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OPTIMISING PRESCRIBING FOR PATIENTS WITH POLYPHARMACY IN PRIMARY CARE

- **Potentially inappropriate prescribing (PIP) occurs when the risks of prescribed medications outweigh their potential benefits, leaving the patient at increased risk of adverse drug reactions (ADRs)**
- **Risk factors for PIP include polypharmacy, multimorbidity, and older age**
- **Certain medications are higher risk for ADRs and require regular monitoring by the prescriber to mitigate their risks of ADRs**
- **There is some evidence that structured medication review in primary care can optimise prescribing and improve patient outcomes**

INTRODUCTION

The prescription of medication is the most common therapeutic intervention in healthcare.[1] **In Ireland it is estimated that 20% of all adults aged ≥65 years are prescribed ≥10 repeat medications, and that 5% are prescribed ≥15.**[2] Between 1997 and 2012, the proportion of these patients aged ≥65 years prescribed ≥five regular medicines rose from 17.8% to 60.4%.[2] As well as a significant medication burden for patients, this also increases the risk of adverse drug reactions (ADRs). An ADR has been defined by the European Medicines Agency as a response to a medicinal product which is noxious and unintended.[3] This definition includes adverse reactions occurring from off-label use, overdose, misuse, abuse and medication errors.[3] Evidence suggests that most ADRs in primary care are mild or moderate; an Irish cohort study of older community-dwelling people (n=605) found that 71% of participants reported ≥1 ADR over six months follow-up, of which the majority (95.2%) were rated as mild.[4] However, data from a 2018 Heath Information Quality Authority (HIQA) review found that **4% of preventable hospital admissions were attributable to ADRs, and within the elderly cohort this figure was as high as 10%.**[5] These figures were similar to cross sectional data which estimated 8.8% of patients presenting to an Irish Emergency Department (ED) had an ADR related admission, and of these, half were considered avoidable.[6] A UK study found patients taking ≥10 medications are three times more likely to be admitted to hospital as a result of an ADR.[7]

There are several factors which are associated with an increased risk of ADRs. Patient factors include older age and frailty, morbidity burden, polypharmacy and the presence of renal and hepatic impairment.[8] While all medications have the potential to cause ADRs, those with a narrow therapeutic index carry a greater risk, including certain antiarrhythmics, antiepileptics, cytotoxics and oral anticoagulants.[8] **This, the first of two bulletins written in collaboration with the HSE General Practice Fellowship in Medicines Optimisation,** will provide an overview of the factors associated with potentially inappropriate prescribing (PIP) and suggest strategies to optimise prescribing for patients with polypharmacy in primary care.

POTENTIALLY INAPPROPRIATE PRESCRIBING

Potentially inappropriate prescribing (PIP) is where the risks of medications prescribed outweigh any potential benefit[9] and encompasses: 1) misprescribing, such as incorrect dose, frequency or duration of treatment, 2) overprescribing, where medications used have no clear clinical indication and 3) underprescribing, where potentially beneficial medications are omitted.[10] A UK study of community dwelling adults found that 15% of the population were prescribed one potentially inappropriate medication, 7.6% were prescribed two and 6.8% were prescribed three or more.[11] An Australian systematic review reported that exposure to PIP during hospital care had significant associations with ADRs, functional decline, falls and health care costs.[12] An Irish longitudinal study which retrospectively collected data from 44 general practice records found the prevalence of PIP in adults >65 years old (n=38,229) to be 51% using the Screening Tool of Older Persons Prescriptions (STOPP) criteria.[13] There are several factors which increase the likelihood of PIP; these are outlined below.

