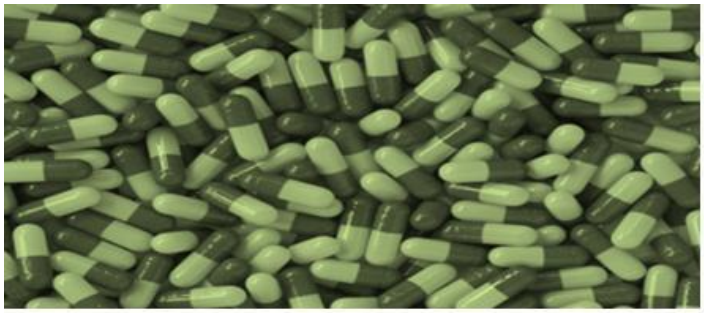
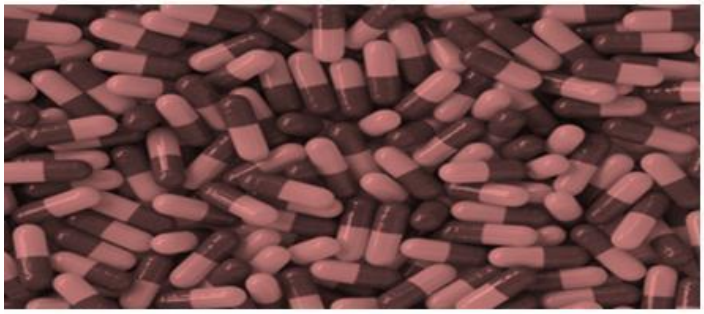
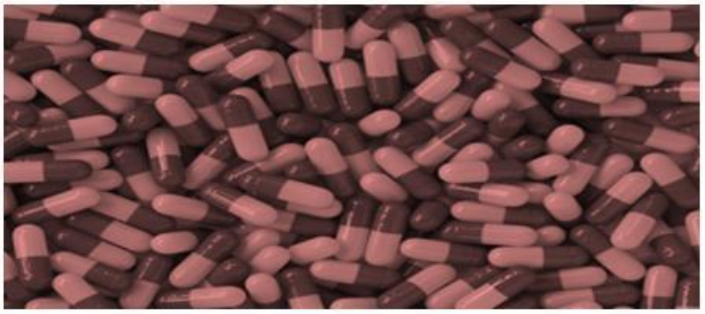
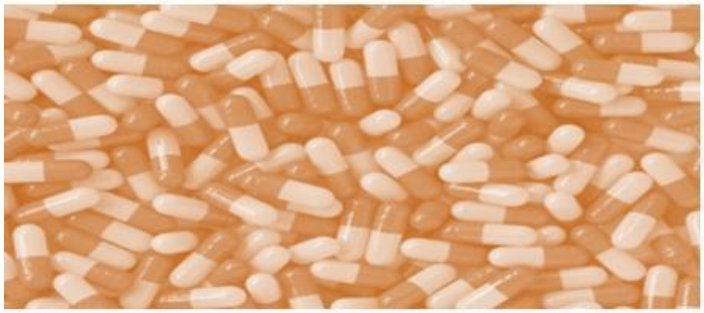
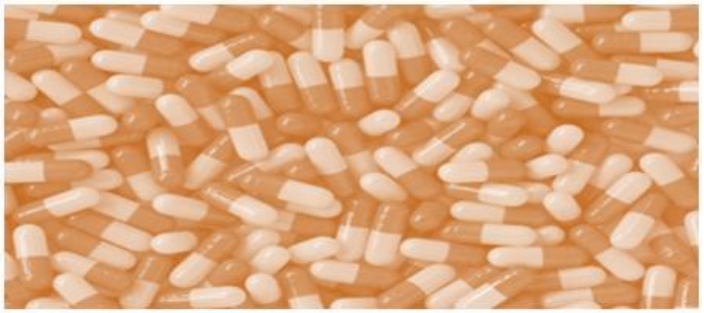
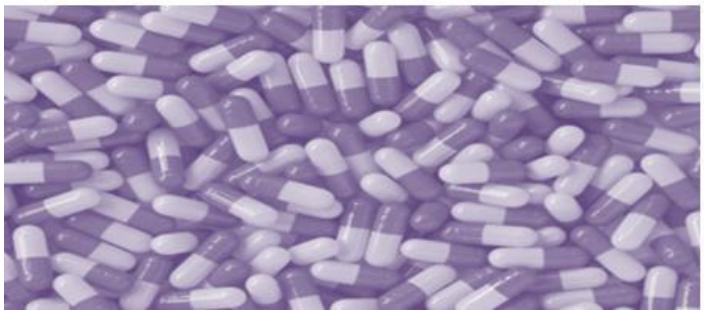


Polypharmacy Guidance

March 2015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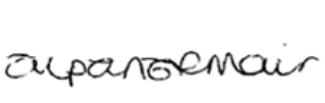
Foreword

The care of patients with multiple medical conditions is one of the greatest challenges now faced by healthcare providers. To date the vast majority of medical research, guidelines and contractual agreements have dealt with single targets for single disease states, whereas in reality many patients have multiple chronic conditions, requiring multiple treatments. The resulting polypharmacy (use of multiple medicines) can be both appropriate and inappropriate and the key healthcare aim for individual patients is to ensure the on-going safe and effective use of their multiple medicines. Research into the management of patients with multiple medical conditions is in relative infancy. Despite this there is the requirement to provide guidance to both patients and healthcare providers based on the best evidence to date.

We are delighted to present the Polypharmacy Guidance 2015, which builds on and refines the previous guidance from 2012. The '7-steps' is a clear structure for the medicines review process, which is centred around the individual adult patient, and presented in a number of forms to facilitate its use across a range of healthcare settings. An electronic version is to be produced as an 'App'. Further clarity is provided for important definitions such as *appropriate* and *inappropriate polypharmacy*, and what is meant by the term *frailty*. The methodology to identify potentially frail patients on potentially inappropriate polypharmacy has been developed since 2012, and case studies are presented to demonstrate the importance of a holistic review of the individual patient when trying to get the best outcomes from medicines. Of particular note is the further work that has been done on the relative efficacy of medicines. Medicines Information resource has developed the use of the relative numbers needed to treat, for key therapeutic areas, in order to help inform patients of the potential benefits and risks of continuing treatment.

The *Appropriate prescribing for patients and polypharmacy guidance* CEL 36 (2012) required that NHS Boards would have plans in place to identify priority patients with potentially inappropriate polypharmacy and to review those patients at greatest risk. It is understood that this work is underway. With the publication of this Polypharmacy Guidance 2015 the requirement now is that the boards will build on the foundational work of the last three years and focus resource on accelerating the capacity of polypharmacy reviews in order to further increase the benefit to patients.



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If using any content from this document, please acknowledge the Scottish Government Model of Care Polypharmacy Working Group

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Contents

1. General Principles

Medication is by far the most common form of medical intervention for many acute and chronic conditions. Drug therapy can be highly effective in preventing disease or slowing disease progression, with guidelines for single diseases recommending the use of a variety of evidence based drug treatments. However, there is often a mismatch between prescribing guidelines for specific medical conditions and the range of clinical complexity found in individual adults. For complex patients with: (1) multiple conditions; (2) frailty; (3) a dominant condition (e.g. dementia) or (4) approaching the end of their lives, the implementation of the sum of evidence based recommendations may: not be rational; increase the risk of adverse drug events and misaligned with the patient's preferences.

Why review polypharmacy?

The term polypharmacy itself just means "many medications" and has often been defined to be present when a patient takes five or more medications. However, it is important to note that polypharmacy is not necessarily a bad thing. For example, secondary prevention of myocardial infarction often already requires the use of four different classes of drugs (antiplatelets, statins, ACE inhibitor, beta blocker). Polypharmacy can be both rational and required. It is therefore crucial to distinguish appropriate from inappropriate polypharmacy.
Inappropriate polypharmacy is present, when one or more drugs are prescribed that are not or no longer needed, either because: (a) there is no evidence based indication, the indication has expired or the dose is unnecessarily high; (b) one or more medicines fail to achieve the therapeutic objectives they are intended to achieve; (c) one, or the combination of several drugs cause inacceptable adverse drug reactions (ADRs), or put the patient at an unacceptably high risk of such ADRs, or because (d) the patient is not willing or able to take one or more medicines as intended.
Appropriate polypharmacy is present, when: (a) all drugs are prescribed for the purpose of achieving specific therapeutic objectives that have been agreed with the patient; (b) therapeutic objectives are actually being achieved or there is a reasonable chance they will be achieved in the future; (c) drug therapy has been optimised to minimise the risk of ADRs and (d) the patient is motivated and able to take all medicines as intended.

Which patients should be targeted?

In the absence of definitive evidence on which patients are most likely to benefit from a holistic review of their medication, the following two groups of patients will be identified as potential candidates for medication review:

A. All patients in care homes age 50+ regardless of the number of medicines that they are on
B. Patients who are:
    - Aged 75 and over, (progressing to 65-74 as resources allow)
    - On 10 or more medicines, one of which is a high risk medication
    - **and** with a SPARRA score in the range 40 to 60%

The numbers in these groups by NHS Board are shown in Tables 1a and 1b. It should be noted that the two groups overlap, so many patients will be in both groups A and B. (Of the patients included in Table 1a as resident in a care home, 6861 aged 75 and over also appear in Table 1b and 7251 aged 65 and over also appear in Table 1b.)

Where there are large numbers using the above process, additional prioritisation may be needed and we suggest focussing on patients who meet one or more of the following criteria for complexity:

(1) Multiple conditions: In Scotland, over half of all people with chronic conditions have two or more conditions. In other words, it is now more common to have two or more long term conditions than only one.[1] Most people aged 65 years or older have two or more long term conditions and the majority of people aged 75 years or older have three or more. Although there is a clear link between

[1] Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *The Lancet*;380(9836):37-43

getting older and the likelihood of having long term conditions it would be wrong to see this as a problem purely associated with older age. In fact quite the reverse is true: the majority of people with two or more chronic conditions are younger than 65. Many of these adults will be attempting to balance the needs and demands of work and family. Deprivation is also strongly linked with multimorbidity, adding in all the complexity this brings to an adult's life.

(2) Frailty: There is an increasing recognition that older age itself should not be a specific focus. Instead, a more functional individualised approach is recommended. To this end the term 'frailty' is becoming the preferred term. A recent Best Practice statement from the British Geriatrics Society notes that:

> Frailty is a clinically recognised state of increased vulnerability. It results from ageing associated with a decline in the body's physical and psychological reserves. Frailty varies in its severity and individuals should not be labelled as being *frail* or *not frail* but simply that they have frailty. The degree of frailty of an individual is not static; it naturally varies over time and can be made better and worse.

Adults who are frail lack the reserve to deal with adverse events. Even minor physical and mental stresses can have a big impact on health. Prescribing in this group needs particular attention as guidelines are unlikely to take the presence or absence of frailty into account when making recommendations. This places frail adults at particular risk of: adverse drug reactions: drug to drug interactions or rapid deterioration if necessary medication is not optimised.

(3) Dominant condition: Standard guidelines will recommend treatment for that single condition rather than in the context of other, often multiple conditions. Certain conditions are recognised to 'dominate' the picture for the adult both practically and prognostically. Of these perhaps dementia is the best example where its impact affects and informs decisions for every other condition.

(4) Approaching the end of their lives: Adults of any age, approaching the end of their life due to any cause, are likely to have different prescribing needs, and risk versus benefit discussions should differ from healthy adults with long life spans.

Table 1a. All SPARRA[A] patients aged 50 and over in care home.
1st September 2014. All risk scores.

	Age 50+
NHS Board	**Number in a care home[D]**
NHS Ayrshire & Arran	2,567
NHS Borders	555
NHS Dumfries & Galloway	979
NHS Fife	2,285
NHS Forth Valley	1,610
NHS Grampian	3,132
NHS Greater Glasgow & Clyde	7,228
NHS Highland	1,969
NHS Lanarkshire	3,033
NHS Lothian	4,233
NHS Orkney	87
NHS Shetland	93
NHS Tayside	2,825
NHS Western Isles	169
Total	**30,765**

Table 1b. Patients in SPARRA[A] on 1st September 2014 with a risk score of 40-60% who were dispensed items from 10 or more BNF sections[B]

	Age 75+					Age 65+				
NHS board	Number of patients	Number with high risk medicines[C]	Number in a care home[D]	Number with high risk medicines and in a care home	Number with dementia[E]	Number of patients	Number with high risk medicines[C]	Number in a care home[D]	Number with high risk medicines and in a care home	Number with dementia[E]
NHS Ayrshire & Arran	3,670	3,592	645	621	558	4,634	4,534	680	655	594
NHS Borders	943	925	109	104	140	1,163	1,133	115	110	149
NHS Dumfries & Galloway	1,360	1,328	210	204	206	1,693	1,649	219	212	227
NHS Fife	2,755	2,672	568	548	649	3,399	3,293	596	574	695
NHS Forth Valley	1,950	1,911	329	319	311	2,447	2,401	344	334	329
NHS Grampian	3,448	3,353	643	614	592	4,207	4,090	688	658	644
NHS Greater Glasgow & Clyde	10,400	10,147	1,637	1,582	1,593	13,234	12,904	1,729	1,668	1,699
NHS Highland	2,305	2,248	372	360	328	2,879	2,799	405	392	356
NHS Lanarkshire	4,521	4,421	655	642	769	5,875	5,742	699	684	835
NHS Lothian	5,449	5,298	990	953	1,107	6,638	6,455	1,039	998	1,186
NHS Orkney	144	140	18	17	30	200	194	21	20	34
NHS Shetland	170	168	25	25	37	215	212	26	26	38
NHS Tayside	3,206	3,127	625	597	538	3,826	3,729	650	622	559
NHS Western Isles	264	263	35	35	40	321	318	40	40	46
Total	**40,585**	**39,593**	**6,861**	**6,621**	**6,898**	**50,731**	**49,453**	**7,251**	**6,993**	**7,391**

[A] SPARRA Version 3 estimates the risk of emergency admission in the next 12 months for approximately 3.6m individuals aged 16 years of age and older.
For the September 2014 release, this is the risk of emergency admission in the period 1st September 2014 to 31st August 2015.

[B] The number of different BNF sections from which a patient's drugs were prescribed and dispensed. SPARRA Version 3 uses the most recent 12 months prescribing data available prior to the start of the risk year.

[C] Defined as medications in any of the following BNF Sections: 2.1, 2.2, 2.4, 2.5, 2.8, 2.9, 4.1, 4.2, 4.3 and 10.1.

[D] Identified by a CHI institution code of 93 or 98.

[E] Evidence of dementia has been determined either by prescribing history (dispensed items within BNF Section 4.11) or previous inpatient admission to hospital where diagnosis at discharge includes ICD10 codes (F00-F03, F051); and ICD9 codes (2900, 2901, 2902, 2904, 2908, 2909).

Requesting SPARRA listings of patients who may be candidates for medication review.

How does this guideline aim to help?

This second edition of the Scottish national guideline on polypharmacy is a major upgrade to the information presented in the last edition and is part of ongoing work aimed at providing more detailed information that is accurate, understandable, and is useful in practice to both prescribers and patients.

1. By providing a clear structure for a drug review that is centred around the individual adult. Clinicians are encouraged to see the adult under review in a holistic manner and include non-pharmacological solutions as well as medication ones.

2. Focus on knowledge and understanding. Large sections of this guideline are set aside to provide information to both clinicians and patients. As a result both are empowered to advise, discuss and make decisions on what to take and why.

3. Worked examples presented as case studies. The four case studies are intended to demonstrate the importance of a holistic review of the individual patient when trying to get the best outcomes from medicines. This includes considering the benefits and risks of treatment in the context of multiple co-morbidities, individual social circumstances and the patient's overall wellbeing. The case studies also illustrate the importance of careful medical assessment in formulating a diagnosis and problem list.

4. Medication safety. Medicines are implicated in 5 - 17 per cent of hospital admissions, of which approximately half are considered potentially preventable. The majority are due to well-known adverse effects of commonly prescribed drugs. There is a clear and steady increase in the number of patients admitted to hospital with adverse drug effects.[2] Information and guidance is given on some of the most common medication safety issues.

5. Drug efficacy and applicability table (Number Needed To Treat (NNT) Chart). Medicines Information Pharmacists across Scotland have collaborated to produce a table that summarises what information is currently available regarding the efficacy of a number of commonly prescribed medications. Being aware of the NNT of different therapies for the same disorder can help to inform rational and patient-centred therapy. The table includes information on the characteristics of adults studied in those trials. This is important as estimating an individual patient's risk in conjunction with the NNT can guide the prescriber and patient in determining the value of a drug intervention where symptomatic relief is not the aim.

Who is this guideline targeted at?

This guidance aims to support those carrying out comprehensive face-to-face medication reviews (defined as Level 3 reviews) with patients and where appropriate carers and welfare proxies (e.g. those with power of attorney regarding health related issues). It also contains much information that patients will find useful.

[2] Co-morbidity and repeat admission to hospital for adverse drug reactions in older adults: retrospective cohort study Zhang, Min et al. BMJ 2009; 338: a2752

The review process

1.1 The '7-steps' approach to medication review

The following seven steps are intended as a guide to structure the review process. An overview of aspects to cover in each step is presented in table 2A. Table 2B lists drugs and drug classes that may be relevant under each step and links to table 2C, where more detailed information on each drug (class) is provided. Table 2C is organised by BNF chapter, which will facilitate access to drug specific information. Where relevant, tables 2A to 2C provide links to section 1.2 (background information for reviewing medication need and effectiveness) and section 1.3 (Tool to assess cumulative risk of drug toxicity and ADRs).

Step 1: Identify aims and objectives of drug therapy. Before embarking on a clinical medication review it is helpful to establish the aims and objectives of drug therapy on the basis of the information available, i.e. patient demographics, medical and drug history, laboratory markers, social situation. Based on this information, likely treatment objectives can often be identified, and will require agreement with the patient (see step 7).

