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OVERVIEW OF DEPRESCRIBING

- **Deprescribing is the process of withdrawing inappropriate medication(s), supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes**
- **There is some evidence that deprescribing is effective in reducing potential inappropriate prescribing and preventing adverse drug reactions (ADRs), as well as reducing morbidity and healthcare resource utilisation as a result of ADRs**
- **Deprescribing should be especially considered in older patients in the event of ADRs and with the use of preventative medications in patients with limited life expectancy**
- **Examples of deprescribing include the cessation of proton pump inhibitors and benzodiazepines, when considered clinically appropriate**

INTRODUCTION

Deprescribing can be defined as "the process of withdrawal of an inappropriate medicine, supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes".[1] Alternative terms used in the literature for deprescribing include rationalisation, de-escalation and withdrawal of medicines.[1]

There are various reasons for stopping or reducing the dose of a medicine such as in patients who are: 1) approaching the end of life, 2) prescribed a medicine where an alternative therapy is more appropriate, 3) prescribed a medicine for an appropriate indication, which becomes inappropriate over time, 4) prescribed a medicine for the short-term which is continued long-term and 5) prescribed a medicine that is ineffective.[2] **The discontinuation of, or a reduction in the dose of a medicine requires careful clinical consideration, and can be just as challenging as the initiation of a medicine.[2,3]** Therefore, it is especially important to consider the benefits/risks of initiating medicines that may be difficult to discontinue (e.g. benzodiazepines).[4] It can be particularly challenging discontinuing a medicine in circumstances where the GP becomes responsible for the long-term prescribing of a medicine which was initiated in secondary care, and where there is a lack of clarity on the indication and the intended duration of treatment.[2]

The benefits and risks of deprescribing should be evaluated for the individual patient following a medication review.[3,5,6] **This bulletin, which was created in collaboration with the HSE General Practice Fellowship in Medicines Optimisation**, will give an overview of the process of deprescribing and provide some examples of how deprescribing in specific therapeutic areas might be enacted.

BENEFITS ASSOCIATED WITH DEPRESCRIBING

There is some evidence that deprescribing is effective in reducing polypharmacy and potentially inappropriate prescribing (PIP),[7-10] which are risk factors for adverse drug reactions (ADRs).[7,9,11-13] In Ireland it is estimated that 20% of all adults aged ≥65 years are prescribed ≥10 repeat medicines, and that 5% are prescribed ≥15.[14] In high risk populations, the risk of ADRs increases from 13% in a person taking 2 medicines, to 58% when taking ≥5 medicines, and to 82% when taking ≥7 medicines.[8] Polypharmacy is a particular concern in older patients as there may be a progressive decline in both hepatic and renal function which can affect the pharmacokinetic (PK) and pharmacodynamic (PD) properties of many medicines, leading to an increased risk of ADRs.[7,11,13] It is important to distinguish appropriate polypharmacy (e.g. secondary preventive therapy following a myocardial infarction) from problematic polypharmacy which can result in PIP.[7,15]

The prevalence of PIP, which varies in the literature, depends on the patient population and healthcare setting; an Irish longitudinal study in the community 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.[16]

Deprescribing, in addition to reducing polypharmacy and PIP also results in reduced morbidity and may reduce healthcare costs.[10,17] Deprescribing may prevent ADRs occurring in older people, where it is estimated that approximately 10 to 25% of preventable hospital admissions are due to ADRs.[18,19] A 2019 systematic review reported that deprescribing interventions based on medication reviews in older patients following a fall, resulted in a relative risk reduction of 24% of further falls.[20]

In addition, evidence suggests that **by discontinuing unnecessary medicines, deprescribing may improve overall adherence to essential medicines.[21]**

Evidence suggests that deprescribing is feasible and does not increase the risk of harm, however there may be a risk of relapse of symptoms.[5,10,13,22] There is evidence that careful withdrawal in suitable older patients under close monitoring can be achieved for medicines such as antihypertensive drugs, psychotropic drugs and benzodiazepines without resulting in harm.[5,21,23-25]

