrel	3.08 (2.32 to 3.91)	13.9% bleed/patient year
Warfarin + aspirin + clopidogrel	3.70 (2.89 to 4.76)	15.7% bleed/patient year
Average age = 70 years Main indication: 82,854 patients surviving hospitalisation with AF Combinations show no benefit over monotherapy with warfarin in the prevention of ischaemic stroke *Risk of bleeding refers to admission to hospital with bleeding related episode or death with bleed		

New oral anticoagulants

(Including apixaban [Eliquis®], dabigatran [Pradaxa®] and rivaroxaban [Xarelto®])

Prescribers should aim to understand and address reasons for non-adherence before switching to an alternative[8]. (Consider use of risk/benefit assessment tool and AWMSG guidance on choice of agent.)

Where a NOAC is deemed appropriate consider the following:

- Follow guidance (including manufacturers' Summaries of Product Characteristics [SPCs]) when switching from warfarin to a NOAC and vice versa (dependent on INR/creatinine clearance [CrCl]).
- Dose reductions may be required in certain patient groups e.g. age, weight, renal function etc. Consult BNF/medicine SPC for specific details.
- The combined use of warfarin and a NOAC is **contraindicated** (except where switching therapy from a NOAC to warfarin as per medicine SPC).
- Dabigatran is not suitable for use in monitored dosage systems.

2.4 Antihypertensives

Older patients are at higher risk of postural hypotension, making them particularly susceptible to adverse drug events such as falls[9].

Points for consideration:

- Optimise antihypertensive therapy bearing in mind falls risk, mobility and postural hypotension (defined as a drop in BP [usually > 20/10 mmHg] within three minutes of standing)[4,10].
- Combination antihypertensives? – Consider reducing the dose or stopping some medicines if signs of postural hypotension or low BP are evident[4].
- Consider indication and other medicine properties when reviewing antihypertensives before deciding which to reduce/withdraw e.g. rate-limiting properties of CCBs, cardio-protective properties of angiotensin-converting enzyme (ACE) inhibitors in heart failure etc.
- Where indicated, stop one antihypertensive at a time, maintaining the dose of the others. Restart if BP increases above desired target[1].
- Patient taking an ACE inhibitor or angiotensin II receptor blocker (ARB) and diuretic with an NSAID? – **Note this is a high-risk drug combination.**
- Prescribed an ACE inhibitor and an ARB? – Combination associated with high rates of renal insufficiency, hyperkalaemia and hypotension with no additional benefit[1]. ACE inhibitors and ARBs should not be used in combination for the treatment of **simple hypertension**.
- Prescribed an alpha blocker? – Reserve for resistant hypertension, due to postural hypotension and increased risk of falls[1].
- Prescribed aliskiren? MHRA Drug Safety Update (2012) highlighted new contraindications and warnings due to risk of cardiovascular (CV) and renal adverse reactions. See 'Aliskiren Prescribing Sheet' on the GP portal for further details.
- Prescribers are reminded of the importance of maintaining treatment with an ACE inhibitor and licensed beta-blocker at the maximum tolerated dose in patients with heart failure due to left ventricular systolic dysfunction[11].
- Prescribed an ACE inhibitor or ARB? – Ensure appropriate monitoring. Monitor renal function and serum electrolytes prior to starting treatment, 1–2 weeks after initiation and 1–2 weeks after each dose increase[11]. Monitor every 6 months thereafter[11]. Earlier/more frequent monitoring may be required in at-risk patient groups[11].

2.5 Digoxin

Doses above 187.5 mcg/day are poorly tolerated in frail patients[1]. In addition, long-term digoxin at a dose of more than 125 mcg/day in patients with impaired renal function can lead to an increased risk of toxicity[1].

Points for consideration:

- eGFR < 50 ml/min? – Review to determine if dose reduction is appropriate (ventricular rate at rest should not fall below 60 bpm, except in special circumstances e.g. concomitant beta-blocker)[1].
- Potentially hazardous drug interactions caused by increased digoxin plasma concentrations may also increase toxicity[1] – see current BNF for full list of interactions.
- Increased risk of toxicity if hypokalaemia occurs (including drug-induced hypokalaemia – e.g. diuretics)[1].
- Regular monitoring of plasma-digoxin concentration during maintenance treatment is not necessary unless problems are suspected[2] (e.g. signs of toxicity). See CKS: Atrial Fibrillation for signs of digoxin toxicity and further information on obtaining blood samples.

2.6 Amiodarone

Amiodarone has an important place in the treatment of severe cardiac rhythm disorders where other treatments either cannot be used or have failed. It has historically been prescribed as a first-line treatment for AF, often started intravenously to treat an acute episode and then continued as tablets. Its use requires regular monitoring due to potential major toxicity. Audit and review of patients taking amiodarone in several areas has revealed inconsistent monitoring. Both primary and secondary care clinicians have therefore recognised that it would be beneficial to review all patients taking amiodarone in Wales to establish the need for ongoing treatment. AWMSG guidance has been developed to assist this process[12]. Further guidance and advice can be found at: www.awmsg.org/awmsgonline/docs/awmsg/medman/Prescribing%20of%20Amiodarone%20in%20Wales.pdf

Loading regimes should only be prescribed by secondary or tertiary care; please refer to the AWMSG Shared Care Template – Amiodarone.

2.7 Diuretics

Loop diuretics prescribed for dependent ankle oedema only (i.e. no clinical signs of heart failure)[13] should be reviewed due to their effects on renal function, serum electrolytes and potential to cause postural hypotension[11].

Points for consideration:

- Consider alternative management of mild ankle oedema e.g. elevation[4]
- Co-prescribed a CCB? – Stopping or reducing dose of CCB may be indicated in ankle swelling resistant to diuretics[4].
- UKMi Q&A reference source provides advice on treating ankle oedema caused by CCBs.
- Thiazide diuretics can exacerbate gout[2].
- Thiazide and related diuretics are ineffective if eGFR < 30 ml/min and should be avoided[2]. Metolazone remains effective (no licensed UK preparation available) but with a risk of excessive diuresis[2].