Polypharmacy

Several definitions exist for polypharmacy ranging from the use of more than 2 medications,[14] to the more generally accepted use of more than 5 medications.[15] **Instead of being related to a defined number of medications, polypharmacy has been more recently described as the prescribing or taking of more medicines than are clinically required,**[16] also referred to as inappropriate polypharmacy. As a result, the reported rates of polypharmacy vary, Irish figures estimate over 60%[2] of patients over the age of 65 years with polypharmacy, while an Australian population-based study estimates polypharmacy prevalence among older adults as 36% with those aged >85 years old the most affected.[17] As the burden of polypharmacy increases, a new area of significant polypharmacy has been described as ≥15 repeat medicines, with Irish dispensing data indicating that it occurs in approximately 5% of those aged ≥65 years.[18] Appropriate polypharmacy is necessary in certain circumstances; an example of this would be the essential drug therapy recommended in secondary prevention post stroke or myocardial infarction. A patient may require an antiplatelet, a statin, an angiotensin converting enzyme inhibitor (ACEi), a beta blocker as well as additional medications if experiencing comorbid diabetes or heart failure.[19]

Multimorbidity

Multimorbidity is defined as the presence of two or more chronic medical conditions in an individual.[20,21] In the UK it is reported that one in six patients have more than one chronic medical condition, which accounts for one third of all primary care consultations.[22] A 2011 Irish observational study of 3309 patients in the community, estimated the prevalence of

multimorbidity at 66.2% in those >50 years of age; those with four or more chronic illnesses were estimated to have an average of 12 GP consultations a year.[23] Patients with multiple chronic conditions will likely accrue multiple medications, due to disease specific guidelines which do not explicitly consider overall treatment burden in multimorbidity.[19] The evidence base for these guidelines largely comes from clinical trial data from which older people, frail and multimorbid patients are usually excluded.[24] In addition to polypharmacy, patients with multimorbidity face further challenges that may increase their risk of ADRs. This population tend to have poorer functional capacity, reduced health related quality of life,[25] and have a higher prevalence of mental health disorders such as depression and anxiety.[26] **There is evidence to suggest that approximately half of all patients with a chronic disease, taking four or more medications, do not take them as prescribed.[27]**

Transitions of care

Patients with multiple chronic conditions may see several different specialists, who may aim to optimise each disease in isolation.[19] The GP is often required to integrate and rationalise medication lists when transcribing, and take on the responsibility of continuing to prescribe these medications long term. It is recognised that repeat prescribing is an area of both clinical and medicolegal risk in primary care.[28] It is also well recognised that transitions of patient care are associated with higher rates of PIP and medication error.[29] These transitions occur between primary and secondary care on admission to and discharge from hospital, presentation to EDs, attendance at outpatient clinics (OPD) and also in the community on admission to nursing home or respite care.[19] **Between 30% and 70% of patients may have experienced an error or unintentional changes to their treatment at transfer of care between services.[30]** It has been estimated from Irish data that admission to hospital is associated with a 24% increase in the occurrence of PIP, compared to pre-admission.[13] Even within primary care, a patient seeing multiple GPs can be associated with PIP. A recent study involving patients with dementia found that higher levels of continuity of GP care are associated with fewer drugs deemed potentially inappropriate and with a lower medication burden.[31]

Prescribing cascades

A further issue which can result in PIP, is that the presenting signs and symptoms of an ADR may not be recognised as such, but interpreted as a new illness or disease. This can result in the addition of further prescribed medication, in what is known as a prescribing cascade.[32] This may happen as adverse symptoms may be vague or overlap with symptoms of other illness such as dizziness or ankle swelling. ADR symptoms in older adults are often non-specific for example, delirium, falls, dizziness, fatigue and constipation, and can be very challenging to identify as medication-related. These symptoms have several potential causes and may overlap with existing multimorbidity. There are several commonly encountered prescribing cascades in primary care (see table 1).[9]

Table 1: Examples of common prescribing cascades in primary care[9]