Step 2: Identify essential drug therapy. A rational first step of the medication review is to separate the list of drugs the patient is currently taking into those that are essential and should usually not be stopped from those that could potentially be stopped. Essential drugs in this respect are those that have a replacement function or may cause rapid symptomatic decline or loss of disease control if stopped.

Step 3: Does the patient take unnecessary drug therapy? For the remaining drugs, it should be verified that each has a function in achieving the above defined therapeutic objectives and whether their use is supported by a sufficient up to date evidence base. In addition to stopping drug therapy with expired indications, the continued need for prophylactic treatments in patients with a short life expectancy should be considered.

Step 4: Are therapeutic objectives being achieved? The next step is to check whether the remaining drugs are the most effective for the indication they are used for and whether they are actually achieving what they are intended to achieve. If this is not the case, the possibility of patient non-adherence should be investigated as a potential explanation. Otherwise, the need for intensifying doses or adding or replacing drugs may also be considered.

Step 5: Is the patient at risk of ADRs or suffers actual ADRs? The presence of ADRs can sometimes be identified from laboratory data (e.g. hypokalaemia from diuretic use), or the patient reports such symptoms. However, ADR identification often requires a more pro-active approach of identifying ADR *risks* (including drug-drug and drug-disease interactions, but also the patient's ability to self-medicate) and asking the patient specific questions (e.g. about the presence of anticholinergic symptoms, dizziness or drowsiness).

Step 6: Is drug therapy cost-effective? Opportunities for cost minimisation should be explored, but changing drugs for cost reasons should only be considered if effectiveness, safety or adherence are not comprised.

Step 7: Is the patient willing and able to take drug therapy as intended? Assessment of adherence has been mentioned in steps 4 and 5 as a way to explain drug therapy failure or identify drug therapy risks, but this steps aims at optimising the drug regimen so that adherence is as easy as possible. In order to maximise their involvement and cooperation, patients should be explicitly asked what they hope to achieve from drug therapy and be empowered to make decisions regarding effectiveness versus safety as well as symptom control versus longevity.

Table 2a: An overview of the '7-steps' with Links to section of greater detail

Domain	Steps	Process
Aims	1. Identify objectives of drug therapy	**Review diagnoses and identify therapeutic objectives with respect to:** ➢ Management of existing health problems ➢ Prevention of future health problems
Need	2. Identify essential drug therapy	**Identify essential drugs (not to be stopped without specialist advice)** ➢ Drugs that have essential replacement functions (e.g. thyroxine) ➢ Drugs to prevent rapid symptomatic decline (e.g. drugs for Parkinson's disease, heart failure)
	3. Does the patient take unnecessary drug therapy?	**Identify and review the (continued) need for drugs** ➢ with temporary indications ➢ with higher than usual maintenance doses ➢ with limited benefit in general for the indication they are used for ➢ with limited benefit in the patient under review (see Drug efficacy & applicability (NNT) table)
Effectiveness	4. Are therapeutic objectives being achieved?	**Identify the need for adding/intensifying drug therapy in order to achieve therapeutic objectives** ➢ to achieve symptom control ➢ to achieve biochemical/clinical targets ➢ to prevent disease progression/exacerbation
Safety	5. Does the patient have ADR or is at risk of ADRs?	**Identify patient safety risks by checking for** ➢ drug-disease interactions ➢ drug-drug interactions (see ADR table) ➢ robustness of monitoring mechanisms for high-risk drugs ➢ drug-drug and drug-disease interactions ➢ risk of accidental overdosing **Identify adverse drug effects by checking for** ➢ specific symptoms/laboratory markers (e.g. hypokalaemia) ➢ cumulative adverse drug effects (see ADR table) ➢ drugs that may be used to treat ADRs caused by other drugs
Cost-effectiveness	6. Is drug therapy cost-effective?	**Identify unnecessarily costly drug therapy by** • Consider more cost-effective alternatives (but balance against effectiveness, safety, convenience)
Adherence/ Patient centeredness	7. Is the patient willing and able to take drug therapy as intended?	**Identify risks to patient non-adherence by considering** • Is the medicine in a form that the patient can take? • Is the dosing schedule convenient? • Is the patient able to take medicines as intended? • Might the patient benefit from the Chronic Medication Service (CMS)? • Is the patient's pharmacist informed of changes to regimen? **Ensure drug therapy changes are tailored to patient preferences by** • Discuss with the patient/carer/welfare proxy therapeutic objectives and treatment priorities • Decide with the patient/carer/welfare proxies what medicines have an effect of sufficient magnitude to consider continuation or discontinuation

Table 2b: Drug groups for the '7-steps' with Links to greater detail by BNF chapter

Essential drug therapy – Only consider stopping following specialist advice

Discuss with expert before stopping

- Diuretics - in LVSD (7)
- ACE inhibitors - in LVSD (17)
- Steroids
- Heart rate controlling drugs

Discuss with expert before altering

- Anti-epileptics
- Antidepressant
- Antipsychotic
- Mood stabilisers
- Amiodarone
- DMARDs
- Thyroid hormones

Potentially unnecessary drug therapy

Check for expired indication

- PPI(1) /H2 blocker (2)
- Laxatives (3)
- Antispasmodics (4)
- Oral steroid (22, 36)
- Hypnotics/anxiolytics (24)
- H1 blockers (29)
- Metoclopramide (28)
- Antibacterials (oral/topical) (32)
- Antifungals (oral/topical) (33)
- Sodium/potassium suppl. (44, 45)
- Iron supplements (44)
- Vitamin suppl. (44)
- Calcium/Vitamin D (44)
- Sip feeds (44)
- NSAIDs (46)
- Drops, ointments, sprays etc. (49)

Check for valid indication

- Anticoagulant (5)
- Anticoagulant + antiplatelet (6)
- Aspirin (6)
- Dipyridamole (6)
- Diuretics (7)
- Digoxin (9)
- Peripheral vasodilators (10)
- Quinine (11)
- Antiarrhythmics (13)
- Theophylline (21)
- Antipsychotics (25)
- Tricyclic antidepressants (27)
- Opioids (30)
- Levodopa
- Nitrofurantoin (32)
- Alpha-blockers (39)
- Finasteride (40)
- Antimuscarinics (urological) (41)
- Cytotoxics/immunosuppressant (43)
- Muscle relaxants (47)

benefit versus risk

- Antianginals (12)
- BP control (15)
- Statins (14)
- Inhaled steroids (20)
- Dementia drugs (26)
- Bisphosphonates (37)
- HbA1c control (34)
- Female hormones (42)
- DMARDs (48)

(see Drug efficacy & applicability (NNT) table)

Effectiveness

If therapeutic objectives are not achieved: **Consider intensifying existing drug therapy**

- Laxative - Constipation (3)
- Antihypertensives - BP control (15)
- Antidiabetics - HbA1c control (34)
- Warfarin - INR control
- Rate limiting drugs - Heart rate?
- Respiratory drugs – Symptoms?
- Pain control

For patients with the following potential indications: **Consider if patient would benefit from the specified drug therapy**

- (see Drug efficacy & applicability (NNT) table)
- CHD - Antithrombotic, statins, ACEI/ARB, beta blocker
- Previous stroke/TIA - Antithrombotic, statin, ACEI/ARB
- LVSD - Diuretic, ACEI/ARB, beta blocker
- AF - Antithrombotic, rate control
- DMT2 - Metformin
- High fracture risk - Bone protection

Safety

Drugs poorly tolerated in frail adults

See Gold National Framework on frailty

- Antipsychotics (incl. phenothiazines)
- NSAIDs (46)
- Digoxin (doses ≥ 250 mcg) (9)
- Benzodiazipines (24)
- Anticholinergics (incl. TCAs) (27)
- Combination analgesics

High-risk clinical scenarios

See ADR table

See "Sick day rules" cards

- Metformin + dehydration
- ACEI/ARBs + dehydration
- Diuretics + dehydration
- NSAIDs + dehydration
- NSAID + ACEI/ARB + diuretic
- NSAID + CKD
- NSAID + age >75 (without PPI)
- NSAID + history of peptic ulcer
- NSAID + antithrombotic
- NSAID + CHF
- Glitazone + CHF
- TCA + CHF
- Warfarin + macrolide/quinolone
- ≥2 anticholinergics (see Anticholinergics)

Cost-effectiveness

Check for

- Costly formulations (dispersible)
- Costly unlicensed 'specials'
- Branded products
- >1 strength of same drug
- Unsynchronised dispensing intervals (28 or 56 day supplies)

Adherence/patient centeredness

Check self-administration (cognitive)

- Warfarin/New OAC's
- Anticipatory care meds eg COPD
- Analgesics
- Methotrexate

Check self-administration (technical)

- Inhalers
- Eye drops
- Any other devices
- Bisphosphonates/calcium

Table 2c: Information on targeted drugs (by BNF) with Links to section of greater detail

The table below briefly provides the rationale behind targeting each drug or drug group as well as some practical guidance. It may be used as a reference while preparing for a face to face medication review. The list is an amalgamation of existing collections of explicit medication assessment tools (including START/STOPP, DQIP and others), but **it is important to note that no list can be comprehensive and the reviewer's clinical judgement and experience continue to be essential in tailoring the advice given to the needs of an individual patient and to identify any additional medication related problems**.

BNF Chapter 1: Gastrointestinal system		
1	PPIs	○ If long term treatment is necessary, ensure doses don't exceed usual maintenance doses ○ CAUTION: Clostridium difficile, osteoporosis, hypomagnesaemia
2	H2 blockers	○ CAUTION: Anticholinergic ADRs! See Anticholinergics, See ADR table
3	Laxatives	○ CAUTION: Vicious cycle of fluid loss > hypokalaemia > constipation ✓ If >1 laxative: Do not stop abruptly. Reduce stimulant first and monitor effect ✓ See advice here on non-pharmacological options:
4	Antispasmodics	○ Rarely effective; rarely indicated long term ○ CAUTION: Anticholinergic side effects
BNF Chapter 2: Cardiovascular system		
5	Anticoagulants	○ Check for expired indications (e.g. temporary loss of mobility that has now resolved) ○ Much more effective for stroke prevention in AF than antiplatelets - See NNT table ○ CAUTION: Bleeding events. Avoid combinations of anticoagulants, antiplatelets, NSAIDs ○ Ensure patient adherence to dosing/monitoring regimen ✓ If patient is unfit for warfarin for cognitive reasons (NOACs may not be indicated either)
6	Antiplatelets	○ NOTE: Antiplatelets are no longer indicated for 1° prevention of CHD ○ Aspirin plus clopidogrel indicated for a maximum of 12 months after ACS only ○ CAUTION: Bleeding events. Avoid combinations of anticoagulants, antiplatelets, NSAIDs ✓ Consider PPI in those with additional GI risk factors (but avoid clopidogrel+ [es]omeprazole) ○ Consider antiplatelets as part of 2° prevention strategy after CVD events - See NNT table ✓ First line antiplatelet for 2° stroke prevention is clopidogrel (rather than dipyridamole)
7	Diuretic	○ Usually essential for symptom control in heart failure ○ Note: Not indicated for dependent ankle oedema (consider medication causes, e.g. CCBs) ○ CAUTION: AKI and electrolyte disturbances ○ Advise patient to stop during intercurrent illness; Is U&E monitoring robust?
8	Spironolactone	○ CAUTION: Hyperkalaemia. Risk factors include: CKD (CI if eGFR<30ml/min), dose >25mg/d, co-treatment with ACEI/ARBs, amiloride, triamterene, potassium supplements
9	Digoxin	○ CAUTION: Toxicity! Risk factors are: CKD, dose>125mcg/d, poor adherence, hypokalaemia, drug-drug interactions
10	Periph. vasodil.	○ Rarely effective; rarely indicated long term
11	Quinine	○ Use short term only when nocturnal leg cramps cause regular disruption of sleep ○ Review effectiveness regularly ○ CAUTION: Thrombocytopenia, blindness, deafness
12	Antianginals	○ Consider reducing antianginal treatment if mobility has decreased

		○ CAUTION: Hypotension (Consider use of other BP lowering drugs; avoid combination with sildenafil)
13	Antiarrhythmic *Amiodarone*	○ In AF: Rate control usually has better benefit/risk balance than rhythm control ○ CAUTION: Overdosing. Maintenance should be max 200mg/day ○ CAUTION: Thyroid complications. Ensure monitoring tests are being done ○ Monitor LFTs
14	Statins	○ Recommended for 1° and 2° prevention in patients at high risk of CVD See NNT table ○ CAUTION: Rhabdomyolysis: Check interactions (e.g. fibrates, dihydropyridines, antiinfectives) ○ Consider need for and intensity of treatment in light of life expectancy and ADR risk See NNT table
15	BP lowering drugs	○ Limited evidence supporting tight BP control in the older frail group ○ Individualise BP targets for primary and secondary prevention of CVD guidelines ○ Consider need for and intensity of treatment in light of CVD risk life expectancy and ADR risk See NNT table
16	Beta blockers	○ Usually essential for rate and angina control in CHD and CHF (and often in AF) ○ BNF recommends up-titration of BB doses in CHF to evidence based target doses ○ CAUTION: Bradycardia in combination with diltiazem/verapamil, digoxin and amiodarone
17	ACEI/ARBs	○ Usually essential for symptom control in CHF. For other potential benefits: See NNT table ○ BNF recommends up-titration of ACEI/ARB doses in CHF to evidence based doses ○ CAUTION: AKI. Avoid combination with NSAIDs and advise pt to stop when at risk of dehydration
18	CCBs	○ CAUTION: Constipation, ankle oedema ○ Dihydropyridines - CAUTION: Reflex tachycardia/cardiodepression: Avoid nifedipine in CHD/CHF ○ Diltiazem/verapamil - CAUTION: Bradycardia in comb. with BBs or digoxin (digoxin levels ↑↑)
19	Spironolactone	○ Recommended in moderate to severe CHF: See NNT table ○ CAUTION: Hyperkalaemia. Risk factors: CKD, combination with ACEI/ARB, triamterene, amiloride ○ CAUTION: AKI. Avoid combination with NSAIDs and advise pt to stop when at risk of dehydration
BNF Chapter 3: Respiratory system		
20	Inhalers	○ Assess symptom control (NICE recommends : Ask specifically about frequency of inhaler use) ○ Assess inhaler technique and adherence to dosing schedule ○ Also see Respiratory Prescribing Strategy
21	Theophylline	○ Monotherapy in COPD is not appropriate - safer, more effective alternatives are available ○ CAUTION: Toxicity (tachycardia, CNS excitation) ○ Avoid combination with macrolides and quinolones
22	Steroids	○ Long term oral use for respiratory disease rarely indicated. ✓ Withdraw gradually if: use >3 weeks, >40mg prednisolone/d ✓ When stepping down use of steroid inhalers: Reduce dose slowly (by 50% every 3 months) ○ CAUTION: Osteoporotic fractures: Consider bone protection if long term treatment necessary ○ Ensure use of steroids aligned with COPD GOLD guideline
23	Antihistamines (1st generation)	○ Rarely indicated long term ○ CAUTION: Anticholinergic ADRs! See Anticholinergics
BNF Chapter 4: Central nervous system and psychotropic medication		
24	Hypnotics and	○ CAUTION: Risk of falls/fractures, confusion(!), memory impairment ✓See section 3.4 for specific information on benzodiazepines and Z drug withdrawal

	anxiolytics	and insomnia guidelines here • CAUTION: Risk of dependency
25	Antipsychotics	○ CAUTION: Risk of stroke and death in elderly patients with dementia! See Antipsychotics ○ CAUTION: Anticholinergic ADRs for phenothiazines (eg chlorpromazine)! See Anticholinergics ○ CAUTION: Worsening of Parkinson's disease (specialist advice is recommended)
26	Antidementia drugs	○ Formally assess benefit: ✓ If MMSE score is ≥10: Continue if drug benefits global, functional or behavioural symptoms ✓ If MMSE <10, only continue if drug helps with behaviour (NICE recommends memantine)
27	Antidepressant	○ Confirm need (First episode: Treat for 6-9 months; Second + episode: Treat for ≥2 years)
	Tricyclics	○ CAUTION: Anticholinergic ADRs! See Anticholinergics SSRIs are better tolerated in the elderly
	SSRIs	○ CAUTION: Risk of GI bleeding may be increased ○ Avoid combination with MAOIs because of the risk of serotonine syndrome
28	Metoclopramide	○ Now only licensed for use for a max of 5 days (does not apply to off label use in palliative care) ○ CAUTION: Worsening of Parkinson's disease (domperidone more suitable but note contra-indications in cardiac disease and severe liver disease)
29	Antihistamines	○ Rarely indicated long term for treatment of vertigo ○ CAUTION: Anticholinergic ADRs! See Anticholinergics
30	Opioids	○ Assess effectiveness/choice (is pain neuropathic or otherwise not responsive to opiates? e.g. chronic back pain, widespread pain, fibromyalgia, medically unexplained symptoms) ➢ See : Chronic Pain Scotland ➢ SIGN 136 Management of Chronic Pain ➢ SIGN 106; Control of Pain in Adults With Cancer ○ CAUTION: Constipation. Use laxatives ○ CAUTION: Cognitive impairment and respiratory depression, dependency,
31	Paracetamol	○ CAUTION: overdosing ✓ Ensure patient is aware of minimum interval between doses and max daily dose ✓ Avoid >1 paracetamol product ✓ Consider dose reduction where low body weight, renal or hepatic impairment
32	Antiepileptics	○ Assess effectiveness/dose if used for pain management: Is pain neuropathic, use DN4 or LANSS to aid diagnosis. Titrate dose up to assess efficacy. Limited evidence for musculoskeletal pain / Fibromyalgia) See chronic pain Scotland and SIGN 136 Management of Chronic Pain ○ CAUTION: Dizziness, blurred vision and sedation. Reduced dose in CKD. Check renal function
BNF Chapter 5: Infections		
32	Antibacterials (oral)	○ Evidence of no benefit for treating asymptomatic bacteriuria (ASB) in diabetes or older adults ○ Review use of long term antibiotics for recurrent UTI (every 6 months) ○ Lack of evidence for antibiotic use in preventing catheter associated ASB
	Nitrofurantoin	○ CAUTION: Pulmonary/renal ADRs; avoid in renal impairment; contraindicated if GFR<30ml/min
33	Antifungals	○ CAUTION: Risk of arrhythmia and HF exacerbation with azole antifungals
BNF Chapter 6: Endocrine system		
34	Antidiabetics	○ Indicated to control symptoms of hyperglycaemia (metformin is first line in DMT2) ○ Note: It takes years for the benefit (mostly microvascular risk) of tight HbA1C control to accrue. Establish individual HbA1c targets balancing any benefits vs hypoglycaemia risk See NNT table
35	Metformin	○ CAUTION: Risk of lactic acidosis. Avoid if eGFR < 30ml/min. Stop when at risk of dehydration
	Sulfonylureas	○ CAUTION: Hypoglycaemia: Active metabolites can accumulate when renal function is impaired
	Glitazones	○ Avoid in patients with heart failure
36	Steroids	○ Rarely indicated for long term use. Consider dose reduction/withdrawal where