2.8 Lipid-modifying drugs

Myopathy is a potential adverse drug reaction for all statins[1]. The risk appears to be related to dose and more common in renal impairment[1]. There is some evidence to suggest lipophilic statins, e.g. simvastatin, atorvastatin, are more likely to produce muscular effects than the relatively hydrophilic agents, e.g. pravastatin[14].

Points for consideration:

- ***Drug choices*** – Low acquisition cost statins (simvastatin, atorvastatin, pravastatin) should be used first line[15], and the use of rosuvastatin reserved due to evidence base. Re-evaluate patient risk profile for primary and secondary prevention of CVD[1].
- Consider stopping statins in frail elderly patients with limited life expectancy for other reasons i.e. where there is no prognostic benefit.
- Consider benefits of starting/continuing statins in patients > 80 years, but do not stop statins based on age alone[1].
- Prescribed a ***high-intensity statin***?
  - Any decision to offer a higher intensity statin should take into account informed preference, co-morbidities, multiple drug therapy, and benefits/risks of treatment[15].
  - Consider MHRA Drug Safety Update (2010), which discusses increased risk of myopathy with simvastatin 80 mg.
  - Prescribe in line with current NICE guidelines and local formulary.
- Risk of myopathy increased with statins following concomitant use of a number of commonly prescribed drugs e.g. amiodarone, amlodipine, azole antifungals,

diltiazem, macrolide antibiotics – dose modifications are required in some cases[2]. Note updated advice on drug interactions/contraindications for simvastatin (MHRA 2012). See current BNF for full list of interactions.

- There is currently limited evidence to demonstrate ***ezetimibe*** as monotherapy has a positive impact on patient-oriented outcomes[16]. Wherever possible, patients should be managed on statin monotherapy[16].
- ***Omega-3 fatty acids*** – Removed from formulary for use in secondary prevention of myocardial infarction (MI) following publication of updated NICE CG172. Do **not** offer or advise people to use omega-3 fatty acid capsules or omega-3 fatty acid supplemented foods to prevent another MI[17]. If people choose to take omega-3 fatty acid capsules or eat omega-3 fatty acid supplemented foods, be aware that there is no evidence of harm[17].
  - See 'Omega-3 Fatty Acids Prescribing Sheet' on the GP portal for further details.

2.9 Peripheral vasodilators and oxerutins

Points for consideration:

- The following are considered 'drugs less suitable for prescribing' (◪) by the BNF:
  - **Peripheral vasodilators** – Naftidrofuryl oxalate is the only peripheral vasodilator recommended by NICE for peripheral arterial disease (PAD)[18]. Review after 3–6 months and discontinue if no symptomatic benefit[18].
  - **Moxisylyte** – Licensed for short-term use in Raynaud's syndrome[2]. Not established as an effective treatment and alternatives e.g. nifedipine maybe more appropriate[2].
  - **Rutosides (oxerutins)** – e.g. Paroven®.

3.0 RESPIRATORY SYSTEM

3.1 Short-acting beta$_2$ agonists

- Review ordering/use of short-acting beta$_2$ agonists (SABAs).
  - Are SABA inhalers being used too frequently? – Marker of poorly controlled asthma/chronic obstructive pulmonary disease (COPD) or poor inhaler technique.
  - Is the patient over-ordering/hoarding medication?

3.2 Inhaler devices and technique

- Is the patient (or carer) able and aware how to use their inhaler devices?
- Do they require an alternative device e.g. breath-actuated or the addition of a spacer?
  For patients with poor inspiratory effort, a metered dose inhaler plus spacer may be easiest to use.
- Is the patient non-adherent? Would they benefit from a licensed combination inhaler?
  - British Thoracic Society asthma guidelines and NICE COPD guidelines advocate the use of combination inhalers where a long-acting beta$_2$ agonist (LABA) and inhaled corticosteroid (ICS) are indicated[19,20].
  - Combination inhalers guarantee that the LABA is not taken without ICS and help to improve inhaler adherence[19].
  - Be aware of differences in licensing in asthma and COPD for combined LABA/ICS inhalers and the constraints they pose during titration.
  - There may be a cost benefit associated with some switches to combination inhalers.

3.3 Corticosteroids in COPD

Use of an ICS in COPD confers only marginal benefits, reducing exacerbations a little and possibly improving quality of life[20]. Patients most likely to benefit are those with severe COPD (defined as FEV_1 < 50%) and those who exacerbate most frequently[20]. Furthermore, use of a high-dose ICS in COPD is associated with systemic side effects such as pneumonia, osteoporosis, diabetes and adrenal suppression[21].

A large observational study found that use of fluticasone/salmeterol in COPD was associated with a greater risk of pneumonia, and death associated with pneumonia, than budesonide/formoterol[21]. As a result, Symbicort® (budesonide/formoterol) should be used in preference to Seretide® (fluticasone/salmeterol) in appropriate patients with COPD.

Remember to remain vigilant for pneumonia/other lower respiratory tract infections (i.e. bronchitis) in patients with COPD treated with an ICS[22]. Patients should be counselled appropriately and ICS only prescribed for COPD in line with current NICE guideline CG101, following consideration of previous treatment (LABA/long-acting muscarinic antagonist) and FEV_1.

3.4 Corticosteroids in asthma

Points for consideration:

- Patients should be maintained at the lowest possible dose of ICS[19].
- Stepping down therapy once asthma is controlled is recommended, but often not implemented, leaving some patients over-treated[19].
- When deciding which drug to step down first and at what rate, consider: severity of asthma, side effects, time on current dose, benefit achieved and patient preference[19].
- Reduction in ICS dose should be slow as patients deteriorate at different rates. Consider reductions every three months, decreasing dose by approximately 25–50% each time[19].
- Regular review of patients as treatment is stepped down is important[19].

4.0 CENTRAL NERVOUS SYSTEM

4.1 Anticholinergics

Anticholinergics should be prescribed with caution as elderly patients are more likely to experience adverse effects such as constipation, urinary retention, dry mouth/eyes, sedation, confusion, delirium, photophobia, falls, reduced cognition (may lead to wrong diagnosis of dementia), decreased sweating and increased body temperature[1]. Research also suggests a link to increased mortality with the number and potency of anticholinergic agents prescribed[23].