Initial drug/drug group	Adverse drug reaction	New drug/drug group
Angiotensin converting enzyme inhibitor	Cough	Antibiotics
Anticholinergics	Cognitive impairment	Donepezil
Antipsychotics	Parkinsonism	Antiparkinsonian agents
Cholinesterase inhibitors	Urinary incontinence	Anticholinergics
Antiemetic	Parkinsonism	Antiparkinsonian agents
Thiazide diuretics	Gout	Anti-gout agents

One of the most common prescribing cascades is the initiation of a diuretic to treat ankle oedema secondary to calcium channel blockers (CCB) such as amlodipine. A recent study found patients who were newly prescribed a CCB had an increased risk of being dispensed a loop diuretic in the following 30 days, compared to patients who were prescribed an ACEi or angiotensin receptor blocker (ARB).[33] This highlights the importance of being familiar with common side effects of frequently prescribed medications and to consider ADRs in the differential for patients presenting with new symptoms.

OPTIMISING PRESCRIBING SAFETY AND QUALITY

There are significant challenges in prescribing for patients with multimorbidity and polypharmacy, not least the implementation of disease specific guidelines in a population which are often excluded from their original evidence base.[19] A UK study of primary care patients found 7.92% patients were defined as being particularly vulnerable to ADRs because of their age, pre-existing disease, or co-prescription.[34] A holistic approach to prescribing in multimorbidity is required to reduce the risks for ADRs; the prevalence of PIP can be reduced through improvements in prescribing safety and quality.

High risk medications

There are several high risk medications that are associated with the greatest risk of ADRs (see table 2).[35] **The medications most commonly associated with serious ADRs resulting in hospital admission are antiplatelets, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), warfarin, opioids, beta blockers, and ACEi/ ARB.[35]** These are amongst the most commonly prescribed medications in primary care. The leading cause of fatal ADRs is haemorrhage, with gastrointestinal (GI) haemorrhage being the most common site,[36] and the most common cause being an NSAID co-administered with an anticoagulant.[37]

Table 2: Examples of high risk medications for adverse drug reactions[14,35]

Drug class (as per BNF)	Examples
Positive inotropic medicines	Digoxin
Diuretics	Bendroflumethiazide, furosemide, spironolactone
Antihypertensives/heart failure	Ramipril, enalapril, losartan
Anticoagulants	Warfarin, rivaroxaban, edoxaban, apixaban, dabigatran
Antiplatelets	Clopidogrel, dipyridamole
Hypnotics and anxiolytics	Diazepam, zolpidem
Antipsychotics	Amisulpride, risperidone
Antidepressants	Amitriptyline, fluoxetine, paroxetine
Opioid analgesics	Tramadol, codeine, morphine, fentanyl
Rheumatic diseases	NSAIDs, corticosteroids, methotrexate
Anticholinergics	Chlorpromazine, oxybutynin, tolterodine.

BNF-British National Formulary; NSAIDs-non-steroidal anti-inflammatory drugs

Anticholinergic agents are used to manage several common issues presenting to primary care such as vertigo or overactive bladder, with their adverse effects displaying significant inter-individual variation.[14] The types of ADRs range from dry mouth, constipation and urinary retention to impaired cognition, physical decline, falls, and cardiovascular events.[38] The NHS Scotland Polypharmacy Guidance and Realistic Prescribing document has a useful section outlining anticholinergic drugs and potential alternatives for several indications commonly seen in primary care.[14]

Drug monitoring

Many high risk medications require ongoing laboratory monitoring to reduce their risk of drug-related morbidity. Table 3 provides examples of laboratory monitoring of medicines that may be required at initiation, after initiation or change in dose and ongoing monitoring, once therapy is established; please note that more frequent monitoring may

be required in individual patients at higher risk of ADRs.[39] **While some high risk medications may be initiated in secondary care, the responsibility for ongoing monitoring lies with the prescribing clinician.[40]** In addition to laboratory monitoring, further clinical monitoring may be necessary to reduce the risk of ADRs, for example, clinical review for signs and symptoms of adverse drug effects, such as in opioid prescribing.[14]