		possible
37	Bisphospho-nates	○ Consider need for treatment in light of risk factors for osteoporotic fractures: previous osteoporotic fragility fracture, parental history of hip fracture, alcohol intake ≥4 units/d, rheumatoid arthritis, oral steroids, BMI<22 kg/m2), ankylosing spondylitis, Crohn's disease, prolonged immobility, untreated menopause. See NNT table ○ Check patient's ability and willingness to take bisphosphonates (and calcium) as instructed ✓ There are no current guidelines for bisphosphonate holidays/discontinuation in the UK ✓ There is no evidence to guide monitoring after discontinuation of bisphosphonate therapy ✓ Women who stop alendronate after 5 years rather than continuing for 10 years show moderate decline in bone mineral density and a gradual rise in biochemical markers but no high fracture risk except clinical vertebral fractures. ✓ Women at high fracture risk may benefit from continuing alendronate beyond 5 years but this should be a considered decision rather than automatic continuation[3]
BNF Chapter 7: Gynaecology and urinary-tract disorders		
39	Alpha-blockers	○ Generally not indicated if a patient has a long term catheter
40	Finasteride	○ Generally not indicated if a patient has a long term catheter - discuss with urology re: stopping
41	Antimuscarini	○ Review continued need/effectiveness after 3-6 months ○ CAUTION: Anticholinergic ADRs (oxybutynin may decrease MMSE score in people w dementia)
42	Female hormones	○ NOTE: There is no cardio-protective effect or cognitive protection in older women ○ CAUTION: Carcinogenic potential in breast and endometrium ○ Discuss with patient individual balance of benefits and risks
BNF Chapter 8- Malignant Disease and Immunosuppression		
43	Cytotoxics etc	○ Is treatment still consistent with treatment objectives? Refer to doctor who initiated treatment
BNF Chapter 9 - Nutrition & blood		
44	Supplements	○ Confirm continued need/effectiveness and set a stop/review date; ○ Monitor weight
45	Potassium	○ CAUTION: Hyperkalaemia. Risk factors: Use without stop/review date, CKD, co-treatment with ACEI/ARBs, spironolactone, amiloride, triamterene, trimethoprim)
BNF Chapter 10: Musculoskeletal and joint diseases		
46	NSAIDs	○ CAUTION: Gastro-intestinal ADRs (Risk factors: age>75, GI ulcer, antithrombotics, steroids, SSRIs, high alcohol use) ✓ If NSAIDs are essential: Consider gastro-protection with a PPI in those with GI risk factors ○ CAUTION: Cardiovascular ADRs (Risk factors: CVD risk>20%, previous CVD events, heart failure) ○ CAUTION: Renal ADRs (Risk factors: age>65, on ACEI/ARBs and/or diuretics, CKD or heart failure) ✓ If NSAIDs are essential: Monitor eGFR; advise patient to stop during intercurrent illness
47	Skeletal muscle relaxants	○ Rarely indicated long term (except for patients with spacicity) ○ CAUTION: Anticholinergic ADRs
48	DMARDs *Methotrexate*	○ Assess effectiveness and discuss any need for changes with secondary care specialist ○ CAUTION: Overdosing. Avoid preparations with different strength ○ Ensure patient adherence to dosing/monitoring regimen
BNF Chapter 11 to 13 – Eye, skin, ear, nose & oropharynx		
49	Drops, sprays Ointments	○ Set a review/stop date for topical antibacterial/antifungal and sympathomimetic preparations ○ Review need for preservative free eye drops (e.g. previous preservative toxicity)

1.2 Reviewing medication need and effectiveness

1.2.1 Assessing the need for preventative treatment in patients with shortened life expectancy/frailty

Identifying patients with shortened life expectancy

We suggest that following guidance contained in the prognostic indicators guidance from the Gold Standards Framework incorporated into the 'Living Well/Dying Well' strategy enables better identification of patients who may need supportive/ palliative care. A full copy is available here.

Characteristics which can be used to identify patients with shortened life expectancy include:

1. Where the answer to the question 'would you be surprised if this person were to die in the next 6 to 12 months?' is 'no'
2. Where a patient with advanced disease is making a choice for comfort care rather than 'curative' treatment
3. Where help is required for multiple activities of daily living, either at home or in care home due to:
    a. advanced organ failure
    b. multiple co-morbidity giving significant impairment in day to day function
    c. advanced dementia

The Gold Standards Framework gives specific information as to what tends to indicate poor prognosis in a number of conditions, for example frailty. The Supportive and Palliative Care Indicators Tool (SPICT) is a further tool developed in Scotland that also gives a picture of adults where end of life issues may need to be considered. It is available here.

Identifying frailty

Frailty is well defined as a 'reduced ability to withstand illness without loss of function'. The Gold Standards Framework defines this further as:

1. Multiple co-morbidities with signs of impairment in day to day functioning
2. Combination of at least three of:
    a. Weakness
    b. Slow walking speed
    c. Low physical activity
    d. Weight loss
    e. Self-reported exhaustion

1.2.2 Understanding numbers needed to treat (NNT)

The **'number needed to treat' (NNT)** is a measure used in assessing the effectiveness of a particular medication, often in relation to a reduction in risk over a period of time. The NNT is the *average* number of patients who require to be treated for one to benefit compared with a control in a *clinical trial*. It is defined as the inverse of the absolute risk reduction. So if treatment with a medicine for one year reduces the death rate over five years from 5% to 1% (a very effective treatment), the absolute risk reduction is 4% (5 minus 1), and the NNT is 100/4 =25.

In other words, the number needed to treat with that medicine for one year to prevent one death is 25. The ideal NNT is 1 where everyone improves with treatment. The higher the NNT, the less effective is the treatment. There is always a need to consider:

- What is the outcome being avoided? Death is more significant than a vertebral fracture, but different outcomes will be more or less significant to individual patients
- Over what period does the benefit accrue? Two drugs may have the same NNT to avoid one death, but the drug that achieves that over 6 months is more effective than the drug which takes 10 years. You can put NNTs on the same timescale by multiplying or dividing the NNT appropriately, but there is an assumption that benefit accrues consistently over time (a not unreasonable assumption, but one that is difficult to test)
- What are the TRUE costs of the drug? This will include monetary costs, but also costs associated with treatment burden, and harm/side effects. A medicine might save the life of one of the 25 people who take it, but if it led to all 25 suffering a debilitating side effect, its costs may outweigh its benefits

NNTs are only estimates of average benefit, and it is rarely possible to know precisely what the likely benefit will be in a particular patient. Clinicians and patients should also be aware of a degree of 'uncertainty' in the number since it is usually not possible to calculate valid confidence intervals around NNTs.

'Number needed to harm' (NNH) is a related measure which is the *average* number of people exposed to a medication for one person to suffer an adverse event. Again, a defined end point (e.g. GI bleeding or renal failure) requires to be specified and confounders may require correction of the raw data i.e. in very elderly patients the risk of particular side effects such as confusion and falls may be higher than on average . In discussion, the overall benefit – risk ratio (NNT / NNH) requires to be 'weighed' in the individual patient and may vary considerably in people with polypharmacy depending on absolute risk, life expectancy and vulnerability to adverse drug events.

Example:
The reference below illustrates that for benzodiazepines for night sedation NNT is 13 but the NNH is 6
Glass, J. et al. Sedative hypnotics in older people with insomnia: a meta-analysis of risks and benefits. BMJ 2005; 331: 1169

Applicability of Trial Data to Individual Adults
Included in the Drug Efficacy chart is information on the trial population and the duration of the trial. The closer an adult is in terms of their own characteristics and duration of treatment to the trial the more likely the trial is to give a good estimate of what they can expect to obtain from the treatment. Conversely the further away they are the less likely the information is to be applicable. This can work in both directions and treatment could be either more or less effective.

An example would be the comparison between a 'Frail' and 'Non – Frail' adult. If two adults present on the same medication and with the same range of diagnoses the answer to how effective their medication would be in terms of both benefit and harm depends on their other attributes. One may be functioning well and still working despite their ill health. The other may be more clearly nearing the end of their life and in a phase of increasingly high dependence. The latter adult is unlikely to have been represented (or even thought of) in a trial situation.

Adults approaching end of life have an increased risk of many events, so each individual event has a higher Absolute Risk. This means that interventions may have a much lower NNT for that adult. This should be balanced against the shorter time they have in life to obtain a benefit and the increased risk that any harm, even small, may have a higher impact.

Efficacy data must only be considered as one aspect of the whole drug review process keeping in mind particularly Steps 1 (objectives of treatment) and 7 (willingness for treatment) which consider the Patient Centred goals and aims in the context of their life as a whole.

Drug Efficacy Chart								
Medicine or intervention	Comparator	Study population	Outcome	Duration of trial	Number needed to treat (NNT)	Annualised number NNT	Comments	
HYPERTENSION								
1 BP control (<140/90mmHg)	No treatment	Patients with hypertension and age > 80yrs	Total mortality	2 years	**333**	**666**	High risk is defined as patients with a previous history of stroke Cardiovascular mortality and morbidity includes fatal MI and non-fatal MI, sudden cardiac death, aneurysms, congestive heart failure, fatal and non-fatal stroke and transient ischaemic attacks Total mortality is death from all causes NB the evidence base to support the NNT for impact on mortality in the over 80's is very limited	
			Cardiovascular mortality and morbidity	2 years	**35**	**70**		
2 BP control (<140/90mmHg)	No treatment	Patients with hypertension High risk and greater than 80 years	Total mortality	2 years	**333**	**666**		
			Cardiovascular mortality and morbidity	2 years	**16**	**32**		
3 BP control (<140/90mmHg)	No treatment	Patients with hypertension age > 60yrs	Total mortality	4.5 years	**83**	**374**		
			Cardiovascular mortality and morbidity	4.5 years	**23**	**104**		
4 BP control (<140/90mmHg)	No treatment	Patients with hypertension High risk and > 60 years	Total mortality	4.5 years	**33**	**149**		
			Cardiovascular mortality and morbidity	4.5 years	**9**	**41**		

HEART FAILURE							
5 ACE inhibitor (ramipril 10mg/day)	Placebo	**Patients at high-risk of cardiovascular disease without LVSD or heart failure** High-risk of CVD defined as: history of CHD, stroke, PAD or DM plus one other CVD risk factor (HTN, elevated total cholesterol, low HDL, smoking or micro-albuminuria)	Prevent one death (all cause)	60 months	**54**	**270**	Mean age of enrolled patients was 66 years. >50% of patients had a history of MI Ramipril reduced the risk of myocardial infarction, stroke, coronary revascularisation and heart failure There is no data to support ARBs for this indication
6 ACE inhibitor (enalapril 2.5 - 40mg/day (up-titrated as tolerated)	Placebo	**Patients with severe heart failure** NYHA class IV Co-morbidities included CHD, previous MI , HTN and DM	Prevent one death (all cause)	188 days (mean follow-up)	**7**	**3**	Mean age of patients was 70 years[3] Symptomatic improvement was observed i.e. A significant improvement in NYHA classification NB Patient numbers in the study were low (n=253)

[3] The Consensus Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. The New England Journal of Medicine. 1987; 316(23): 1429-1435

7 ACE inhibitor (enalapril 2.5 - 20mg/day (up-titrated as tolerated)	Placebo	**Patients with mild to moderate heart failure** NYHA II – III	Prevent one death (all cause)	55 months	**21**	**98**	Mean age of patients was 61 years. Approximately 80% were male [4] Treatment also reduced hospital admissions for heart failure
8 ACE inhibitor (enalapril 2.5 - 20mg/day (up-titrated as tolerated)	Placebo	**Patients with asymptomatic heart failure** NYHA I LVEF ≤ 0.35	Prevent one death (all cause)	34 months (mean follow-up)	**88**	**251**	Mean age of enrolled patients was 60 years[5] Treatment reduced the incidence of congestive heart failure and related hospital admissions
9 ACE inhibitor and indapamide (perindopril 4mg/day and idapamide	Placebo	Patients who had a history of stroke or TIA in the last 5 years.	Prevent one stroke	3.9 years (mean follow-up)	**17**	**68**	Mean age of patients was approximately 64 years [6] 70% of patients in the trial had ischaemic stroke There were similar reductions in the risk of stroke in hypertensive v. non-hypertensive patients
10 Angiotensin II receptor antagonist (telmistartan 80mg/day)	Placebo	**Patients intolerant of ACE Inhibitors with established CVD:**	Prevent one of a composite of cardiovascular death, MI or stroke	56 months (median follow-up)	**55**	**258**	Mean age of patients was approx. 67 years [7] Death rate (of any cause) was higher in treatment group than placebo group. When hospitalisations for cardiac failure were added to the composite endpoint as a primary outcome, the results were non-significant. Study concluded that telmisartan

[4.] The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. 1991; 325(5): 293-302

[5.] The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The New England Journal of Medicine. 1992; 327 (10): 685 – 691

[6.] PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. The Lancet. 2001; 358: 1033-42

[7.] Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I et al. Telmisartan Randomised Assessment Study in ACE intolerant subjects with cardiovascular disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. The Lancet. 2008; 372: 1174-1183

11 Angiotensin II receptor antagonist (candesartan 4-32mg/day)	Placebo	**Patients with intolerance to ACE inhibitors with symptomatic heart failure** NYHA II-IV LVEF ≤ 0.4	Prevent one death (cardiovascular cause) or	33.7 months	**14**	**40**	Mean age of enrolled patients was approximately 66 years [8] Patients were already taking other drugs as part of therapy for heart failure Approximately 70% had heart failure of ischaemic cause
			Prevent one death		**34**	**94**	
12 Beta-blocker (bisoprolol titrated to target dose of 10mg/day)	Placebo	**Patients with moderate to severe heart failure** NYHA III-IV LVEF ≤ 0.35	Prevent one death (all cause)	1.3 years (mean follow-up)	**18**	**24**	Mean age of patients was 61 years [9] 83% of which were NHYA III Current treatment had to include a diuretic and an ACE inhibitor although other vasodilators were allowed if patients were intolerant of ACE inhibitors. 96% of patients were on ACE inhibitors
13 Beta-blocker (carvedilol titrated to target dose of 25mg twice daily)	Placebo	**Patients with severe heart failure** NYHA IV LVEF < 0.25 (despite appropriate conventional therapy)	Prevent one death (all cause)	10.4 months (mean follow-up)	**18**	**16**	Mean age of patients was 63 years [10] Conventional therapy included diuretics and an ACEI or ARB. 97% of patients were already on an ACE inhibitor or ARB

[8.] Granger C, McMurray J, Yusuf S, Held P, Michelson E. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting enzyme inhibitors: the CHARM-Alternative trial. The Lancet. 2003; 362: 772-776

[9.] CIBIS-II Investigators or Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. The Lancet. 1999; 353: 9-13.

[10.] Packer M, Coats A, Fowler M, Katus H, Krum H et al. Effect of carvedilol on survival in severe chronic heart failure. New England Journal of Medicine. 2001; 344 (22): 1651-1658

14 Beta-blocker (Metoprolol modified-release titrated to a target dose of 200mg/day)	Placebo	**Patients with mild to severe heart failure** NYHA II – IV LVEF ≤ 0.40 (despite optimum standard therapy)	Prevent one death (all cause)	12 months (mean follow-up)	**28**	**28**	Mean age of patients was 64 years [11] Optimum standard therapy was defined as any combination of ACE inhibitors, ARB and diuretics 97% of patients were on an ACE inhibitor or ARB
15 Beta-blocker (nebivolol titrated to a target dose of 10mg/day)	Placebo	**Patients >70 years old with mild-severe heart failure (NYHA I-IV) irrespective of LVEF.**	Prevent one death (all cause)	21 months (mean follow-up)	**44**	**78**	Median age of patients was 75 years [12] 64% of patients had a LVEF of </=0.35. >95% of enrolled patients were NYHA class II or III >87% were already taking an ACE inhibitor or Angiotensin receptor blocker
16 Spironolactone 25mg daily	Placebo	**Patients with heart failure** Patients had NYHA Class IV heart failure in the 6 months prior to enrolment, but were NYHA class III or IV at enrolment.	Prevent one death (all cause)	24 months (mean follow-up)	**9**	**18**	The mean age of patients was 65 years [13] Spironolactone also reduced the frequency of hospitalisation for heart failure and produced a significant improvement in the symptoms of heart failure Patients in the trial were on an ACE inhibitor (if tolerated) and a diuretic. 10% of patients were also on a beta-blocker

[11.] Merit H-F Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised intervention Trial in Congestive Heart Failure (MERIT-HF). The Lancet. 1999; 353: 2001-2006

[12.] Flather M, Shibata M, Coats A, Van Velhuisen D, Parkhomenko A. Randomised trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). European Heart Journal. 2005; 26: 215-225.