The *Anticholinergic Risk Scale* is useful to raise awareness of anticholinergic effects of different medicines. A number of studies have been published which aim to assign drugs with one, two or three points; the higher the number, the stronger the anticholinergic effect. The number of points allocated to drugs varies between studies; examples of drugs with a high anticholinergic burden include[23,24]:

Table 2. Medicines with a high anticholinergic burden

1 Point	2 Points	3 Points
• Haloperidol • Quetiapine • Mirtazapine • Paroxetine • Trazodone • Ranitidine	• Clozapine • Nortriptyline • Baclofen • Cetirizine • Loratadine • Cimetidine • Loperamide • Prochlorperazine	• Chlorpromazine • Amitriptyline • Imipramine • Chlorpheniramine • Hydroxyzine • Oxybutynin

Further details of these studies can be found at:
1) http://archinte.jamanetwork.com/article.aspx?articleid=414049
2) http://onlinelibrary.wiley.com/doi/10.1111/j.1532-5415.2011.03491.x/pdf
3) http://www.uea.ac.uk/mac/comm/media/press/2011/June/Anticholinergics+study+drug+list

Points for consideration:

- Minimise use of anticholinergics wherever possible[1].
- Consider anticholinergic burden scale when prescribing anticholinergic combinations.
- Avoid prescribing anticholinergics with acetylcholinesterase inhibitors e.g. donepezil, rivastigmine (can worsen cognitive impairment)[1].
- Proactively monitor at regular intervals for efficacy and tolerance[1] e.g. annually (or 6-monthly in patients over 75 years) once clinically stable.
- Consider switching if side effects are troublesome and clinically appropriate e.g. oxybutynin to mirabegron. (Check local formulary status.)
- If suspicion of anticholinergic-induced impaired cognition, carry out a mini mental state examination (or equivalent) and consider switching or stopping if confirmed and clinically appropriate[1].
- For patients taking long-term, high-potency anticholinergic drugs, withdraw slowly[1].
- Refer patients suffering from significant anticholinergic side effects due to psychotropic medication to an appropriate specialist[1].

4.2 Antidepressants

TCAs have anticholinergic properties and are poorly tolerated in the elderly[2]. Furthermore, their use is associated with adverse CV effects (avoid in heart failure), increased risk of fracture, drowsiness and toxicity in overdose[2].

SSRIs are associated with increased risk of bleeding especially in the elderly or those taking drugs which damage GI mucosa/interfere with clotting[25] (e.g. aspirin, NSAIDs, warfarin). See current BNF for full list of interactions.

Points for consideration:

- Consider low-intensity psychosocial interventions e.g. cognitive behavioural therapy, 'Mindfulness' or physical group activity programmes first line in persistent subthreshold depressive symptoms or mild to moderate depression[26].
- Where an antidepressant is indicated, an SSRI e.g. sertraline should normally be prescribed first line (equally effective as other antidepressants and a more favourable risk–benefit ratio)[25].
- Concomitant use of drugs which damage GI mucosa/interfere with clotting? – Review need for all applicable drugs and consider gastroprotection if prescribing is to continue.
- Citalopram and escitalopram are associated with dose-dependent QT interval prolongation. Maximum daily dose of citalopram in patients > 65 years is 20 mg/day[2]. See MHRA Drug Safety Update (2011) for further details.
- Review combinations of antidepressants (such as TCAs for analgesia used in combination with another antidepressant for depression)[4].

- Do not switch to or start dosulepin due to its tolerability, increased cardiac risk and toxicity in overdose[25]. Review any patients still prescribed dosulepin with a view to discontinuation or switching to a more appropriate alternative.
- Review patients on antidepressants every 3 months.
- Continue treatment for at least 6 months in depression to reduce the risk of relapse.
- Consider continuing for at least 1 year after remission in patients with any increased risk of relapse.
- Consider continuing for at least 2 years in higher risk patients (e.g. more than five lifetime episodes and/or two episodes in the last few years).
- Continue for 1 year in generalised anxiety disorder.
- Don't stop antidepressants abruptly, reduce slowly over 4 weeks (or longer for drugs with short half-life, such as paroxetine and venlafaxine) to avoid discontinuation symptoms. The exception is fluoxetine, which has a long half-life; a 20 mg fluoxetine dose can be stopped immediately.
- Care is required when switching between antidepressants.
  - Switching between tricyclic, SSRI and related antidepressants
  - Switching between monoamine oxidase inhibitors and SSRI, tricyclic or related antidepressants

4.3 Treatment of vertigo

Points for consideration:

- Betahistine is generally well tolerated even in long-term use; however, little evidence to show symptomatic improvement in the long term[27]. Review patients every 3–6 months to see if they are still obtaining benefit[28].
- Prochlorperazine should be reserved for the treatment of acute symptoms[2]. Elderly patients are particularly susceptible to adverse central nervous system disorders (parkinsonism, confusion) and postural hypotension[29].
- Sedating antihistamines (e.g. cinnarizine, cyclizine, promethazine) are also associated with increased drowsiness and anticholinergic side effects in the elderly[2].

4.4 Antipsychotics for behavioural and psychological symptoms of dementia

More than 90% of people with dementia will experience behavioural and psychological symptoms of dementia (BPSD) as part of their illness[30]. Although NICE dementia guidelines recommend psychosocial interventions first line, in practice pharmacological interventions i.e. antipsychotic medication, are still sometimes used first line[30].