RISKS ASSOCIATED WITH DEPRESCRIBING

While the discontinuation of most long-term potentially inappropriate medicines may produce little or no adverse effects for some patients, it can result in potential risks including increased patient anxiety and precipitation of an adverse drug withdrawal event (ADWE).[3,26,27] An ADWE can be defined as recurrence of the condition for which the medicine was prescribed or a physiological reaction to the medicine's discontinuation;[28] it can present as a physiological withdrawal reaction (e.g. tachycardia with beta-blocker discontinuation), appearance of new symptoms (e.g. sweating with antidepressant withdrawal), or exacerbation of an underlying condition (e.g. depression relapse after stopping antidepressants).[4,9] **There is evidence however that ADRs are far more prevalent than ADWEs.[29]** A

randomised controlled trial of 51 Irish GP practices (n=404 patients), which compared structured medication review and deprescribing of medicines to standard care, reported a small but significant reduction in the number of medicines prescribed and <2% resulted in ADWEs (including hospitalisation with depression relapse).[30] **Factors that are associated with an increased risk of ADWEs include long duration of use (e.g. benzodiazepines), higher doses (e.g. corticosteroids) and medicines with a short half-life (e.g. paroxetine).[9]**

WHEN SHOULD DEPRESCRIBING BE CONSIDERED?

Deprescribing is not about denying effective treatment to eligible patients; it is a patient centred intervention, which requires shared decision making and monitoring for adverse effects.[21] Deprescribing should be considered (especially in older patients) in the following scenarios: 1) patients presenting with a new symptom or clinical syndrome suggestive of an ADR (e.g. ankle oedema following initiation of a calcium channel blocker), 2) the use of preventative medicines in patients with limited life expectancy (e.g. statins) or 3) patients receiving "high-risk" medicines or combinations (e.g. non-steroidal anti-inflammatory drugs [NSAIDs]).[21,31]

A medical event such as a fall, an admission to hospital or a residential care facility, can also serve as a trigger for deprescribing,[27] although deprescribing ideally occurs before an ADR occurs. Consideration should be given to the likelihood of meaningful benefit from preventative agents in an older cohort, for example it requires 2 to 5 years of statin use to reduce the risk of stroke or myocardial infarction.[32] As the risk of ADRs from preventative drugs increase with age due to PK and PD changes, consideration should be given to realistic treatment objectives and the likelihood of a patient with reduced life expectancy benefiting from the initiation or continuation of these agents.[33]

As discussed earlier, **the discontinuation of a medicine that was started for an appropriate indication, that is no longer appropriate and/or for treatment that is no longer effective should be considered, even if these medicines are well tolerated.[21]** Examples of unnecessary continuation of medicines include gastroprotective proton pump inhibitors (PPIs) following cessation of non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics for acute pain that has resolved (e.g. opioids).[4,21]

The deprescribing of a medicine may also be considered appropriate for patients taking medicines that are associated with dependence (e.g. benzodiazepines and z-drugs [BZRA] and opioids).[4] As the deprescribing of these types of medicines can be challenging, it is important that before starting or continuing these medicines that all suitable management options including non-pharmacological therapies have been considered and discussed with the patient.[4] The gradual withdrawal of antidepressants in individual patients with a resolved episode of depression and close follow-up may also be considered.[4]

BARRIERS TO DEPRESCRIBING

There are multiple barriers to deprescribing in primary care. These include time constraints for a medication review, especially in clinically complex older patients with multimorbidity and polypharmacy who may have multiple prescribers.[21,25] There may be fragmented care of a patient across primary and secondary care with communication difficulties (due to a lack of integrated IT system for a shared patient medication record) resulting in incomplete information of a patient's medicines (e.g. indication and duration of therapy).[21,34,35] A GP may be reluctant to discontinue a medication that was prescribed elsewhere, particularly if this was initiated by another prescriber (e.g. specialist in secondary/tertiary care).[2,9,22] There may also be uncertainty about the benefits and harms of discontinuing specific medicines and concern about ADWEs.[2,9,25] There may be pressure to prescribe according to disease specific guidelines, which while intending to optimise care, may not be applicable to older multimorbid patients with polypharmacy.[2]

It is important to involve patients in the decision to discontinue medicines, and to get the patient's views on the benefits and risks of the medicines.[9,27,36] Patients may be reluctant to discontinue medicines if they think that the medicine is necessary for their condition, and in particular there may be resistance from patients to discontinue medicines that are associated with dependency,[27] especially if there is difficulty getting access to non-pharmacological therapy.[4] Patient engagement and education of the deprescribing process is important as these have been associated with positive outcomes.[25,37]