CEREBROVASCULAR/ CARDIOVASCULAR DISEASE							
17 **Warfarin** (target INR 2 - 3)	Aspirin 75mg daily	Age > 75yrs with AF	1st occurrence of fatal or non fatal disabling stroke (ischaemic or haemorrhagic), other intracranial haemorrhage or	2.7 years (mean follow-up)	**20**	**54**	Mean age of patients prescribed warfarin was 81.5 years [14] 73% of patients had a CHADS2 score of 1-2 67% of patients on warfarin remained on this treatment for the complete duration of the trial
18 **Aspirin**	Placebo or no treatment	**Primary prevention of CVD** Individuals without history of occlusive disease	Serious vascular event (Defined as MI, stroke or vascular death)	5.8 years (mean follow-up)	**246**	**1428**	Age range in trials was 19-94yrs [15] Patients had hypertension or coronary risk factors without overt disease
19 **Aspirin or other antiplatelet**	Placebo or no treatment	**Secondary prevention of CVD in patients with history of stroke or TIA (outwith acute period)**	Serious vascular event (Defined as non-fatal MI, non-fatal stroke or vascular death)	29-31 months	**28-40**	**68 – 94**	Antiplatelets include aspirin (most widely studied), clopidogrel, dipyridamole, and other antiplatelets not commonly used in UK practice [16] [17]

[13]. Pitt B, Zannad F, Remme W, Cody R, Castaigne W et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. The New England Journal of Medicine. 1999; 341(10): 709-717

[14].Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA) : a randomised controlled trial. Lancet 2007; 370: 493 - 503

[15]. ATT Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009; 373: 1849-60.

20 Antiplatelet	Placebo or no treatment	**Secondary prevention in patients at high risk of cardiovascular events** Included patients with previous MI, acute MI, previous stroke/TIA, and other high risk **(excluding**	Serious vascular event (Defined as non-fatal MI, non-fatal stroke or vascular death)	26 months	**15**	**32**	Antiplatelets include aspirin (most widely studied), clopidogrel, dipyridamole, and other antiplatelets not commonly used in UK practice [18]
21 Aspirin & dipyridamole	Placebo	**Secondary prevention of CVD in patients with arterial vascular disease**: (Defined as: coronary artery disease, MI, angina, retinopathy, nephropathy,	Vascular event. (Defined as vascular death, non-fatal stroke or non-fatal myocardial infarction)	30 months	**25**	**163**	Mean age of patients 54 years [19]

[16]. Antithrombotic trialists collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, MI and stroke in high risk patients. BMJ 2002;358:71-86
[17]. McGrath E et al. Validity of composite outcomes in meta-analyses of stroke prevention trials: the case of aspirin. Cerebrovascular Diseases 2011; 32(1):22-7.
[18]. Antithrombotic trialists collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, MI and stroke in high risk patients. BMJ 2002;358:71-86
[19]. The Cochrane Collaboration. Dipyridamole for preventing stroke and other vascular events in patients with vascular disease. *The Cochrane Library* 2007, Issue 3

22 Aspirin & dipyridamole	Aspirin	peripheral arterial disease, stroke, TIA, amaurosis fugax)		29 months	**50**	**121**	Mean age of patients 55 years [20]
23 Thienopyridine derivative (Ticlopidine or clopidogrel)	Aspirin	**Secondary prevention of CVD in patients with history of ischaemic stroke or TIA**	Stroke (all types)	22 months	**100**	**184**	Mean age of patients was 63yrs [21] Ticlopidine is not available in the UK but has similar mode of action to clopidogrel
			Stroke, MI or vascular death	28 months	**100**	**223**	
24 Statin (Simvastatin 40mg daily, atorvastatin 80mg daily, pravastatin 40mg daily)	Placebo	Secondary prevention of CVD Patients had a history of ischaemic or haemorrhagic stroke or TIA	Ischaemic or haemorrhagic stroke	48 months	**100**	**400-420**	Serious vascular events (non-fatal stroke, non-fatal myocardial infarction, vascular death) and all-cause mortality including sudden deaths [22]
			Serious vascular event	41- 44 months	**20**	**68-74**	

[20]. Dipyridamole for preventing stroke and other vascular events in patients with vascular disease. *The Cochrane Library* 2007, Issue 3
[21]. The Cochrane Collaboration. Thienopyridine derivatives versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients. The Cochrane Library 2009, Issue 4
[22]. The Cochrane Collaboration. Interventions in the management of serum lipids for preventing stroke recurrence. *The Cochrane Library* 2009, Issue 3

DIABETES							
25 Intensive sulphonylurea with insulin to achieve fasting plasma glucose less than 6.0mmol/ (Sulphonylureas: chlorpropamide, glibenclamide or glipizide) (Insulins: Ultratard or Humulin Zn or isophane insulin)	Conventional treatment with diet to aim for fasting blood glucose less than 15mmol/l (Metformin and sulphonylurea could be added or patients changed to insulin if target not achieved)	Newly diagnosed type 2 diabetes patients - between 25-65 years	Any diabetes end point	10 years (median duration of follow-up)	**20**	**200**	Mean age of patients was 54 years [23] Any diabetes-related endpoint was defined as sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, digital amputation, vitreous haemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction Diabetes-related death was death due to myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia, and sudden death Median HbA1c over 10 years 7.0% in intensive group versus 7.9% in conventional group Intensive group had more hypo-glycaemic episodes per year and higher weight gain than conventional group Reduction in micro-vascular events were mostly retinal
			Diabetes related death		**91**	**910**	
			Micro-vascular complications		**36**	**360**	

[23] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-53.

DIABETES							
Metformin to achieve fasting blood glucose <6.0mmol/l (maximum dose 2550mg) Glibenclamide was added if this was not achieved and if unsuccessful changed to insulin to achieve fasting blood glucose <6.0mmol/l (or 7.0 if on insulin)	Diet alone to achieve fasting blood glucose <15mmol/l. If unsuccessful sulphonylurea (chlor-propamide or glibenclamide) or metformin or insulin to achieve fasting blood glucose <15mmol/l could be added	Newly diagnosed type 2 diabetes patients - between 25-65 years Overweight defined as >120% ideal body weight	Any diabetes end point	10.7 years (median follow-up)	**7**	**80**	Mean age of patients was 53 years; mean weight 87kg ; BMI 31 [24] Any diabetes-related endpoint or death was defined as for the scenario above sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous haemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction Median HbA1c during 10 years was 7.4% in metformin group and 8.0% in conventional group Hypoglycaemic episodes were higher in metformin group compared to diet alone but lower than the sulphonylurea group. Hypoglycaemia rates increased over time in insulin group as higher doses were required
			Diabetes related death		**19**	**203**	
			Microvascular disease		**45**	**481**	

[24.] UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998; 352: 854-65

DIABETES							
26 Intensive control of glucose **I**ncluded the addition of Gliclazide mr tablets 30-120mg daily, to existing medication (which could also be adjusted) to achieve a glycated haemoglobin (HbA1c) value of 6.5% or less.	Hypo-glycaemia agents chosen by the treating physician	Patients with type 2 diabetes mellitus at least 55 years old with a history of major macro-vascular or micro-vascular disease or at least one other risk factor for vascular disease	Major microvascular or macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke)	5 years (median follow-up)	**53**	**263**	Mean HbA1c in control group was 7.3% and intensive (gliclazide mr) arm was 6.5% after 5 years follow up Microvascular benefits were mostly due to reduction in nephropathy [25] No significant effect on major macrovascular events alone Severe hypoglycaemia occurred in 2.7% of patients on intensive therapy compared with 1.5% of patients in the standard therapy group (Number needed to harm =80)
			Major micro-vascular events (new or worsening nephropathy or retinopathy)		**67**	**333**	

[25.] ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560-2572.

OSTEOPOROSIS									
27 **Alendronate** 10mg tablets	Placebo	**Post-menopausal women: Secondary prevention** in women who had experienced previous vertebral compression fractures	Rate of vertebral, non-vertebral or hip fractures (as below) over a 5 year period	60 months (5 years)	As per age range below		As per age range below		Age range 42-85 but >62 for secondary prevention These NNTs apply to the <u>first 5 years of treatment only</u>
			Vertebral **secondary** prevention		65-69	16	65-69	**80**	
					70-74	13	70-74	**65**	
					75-79	9	75-79	**45**	
					80-84	12	80-84	**60**	
					85-89	11	85-89	**55**	
					90+	8	90+	**40**	
			Non-vertebral **secondary** prevention		65-69	52	65-69	**260**	
					70-74	39	70-74	**195**	
					75-79	36	75-79	**180**	
					80-84	27	80-84	**135**	
					85-89	24	85-89	**120**	
					90+	12	90+	**60**	
			Hip **secondary** prevention		65-69	210	65-69	**1050**	
					70-74	86	70-74	**430**	
					75-79	36	75-79	**180**	
					80-84	21	80-84	**105**	
					85-89	9	85-89	**45**	
					90+	8	90+	**40**	

OSTEOPOROSIS										
28 **Alendronate**	Placebo	**Post-menopausal women: primary prevention** average T-score was within 2 standard deviations of the mean for bone density vertebral compression fractures	Rate of vertebral, non-vertebral or hip fractures (as below) over a 5 year period	60 months (5 years)	As per age range below		As per age range below		Age range 42-85 but >62 for secondary prevention These NNTs apply to the <u>first 5 years of treatment only</u>.	
			Vertebral **primary** prevention		65-69	148	65-69	**740**		
					70-74	123	70-74	**615**		
					75-79	67	75-79	**335**		
					80-84	97	80-84	**485**		
					85-89	89	85-89	**445**		
					90+	47	90+	**235**		
			Non-vertebral **primary** prevention		65-69	104	65-69	**520**		
					70-74	67	70-74	**335**		
					75-79	59	75-79	**295**		
					80-84	42	80-84	**210**		
					85-89	32	85-89	**160**		
					90+	12	90+	**60**		
			Hip **primary** prevention		65-69	236	65-69	**1180**		
					70-74	118	70-74	**590**		
					75-79	50	75-79	**250**		
					80-84	27	80-84	**135**		
					85-89	11	85-89	**55**		
					90+	9	90+	**45**		

1.3 Tool to assess cumulative risk of drug toxicity and ADRs

The chart below cross-tabulates medication and ADR risks associated with them. It is intended as an aid to identify actual ADRs or medication safety risks that are the consequence of cumulative ADRs. For example, if a patient reports constipation, the chart can identify drugs that may contribute to it. Inversely, the risk of constipation can be anticipated if a patient is taking multiple drugs that may cause this side effect. **Please, note that the list focuses on commonly used drugs and commonly preventable ADRs, and is not meant to replace more detailed medicines information sources.**

Table 3a: ADR Table

A - STRONG anticholinergics are: dimenhydrinate, scopolamine, dicyclomine, hyoscyamine, propantheline; B - STRONG anticholinergics are: tolterodine, oxybutynin, flavoxate; C - STRONG anticholinergics are: amitriptyline, desipramine, doxepine, imipramine, nortriptyline, trimipramine, protriptyline; D - STRONG anticholinergics are: promethazine; E - STRONG anticholinergics are: diphenhydramine, clemastine, chlorphenamine, hydroxyzine. Please see here for full list of anticholinergics! See here for full list of medicines linked to falls.

2.Case studies: The ‘7 steps’ approach in action

Case 1: Multimorbidity without frailty

Case summary

Patient details

58 year old woman

Current medical history

- Diabetes Type 2 (diagnosed 5 years ago)
- Coronary Heart Disease (NonSTEMI 1 year ago)
- Hypertension
- Atrial Fibrillation
- COPD
- Chronic Back Pain
- Depression (2 episodes)
- Hypothyroidism

Results

- HbA_{1c} 86 mmol/mol (10%)
- BP 150/85 mmHg
- BMI 35kg/m^2
- PFTs mild obstruction
- No urinary protein detected
- eGFR 55ml/min

Lifestyle

- Smoking: 10 – 15 cig/d
- Alcohol: 20 units/week

Current Medication

- Aspirin 75mg od
- Metformin 1g tds
- Gliclazide 80mg bd
- Pioglitazone 30mg od
- Salbutamol inhaler prn
- Becotide inhaler 100 bd
- Thyroxine 75 mcg od
- Citalopram 20mg od
- Bendroflumethiazide 2.5 mg
- Lisinopril 30mg od
- Amlodipine 10mg od
- Atenolol 50mg od
- Furosemide 40 mg od
- Gabapentin 400mg tds
- Co-codamol 8/500mg 2 tabs up to qds
- Diclofenac 50mg up to tds
- Omeprazole 40mg bd

Current Function

Receptionist in local garage. Works 6 half days per week. Provides support for elderly mother who lives alone and has early dementia. Lives with husband - out of work long term. Two previous acute admissions to hospital. Flu-like illness leading to exacerbation of COPD two years ago. Chest pain 12 months ago - found to be in atrial fibrillation on admission and troponin positive. Angiogram showed widespread coronary artery disease but not severe enough to warrant revascularisation. Echocardiography showed normal left ventricular systolic function. On dual aspirin and clopidogrel for 1 year. Recently moved to aspirin monotherapy.

Most recent consultations

Ongoing problems with ankle swelling. Back pain difficult to manage and resistant to several strategies. Occasional palpitations, and persistent indigestion with heartburn. Chronic financial worries. Increasing carer strain.

Applying the 7 steps

Checks	Medication related risks /problems identified
1. Therapeutic objectives ➢ Existing problems ➢ Prevention	• Secondary prevention of CVD events (incl. stroke prevention in AF) • Rate control in AF • Management of CKD • Management of COPD • Pain control • Management of depression • Control of hypothyroidism
2. Essential drugs ➢ Essential replacement function ➢ Preventing rapid deterioration	• Thyroxine to treat hypothyrodism • Antidiabetic medication to control diabetes • Atenolol is needed for rate control in AF
3. (Continued) need for drugs ➢ Temporary indications ➢ Maintenance doses ➢ Limited benefit in general ➢ Limited benefit in this patient	• Pain control: Is the gabapentin for neuropathic pain (from DM) or mechanical back pain; co-codamol v paracetamol; NSAID required? • Duration of antidepressant? • High dose omeprazole. Active peptic ulcer or oesophagitis? Check symptoms are of gastric origin rather than angina; may require endoscopy or trial without NSAID?
4. Therapeutic objectives achieved? ➢ Symptom control ➢ Biochemical/clinical targets ➢ Prevention	• Secondary prevention of coronary events: - Young and active so potentially a long time to obtain benefit - Not on statin despite high CVD risk (check if omission or due to side effects. If side effects, consider alternative statin - HbA_{1c} high despite 3 antidiabetic drugs; discuss adherence and HbA_{1c} target - Check BP control, lipid control and life style • Stroke prevention in AF: - CHADS score = 2 - consider replacing aspirin for warfarin • Rate control in AF: Check pulse • Management of COPD: Discuss symptom control with patient • Pain control: Discuss symptom control; gabapentin indicated for neuropathic pain. Consider withdrawal if not effective or misprescribed for mechanical back pain. Review efficacy of NSAID • Management of depression: Discuss symptom control with patient • Control of hypothyroidism: Recent TFTs? • Management of CKD: OK at the moment (no proteinuria) but need to monitor regularly

5. Safety ➢ Drug-disease interactions ➢ Drug-drug interactions ➢ Monitoring robust? ➢ ADRs	**Risk of ADRs** • Risk of GI bleeding: NSAID + citalopram + aspirin (or warfarin if changed in step 3) • Risk of acute kidney injury: - NSAID + CKD (eGFR 55ml/min). Consider stopping. - co-prescribed diuretic,ACEI/ARB and NSAID ('triple whammy') - co-prescribed thiazide + loop diuretic. Stop one - consider more frequent U&Es monitoring • Risk of CVD/cardiac events: - NSAID + IHD - diclofenac (ibuprofen and naproxen preferred) - Pioglitazone [Ankle swelling + ischaemic heart disease] • Risk of arrythmia: QTc prolongation: omeprazole/citalopram/gabapentin. **Actual ADRs** • Ankle swelling - due to amlodipine? pioglitazone?
6. Cost-effectiveness	Opportunities for cost minimisation (eg generic substitution) should be explored
7. Risks to patient-adherence ➢ Convenient form/dosing schedule? ➢ Technical/cognitive ability? ➢ Continuity of care/CMS beneficial? ➢ Aligned with patient preferences?	• Secondary CVD prevention: Consider how to prioritise discussions (and allocate time for this in consultation) - Most effective intervention would be stopping smoking followed by Warfarin for AF, BP control, weight reduction, HbA_{1c} control - Offer and support smoking cessation, diet, exercise • COPD management: - Check inhaler technique and inhaler use - Adjust dose/formulation if necessary • Patient cooperation: - Check this lady is aware of the rationale for medication - Check this lady is aware of safety advice eg what medication to stop if at risk of dehydration - Check patients willingness to make lifestyle changes (smoking, diet, exercise) • Social support: Impact of stress. Signpost to Alzheimer's Scotland helpline (for carers), or self-help for anxiety/ depression

SUMMARY: KEY CONCEPTS IN THIS CASE

1. Large number of medications likely to be needed and effective. High number of medications on its own not an indicator or problematic prescribing but of high risk patient requiring more support
2. Long medication list making it harder to pick up problems without focused review
3. Potential to usefully detect and treat conditions (in this case AF)
4. Potential for high risk drug combinations particularly in patients on multiple medications
5. Need for direct to patient advice on medication, e.g. regarding dehydration
6. Link with non-pharmacological management
7. Time required in consultation likely to have to be longer than standard to cover the patients concerns and issues and focus on medication