Points for consideration:

- Associated with adverse events and side effects including sedation, parkinsonism, gait disturbances, dehydration, falls, chest infections, cognitive decline, stroke and death[30].
- Review ongoing need for antipsychotics. Antipsychotics should be used at the lowest possible dose for the shortest possible time.
- Consider causes of agitation e.g. undertreated pain, infection, dehydration etc[30].
- Review anticholinergics, long-acting SSRIs, opioids.
- Undertake person-centred assessment e.g. lifestyle preferences, communication needs (glasses, hearing aids etc.), environmental factors (noise, heat, cold etc.)[30].
- Consider non-drug treatments first line[30]:
  - Development of a life story book, frequent short conversations (as little as 30 seconds has proven effective).
  - Soothing and creative therapies e.g. aromatherapy, music, dancing.
  - Aim to improve sleep hygiene.
  - Psychosocial interventions e.g. exercises, problem solving, personalised activities.

- Consider dose reduction where stopping treatment is not appropriate.
- Risperidone is the only antipsychotic licensed for persistent aggression in Alzheimer's dementia[2].
- ***Priority groups for review –*** patients in care homes, patients with vascular dementia, patients with dementia who also have a history of CVD, cerebrovascular disease (CeVD) or vascular risk factors[4].
- ***When not to stop antipsychotics –*** patients with a co-morbid mental illness treated with antipsychotic medication should not be reduced/stopped without specialist advice[4].
- See 'Optimising Treatment and Care for Behavioural and Psychological Symptoms of Dementia' for further details.

Strategies for reducing antipsychotics:

- ***Reduction of antipsychotics[4]***
  - Reduction should be slow with careful monitoring of the effect.
  - Start with a reduction of 25% of total daily dose (TDD).
  - If the current dose is low, e.g. at the suggested starting dose, medication may be stopped without tapering the dose.
- ***Review process[4]***
  - Review the effects after 1 week and assess for:
    - The re-emergence of initial "target" symptoms.
    - Discontinuation symptoms (e.g. nausea, vomiting, anorexia, diarrhoea).
  - If either of the above occur, assess the risks and benefits of re-instating the previous dose; any further attempts to reduce should be made 1 month later with smaller decrements (e.g. 10% of TDD).
  - If there are no problems after week 1 the dose should remain the same and be reviewed after week 4 (risperidone and haloperidol) or fortnightly (quetiapine).
  - If the reduction is tolerated without any signs of withdrawal then reduce the TDD by a further 25% and repeat process.
- ***Stop antipsychotic[4]***
  - Once the TDD is reduced to the recommended starting dose for the individual antipsychotic, it may be stopped.

4.5 Hypnotics and anxiolytics

Prolonged use of benzodiazepines and 'Z' drugs can lead to issues with tolerance and dependence[31] as well as potential adverse effects such as drowsiness, falls, impaired judgement, confusion and irritability[32].

Points for consideration:

- Discuss reducing long-term therapy with the aim of stopping.
- Discuss good sleep hygiene and factors which can disturb sleep e.g. alcohol, drugs, caffeine.
- Investigate and treat alterative causes e.g. depression, pain etc.
- Additional support including sleep/anxiety diaries, patient information leaflets, reduction protocols and sample GP practice prescribing policies can be obtained from The Welsh Medicines Partnership Educational Pack.
- Where prescribing in the elderly is deemed appropriate, consider the following[32]:
  - Prescribe with caution and start at a lower dose.
  - Only indicated for short-term use; prescribing should be in line with drug licences.
  - Monitor the response as elderly patients may be more sensitive to these medicines e.g. increased risk of 'hangover' effect, increased risk of ataxia, confusion and falls.

4.6 Metoclopramide and domperidone

An MHRA Drug Safety Update (2013) highlighted and confirmed the risks of neurological effects such as short-term extrapyramidal disorders and tardive dyskinesia with metoclopramide. It concluded that these risks outweigh the benefits in long-term or high-dose treatment and that treatment should be reviewed. See report for full details of the new restrictions to dose and duration.

Restrictions have been applied to the licensed use of domperidone due to small increased risk of serious cardiac events[33]. Its use is now restricted to the relief of nausea and vomiting, and the dosage and duration have been reduced.

4.7 Opioid analgesics

Starting doses of opioids should be cautious in the elderly and lower doses are generally recommended[34,35]. Elderly patients are more susceptible to adverse effects of opiates (e.g. drowsiness, postural hypotension, vertigo) leading to increased risk of falls[13]. Slow-release preparations may reduce the incidence of side effects; however, short-acting opioids may be more appropriate in renal failure to prevent the risk of accumulation. Assess needs on an individual patient basis and adjust doses according to response.

Points for consideration:

- Review the use of long-term strong opioids for mild to moderate pain.
  - Review diagnosis and type of pain (e.g. is pain neuropathic or otherwise not responsive to opiates?)[4].
  - Review effectiveness of prescribed analgesia – is the patient demonstrating any improvement in function? (N.B. the primary measurement of effectiveness is functional improvement and not simply a reduction in pain levels).
  - Consider the use of 'pain scales' to assess improvement and consider appropriateness of opioids if no improvement is seen.
  - Step analgesia up or down in accordance with local pain guidelines or World Health Organisation (WHO) analgesic ladder (palliative).
  - Reduce dose if appropriate – consider patient age, weight, renal/hepatic function, adverse effects, concomitant medication etc.
- Prescribed base line analgesia i.e. regular paracetamol?
  - Patients should be prescribed regular paracetamol (1 g 3–4 times a day); however, consider a dose reduction in frail elderly or malnourished patients, potential hepatic enzyme induction, evidence of ongoing liver injury or patients with low body weight (< 50 kg).
  - Check for inappropriate co-prescribing or co-administration (may be purchased over the counter [OTC]) of other paracetamol-containing products.
- Co-prescribed multiple opioids (including the use of multiple 'weak' opioids e.g. co-codamol and BuTrans)?
- Ensure directions include a minimum interval between doses and maximum dose per day.
- Do not prescribe in ranges; prescribe the lowest dose first and review prior to increasing.
- Modified-release morphine, fentanyl patches and oxycodone should be prescribed by brand.
- Is a laxative required? Laxatives should normally be prescribed with opioids at the point of initiation as constipation is generally a 'given'[4].
- Consider appropriate non-pharmacological treatments e.g. gentle exercise, relaxation, or TENS to help reduce the need for opioid analgesics[4].
- AWMSG Medicines for Mild to Moderate Pain Relief patient information leaflets are also available.