Table 3. Ongoing laboratory monitoring for selected high risk medications[9,39-48]

Drug	Laboratory monitoring	Interval*
Angiotensin converting enzyme inhibitors/ Angiotensin receptor blockers [9,41]	Renal function and electrolytes	Baseline, within 2 weeks after initiation and following dose increase, thereafter every 6 to 12 months depending on indication
Direct oral anticoagulants [42-44]	FBC, renal and hepatic function	Baseline, then at least annually, or every 4 months if ≥75 years. Additional monitoring required, if CrCl <60 ml/min, variable = (CrCl/10)** or in intercurrent illness which may affect hepatic or renal function.
Methotrexate[9,45]	FBC, renal and hepatic function	Baseline in secondary care, and once stabilised at least every 3 months. (May need to liase with secondary care.)
Lithium[46]	Lithium level, renal function, electrolytes, serum calcium, TFTs	Lithium levels at baseline and once stabilised at least every 3 months; U&E, TFTs every 12 months (May need to liase with secondary care)
Diuretics[9,47,48]	Creatinine and electrolytes	Consider monitoring at baseline, within 8 weeks of initiation of therapy and 6 to 12 months thereafter in stable patients

*Always consult manufacturer's Summary of Product Characteristics (SmPC) for full prescribing information; FBC - Full blood count; U&E - Urea and Electrolytes; CrCl - Creatinine Clearance; INR - International normalised ratio; LFTs - Liver Function Tests; TFTs - Thyroid Function Tests;. ** for those with CrCl of 50ml/min do bloods every 5 months, if CrCl is 40ml/min then do bloods every 4 months, if CrCl is 30ml/min do bloods every 3 months etc

In addition to regular interval laboratory monitoring, high risk medications may require additional monitoring during periods of acute illness, owing to both pharmacodynamic and pharmacokinetic changes. For example, it is recommended that patients prescribed a direct oral anticoagulant should have renal and liver function tests performed in the event of intercurrent illness that may impact renal or hepatic function.[43]

Appropriate polypharmacy

As well as monitoring for safety, prescribing should also be assessed for quality, with the ultimate aim that any polypharmacy is appropriate. Assessing prescribing for quality includes determining that; 1) an ongoing indication is present, 2) that treatment is achieving the desired effect and, 3) that this is weighed against any adverse effects or difficulties for the patient taking the prescribed therapy.[14] For example, an Irish study reports that one of the most common indicators of PIP in older patients in primary care is the long term use of proton pump inhibitors (PPIs).[13] The UK NICE guidelines recommend an eight week PPI course for gastritis,[49] but very often PPIs are continued inappropriately on repeat prescriptions when the clinical indication no longer exists. This is particularly relevant for older people where the risk of ADRs, such as *Clostridium difficile* infection, can outweigh any benefits, if PPIs are inappropriately prescribed.[50]

For preventative or disease modifying medications, it is important to determine the appropriate treatment targets for each individual patient, and that these targets are being met.[14] In the case of hypertension, for example, for a diabetic patient with microvascular disease a treatment target of <135mmHg for systolic blood pressure is recommended.[51] However this may not be an appropriate target for an older diabetic patient where the risks of aggressive blood pressure control e.g. falls, may outweigh the benefit. In that instance, a target systolic blood pressure of <150 mmHg[52] may confer more overall benefit by reducing the risks of ADRs associated with strict BP correction in elderly patients.