Case 2: Frailty without overt multimorbidity

Case summary

Patient details
69 year old man. Care home resident 2 years. Long term heavy alcohol use in the past. Developed dementia exacerbated by alcohol related brain damage. Fell at home leading to fractured hip. Very confused and distressed post surgery. When settled, unable to manage at home post fracture and transferred to care home. Lacked capacity at time of admission. Rallied and put weight on initially. Slowly fading over years
Current medical history
• Fracture neck of femur 2 years ago • Dementia – mixed Alzheimer's disease / alcohol abuse
Results
• BP 120/84mmHg • eGFR > 60ml/min
Current Medication [stable since admission]
• Trazodone 150mg nocte • Thiamine 50mg tds • Bendroflumethiazide 2.5mg od • Tramadol 50mg qds • Cetirizine 10mg od • Amisulpiride 100mg bd • Diprobase cream as required • Fucibet cream topically bd
Current Function
Assistance of two to transfer to chair. Regular falls as attempts to mobilise unaided. Conversation confused. Short term memory poor. Prompting required to ensure he eats and drinks. Over the last 12 months has developed ankle swelling and shortness of breath

Applying the 7 steps

Checks	Outputs
1. Therapeutic objectives ➢ Existing problems ➢ Prevention	• Increase/prevent further deterioration of ability to self-manage; ankle swelling; shortness of breath • Prevent falls/fractures
2. Essential drugs ➢ Essential replacement function ➢ Preventing rapid deterioration	• None
3. (Continued) need for drugs ➢ Temporary indications ➢ Maintenance doses ➢ Limited benefit in general ➢ Limited benefit in this patient	• Thiamine - may be redundant if well-nourished in care home. • Bendroflumethiazide - No longer hypertensive. Potential for withdrawal • Tramadol - Indication unclear (may have been started after surgery). • CNS medication (Trazodone, amisulpride) - Indication unclear. Consider staged withdrawal if not agitated • Cetirizine /topicals (Diprobase cream, Fucibet cream). - Required for itch? Clarify cause (i.e. dermatological versus CNS problem or drug side effect). If dermatological problem, non-pharmacological measures e.g. attention to washing powder, natural fabrics, reducing use of perfumed products etc, as well as proper use of emollients regularly and in sufficient quantity can make a difference) • Antimicrobial cream: Use should be limited to short term (e.g. one week)
4. Therapeutic objectives achieved? ➢ Symptom control ➢ Disease management ➢ Disease prevention	• Prevent falls/fractures: Possible role for calcium/vitamin D to reduce falls risk, and for osteoporosis prevention using bisphosphonates or denosumab • Ankle swelling and shortness of breath: Consider presence of LVSD. Potentially highly effective treatment available (ACEI/ARB, BB) if present. Consider ECG +/ ECHO /BNP • Ensure thyroid function checked. If deficient treat to replace
5. Safety ➢ drug-disease interactions ➢ drug-drug interactions ➢ Monitoring robust? ➢ ADRs	**ADR risks** • Risk of CVD events: - Antipsychotics • Risk of cognitive deterioration: - Antipsychotics, antihistamines, tramadol • Risk of falls/fractures: - Antipsychotics, antidepressant (sedative), antihistamines • Risk of serotonin syndrome: - Tramadol and antidepressant • Risk of steroid adverse effects (topical and systemic): - High dose topical steroid **Actual ADRs** • Subacute serotonin syndrome may contribute to confusion

6. Cost-effectiveness	• Opportunities for cost minimisation (eg generic substitution) should be explored
7. Risks to patient-adherence ➢ Convenient form/dosing schedule? ➢ Technical/cognitive ability? ➢ Continuity of care/CMS beneficial? ➢ Aligned with patient preferences?	• Prevention of falls/fractures - Decision to start bisphosphonate: Balance ability to take versus expected benefit. Intravenous bisphosphonate or subcutaneous denosumab alternative options • Patient cooperation: - Involve patient where possible. If deemed to lack capacity, ensure "Adults with Incapacity Documentation" in place. Discuss with relevant others e.g. Welfare Guardian, Power of Attorney, nearest relevant if one exists
KEY CONCEPTS IN THIS CASE **1.** Low number of conditions and medications but still high potential for drug related issues **2.** Ongoing review of medication commenced for symptomatic relief **3.** **Apparent** low level of multimorbidity but potential for undiagnosed treatable conditions	

Case 3: Frailty with Multimorbidity

Patient details

87 year old woman

Current medical history

- Cerebrovascular Disease
  - Partial anterior circulation stroke 5 years ago
  - Vascular Dementia diagnosed 3 years ago
- Hypertension
- Ischaemic Heart Disease
  - Atrial Fibrillation 2 years
  - MI 15 years ago
- Type 2 Diabetes
- Osteoporosis: Fracture vertebra L2 1 year ago; T score -3.2 at hip on DXA scan
- Recurrent UTIs
- MMSE 22/30 ACE-R 66/100
- COPD with moderate airflow obstruction
- Hypothyroidism

Results

- BP 106/76 mmHg
- HbA_{1c} 40mmol/mol
- Urine Albumin/Creat ratio: trace micro-albuminuria
- Creatinine 124umol/L; eGFR 45ml/min and stable at this level
- Weight 43kg

Current Medication

- Thyroxine 150mcg once a day
- Alendronate 70mg once a week
- Calcichew D3 forte 1 tab twice a day
- Metformin 1g TDS
- Gliclazide 160mg bd
- Perindopril 4mg once a day
- Indapamide 2.5mg once a day
- Warfarin as per INR
- Clopidogrel 75mg once a day
- Atorvastatin 80mg once a day
- Mirtazapine 30mg nocte
- Zopicolone 7.5mg at night
- Paracetamol 1g QDS
- Omeprazole 20mg once a day
- Seretide 250 1 puff twice/day
- Salbutamol as required
- Ipratropium inhaler 4 times/day
- Oxybutinin 5mg bd
- Trimethoprim 200mg once a day prophylaxis

Current Function

Lives at home with husband who is cognitively intact but limited due to heart failure. Vascular dementia diagnosed 3 years ago. Steadily worsening memory. Needs regular reorientation by husband. Marked increase in confusion with infection. Continence a particular issue with multiple nocturnal trips to toilet. Needs a lot of encouragement to eat and drink enough. Main trips out the house are to clinics and GP. Speciality hospital clinics.

Most recent consultations

Recent Admissions: Osteoporotic fracture leading to sudden loss mobility one year ago. Delirium in hospital. Flu-like illness 3 months ago. Admitted with confusion, hypoglycaemia and acute kidney injury.

Applying the 7 steps

Checks	Medication related risks /problems identified
1. Therapeutic objectives ➢ Existing problems ➢ Prevention	• Reduce potential for harms from drugs • Ameliorate effects of dementia • Minimise potential for future episodes of delirium • Maintain physical function and minimise symptoms
2. Essential drugs ➢ Essential replacement function ➢ Preventing rapid deterioration	• Thyroxine
3. (Continued) need for drugs ➢ Temporary indications ➢ Maintenance doses ➢ Limited benefit in general ➢ Limited benefit in this patient	• Huge medication burden • Consider relaxing diabetes, BP and lipid control • Consider continued need for osteoporosis treatment • Review ongoing need for night sedation, antidepressant, PPI and oxybutynin • Clopidogrel plus warfarin is rarely indicated • Thyroxine - Check dose and recent TFTs in case over replaced • Trimethoprim prophylaxis- no evidence beyond 6 months – see SAPG • Review evidence for accuracy of UTI diagnoses
4. Therapeutic objectives achieved? ➢ Symptom control ➢ Biochemical/clinical targets ➢ Prevention	• Check INR • Pursuing surrogate targets (BP, HbA_{1c}, cholesterol) may not be appropriate in this case • Symptoms and daily function likely to assume greater importance
5. Safety ➢ Drug-disease interactions ➢ Drug-drug interactions ➢ Monitoring robust? ➢ ADRs	• Risk of metformin adverse effects (lactic acidosis) • Risk of acute kidney injury/lactic acidosis: ○ ACEI + diuretic + metformin: Advise patient / carer to stop if dehydrated ○ Renal impairment(eGFR 38 in keeping with Stage 3 CKD; using body weight, the estimated creatine clearance is 19 ml/min) • Risk of paracetamol intoxication (max 4g/24 hours paracetamol in 45kg lady). Consider reducing dose or extending dosing interval • Risk of hypoglycaemia: Tight blood sugar control ○ Risk of hypotension/falls: Tight BP control, mirtazapine, zopiclone • Risk of bleeding events: Combination of warfarin and clopidogrel. Stop one or other (warfarin is more effective in preventing stroke in AF) • Anticholinergic effects: Consider oxybutynin having any effect v risk of increased confusion • Myalgia: Enquire about statin (high dose) related side effects?
6. Cost-effectiveness	Opportunities for cost minimisation (e.g. generic substitution) should be explored

7. Risks to patient-adherence ➢ Convenient form/dosing schedule? ➢ Technical/cognitive ability? ➢ Continuity of care/CMS beneficial? ➢ Aligned with patient preferences?	• COPD management: - Check inhaler technique and inhaler use - Adjust dose/formulation if necessary • Prevention of falls/fractures: - Verify cognitive/technical ability to take alendronate as intended. - Consider change to denosumab to aid adherence • Patient cooperation: - Ensure patient/carer awareness of likely benefit v burden/adverse effects - Consider whether patient has capacity to engage with review process - Ensure that carers views and expectations are heard and balanced against professional advice and patient preferences – especially if carer has power of attorney - Discuss effort on both patient and carer in taking medication - Balance against focussing on nutrition - Consider narrowing medication to most effective agents - Ensure that medication review is incorporated into wider anticipatory care planning discussions

KEY CONCEPTS IN THIS CASE

1. Although most of the medications in this case have a clear indication the cumulative effect is an enormous drug burden with 'pernicious' ADR potential. Careful consideration required to balance the potential for benefit for this specific patient v a reasonable estimation of life expectancy
2. Consideration of potential adverse impact of high drug burden on other vital areas e.g. nutrition
3. Strong potential for inadvertent high risk co-prescription on a long drug list
4. Difference in risk between trial populations and frail elderly
5. Likely to have intercurrent illnesses and stressors requiring 'acute' / 'emergency' therapeutic review
6. Opportunity costs and potential savings from dispensing / administration /aberrant concordance through rational prescribing

Case 4: Care home resident with multiple morbidity

Patient details	
79 year old man	
Current medical history	
• Stroke 2 years ago • Dense left hemiparesis • Cognitive impairment (post CVA)	• Coronary Heart Disease • Impaired left ventricular systolic function on ECHO
Results	
• BP 160/80 • Continues to smoke 5-10 cigs per day	• U&Es all within normal range
Current Medication	
• Lansporazole 30mg od • Simvastatin 40mg nocte • Clopidrogel 75mg od • Bisoprolol 2.5mg od • Enalapril 20mg od	• Amlodipine 10mg od • Furosemide 40mg od • Trazadone 100mg nocte • Tolteridine MR 4mg nocte • Salbutamol MDI 2 puffs prn
Current Function	
Has been in care home for 12 months. Intermittent behavioural upset . Diet and general personal hygiene improved since been in care home. Shows signs of early dementia and can be difficult to engage depending on mood.	
Most recent consultations	
Nursing staff tell you that they have recently requested salbutamol as they think he has asthma as he's a little breathless. Persistent issues with peripheral oedema.	

Applying the 7 steps

Checks	Medication related risks /problems identified
1. Therapeutic objectives ➢ Existing problems ➢ Prevention	• Manage the breathlessness • Manage heart failure (HF) • Manage use of preventative treatments • Minimise medication related harm • Help patient quit smoking
2. Essential drugs ➢ Essential replacement function ➢ Preventing rapid deterioration	• None for essential drug • The drugs for symptomatic deterioration of HF need to be titrated for optimal benefit
3. (Continued) need for drugs ➢ Temporary indications ➢ Maintenance doses ➢ Limited benefit in general ➢ Limited benefit in this patient	• Review need for on-going PPI : If still needed - aim for dose reduction (maintenance dose is 15mg/day) • Patient examined and breathlessness due to HF: Stop salbutamol? • Trial reduced dose of trazadone
4. Therapeutic objectives achieved? ➢ Symptom control ➢ Biochemical/clinical targets ➢ Prevention	• HF symptoms: Titrate all relevant medicines and monitor U&E • Consider options for smoking cessation
5. Safety ➢ Drug-disease interactions ➢ Drug-drug interactions ➢ Monitoring robust? ➢ ADRs	• Drug-drug interaction: Simvastatin and amlodipine - reduce dose of amlodipine as ACE dose is titrated up • Possible drug-drug interaction with clopidrogel and lansoprazole
6. Cost-effectiveness	• Opportunities for cost minimisation (e.g. generic substitution) should be explored
7. Risks to patient-adherence ➢ Convenient form/dosing schedule? ➢ Technical/cognitive ability? ➢ Continuity of care/CMS beneficial? ➢ Aligned with patient preferences?	• May need support with inhaler and inhaler technique if continuing treatment
KEY CONCEPTS IN THIS CASE: 1. Low number of conditions and medications but still high potential for drug related issues 2. On-going review of medicines needed for those for symptomatic relief for heart failure	

3. Hot topics: Further background reading

3.1 Anticholinergics

Why are anticholinergics problematic?

Anticholinergics have long been linked to impaired cognition and falls risk, but (more recently) have also been linked to increased morbidity and mortality. Anticholinergics may also be a cause of constipation and urinary retention. The table below shows that anticholinergic effects are dose dependent (adapted from reference[26]). Of note is, however, that there is significant inter-individual variability regarding anticholinergic dose and manifestations of signs and symptoms of toxicity.

Table 4a: Anticholinergic effects

Atropine dose equivalent	Digestive tract	Urinary tract	Skin	Eyes	Cardiovascular	CNS
10 mg			Red, hot, dry	+++Mydriasis +++Blurred vision	+++ Tachycardia Fast and weak pulse	Ataxia Agitation Delirium Hallucinations Delusions Coma
5 mg	Decreased gut motility	Urinary retention	Hot and dry	++Mydriasis	++ Tachycardia	Restlessness Fatigue Headache
2 mg	++ Mouth dryness			+Mydriasis Blurred vision	+ Tachycardia Palpitations	
1 mg	+ Mouth dryness Thirst			Mydriasis	Tachycardia	
0.5 mg	Mouth dryness		Anhidrosis			

Drugs with anticholinergic properties continue to be commonly prescribed to older people and those with mental illness, who are particularly susceptible to adverse effects, even at therapeutic doses. A recent study in NHS Tayside[26] found that use of anticholinergics among older patients had increased to 24% in 2010, with 7% being classified as carrying a high anticholinergic drug burden.

How to assess and reduce the anticholinergic burden

Not all drugs with anticholinergic properties may individually put patients at risk of severe adverse effects. However, a wide range of commonly used drugs have anticholinergic properties and their effects may accumulate. A scale or table that lists the anticholinergic activity of commonly prescribed drugs can guide clinical decision-making to limit anticholinergic load. One such tool is the Anticholinergic Risk Scale (ARS), which was developed using 500 most prescribed medications.[27] They ranked medication with anticholinergic potential on a scale of 0–3 (0. limited or none; 1. moderate; 2. strong; 3. very strong potential) based on information available on the dissociation constant for

[26] Sumukadas D, McMurdo MET, Mangoni AA, Guthrie B. Temporal trends in anticholinergic medication prescription in older people: repeated cross-sectional analysis of population prescribing data. *Age and Ageing* 2014 July 1, 2014;43(4):515-21.

[27] Rudolph JL SM, Angelini MC, McGlinchey RE The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Arch Intern Med* 2008;168:508-13.

the muscarinic receptor and rates of anticholinergic adverse effects, i.e. based on in vitro data which may not always reflect in vivo effects.[28] The scale may not always reflect *in vivo* actions however. The ARS has since been modified (subsequently referred to as mARS) to include newer medications with anticholinergic properties that are available in the United Kingdom (see table overleaf).[28] Medications with moderate to severe anticholinergic effects according to other scales (Anticholinergic Burden Scale[29] and Anticholinergic Drug Scale[30]) were added to the list. Medications identified as having significant anticholinergic properties in the BNF were also included and medications not available in the UK were excluded. The table overleaf also lists therapeutic alternatives with no or minimal anticholinergic effects.

Table 4B: Modified Anticholinergic Risk Scale (mARS)[28]

mARS category 3	mARS category 2	mARS category 1	Guidance
Antidepressants			
Amitriptyline Imipramine	Desipramine Trimepramine Nortriptyline Clomipramine Sertraline	Trazodone Mirtazapine Paroxetine Lofepramine	Venlafaxine, duloxetine, bupropion and trazadone have low-to-nil systemic anticholinergic activity
Antipsychotics			
Thioridazine Fluphenazine Perphenazine Chlorphenamine Chlorpromazine Promethazine Trifluorperazine	Clozapine Doxepine Olanzapine Levomepromazine Pericyazine	Quetiapine Risperidone Haloperidol	Avoid phenothiazines Among atypical antipsychotics, aripiprazole and ziprasidone are the least anticholinergic
Nausea and vertigo			
	Prochlorperazine	Metoclopramide	Domperidone (antiemetic) does not penetrate CNS
Urinary antispasmodics			
Oxybutynin	Fesoterodine Flavoxate Darifenacin Trospium Dosulepin Solifenacin Tolterodine		
Sedatives			
Clemastine Hydroxyzine Cyproheptadine			Avoid antihistamine sedatives

[28] Sumukadas D, McMurdo MET, Mangoni AA, Guthrie B. Temporal trends in anticholinergic medication prescription in older people: repeated cross-sectional analysis of population prescribing data. *Age and Ageing* 2014 July 1, 2014;43(4):515-21.