Buprenorphine and fentanyl patches

- Third-line 'strong' opioid options – Reserve for patients with a clear indication for a patch formulation e.g. swallowing difficulties.
- Should only be prescribed in patients with stable opioid requirements[1].

Tramadol

- Associated with an increased risk of seizures in at-risk groups (e.g. epilepsy, history of stroke/head injury etc.)[36]. Seizure threshold can also be lowered by concomitant use of TCAs, SSRIs, antipsychotics[2]. See current BNF for full list of interactions.
- Elderly patients are often more susceptible to the psychiatric side effects of tramadol.
- Can cause serotonin syndrome particularly when used in high dose or in combination with other drugs that increase serotonin levels[37] e.g. SSRIs, duloxetine, monoamine oxidase inhibitors. See current BNF for full list of interactions.
- Consider dose equivalences of moderate and strong opioids when prescribing in elderly patients:
  - Opioid equivalence – estimated only. Always titrate dose to individual patient's needs. Check patient's compliance with current prescribed regimen before switching to avoid inadvertent overdose[38].

Table 3. Dose Comparison Table[38]

Codeine/dihydrocodeine	Tramadol	Morphine SR
240 mg total daily dose	50 mg four times a day	20 mg twice daily minimum

- Be alert for the potential of tramadol misuse. At the time of writing, an All Wales review of tramadol is underway.
- A range of Tramadol Educational Resource Materials are available on the AWMSG website.

5.0 INFECTIONS

5.1 Antibiotics

- Local Antimicrobial Guidelines, BNF Clinical Evidence (http://clinicalevidence.bmj.com/x/index.html) or HPA prescribing guidelines (www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/PrimaryCareGuidance/) should be followed.
- Review the need for long-term antibiotic prophylaxis.
- Nitrofurantoin for urinary tract infections is contraindicated in patients with a CrCl < 60 ml/min (MHRA 2013).

5.2 Topical preparations

- Review the need for long-term antibiotic, antifungal and steroid creams.

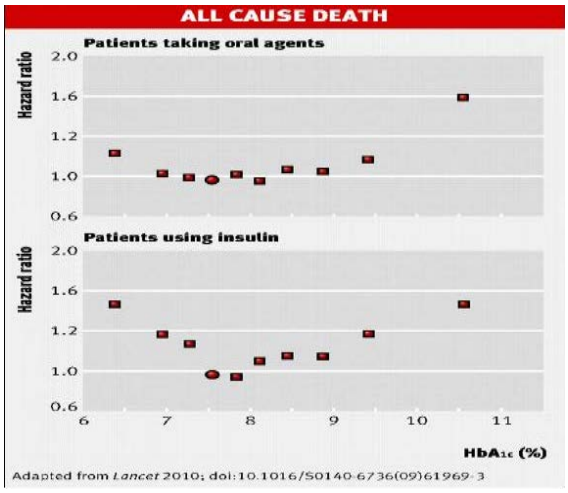
6.0 ENDOCRINE SYSTEM

Potential dangers of a lower HbA_{1c}[4]

The evidence from three randomised controlled trials (UKPDS 33[39], ACCORD[40] and ADVANCE[41]) shows that whilst intensive control can have benefits in terms of reducing microvascular events, there are also harmful effects, in particular increase in hypoglycaemia (increase of 42 events per 1,000 treated patients over 4.4 years: CI 25.8–61.7). The study by Currie et al.[42] described below shows that the optimal level of HbA_{1c} of 7.5% (58 mmol/mol) was associated with lowest all-cause mortality.

Researchers analysed data from nearly 48,000 primary care patients who had stepped up their hypoglycaemic treatment. HbA_{1c} of around 7.5% had the lowest mortality. Risk of death rose significantly on both sides of this reference group. Reaching a hazard ratio of 1.52 (1.32 to 1.76) for patients in the bottom 10th of HbA_{1c} concentration (median: 6.4%), and 1.79 (1.56 to 2.06) for patients in the top 10th (median: 10.5%).

Figure 1. Chart illustrating potential link between all-cause death and HbA_{1c} levels[4]



These results are of particular concern for the frailer groups of patients covered by the Polypharmacy Guideline who, given the long lead time to obtain benefits from low HbA_{1c}, may nonetheless suffer adverse outcomes.

Patients who suffer from hypoglycaemia are at increased risk of falls.

6.1 Antidiabetic agents

Points for consideration:

- Long-acting sulphonylureas e.g. glibenclamide should be avoided in the elderly due to increased risk of hypoglycaemia[2].
- Sulphonylureas should be used with care in mild to moderate renal impairment due to the hazard of hypoglycaemia[2]. See current BNF for specific drug details.
- Metformin should be used with caution in renal impairment due to increased risk of lactic acidosis[2]. Dose reductions may be required; see current BNF/SPC for details.
- Combination therapy with a sulphonylurea and DPP-4 inhibitor/glitazone/GLP-1 analogue can potentiate hypoglycaemia. Be aware of the increased risk with combination therapy and ensure treatment is optimised before adding additional agents.
- Prescribed pioglitazone?
  - Should not be used in patients with heart failure, history of fractures (especially postmenopausal) or bladder cancer[4].
  - Use with caution in the elderly. Regularly review its safety and efficacy[43].
- Check latest local/national guidelines for the current place in therapy of new agents e.g. dapagliflozin.

6.2 Home blood glucose monitoring for type II diabetics

Points for consideration:

- Is home blood glucose monitoring in line with local guidelines (if available)?
  - e.g. type II diabetic managed with diet and exercise plus sulphonylureas – advise home blood glucose monitoring up to 3 times a week at varied times.
- Is monitoring negatively affecting a patient's quality of life?
- Are additional home visits by domiciliary carers/health care support workers required as a result?
- Is the quantity prescribed on repeat/patient ordering appropriate?