Identifying PIP

There are various tools available to assist GPs in optimising prescribing. For older people, the STOPP tool is a valuable resource to identify PIP,[53] while the START tool lists common significant prescribing omissions.[53] It is estimated that significant omissions have been found in 58% of hospitalised patients and 23% of primary care patients.[53] Failing to initiate an ACEi in a diabetic patient with evidence of dipstick proteinuria or persistent microalbuminuria would be an example of such an omission.[51,54] A significant proportion of multimorbidity now occurs in middle age, with approximately 30% of middle-aged adults (aged 45 to 64 years) affected.[55] The Prescribing Optimally in Middle-aged People's Treatments (PROMPT) criteria is available to support optimising prescribing in this specific patient group.[55] **Clinical decision support systems at the point of care have been shown to increase the effectiveness of these tools in practice,[56] and would therefore be of significant support to GPs if these tools were integrated into general practice software.**

MEDICATION REVIEWS

To optimise prescribing it is recommended that regular medication reviews should be conducted in primary care. **There is increasing evidence that GP-led medication reviews can improve both the safety and quality of prescribing,[57,58]** and that alerting GPs to high risk prescribing can reduce the risk of hospital admissions for ADRs.[59] The maximum benefit is derived from in person medication review, with carers present if appropriate, and when the patient has the medications that they are currently taking with them.[14] It is also recommended the review is done with a patient's regular GP, as continuity of care in patients with multimorbidity has been demonstrated to improve patient outcomes and reduce preventable hospital admissions.[60,61] Barriers to medication reviews include lack of protected time to undertake a review, difficulty in assimilating the necessary information due to multiple prescribers and lack of a shared patient medication record.

The NHS Scotland Polypharmacy Guidance and Realistic Prescribing document has devised a *7 step* approach to undertaking a structured medication review in primary care (see table 5 for a link to this guidance).[14] **The guidance recommends specific patient groups that should be prioritised for regular medication review that include: 1) patients aged ≥50 years in residential care (regardless of the number of medications prescribed), 2) patients approaching the end of life, 3) patients prescribed ≥10 medications, and 4) patients prescribed high risk medications** (see table 2). The *7-Steps* structured medication review is outlined in table 4.

The NHS Scotland guidance document also provides 27 case finding indicators to identify PIP within a practice; for example, patients aged >65 years prescribed an ACEi/ARB and an NSAID, or patients aged ≥65 years prescribed three or more drugs with sedating or anticholinergic effects other than antiepileptics.[14]

There are several considerations and challenges in adapting this *7-Step* type of medication review to the Irish primary care setting. Adaption can be challenging due to current capacity issues in primary care and given that the average

consultation duration in Irish general practice has been estimated at 13.7 minutes.[62] The GP may have to perform this type of a medication review over several visits.[20]

Table 4. The *7-steps* medication review[14]

1 Aim	**Review diagnoses and identify therapeutic objectives** *What matters to the patient?* Identify what matters to the patient and determine their understanding of treatment indications and objectives.
2 Need	**Identify essential drugs (not to be stopped without specialist advice)** Those that perform essential replacement function or prevent rapid symptomatic decline.
3 Need	**Identify and review the (continued) need for drugs** *Does the patient take unnecessary therapy?* Identify drugs that had temporary indications, that are at higher than usual maintenance doses, that have limited benefit in general for the indication they are being used for and with limited benefit to the patient under review.
4 Effectiveness	**Identify the need for adding/intensifying drug therapy in order to achieve therapeutic objectives** *Are therapeutic objectives being achieved?* Aim to achieve symptom control, biochemical and/or other clinical targets and prevention of disease progression/exacerbation.
5 Safety	**Identify patient safety risks and adverse drug effects** *Does the patient have or is the patient at risk of ADRs/side effects?* Assess for potential drug-drug and drug-disease interactions, and the monitoring systems in place especially for high risk medications, assessing specific symptoms or laboratory markers, assessing for cumulative ADRs and the presence of prescribing cascades.
6 Efficiency	**Identify unnecessarily costly drug therapy** Consider if there is a more cost effective alternative balanced against effectiveness, safety and convenience.
7 Patient centred	**Ensure patient understands the outcomes of the review, ensure drug therapy changes are tailored to patient preferences and agree plan.** *Is the patient willing and able to take drug therapy as intended?* Determine that the patient understands the outcome of the review, check if the medication is in a form the patient can take, if the patient will need any assistance and decide with the patient which medications have sufficient effect to consider continuation or discontinuation.