[29] Boustani MA CN, Munger S, Fox C. Impact of anticholinergics on the aging brain: a review and practical application. Aging Health 2008;4:311-20.

[30] Carnahan RM LB, Perry PJ, Pollock BG, Culp KR. The anticholinergic drug scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. *J Clin Pharmacol 2006*;46:1481-6

Antiallergics			
	Cetirizine Loratadine		Desloratadine may be an alternative
H2 blockers			
	Cimetidine	Ranitidine	PPIs may be an alternative
Antiparkinson			
Procyclidine Benzatropine	Amantadine	Levodopa/Carbidopa Selegeline Entacapone Pramipexole	
Others			
Atropine Dicyclomine Orphenadrine Tizanidine	Loperamide Tiotropium Pseudoephedrine Baclofen Propiverine	Methocarbamol Reboxetine	

3.2 Medication & The Risk of Falls in the Older Person

Reproduced from BHPS at [this link]

This classification has been based upon a review of the clinical evidence of medicines implicated in falls and from an analysis of the most commonly used drugs with side effect profiles associated with an increase in falls risk. The list is not meant to be fully comprehensive but intended to raise awareness of the types of drugs that can contribute to falls. Drugs have been graded as either a high, moderate or low risk in terms of their 'potential to cause falls'.

Highest risk	Guidance
Antidepressants	Avoid tricyclic antidepressants especially with high anti-muscarinic activity e.g. amitriptyline. SSRIs are associated with a reduced incidence of side effects in the elderly. Trial of gradual withdrawal should be attempted for all anti-depressants after 6 –12 months of initial treatment
Antipsychotics including atypicals	Risk of hypotension is a dose related effect reduced by the 'start low go slow approach.' Atypical antipsychotics are associated with a similar falls risk than traditional ones. Attempted withdrawal **MUST** always be gradual to avoid precipitation of withdrawal symptoms e.g. rebound agitation, etc. The phenothiazine prochlorperazine (Stemetil) is frequently inappropriately prescribed for dizziness due to postural instability and the most frequently implicated drug causing drug induced Parkinson's disease
Anti-muscarinic drugs (Anticholinergics)	Anti-muscarinic drugs are used in treatment of urinary incontinence and in Parkinson's disease. Oxybutynin may cause acute confusional states in the elderly especially those with pre-existing cognitive impairment
Benzodiazepines & Hypnotics	Whilst complete withdrawal may not be an achievable goal there is still benefit to be gained in reducing use to the minimum effective dose. Avoid long acting benzodiazepines e.g. nitrazepam. Newer hypnotics e.g. zopiclone are associated with reduced hangover effects but all licensed for short-term use only
Dopaminergics used in Parkinson's disease	Sudden excessive daytime sleepiness can occur with levodopa and other dopamine receptor agonists. Careful dose titration is particularly important in initiation of treatment because of additional risk of inducing confusion. As the patient ages, maintenance doses may need to be reduced
Moderate risk	
Anti-arrhythmics	Dizziness and drowsiness are possible signs of digoxin toxicity – risks of toxicity are greater in renal impairment or in the presence of hypokalaemia. Flecainide has a high risk for drug interactions and can also cause dizziness
Anti-epileptics	Group with high risk for potential drug interactions. Important side effects include: Dizziness, drowsiness and blurred vision (dose related)
Opiate analgesics	Drowsiness and sedation common with initiation of treatment but tolerance to these side effects is usually seen within 2 weeks of continuous treatment. Drowsiness and sedation is rare with codeine unless concurrently used in combination with other drugs with CNS effects. Confusion also reported with tramadol
Anti-histamines	Somnolence may affect up-to 40% of patients with older antihistamines e.g. chlorpheniramine. The newer anti-histamines e.g. desloratidine cause less sedation and psychomotor impairment. Risk of hypotension with cinnarizine is a

	dose related side effect
Alpha – blockers	Doses used for treatment of BPH less likely to cause hypotension than those required to treat hypertension
ACEI/ARB	Risk of hypotension is potentiated by concomitant diuretic use. Incidence of dizziness varies from 4-12% of patients but affects twice as many patients with heart failure than hypertension
Diuretics	Postural hypotension, dizziness and nocturia are the most frequent problems seen in the elderly. Diuretics should **not** be prescribed for long-term use in the treatment of gravitational oedema
Beta-blockers	Reports of dizziness may be due to postural hypotension and can affect up to 10% of patients. Water-soluble beta-blockers can accumulate in renal impairment and therefore dose reduction is often necessary
Lower risk	
CCBs	Incidence dizziness low especially for once daily dihydropyridine calcium channel blockers e.g. felodipine
Nitrates	Dizziness may be due to postural hypotension. Advise patient to sit when using GTN spray or tablets
Oral anti-diabetic drugs	Dizziness due to hypoglycaemia, but usually avoidable. Avoid long acting sulphonylureas e.g. chlorpropamide.
PPIs & H2 Antagonists	Avoid cimetidine in polypharmacy patients – high risk of potential drug interactions. Cimetidine also associated with causing confusion in the elderly. Reports of dizziness, somnolence are uncommon and mental confusion or blurred vision rare with the other PPIs and H2 antagonists

3.3 Stopping antipsychotics in patients with dementia

Reproduced from QI Hub at this link

Antipsychotic drugs are frequently prescribed with the aim of reducing behavioural and psychological symptoms of dementia (BPSD) in older people. In Scotland in 2007, 17.7% of people with a diagnosis of dementia were prescribed an antipsychotic, compared to approximately 12% in 2005–2007 in one US study. Despite this high rate of use, antipsychotics have only limited benefit in treating BPSD in older people with dementia and carry significant risk of harm. In 2009, antipsychotics were estimated to cause approximately 1800 deaths and 1620 cerebrovascular events in people with dementia in the UK annually. However, clinical trial evidence in nursing home patients with dementia indicates that chronically prescribed antipsychotic drugs can be safely discontinued in most patients, with longer term follow-up suggesting a significant reduction in mortality.

Which patients should be prioritised for review?
Patients who have dementia and who have been on antipsychotics for more than 3 months and have stable symptoms should be reviewed with a view to reducing or stopping antipsychotic medication. Antipsychotics are associated with an increased risk of falls, delirium, cerebrovascular events and all-cause death. Priority groups for reducing antipsychotic medication include:

1. People in care homes: the prescription of antipsychotics for BPSD is most common in these people, who are also more frail than other populations
2. People with vascular dementia: the risk of cerebrovascular events associated with antipsychotic medication may be higher in this population
3. People with dementia who also have a history of cardiovascular disease, cerebrovascular disease or vascular risk factors: The risk of cerebrovascular events associated with antipsychotic medication may be higher in this population

When should antipsychotic medication NOT be stopped?
Patients who have a co-morbid mental illness that is treated with antipsychotic medication, such as schizophrenia, persistent delusional disorder, psychotic depression or bipolar affective disorder should not have antipsychotic medication reduced without specialist advice.

How to reduce antipsychotic medication?

1. As with initiation of medication, reduction should be carried out slowly with monitoring of effect. Start with a reduction of 25% of the total daily dose. If the current dose is low, e.g. at the suggested starting dose, the medication may be stopped without tapering the dose
2. Review the effect after one week to assess for: the re-emergence of the initial 'target' symptoms. Discontinuation symptoms such as nausea, vomiting, anorexia, diarrhoea, rhinorrhoea, sweating, myalgia, paraesthesia, insomnia, restlessness, anxiety and agitation. These symptoms are more common with abrupt withdrawal of antipsychotic medication, and generally begin within 1 to 4 days of withdrawal and abate within 7 to 14 days
3. If either of the above occurs the clinician should make an assessment of the risks and benefits of re-instating the previous dose of antipsychotic. Further attempts to reduce the antipsychotic should be made one month later with smaller decrements, for example 10% of the total daily dose
4. If there are no particular problems after week 1 then the dose should remain the same with further review after week 4 (for risperidone and haloperidol) or fortnightly (for Quetiapine).
5. If the reduction has been tolerated without any of the effects described above then reduce by a further 25% and repeat the process
6. There will be practical issues when reducing the dose, for example the availability and form of small doses of medication. It is recommended that this is discussed with a pharmacist
7. It is suggested that once the total daily dose is reduced to the recommended starting dose for the individual antipsychotic, it may be stopped

A best practice guide for optimising treatment and care for behavioural and psychological symptoms of dementia is also available from Alzheimer's Society at this link.

3.4 Stopping benzodiazepines and z-drugs

Reproduced from NICE at this link.

How do I assess someone who wants to stop benzodiazepines or z-drugs?

- **Assess whether this is a suitable time for the person to stop taking the drug (**chances of success are improved when a person's physical and psychological health and personal circumstances are stable)
- **Enquire about:**
  - **Symptoms of depression.** Withdrawing these drugs can worsen symptoms of clinical depression. The priority is to manage depression first, before attempting drug withdrawal
  - **Symptoms of anxiety** Withdrawing treatment when significant symptoms of anxiety are present is likely to make symptoms worse and is therefore unlikely to succeed. However, when symptoms are reasonably well controlled and stable it may be possible to attempt careful drug withdrawal
  - **Symptoms of long-term insomnia.** If insomnia is severe, consider treating this with non-drug treatments prior to starting withdrawal of a benzodiazepine or z-drug
  - **Any medical problems and whether these are well controlled and stable.** If problems are causing significant distress, consider managing these first, prior to starting withdrawal of benzodiazepines or z-drugs
  - **Consider whether the withdrawal of the benzodiazepine or z-drug can be appropriately managed in primary care (i.e. whether they are** willing, committed, and compliant, and have adequate social support, have no previous history of complicated drug withdrawal and are able to attend regular reviews
  - **Consider seeking specialist advice or referral to a specialist centre for people with:** A history of alcohol or other drug use or dependence. Concurrent, severe medical or psychiatric disorder or personality disorder. A history of drug withdrawal seizures — these generally occur in people who suddenly stop high doses of the drugs. Slow tapering is recommended for these individuals

How do I manage someone who wants to stop benzodiazepines or z-drugs?

- **Decide if the person can stop their current benzodiazepine or z-drug without changing to diazepam**
- **Switching to diazepam** is recommended for:
- People using the short-acting potent benzodiazepines (that is, alprazolam and lorazepam)
- People using preparations that do not easily allow for small reductions in dose (that is alprazolam, flurazepam, loprazolam and lormetazepam)
- People taking temazepam or nitrazepam who choose to withdraw from diazepam after discussing the advantages and disadvantages
- People experiencing difficulty or who are likely to experience difficulty withdrawing directly from temazepam, nitrazepam, or z-drugs, due to a high degree of dependency (associated with long duration of treatment, high doses, and a history of anxiety problems)
- **Seek specialist advice (preferably from a hepatic specialist) before switching to diazepam in people with hepatic dysfunction** as diazepam may accumulate to a toxic level in these individuals. An alternative benzodiazepine without active metabolites (such as oxazepam) may be preferred
- **Negotiate a gradual drug withdrawal schedule (dose tapering) that is flexible. Be guided by the person in making adjustments so that they remain comfortable with the withdrawal**
- Titrate the drug withdrawal according to the severity of withdrawal symptoms
- Drug withdrawal may take 3 months to a year or longer. Some people may be able to withdraw in less time
- **Review frequently, to detect and manage problems early and to provide advice and encouragement during and after the drug withdrawal**
- **If they did not succeed on their first attempt, encourage the person to try again**

- Remind the person that reducing benzodiazepine dosage, even if this falls short of complete drug withdrawal, can still be beneficial
- If another attempt is considered, reassess the person first, and treat any underlying problems (such as depression) before trying again

How should I withdraw a benzodiazepine or a z-drug?

- **Withdrawal should be gradual** (dose tapering, such as 5–10% reduction every 1–2 weeks, or an eighth of the dose fortnightly, with a slower reduction at lower doses), and titrated according to the severity of withdrawal symptoms
- This may take 3–4 months to a year or longer. Some people may be able to withdraw in less time
- For advice on withdrawal, see Advice
- **Withdrawal may be undertaken with or without switching to diazepam.**
- See Additional information for examples of withdrawal schedules. These should be tailored to meet individual needs
- For more information on withdrawal schedules for other benzodiazepines and z-drugs, see the Ashton Manual (available online at www.benzo.org.uk)

Managing withdrawal symptoms

- How should I manage withdrawal symptoms?
- **Review frequently** to detect and manage problems early, and to provide encouragement and reassurance during and after drug withdrawal
- **Manage anxiety:** Explain that anxiety is the most common acute withdrawal symptom
- Reassure that anxiety is likely to be temporary. Consider slowing or suspending withdrawal until symptoms become manageable. Consider additional use of non-drug treatments
- **Adjunct drug therapy should not be routinely prescribed** but may be considered: Propranolol: for severe, physical symptoms of anxiety (such as palpitations, tremor, and sweating) *only* if other measures fail
- Antidepressants: *only* if depression or panic disorder coexist or emerge during drug withdrawal.
- Do *not* prescribe antipsychotics which may aggravate withdrawal symptoms
- Seek specialist advice if symptoms are severe or difficult to manage
- **Manage depression**
- If depression emerges or coexists with withdrawal symptoms:
- Consider suspending drug withdrawal until the depression resolves
- See the CKS topic on Depression for further information on the management of depression
- **Manage insomnia**

What should I advise people undergoing withdrawal?

- Advise that drug withdrawal should be gradual to minimize the risk of withdrawal effects
- Offer reassurance that the person will be in control of the drug withdrawal and that they can proceed at a rate that suits them. Drug withdrawal may take 3 months to a year or longer if necessary. Some people may be able to withdraw in less time
- If the person reaches a difficult point in the drug withdrawal schedule, maintain the current dose for a few weeks if necessary. Try to avoid going backwards and increasing the dosage again if possible
- Avoid taking extra tablets in times of stress
- Avoid compensating for benzodiazepines or z-drugs by increasing the intake of alcohol or other drugs (prescription, non-prescription, or illicit drugs) or smoking
- Stopping the last few milligrams is often seen as being particularly difficult
- Reassure the person that this is usually an unfounded fear derived from long-term psychological dependence on benzodiazepines
- Warn the person not to be tempted to prolong the drug withdrawal to an extremely slow rate towards the end (such as reducing by 0.25 mg diazepam each month). Advise the person to consider stopping completely when they reach an appropriate low dose (such as diazepam 1 mg daily)

- Give information on withdrawal symptoms
- With slow tapering, many people experience few or no withdrawal symptoms
- If withdrawal symptoms are present with slow tapering, some users will have lost all their symptoms by the end of the drug withdrawal schedule. For most people, symptoms will disappear within a few months
- Only a very small number of people will suffer from protracted withdrawal symptoms which will gradually improve over a year or longer
- Inform the person that nearly all the acute symptoms of withdrawal are those of anxiety
- Explain that some of the withdrawal symptoms may be similar to the original complaint and do not indicate a return of this
- It is not possible to estimate the severity and duration of withdrawal symptoms as these will depend on a number of factors (such as severity of dependence and speed of withdrawal)
- For information on managing withdrawal symptoms, see Managing withdrawal symptoms

What if someone does not want to stop taking benzodiazepines or z-drugs?

- **Do not pressurize the person to stop if they are not motivated to do so**
- **Listen to the person, and address any concerns they have about stopping**
- Explain that for most people who withdraw from treatment slowly, symptoms are mild and can usually be effectively managed by other means
- Reassure the person that they will be in control of the drug withdrawal and that they can proceed at a suitable rate
- **Discuss the benefits of stopping the drug.** The discussion should include an explanation of tolerance, adverse effects, and the risks of continuing the drug. See Reasons for stopping for further information
- **Review at a later date** if appropriate, and reassess the person's motivation to stop
- **In people who remain concerned** about stopping treatment despite explanation and reassurance, persuading them to try a small reduction in dose may help them realize that their concerns are unfounded

3.5 Management of constipation

Reproduced from NICE at this link.

What drugs commonly cause constipation in adults?

- Many drugs are constipating. The most common are:
- Aluminium antacids
- Antimuscarinics (such as procyclidine, oxybutynin)
- Antidepressants (most commonly tricyclic antidepressants, but others may cause constipation in some individuals)
- Some antiepileptics (for example carbamazepine, gabapentin, oxcarbazepine, pregabalin, phenytoin)
- Sedating antihistamines
- Antipsychotics
- Antispasmodics (such as dicycloverine, hyoscine)
- Calcium supplements
- Diuretics
- Iron supplements
- Opioids
- Verapamil

How should chronic constipation be treated in adults?