6.3 Long-term oral corticosteroids

Points for consideration:

- Maintenance doses should be kept as low as possible with withdrawal considered where clinically appropriate[4].
- Polymyalgia rheumatica? Consider slowly reducing the dose of prednisolone once symptoms are fully controlled[44]. Typically, treatment is required for between 1 and 3 years (smaller dose reductions and longer durations may be needed to avoid relapse in some patients)[44]. A suggested schedule for reduction and further information can be found at CKS: Polymyalgia rheumatic.
- Patients prescribed long-term corticosteroid treatment should carry a Steroid Treatment Card[2].
- Consider therapeutic options for the prophylaxis of corticosteroid-induced (glucocorticoid) osteoporosis, in patients taking corticosteroids for 3 months or longer (aged 65 years and over are at greater risk)[2].
- Where possible, local treatments e.g. inhalers, creams etc. should be used in preference to systemic treatments[4].
- Review use of enteric-coated and soluble preparations of prednisolone
  - Currently no conclusive evidence that use of enteric-coated preparations reduces risk of peptic ulceration[2]. However, may be theoretical clinical implications to consider when switching between formulations. (See UK Medicines Information [UKMi] Q&A for further details.)
  - Soluble preparations should be reserved for patients with swallowing difficulties.

6.4 Bisphosphonates

The need to continue bisphosphonates for osteoporosis should be re-evaluated periodically, particularly after 5 or more years of use[45]. Due to their complex directions for administration, compliance with bisphosphonates is often difficult. Subsequently, administration can also be problematic in patients receiving domiciliary care due to the need for additional calls.

It is worth noting that each of the bisphosphonates has a different set of directions for administration (see current BNF for full details). Therefore some patients may be able to comply with administration of one bisphosphonate but not another.

Points for consideration:

Reviewing treatment with bisphosphonates

- Consider the need to continue treatment for osteoporosis periodically, particularly after 5 years or more of use[45].
- Treatment should be continued in high-risk individuals and those with severe osteoporosis, as the benefits of osteoporotic fracture prevention outweigh risks[46].
- If treatment is discontinued, fracture risk should be reassessed after a new fracture regardless of when this occurs and if no new fracture occurs, after two years[46].

- Further information can be obtained from National Osteoporosis Guideline Group.
- Prescribed a bisphosphonate and PPI? – Emerging evidence suggests a possible link between the use of PPIs (especially high doses for > 1 year) with increased risk of fracture. The mechanism responsible for this increase and strength of evidence has not yet been established; however, it may be prudent to ensure patients have a valid indication for a PPI and prescribed the lowest dose for shortest duration. For further information see UKMi Q&A which provides advice on the interaction between bisphosphonates and PPIs.

Table 4. Potential disadvantages to continuing/stopping treatment

Potential disadvantages to continuing treatment[1]
▪ Fragility fractures may still occur and adverse effects are possible. ▪ Atypical femoral fractures reported rarely with bisphosphonate therapy, mainly in long-term treatment[45]. MHRA Drug Safety Update (2011) provides advice to clinicians on identifying and managing atypical femoral fractures. ▪ Concerns long-term treatment may also increase risk of osteonecrosis of the jaw (ONJ) or oesophageal cancer (**N.B.** associations are rare and causality has not been established). ▪ ONJ may be a particular risk for people with cancer receiving i.v. bisphosphonates.
Potential disadvantages to stopping treatment[1]
▪ Any increase in risk of atypical subtrochanteric fracture is more than offset by decreased risk of fracture at hips and other sites. ▪ Risk of oesophageal cancer is low and does not outweigh benefits of treatment. ▪ If alendronate is stopped, its benefits reduce over 3–5 years. For other drugs, the benefits are lost more rapidly after cessation.

Initiating bisphosphonates

- Alendronate has been shown to reduce the risk of osteoporotic fragility fractures (vertebral, non-vertebral and hip) in postmenopausal women[47].
- Consider risk factors for osteoporotic fragility fractures in line with current NICE Osteoporosis overview guidance and the benefits of treatment in primary and secondary prevention.
- ***Risk factors for osteoporotic fragility fractures[48]:***
  - female
  - age (women over 65 years and men over 75 years)
  - previous fragility fracture
  - current/frequent recent use of oral or systemic glucocorticoids
  - history and/or increased risk of falls[47]
  - family history of hip fracture
  - secondary causes of osteoporosis e.g. rheumatoid arthritis (see NICE CG146 for full list)
  - low body mass index (BMI) (< 18.5 kg/m^2)
  - smoking
  - alcohol intake (> 14 units/week for women or 21 units/week for men)

6.5 Strontium ranelate

MHRA Drug Safety Updates have highlighted the risk of serious cardiac disorders associated with the use of strontium ranelate. Subsequently, new restricted indications, contraindications and warnings have been published. See MHRA for full details.

Strontium ranelate should only be used in severe osteoporosis where other treatments have failed[49]. Its use is contraindicated in patients with ischaemic heart disease (IHD), PAD and/or CeVD or those with uncontrolled hypertension[49]. The patient's CV risk should be assessed prior to initiation and at regular intervals during treatment (i.e. every 6 to 12 months)[49]. Strontium ranelate is also associated with an increased risk of venous thromboembolism[2].

7.0 UROGENITAL SYSTEM

7.1 Antimuscarinics

Points for consideration:

- Review the use of antimuscarinics (anticholinergics) e.g. oxybutynin, tolterodine for the treatment of urinary incontinence.
- **Oxybutynin (immediate release) should not be used in the frail elderly due to adverse effects on cognitive function** (see NICE CG171)[50].
- Tolterodine (immediate release) and darifenacin (once daily) are appropriate first-line alternatives[50]. Check local formulary.
- Consider anticholinergic load (i.e. the number of anticholinergics prescribed) when initiating treatment for overactive bladder symptoms.
- Mirabegron is a beta-3-adrenoceptor agonist recommended as a treatment option for the symptoms of overactive bladder **only** where antimuscarinic drugs are contraindicated/clinically ineffective or have unacceptable side effects[51]. Check local formulary.
- Do not use flavoxate, propantheline and imipramine for the treatment of urinary incontinence or overactive bladder[50].