It may also be time efficient for the patient to attend the practice nurse to record certain clinical monitoring parameters in advance of the medication review, such as blood pressure and weight, as well as phlebotomy for required laboratory monitoring.[20] The HSE Structured Chronic Disease Management programme for patients eligible for GMS and Doctor Visit cards provides this opportunity for practices participating in this programme, and affords additional resourced GP consultation time to perform a patient centred medication review.[63] At present however, this programme only extends to patients with Type 2 diabetes, asthma, chronic obstructive pulmonary disease, cardiovascular disease, including heart failure, angina, atrial fibrillation and stroke; further expansion to other conditions and across the whole population would afford GPs greater opportunities to review patient medications.[64]

In terms of cost effectiveness in the Irish setting, it is recommended that generic prescribing be used to reduce costs to patients who pay out of pocket for prescribed medications and to the state for those provided under the General Medical Service (GMS).[65] The HSE in conjunction with the Medicines Management Programme have implemented a Preferred Drug Initiative, which offers prescribers useful guidance on selecting, prescribing and monitoring a preferred drug for 10 separate therapeutic classes.[66-74]

Adherence

As well as improving prescribing safety and quality, a further aim of a medication review is to improve medication adherence. It is important to explore and address patient concerns and barriers to compliance.[75] Non-adherence may be due to "non-initiation", "non-persistence" or the patient not correctly adhering to the daily schedule of medicines.[76] Studies report medication non-adherence rates of 50% for chronic conditions, which is higher in patients with cardiovascular disease.[77] It has been found that patients living in socio-economically disadvantaged areas have the lowest rates of medication adherence, with lack of health literacy and declining cognitive function identified as other factors associated with reduced medication adherence.[78] Increasing multimorbidity is also associated with reduced compliance, as is increasing number of medications and multiple dosing regimens.[76,77] A medication review allows the opportunity to discuss strategies with patients to improve adherence; these may include a change in medication formulation, medication reminders (e.g. technology interventions such as mobile phone applications) and streamlining dosing to once daily dosing where available, and blister packing.[79,80]

DEPRESCRIBING

One of the most effective interventions in optimising prescribing and reducing the risk of ADRs is that of deprescribing, which involves the discontinuation of medications that are no longer indicated, have inadequate prognostic benefit, or are causing side effects.[81] The next NMIC bulletin (Number 3, 2022) will outline the benefits of deprescribing, and the process of deprescribing in primary care.

SUMMARY

Optimising prescribing is an essential component of the management of patients in primary care and in reducing the risk of medication-related harm. Performing a medication review in primary care has been demonstrated to reduce the risk of ADRs, and is associated with improved medication adherence. It is important that robust systems are in place in general practice for the monitoring of higher risk medications prescribed in primary care. There are several helpful tools to aid GPs to optimise prescribing (see table 5). Strategies such as individualising guideline recommendations to maximize overall individual care and deprescribing are proven interventions to optimise prescribing in primary care.

Table 5: Tools for medication optimisation in polypharmacy.

Tools for addressing polypharmacy and potentially inappropriate prescribing in Primary Care	
STOPP/START version 2	https://www.cgakit.com/m-2-stopp-start
PROMPT criteria	https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-014-0484-6
NHS Scotland Polypharmacy	https://www.therapeutics.scot.nhs.uk/wp-content/uploads/2018/04/Polypharmacy-Guidance-2018.pdf
ICGP QRG on Medication Review[8]	www.icgp.ie available on subscription only
NICE Multimorbidity	https://www.nice.org.uk/guidance/ng56
Deprescribing	https://www.deprescribingnetwork.ca/

List of references available on ePublication on www.nmic.ie.
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Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue.

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