- Begin by relieving faecal loading/impaction, if present
- Set realistic expectations for the results of treatment of chronic constipation
- Advise people about lifestyle measures — increasing dietary fibre (including the importance of regular meals), drinking an adequate fluid intake, and exercise
- Adjust any constipating medication, if possible

Laxatives are recommended:

- If lifestyle measures are insufficient, or whilst waiting for them to take effect
- For people taking a constipating drug that cannot be stopped
- For people with other secondary causes of constipation
- As 'rescue' medicines for episodes of faecal loading

If laxative treatment is indicated:

- Start treatment with a bulk-forming laxative
- It is important to maintain good hydration when taking bulk-forming laxatives. This may be difficult in the elderly
- If stools remain hard, add or switch to an osmotic laxative (use macrogols as first choice of an osmotic laxative and lactulose if macrogols are not effective, or not tolerated)
- If stools are soft but the person still finds them difficult to pass or complains of inadequate emptying, add a stimulant laxative
- Adjust the dose, choice, and combination of laxative according to symptoms, speed with which relief is required, response to treatment, and individual preference
- The dose of laxative should be gradually titrated upwards (or downwards) to produce one or two soft, formed stools per day
- If at least two laxatives (from different classes) have been tried at the highest tolerated recommended doses for at least 6 months, consider the use of 5-HT_4-receptor agonist or guanylate cyclase-C receptor agonist as per their recommended place in therapy
- Before prescribing, ensure National Institute for Health and Care Excellence criteria are fulfilled

If the person has opioid-induced constipation:

- Advise them to increase the intake of fluid and fruit and vegetables if necessary
- Avoid bulk-forming laxatives
- Use an osmotic laxative and a stimulant laxative
- Adjust the laxative dose to optimize the response
- More information on the pros and cons of the various laxatives, is available here

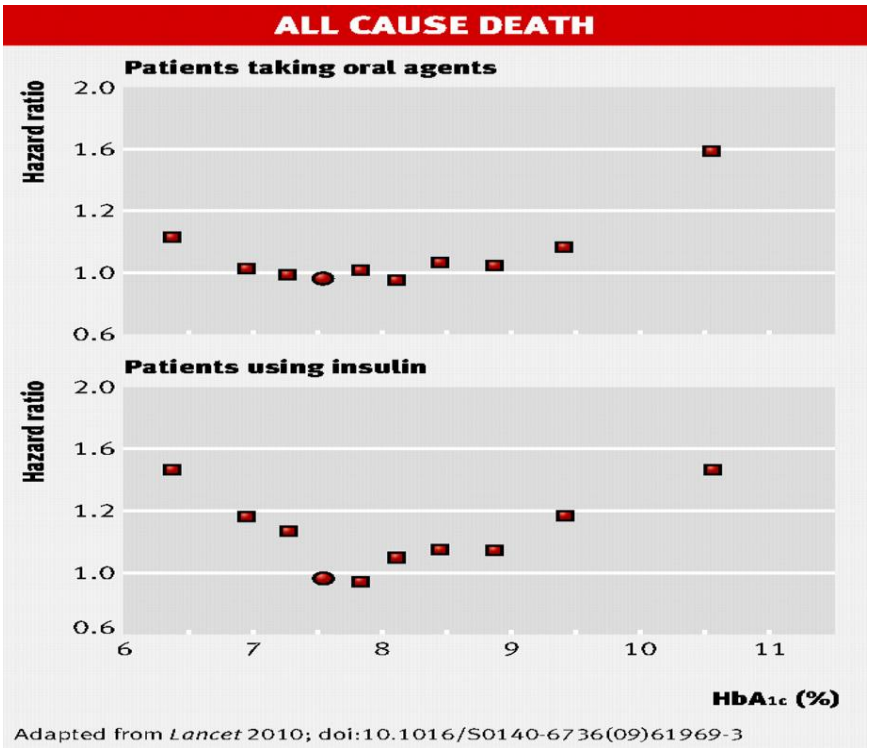
3.6 Management of blood glucose control- effects of intensifying control

Reproduced from QI hub at this link.

See this link for diabetes prescribing strategy

What is the optimal level of blood glucose control?

Intensive blood glucose control can have benefits in reducing microvascular events, but four key randomised controlled trials (UKPDS 33, ACCORD, ADVANCE and VAT) also show that this is at the cost of increases in hypoglycaemia (increase 42 events per 1000 treated patients over 4.4 years (CI 25.8-61.7)). The figure below shows that an HbA1c level of 7.5% is associated with lowest all-cause mortality. In nearly 48,000 primary care patients who had stepped up their hypoglycaemic treatment, risk of death rose significantly on both sides of the reference group achieving this reference level. The patient subgroup with the lowest HbA1c levels (median HbA1c of 6.4%) had a 1.52 (1.32 to 1.76) fold increased risk of death and the patient subgroup with the highest HbA1c levels (median 10.5%) had a 1.79 (1.56 to 2.06) –fold increased risk of death.



What are the implications for clinical practice?

The observational nature of the above cited study implies that causes of death other than hypoglycaemia may not have been completely controlled for. However, older people were identified as being at greatest risk. These results are of particular concern for the frailer groups of patients, who given the long lead time to obtain any supposed benefits from low HbA1c, may nonetheless suffer adverse outcomes. In addition, patients who suffer from hypoglycaemia are at increased risk of falls. [Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study *The Lancet*, 2010 Volume 375, Issue 9713, Pages 481-489C. Currie, et al.]

Appendix A: General Medication Review leaflet

The below patient information leaflet is available for download from this link, created by NHS Highland.

MEDICINES REVIEW: IMPORTANT INFORMATION FOR PATIENTS AND CARERS

NHS Highland

Introduction

A medicines review is a meeting with your doctor, pharmacist or nurse to talk about your medicines.

Your medicines should be reviewed regularly (usually once a year) to check that they are right for you.

Why are medicines reviews needed?

When you are first prescribed a medicine, your doctor, pharmacist and/or nurse checks that it is the best medicine for you. However, things can change, for example:

- You might have developed a side effect from the medicine.
- Your health might have changed, such as developing a long-term condition.
- You might have started taking other additional medicines.
- The guidelines for treating your condition might have changed.
- You may be taking a large number of medications (known as "polypharmacy").
- A medication you are on may be no longer essential for your health day to day.

All of these factors can affect whether a medicine remains the best choice for you.

What is "polypharmacy"?

You might have heard your doctor, pharmacist or nurse talk about "polypharmacy". Polypharmacy just means "lots of pharmacy" or, in other words, taking a large number of medicines.

Medicines reviews are particularly useful for people who take lots of medicines so they are sometimes called "polypharmacy reviews".

What happens at a medicines review?

You will be asked to make an appointment with your doctor, pharmacist or nurse for a medicines review. The review will take between 10 and 30 minutes.

The review will involve the doctor/pharmacist/nurse gathering information from you and from your medical record. This information will be used to check that you are taking the most appropriate medicines.

You will also be able to ask any questions or raise any concerns you have about your medicines.

It might be necessary for the doctor/pharmacist/nurse to recommend some changes to your medicines. The reasons for these changes will be explained to you and you will be asked for your agreement before any changes are made.

What changes to my medicines might be recommended?

Some common changes your doctor/pharmacist/nurse might recommend to your medicines are:

- A medicine may be changed to a form that is easier to take (eg, once a day rather than three times a day).
- A medicine may be started or changed to a newer version.
- A medicine may be stopped.

Do I need to take anything to my medicines review?

It would be very useful if you could bring all of your medicines with you, including any you have bought in a pharmacy or shop. If you buy vitamins or herbal or homoeopathic remedies, please bring them too.

Medicines often have two names (a generic name and a brand name) so having the medicines with you will prevent any confusion if the doctor/pharmacist/nurse calls the medicine by a different name to the name you normally use.

What questions will I be asked at my medicines review?

At the medicines review, you will be asked about how you are getting on with your medicines. Some of the questions you might be asked at your medicines review include:

- Are you taking all of your medicines?
- Are there any you miss out or forget to take?
- Can you take/use the medicine properly?
- Do you feel you are having any side effects from your medicines?
- Do you have any concerns about your medicines?
- Do you take any other medicines, such as those bought in a pharmacy or supermarket?

Where can I get more information?

For further information about your medicines, please contact:

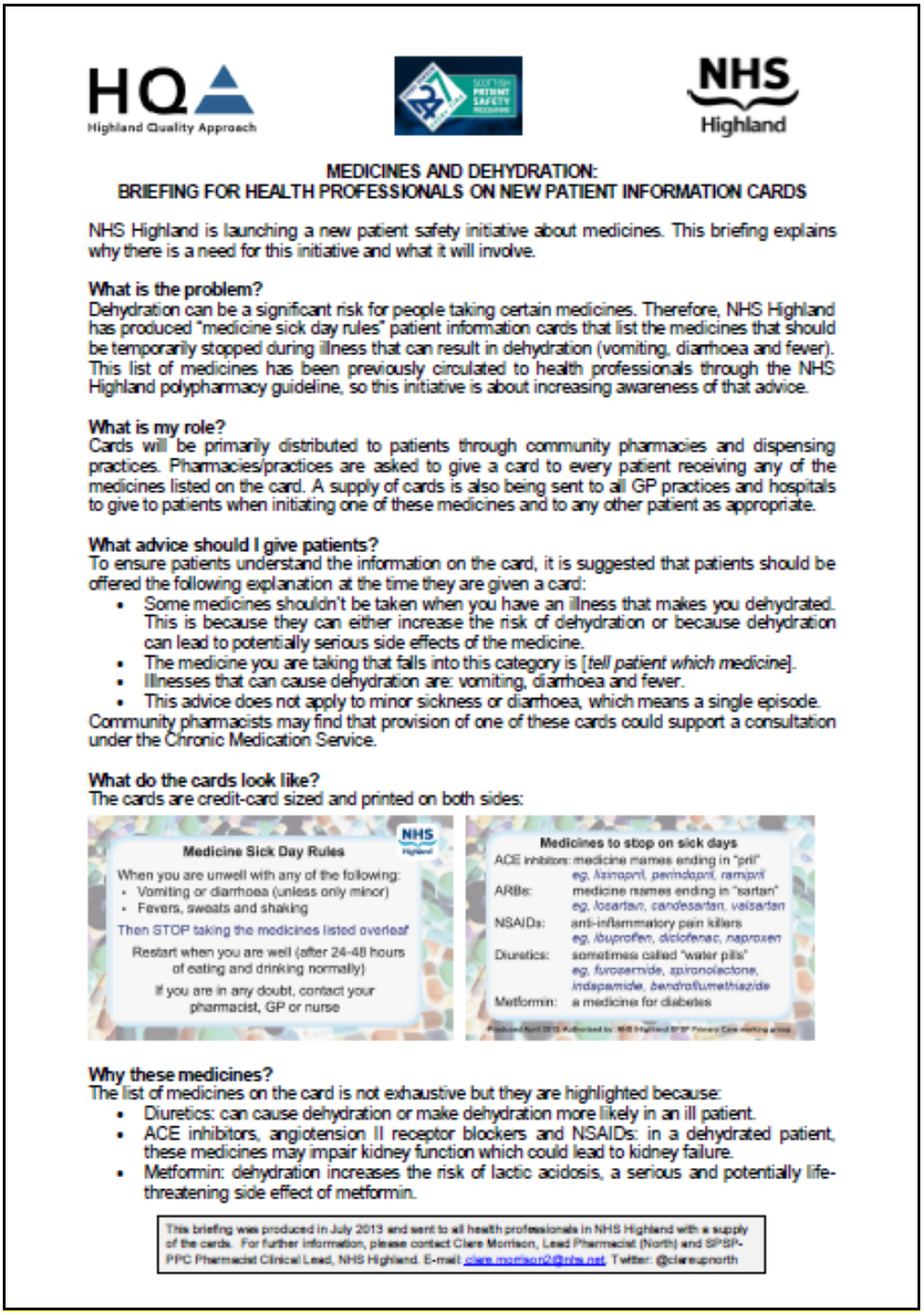
- Your medical practice.
- Your community pharmacy.
- NHS24 (www.nhs24.com or phone: 08454 24 24 24).

Produced by the NHS Highland Polypharmacy Action Group. First produced July 2010. Updated April 2013. To be reviewed April 2015.

Appendix B: Sick Day Rules: Information for healthcare professionals and patients

The following guidance documents for health professionals and patients are available for download, created by NHS Highland.

Health Professionals Guidance (below) is available at this link



HQA Highland Quality Approach

NHS Highland

MEDICINES AND DEHYDRATION:
BRIEFING FOR HEALTH PROFESSIONALS ON NEW PATIENT INFORMATION CARDS

NHS Highland is launching a new patient safety initiative about medicines. This briefing explains why there is a need for this initiative and what it will involve.

What is the problem?
Dehydration can be a significant risk for people taking certain medicines. Therefore, NHS Highland has produced "medicine sick day rules" patient information cards that list the medicines that should be temporarily stopped during illness that can result in dehydration (vomiting, diarrhoea and fever). This list of medicines has been previously circulated to health professionals through the NHS Highland polypharmacy guideline, so this initiative is about increasing awareness of that advice.

What is my role?
Cards will be primarily distributed to patients through community pharmacies and dispensing practices. Pharmacies/practices are asked to give a card to every patient receiving any of the medicines listed on the card. A supply of cards is also being sent to all GP practices and hospitals to give to patients when initiating one of these medicines and to any other patient as appropriate.

What advice should I give patients?
To ensure patients understand the information on the card, it is suggested that patients should be offered the following explanation at the time they are given a card:

- Some medicines shouldn't be taken when you have an illness that makes you dehydrated. This is because they can either increase the risk of dehydration or because dehydration can lead to potentially serious side effects of the medicine.
- The medicine you are taking that falls into this category is [*tell patient which medicine*].
- Illnesses that can cause dehydration are: vomiting, diarrhoea and fever.
- This advice does not apply to minor sickness or diarrhoea, which means a single episode.

Community pharmacists may find that provision of one of these cards could support a consultation under the Chronic Medication Service.

What do the cards look like?
The cards are credit-card sized and printed on both sides:

Why these medicines?
The list of medicines on the card is not exhaustive but they are highlighted because:

- Diuretics: can cause dehydration or make dehydration more likely in an ill patient.
- ACE inhibitors, angiotension II receptor blockers and NSAIDs: in a dehydrated patient, these medicines may impair kidney function which could lead to kidney failure.
- Metformin: dehydration increases the risk of lactic acidosis, a serious and potentially life-threatening side effect of metformin.

This briefing was produced in July 2013 and sent to all health professionals in NHS Highland with a supply of the cards. For further information, please contact Clare Morrison, Lead Pharmacist (North) and SPSP-PPC Pharmacist Clinical Lead, NHS Highland. E-mail: clare.morrison2@nhs.net. Twitter: @clareupnorth

Patient guidance (below) is available at this link

MEDICINES AND DEHYDRATION: PATIENT INFORMATION

NHS Highland

This leaflet is about what actions to take if you develop an illness that causes dehydration. These actions are called "medicine sick day rules".

Who is this leaflet for?

This leaflet is for people who take the following long-term medicines. Your pharmacist, doctor or nurse can tick/highlight your medicine(s) on this list:

- ☐ ACE inhibitors: a medicine for high blood pressure and heart conditions
  Examples: names ending in "pril" such as lisinopril, perindopril, ramipril
- ☐ ARBs: a medicine for high blood pressure and heart conditions
  Examples: names ending in "sartan" such as losartan, candesartan, valsartan
- ☐ NSAIDs: anti-inflammatory pain killers
  Examples: ibuprofen, naproxen, diclofenac
- ☐ Diuretics: sometimes called "water pills" for excess fluid and high blood pressure
  Examples: furosemide, bendroflumethiazide, indapamide, spironolactone
- ☐ Metformin: a medicine for diabetes

Which illnesses cause dehydration?

Dehydration is the loss of fluid from your body. Vomiting, diarrhoea and fever (high temperature, sweats, shaking) can make you dehydrated. If you are sick once or have diarrhoea once, then you are unlikely to become dehydrated. Having two or more episodes of vomiting or diarrhoea can lead to dehydration: in these cases, you should follow the advice on this leaflet.

What is the problem?

Taking certain medicines when you are dehydrated can result in you developing a more serious illness. These are:

- ACE inhibitors, ARBs and NSAIDs: if you are dehydrated, these medicines can stop your kidneys working properly.
- Diuretics: these medicines can make dehydration more likely.
- Metformin: dehydration can make it more likely that you will develop a serious side effect called lactic acidosis.

What actions should I take?

If you develop a dehydrating illness, you should temporarily stop taking the medicines listed above. It is very important that you re-start your medicine(s) once you have recovered from the illness. This would normally be after 24 to 48 hours of eating and drinking normally. When you re-start your medicines, just take them as normal: do not take extra for the doses you have missed.

Reminder cards

The medicine sick day rules are summarised on a reminder card available from pharmacies, GP practices and hospitals (right).

Need more information?

Please contact your pharmacist, doctor or nurse.

Information leaflet produced by Clare Morrison (Lead Pharmacist, North) and Dr Martin Wilson (Consultant Physician, Raigmore Hospital), NHS Highland. Approved by: NHS Highland Medicines Safety Subgroup. Date produced: January 2015. To be reviewed: January 2017.

Appendix C: NNT and the Methodology for NNT used

Inclusion of Number Needed to Treat Data in the Scottish Government Polypharmacy Guidance
Standard Operating Procedure (SOP)

1. Background

The Scottish Government Polypharmacy Guidance 2015 is intended as a practical tool to help prescribers decide when it is appropriate to initiate and continue long-term medicines, especially in the management of long term conditions. In some circumstances, and in consultation with the patient, it may be appropriate to discontinue treatments. Presentation of numbers needed to treat (NNT) for a range of medicines is one tool that prescribers may use to aid discussions with patients about the likely benefit.

The NNT is defined as the expected number of people who need to receive the experimental rather than the comparator intervention for one additional person to either incur or avoid an event in a given time frame. An NNT of 10 can be interpreted that one additional (or less) person will incur an event for every 10 participants receiving the experimental intervention rather than control over a given time frame.

2. Scope

This SOP is intended to describe the roles of the Association of Scottish Medicines Information Pharmacists (ASMIP) in the development and maintenance of the NNTs and to describe a systematic approach to their calculation.

3. Defining NNTs

3.1 Defining the medicine/ intervention and the clinical outcome of relevance

The medicines used in the first edition of the Scottish Government Polypharmacy Guidance 2012 should be included. These will be reviewed to ensure that they are both specific and measurable. Consideration also needs to be given to their relevance to clinical practice, e.g. is the medicine likely to be used in this clinical context and is the comparator described the most relevant to clinical practice?

3.2 Identifying relevant medical literature

The following principles should be applied:

- Cochrane reviews where available should be used
- Systematic reviews should generally be used in preference to individual randomised controlled clinical trials (RCT), unless the RCT includes a greater number of patients than a corresponding systematic review
- Where systematic reviews are not available individual randomised controlled trials may be used

The MI pharmacist should carry out a standard Medline® or Embase® search using relevant Medical Subject Heading (MeSH) terms and Boolean operators. In particular the following should be identified:

- Cochrane systematic reviews
- Other high quality systematic reviews
- Pivotal trials for the medicine in the relevant indication

Ideally studies should be identified from the previous five years, but in exceptional circumstances, e.g. where only a single pivotal trial has been published, or no newer systematic reviews have been published, older clinical trials or systematic reviews may be used.