7.2 Alpha-blockers

Review the use of alpha-blockers (e.g. alfuzosin, tamsulosin) prescribed for more than 2 months for benign prostatic hypertrophy in men with long-term urinary catheters. Consider stopping[4].

7.3 Finasteride

Review the use of finasteride in men with long-term urinary catheters. Discuss with the urology team regarding considering stopping[4].

8.0 NUTRITION AND BLOOD

8.1 Calcium and vitamin D preparations

Points for consideration:

- Calcium and vitamin D supplementation is widely recommended in older people who are housebound or living in residential or nursing homes, where vitamin D deficiency and low dietary calcium intake are common[46].
- Supplementation is also often advocated as an adjunct to other treatments for osteoporosis, as the clinical trials of these agents were performed in patients who were calcium and vitamin D replete[46].
- Avoid sub-therapeutic preparations (e.g. Calcichew D3 = 200 units vitamin D per tablet)[1].
- Preparations should contain 1.5 g calcium and 10 mcg/400 units vitamin D per tablet e.g. Adcal-D_3®, Accrete D_3®[1].
- ***Check compliance –***
  - Some patients are only able to manage one tablet a day due to GI side effects[1].
  - Calcium and vitamin D should be taken in divided doses to improve absorption[1].
  - Supplements are available in a variety of formulations e.g. chewable tables, caplets, sachets etc. Consider an alternative preparation in noncompliant patients.
  - Consider vitamin D alone in patients that cannot tolerate calcium-containing tablets but have a **good dietary calcium** intake[46].
- Calcium and vitamin D preparations can interfere with the absorption of other medicines e.g. bisphosphonates, quinolone/tetracycline antibiotics and iron[1]. Manufacturers of certain preparations advise leaving a 4-hour gap before calcium/vitamin D is taken[52].

8.2 Vitamins and minerals

- Review the need for sodium, potassium, vitamins and iron supplements – is there still a current and valid indication?
- Iron salts should be given orally until haemoglobin has reached reference range and then maintained for 3 months, to replenish iron stores, before stopping.
- Iron salts can affect absorption of other medicines e.g. quinolones/doxycycline and cause therapeutic failure.
- Some vitamins, e.g. cyanocobalamin and vitamin B compound, are considered drugs of limited clinical value by the BNF ( )[2].
- Vitamin B, Compound, Strong is no longer recommended for use in patients with a history of excess alcohol intake due to a lack of efficacy. Current NICE guidance CG100 states that the prescription of thiamine alone at the higher end of BNF recommended dosages may be a more appropriate alternative for those who have a chronic alcohol problem and whose diet is deficient[53].

8.3 Nutritional supplements

Points for consideration:

- Are 'Food First' strategies being encouraged?
- Is the original clinical indication for prescribing still valid?
  - Is the patient under the care of a dietician?
  - Has the patient been reviewed in the last 3 months by a healthcare professional?
  - Is the patient's weight being monitored?
- Have all underlying causes of poor oral intake been addressed and the patient signposted to relevant healthcare professionals e.g. dentist, social worker, speech and language therapy, physiotherapy etc.?
- Is the patient compliant?
  - Would an alternative preparation, flavour or volume be more appropriate?
  - Is there any wastage?
- Is the patient prescribed the most cost-effective preparation?
  - Powder-based supplements should be used first line (require reconstitution with milk) e.g. Complan®/Aymes®.
- Has the patient been referred to Meals on Wheels/alternative supply if appropriate?

9.0 MUSCULOSKELETAL SYSTEM

9.1 Non-steroidal anti-inflammatory drugs

All NSAIDs, including cyclo-oxygenase-2 selective (COX II) inhibitors, are associated (to varying degrees) with a small increased risk of thrombotic events i.e. MI and stroke, independent of baseline CV risk[2]. The greatest risk may be associated with high-dose long-term use[2]. All NSAIDs are also associated with serious GI toxicity; this risk is higher in the elderly[2]. NSAIDs may rarely precipitate renal failure in vulnerable patients[54].

Points for consideration:

Initial prescribing

- Is the pain inflammatory in nature?
  - Is an NSAID still needed and appropriate? – Prescribe lowest dose for shortest duration. Consider non-NSAID options where possible.
- Heart failure? – NSAIDs are contraindicated in heart failure.
- Also prescribed ACE inhibitor or ARB and diuretic? – **High-risk combination**

- At risk of CV events, GI events or nephrotoxicity given current diagnoses and/or prescribed medication?
  - The table[2] below summarises at-risk groups, key drug interactions and potential high-risk combinations with NSAIDs.

Table 5. At-risk groups, key drug interactions and potential high-risk combinations with NSAIDs

At-risk groups*	Key common drug interactions*
Elderly (over 65 years) Renal/hepatic impairment Heart failure (contraindicated) IHD PAD CeVD Uncontrolled hypertension Active GI ulceration or bleeding (contraindicated) History of GI ulceration, bleeding or perforation	ACE inhibitors[1] ARBs[1] Antiplatelets[2] Oral anticoagulants[2] Ciclosporin[1] Oral corticosteroids[1] Diuretics[1] Lithium[3] Other NSAIDs or COX II inhibitors[4] Pentoxifylline[2] SSRIs[2] Tacrolimus[1] Venlafaxine[2]
Potential high-risk combinations	
▪ NSAID plus ACE inhibitor or ARB and diuretic ▪ NSAID and a diagnosis of heart failure ▪ NSAID plus eGFR < 60 ml/min ▪ NSAID plus oral anticoagulant ▪ NSAID in patients aged over 75 years without a PPI ▪ COX II inhibitor or diclofenac and a diagnosis of IHD, PAD or CeVD.	

***See current BNF for a full list of cautions/contraindications and medicine interactions.**

1. Increased risk of nephrotoxicity/renal impairment. Where applicable hypotensive/diuretic effect antagonised.
2. Increased risk of bleeding. Where applicable possible enhanced anticoagulant effect.
3. Reduced excretion of lithium leading to increased risk of lithium toxicity.
4. Increased side effects. Avoid concomitant use.