3.3 Dealing with multiple trials/ meta-analyses

Where more than one review or trial is identified for the relevant indication and intervention the following criteria should be assessed:

- Relevance to the defined medicine/ intervention
- Size of the study or review
- Similarity of review/ study cohort to the Scottish population

A judgement can then be made, using the criteria above to identify the most relevant trial or review from which the NNT can be calculated. Where the studies are very similar, the NNT should be calculated for each individual study and the mean taken for inclusion in the table.

4. Calculating NNTs

The NNT can be calculated from the absolute risk reduction (ARR) taken from a clinical trial or systematic review. ARR = p_1- p_2 , where p_1 is the baseline or placebo rate and p_2 is response rate in the intervention group in a clinical trial. The NNT can be calculated as 1/ (p_1-p_2).[31] Where the benefit is accrued over a number of years, the annual NNT can be calculated by dividing the NNT by the number of years over which the study was conducted.

5. Recording research

The MiDatabank® project management function should be used to record all research. The following information should be recorded:

- The literature search
- Trials/ reviews identified
- Absolute risk reduction figures taken from the study(ies)
- The calculation used to define the NNT

6. Presenting the of NNT data

All NNT data should be tabulated to include the following:

- Intervention - the medicine or other intervention of interest
- The comparator
- Outcome - the desired outcome from the proposed treatment
- NNT - calculated using standard methodology
- Duration of study/ intervention
- Demographics of population - age, sex (where relevant), co-morbidities
- Reference - main reference used to calculate the NNT

7. Referencing

Vancouver style should be used to reference all trials/ reviews used in the calculation of NNTs. Where data has been taken from websites, the web address and the date accessed should be recorded.

8. Checking/ Peer Review

A peer check should be undertaken by another MI or clinical pharmacist prior to publication. The check should include:

- Clarity and completeness
- Any obvious gaps in the information concerning the patient demographics
- A calculation check for the NNT

[31] Hutton JL. Number needed to treat and number needed to harm are not the best way to report and assess the results of randomised clinical trials. Br J Haematol 2009;146

Appendix D: Health Economics Analysis of Polypharmacy reviews

Expected health economic impacts 2015

Polypharmacy reviews can be expected to deliver long-term direct and indirect economic benefits. A direct reduction in the cost of medicines prescribed, and reduction in the waste of medicines is anticipated. In terms of indirect economic benefits, a patient stabilised on fewer medicines will potentially require less contact with health professionals, thereby freeing up healthcare capacity. Of prime aim is the indirect economic benefit of fewer unscheduled hospital admissions due to adverse drug reactions.

Scottish SPARRA population groups

Table 5a below summarises the number of patients in the key target group of 75 years and older, in Scotland, receiving medicines from 10 or more BNF sections, and at risk levels of between 40% and 60%, as identified by the Scottish Patients at Risk of Readmission and Admission (SPARRA) database. Additionally, the number of patients aged 50 years and older in a care home at any risk level and any number of BNF sections is also given. The overall total for these two groups is 64,729 (accounting for some overlap across the two groups).

Table 5a: Target SPARRA[1] population							
Number of patients			Age 75+				Age 50+
SPARRA risk score	BNF sections[2]	**Total**	with high risk medicines[3]	in a care home[4]	with high risk medicines and in a care home	with dementia[5]	in a care home, any risk, any BNF[4]
40%-60%	10+BNF	**40,585**	39,593	6,861	6,621	6,898	30,765

[1] SPARRA Version 3 estimates the risk of emergency admission in the next 12 months for approximately 3.6m individuals aged 16 years and older. For the September 2014 release, this is the risk of emergency admission in the period 1st September 2014 to 31st August 2015

[2] The number of different BNF sections from which a patient's drugs were prescribed and dispensed. SPARRA Version 3 uses the most recent 12 months prescribing data available prior to the start of the risk year.

[3] Defined as medications in any of the following BNF Sections: 2.1, 2.2, 2.4, 2.5, 2.8, 2.9, 4.1, 4.2, 4.3 and 10.1

[4] Identified by a CHI institution code of 93 or 98

[5] Evidence of dementia has been determined either by prescribing history (dispensed items within BNF Section 4.11) or previous admission to hospital where diagnosis at discharge includes ICD10 codes (F00-F03, F051); and ICD9 codes (2900, 2901, 2902, 2904, 2908, 2909).

Cost avoidance – number of drugs stopped

Table 5b below takes these population figures and estimates potential direct savings from stopping drugs. If one prescribed medication, with an average 6 repeats, and with **average unit cost of £9.87** (BNF 2013/14) was stopped for one year, this would equate to about £2.4m avoided cost in the 75+ group. Adding those aged 50+ in care homes to the reviews would give a total of about £3.8m. Stopping two drugs with 6 repeats would double these estimates to £4.8m and £7.7m respectively

These estimates are consistent with the mid-range of estimates of savings from polypharmacy reviews in Craig, J (2013). Here, estimates based on surveys of individual health board experiences ranged from £66 per annum (value of medicine taking ceased), to £155 per annum (made up of: £90 achieved from change in medication; £22 from switching to more cost effective compounds and £43 from cost avoidance measures associated with duplicate prescriptions).

Table 5b: Cost avoidance from stopping repeat medication									
Cost avoidance £m				Age 75+					Age 50+
assumed number of items stopped once	assumed number of repeats stopped per item per year	SPARRA[1] risk score	BNF sections[2]	**Total**	with high risk medicines[3]	in a care home[4]	with high risk medicines and in a care home	with dementia[5]	in a care home, any risk, any BNF[4]
1	6	40%-60%	10+BNF	**£2.4**	£2.3	£0.4	£0.4	£0.4	£1.8
2	6	40%-60%	10+BNF	**£4.8**	£4.7	£0.8	£0.8	£0.8	£3.6

[1] SPARRA Version 3 estimates the risk of emergency admission in the next 12 months for approximately 3.6m individuals aged 16 years and older. For the September 2014 release, this is the risk of emergency admission in the period 1st September 2014 to 31st August 2015

[2] The number of different BNF sections from which a patient's drugs were prescribed and dispensed. SPARRA Version 3 uses the most recent 12 months prescribing data available prior to the start of the risk year.

[3] Defined as medications in any of the following BNF Sections: 2.1, 2.2, 2.4, 2.5, 2.8, 2.9, 4.1, 4.2, 4.3 and 10.1

[4] Identified by a CHI institution code of 93 or 98

[5] Evidence of dementia has been determined either by prescribing history (dispensed items within BNF Section 4.11) or previous admission to hospital where diagnosis at discharge includes ICD10 codes (F00-F03, F051); and ICD9 codes (2900, 2901, 2902, 2904, 2908, 2909).

Table 5c projects these assumptions onto the given SPARRA populations. Overall savings using the base-case of £90 per medication stopped gives savings in the range of £3.7m and £5.8m. For the upper estimate including: medication change; a switching to more cost effective drugs and cost avoidance measures, the range increases to £6.3m and £10.0m.

Table 5c: Range of estimates of savings from polypharmacy reviews			
	Unit cost/saving Scotland	Age 75+, 10+ BNF sections, SPARRA 40%-60%	75+ group plus all care home residents
Number of patients with high risk medicines		40,585	64,729
Cost estimates based on savings per case p.a		£m	£m
1 med stopped; 6 repeats; 1 yr; unit cost £9.87	£9.87	£2.4	£3.8
2 meds stopped; 6 repeats; 1 yr; unit cost £9.87	£9.87	£4.8	£7.7
Lower estimate of value of medicines stopped	£66	£2.7	£4.3
Base-case: change medication only	£90	£3.7	£5.8
Upper estimate: change medication + switching to cost effective + cost avoidance measures	£155	£6.3	£10.0

Indirect impacts – Adverse Drug Reactions

Pirmohamed et al (2004)[32] estimate a prevalence of 6.5% (95% C.I. 6.2% to 6.9%) of admissions judged as being due to an adverse drug reaction (ADR). 80% (78% to 82%) of the ADRs were judged to have been directly responsible for the admission, while 20% (18% to 22%), although not directly responsible for the admission, may nevertheless have contributed to it.

[32] Pirmohamed M et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. BMJ 2004;329:15-19

The study determined avoidability of admissions related to an ADR. Only 28% (25% to 30%) of the ADRs were assessed as unavoidable, while 9% (7% to 10%) were classified as definitely avoidable and 63% (60% to 66%) as possibly avoidable. It was estimated that ADRs were responsible for the death of 0.15% (0.1% to 0.2%) of all the patients admitted and that patients admitted with an ADR had a median stay of 8 days (interquartile range 4-18 days).

These ADR attributable fractions and patient risk scores were estimated[33] to account for around 16,000 hospital admissions, and a median number of bed days of 128,000 in Scotland. Of these, about 1,400 ADRs were estimated to be definitely avoidable, and up to 10,000 possibly avoidable. If these admissions were treated in direct general medicine, the associated estimated cost of bed days would be around £34.3m of which between £3.1m and £21.6m could be avoidable. The drug cost associated with polypharmacy was estimated to be between £33m and £55.4m.

To illustrate the associated cost and welfare loss due to loss of life, the Value of Prevented Fatality (VPF, £1.76m in 2012) was applied to the associated number of deaths, following UK Department for Transport guidance[34] . In Scotland, about 24 fatalities could be attributed to ADRs, with an associated cost of £35.2m, of which £3.8m was definitely and £26.6m possibly avoidable.

Implementation cost

Table 5d provides an overview of estimated activity and associated costs for reviews in Scotland[35]. Total implementation cost will depend on the number of reviews carried out; for the two groups considered here this might be up to £3.4m and £5.4m respectively, not including wider costs such as travel. There could be additional efficiencies to be gained if, e.g. multiple reviews are carried out in one sitting, reducing travel costs, etc.

It should also be stressed that these estimates include the cost of an estimated 15 minutes GP time dedicated to discussion with the patient. This should not create additional costs to the system as that time should also be covered under QOF.

Table 5d: Activity and implementation cost					
Per patient cost of polypharmacy review	Estimated average hours and cost, Scotland			Age 75+, 10+ BNF sections, SPARRA 40%-	75+ group plus all care home
Number of patients with high risk medicines				40,585	64,729
Direct cost					
Activity	Staff involved	Total hours allocated	Cost per review	£m	£m
Patient review	Clinical	1.00	£29	£1.2	£1.9
Discussion between pharmacist and GP	Clinical	0.25	£7	£0.3	£0.5
	GP	0.25	£15	£0.6	£1.0
GP discussion with patient	GP	0.25	£15	£0.6	£1.0
Direct total			**£67**	**£2.7**	**£4.3**
On-costs			£17	£0.7	£1.1
Total			**£84**	**£3.4**	**£5.4**

The review cost is based on: assessment by the pharmacist; consultation with the GP and pharmacist, and follow-up by the nurse or pharmacist.

[33] SG ASDHD (2013) Polypharmacy reviews – cost benefit analysis, Scottish Government, unpublished

[34] http://www.rssb.co.uk/SAFETY/Documents/VPF%20letter%202012%20-%20final.pdf

[35] Based on estimates in Craig, J. (2013) Resources, Costs and Benefits Associated with Implementing Anticipatory Care Plans including Polypharmacy Reviews in Scotland, Scottish Government 2013 http://www.knowledge.scot.nhs.uk/acp-assessment-tool.aspx

Appendix E: Indicators and monitoring

In parallel with the implementation of National Guidance on medication reviews and polypharmacy, the Data Working Group of the Polypharmacy Short Life Working Group have been developing a definition of an indicator of polypharmacy to help monitor trends and the impact of the policy. The definition of the core indicator is shown in the table below.

ISD Scotland have developed standard reports which can be run by NHS Boards on the national Prescribing Information System to identify the numbers of patients experiencing polypharmacy defined in terms of the standard definition. These reports output numbers at the level of NHS Board, Community Health and Care Partnership and GP Practice. Two versions of the reports are available: one with the High Risk drug criterion, one without.

Table 6a: Comparison between the standard indicator and the criteria used to identify potential patients for review (SPARRA listings).
Comparative criteria: SPARRA listings and the standard indicator.

Table 6a	SPARRA listing	Standard Indicator
Core definition	10 or more BNF sections dispensed in a single year	10 or more BNF paragraphs dispensed in a 6 month period with at least one High Risk drug
Unit of counting	BNF section	BNF paragraph
Counting period	One year	Six months
Age threshold	Listings produced for 75+ and 65-74 on request	Aged 50 and over
Use of high-risk criterion	Listings produced regardless of presence of high-risk: but include marker indicating dispensing of at least one high-risk drug	At least one high-risk drug dispensed
High risk drugs	**BNF Sections** 2.1 Positive inotropic med. 2.2 Diuretics 2.5 Hypertension/heart failure 2.8 Anticoagulants and protamine 2.9 Anti-platelets 4.1 Hypnotics and anxiolytics 4.2 Antipsychotic/antimanic drugs 4.3 Antidepressants 10.1 Rheumatic diseases and gout	See definition of indicator Box

Specific High Risk Prescribing Indicators.
As described above the definition of standard version of the indicator of polypharmacy contains a criterion that at least one of the drugs dispensed must be one of a specified list of drugs regarded as being high risk in themselves.

In addition ISD Scotland has developed a series of standard reports relating to specific high risk drugs and combinations of drugs.

These reports have been developed following a study called “Protocol for the Effective Feedback to Improve Primary Care Prescribing Safety (EFIPPS)”, which can be found here. The reports allow patients to be identified by CHI number within each GP Practice and also identify if any Community

Heath and Care Partnership or GP Practice within an NHS Board has a particularly high rate of high risk prescribing. The reports have integrated links to searches of a practice's own local systems which can be used to locate these patients, aiming to improve individual patient safety. The reports are available for a six quarter trend at GP Practice level, or for the most recent quarter at NHS Board level.

There are reports for six specific high risk prescribing indicators, as follows:
1. Older person (>=75 years) prescribed an antipsychotic drug
2. Older person (>=65 years) currently taking an ACE inhibitor/Angiotensin Receptor Blocker and a diuretic, who is prescribed an NSAID (the 'triple whammy')
3. Older person (>=75 years) prescribed an NSAID without gastroprotection
4. Older person (>=65 years) currently taking either aspirin or clopidogrel who is prescribed an NSAID without gastroprotection
5. Current anticoagulant user prescribed an NSAID without gastroprotection
6. Current anticoagulant user prescribed aspirin or clopidogrel without gastroprotection

For more information, contact ISD Scotland's prescribing team at NSS.isdprescribing@nhs.net.

SPARRA and the identification of potential patients for medication review.
As preparations were being made for the issuing of national Polypharmacy Guidance in October 2012, it was recognised that the process would be greatly facilitated if lists of potential candidates for medication review could be generated and distributed to NHS Boards.
Scotland's principal repository of patient-based information on patterns of dispensing is the Prescribing Information System which contains detailed information on all prescriptions dispensed in the community in Scotland. However, the generation and distribution of lists from this system would have been a major undertaking and would not have been possible in the timescale available.
However a system was available for distributing lists of patients to NHS Boards: SPARRA. The SPARRA system (Scottish Patients at Risk of Readmission and Admission) is a risk-prediction tool that calculates the probability that a given patient will be admitted to hospital as an emergency in the following year based on the patient's history of hospital admissions and attendances. In addition, in recent years, a marker, at BNF section level, of drugs dispensed in the previous year has been incorporated into the SPARRA prediction model. Lists of patients at risk of subsequent hospital admission are routinely distributed to NHS Boards so that they can be assessed for possible preventative or anticipatory care.
Hence the SPARRA system provided a means of generating lists of patients who had experienced polypharmacy in the previous year, at a given level of risk of hospital admission, which could be distributed to Boards as potential candidates for medication review as described earlier in this Guidance.

Comparison between SPARRA criteria and the polypharmacy indicator definition.
Hence the use of SPARRA was a pragmatic decision without which potential candidates for medication review could not have been identified as quickly as they were.
However, the 'targeting criteria' involved were dependent upon the information already available as part of the SPARRA system. This meant that polypharmacy and high-risk drugs could only be identified at BNF Section level and the only counting period available is one year.
When the Data Working Group set out to define a standard indicator of polypharmacy to facilitate monitoring and evaluation it was felt that advantage should be taken of the more detailed dispensing information available on the Prescribing Information System.

However this means that the SPARRA listings and the polypharmacy indicator are based on different criteria. To avoid potential confusion the two definitions are outlined in the table 6a above.
It is intended that in future the ability of NHS Boards to derive lists of candidates directly from the Prescribing Information System will be enhanced. As this method is adopted the same criteria will increasingly be used for targeting as are used in the indicator of polypharmacy.

Initial analyses.

The charts below present initial analyses related to the standard indicator. The first shows the distribution of a simple count of BNF paragraphs by 5 year age group. This analysis does not incorporate the high-risk drug criterion. The younger age groups, up to the ages of 60 to 70 broadly speaking, are dominated by individuals who were dispensed either no drugs or drugs from 1 to 4 different BNF paragraphs. In age groups over 70 a majority of individuals are dispensed drugs from 5 or more different BNF paragraphs. However, it can also be seen that age groups below 60 contain significant numbers and proportions of individuals with high levels of polypharmacy.

The second is directly based on the standard indicator. It shows the proportion of the population aged 50 and over who satisfy the criteria for the standard indicator – 10 or more BNF paragraphs at least one of which is a high-risk drug in a six-month period – by five year age group. Overall 13.3% of the population aged 50 and over meet these indicator criteria. For those aged 80 and above, over a quarter of the population satisfy the indicator criteria.