Continued prescribing

- Is the patient prescribed the most appropriate medicine choice?
  - Naproxen (1 g daily) and low doses of ibuprofen (1.2 g daily or less) associated with lower thrombotic risk[55].
  - COX II inhibitors, diclofenac (150 mg daily) and high-dose ibuprofen (2.4 g daily) associated with increased risk of thrombotic events[2].
  - Diclofenac and COX II inhibitors contraindicated in IHD, PAD, CeVD and mild to severe heart failure[2].
  - Use the lowest effective dose for the shortest time possible. Review regularly and stop as soon as appropriate e.g. reserve for 'flare ups' of inflammatory conditions.
  - Topical NSAID? – NICE guidance for Osteoarthritis recommends considering paracetamol and/or topical NSAIDs ahead of oral NSAIDs, COX II inhibitors and opioids[56].
- Increased risk of GI adverse effects? Co-prescribe PPI with NSAID for gastroprotection. See section 1.1 for full details of risk factors associated with adverse GI effects.
- Co-prescribed medicines known to increase upper GI adverse events? See table above, section 1.1 and current BNF for a full list of medicines.
  - If so, are they prescribed a PPI?
  - Can their medication be rationalised to reduce risk?

A document has been produced to help support the clinical review of patients prescribed NSAIDs for the treatment of osteoarthritis; this is available at: http://howis.wales.nhs.uk/sites3/docopen.cfm?orgid=872&id=327994&uuid=6C848294-F9A0-CEF4-356AD6479BF17BE2

10.0 MISCELLANEOUS

10.1 Quinine

Points for consideration:

- Should not routinely be used for treatment of nocturnal leg cramps[57].
- Review use of long-term quinine for nocturnal leg cramps in line with MHRA Drug Safety Update (2010).
- Although generally well tolerated, adverse effects include tinnitus, impaired hearing, headache, nausea, disturbed vision, confusion, flushing and abdominal pain[57]. Rarely thrombocytopenia has also been reported[57].
- Number of potentially significant medicine interactions including increased risk of arrhythmias with other medicines that prolong the QT interval. See current BNF for full list.
- Regularly review and only continue where there is reported benefit[57].

10.2 Antihistamines

Review the ongoing need for long-term antihistamines e.g. promethazine for the treatment of vertigo, skin conditions (itching) and seasonal allergic rhinitis **(suggested audit topic).**

10.3 Risks of common sodium-containing oral medicines

Exposure to sodium-containing formulations of effervescent, dispersible and soluble medicines has been associated with increased odds of adverse CV events compared to standard formulations of the same medicine[58].

The sodium content of some preparations exceeds the recommended daily sodium allowance in adults without accounting for dietary intake[59]. Preparations in which sodium content may be high include: alginates/indigestion remedies, soluble/effervescent analgesics, laxatives and antidiarrhoeal, cold and flu and cystitis preparations[59]. **For example, 8 co-codamol 30 mg/500 mg tablets per day contain approximately 1.5 times the recommended maximum daily intake of salt.** Further examples can be found here: What is the sodium content of medicines?

Prescribers should consider the risks and benefits of sodium-loaded medicines and prescribe with caution[58]. In particular, regular use should be avoided in patients with conditions associated with sodium retention (e.g. hypertension, heart failure, renal impairment) and in patients following a salt-restricted diet[59].

10.4 Shared care medicines

Check the local shared care protocols for rheumatology medicines, lithium, methotrexate and amiodarone etc.

10.5 Medicines prescribed by secondary care

Points for consideration:

- Is the patient prescribed any medicines from other sources i.e. secondary care, specialist clinics etc. (examples include donepezil, antiretrovirals, immunosuppressant, erythropoietins).
- If so, are these medicines clearly recorded on the patient's medical record? – Ensure clear documentation to enable prescribers to be alert to potential drug–drug interactions, adverse effects and monitoring requirements.

10.6 Specialist services

Points for consideration:

- Is the patient prescribed any specialist items such as dressings, lymphoedema, incontinence or stoma products?
- Ensure supply source and review arrangements are clearly documented and specialist nurses consulted as required.

10.7 Unlicensed pharmaceutical specials

Occasionally, patients with swallowing difficulties may require an unlicensed special; as these products are unlicensed, prescribers accept responsibility for the safety and effectiveness of the product[60].

Points for consideration:

- Licensed medicines should be used wherever possible as they are manufactured to specific standards and assessed for safety and efficacy.
- Medicines ***not*** listed in the BNF are likely to be unlicensed (BNF clearly identifies any products needing to be obtained from a specials manufacturer)[60].
- Consider soluble or oro-dispersible preparations and licensed liquids first line in patients who require an alternative formulation. Prescribers should be mindful of the high sodium content in some preparations. See above.
- Where a liquid is required, ensure if available a licensed preparation is prescribed (e.g. furosemide oral solution 20 mg/5 ml [£13.85] is licensed whereas furosemide oral solution 5 mg/5 ml [£66.77] is an unlicensed special). There may also be differences in licensing between oral solutions and syrups.
- There is often wide variation between costs charged by manufacturers for specials. In order to improve transparency 'Specials Tariff' (Part VIIIB in Drug Tariff) has been developed[61]. Prescribe from this list where possible as prices are regulated.
- Although crushing or breaking tablets may be considered as using a licensed product in an unlicensed manner, liquid pharmaceutical specials are also unlicensed[61]. Crushing/dissolving may therefore be an appropriate option in patients where a licensed product is not suitable/available. Advice from locality medicines management teams, local Medicines Information Services or UKMi, (click on map for contact details) should be followed.

Additional resources

- UKMi Medicines Q & A – What are the therapeutic options for patients unable to take solid oral dosage forms?
- Drug Tariff Part VIIIB 'Arrangements for Payment for Specials and Imported Unlicensed Medicines'.
- Information and guidance on the prescribing and use of unlicensed pharmaceutical specials (NHS East of England).

10.8 Medicines or preparations purchased over the counter

Clinicians and healthcare professionals should check if patients are taking any additional medication bought OTC, in order to prevent inadvertent drug duplication e.g. paracetamol overdose.

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