THE PROCESS OF DEPRESCRIBING

The decision to discontinue a medicine can be quite challenging. Factors to encourage deprescribing include a more prudent prescribing culture, tools to support deprescribing, shared decision-making and improved communication with patients and between HCPs in different health settings.[21,34-37] Several deprescribing protocols have been developed, to assist clinicians in the process of deprescribing medications.[21,38] Organisations that have published guidance include NHS Scotland,[33] the Canadian Deprescribing Network[39] and the Australian Deprescribing Network[40] (see useful resources). A structured medication review, such as the NHS Scotland *7 Steps* is an integral step in the process of deprescribing, which may identify the potential for preventable ADRs.[33] This 7 step review forms the basis for a current pilot study in several Irish practices, assessing pharmacy led structured medication review in reducing PIP in primary care.[41] The third step of this process in particular may inform which medicines should be considered for deprescribing.[33] This medication review is outlined below in table 1; a detailed overview of this process can be found in the NMIC bulletin on Optimising Prescribing for Patients with Multimorbidity in Primary Care 2022 28(2).

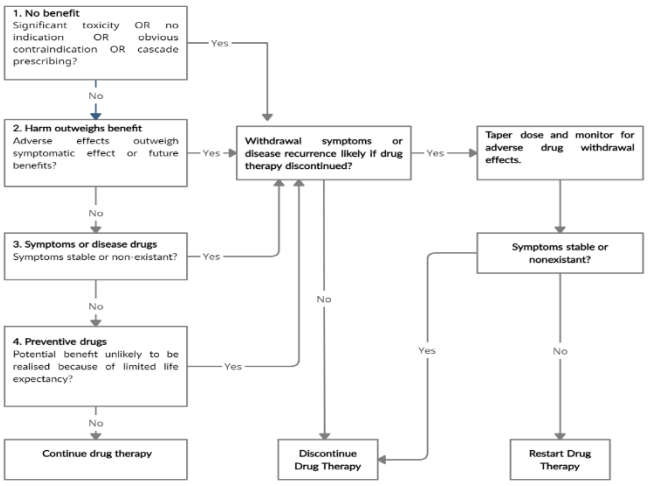
Table 1: *7 Steps* Medication Review[33]

Step 1	Review diagnoses and identify therapeutic objectives
Step 2	Identify essential drugs
Step 3	Identify and review the continued need for drugs
Step 4	Identify the need for adding/intensifying drug therapy in order to achieve therapeutic objectives
Step 5	Identify patient safety risks and identify adverse drug effects
Step 6	Identify unnecessarily costly drug therapy
Step 7	Ensure patient understands the outcomes of the review Ensure drug therapy changes are tailored to patient preferences Agree and communicate plan

There are several screening tools to help identify PIP (e.g. Screening Tool of Older Persons Prescriptions - STOPP, Screening Tool to Alert doctors to Right Treatments – START[42] and Prescribing Optimally in Middle-aged People's Treatments [PROMPT]).[43] The aim of these tools is not deprescribing as such, however the screening tools can be a useful aid in reviewing a patient's medications in order to identify potentially inappropriate medicines that could be deprescribed, although their use does not replace clinical judgement in individual cases. **In certain circumstances, a potentially inappropriate medicine may actually be appropriate, if the benefits outweigh the risks or if following consultation with the patient a shared decision is made to continue its use.[5,9]** STOPPFrail is a further tool that was developed to assist clinicians with deprescribing decisions in older people approaching end of life.[44-47]

Figure 1 provides an algorithm for how a medicine might be discontinued.

Figure 1: Algorithm for deciding order and mode in which drug use could be discontinued[21]



Scott I, Hilmer S, Reeve E et al, Reducing Inappropriate Polypharmacy - The Process of Deprescribing, JAMA Internal Medicine 2015;175(5):827-834

It is important to get as much information as possible about the potentially inappropriate medicine such as 1) the original prescriber, indication and planned treatment duration, 2) whether the medicine is still effective, 3) whether the medicine was originally prescribed to treat an ADR of another medicine (e.g. prescribing cascade) and 4) whether alternative non-pharmacological options are available.[21] **If a number of potentially inappropriate medicines have been identified, one medicine should be deprescribed at a time** so that any benefits (e.g. reduction in ADRs) and harms (emergence of ADWEs) can be attributed to the individual medicine.[9,21] The order of discontinuation of medicines may depend on 1) those with the greatest harm and least benefit, 2) those with the lowest likelihood of ADWEs and 3) those that the patient is most likely to discontinue first.[21] Patients should be informed of the risk of ADWEs and monitored for ADWEs following the deprescribing of a medicine.[21,27]

Gradual tapering of some medicines (e.g. benzodiazepines), may reduce the risk of ADWEs.[27] For certain medicines, where it is uncertain if a condition is a current problem (e.g. PPIs to manage reflux or analgesics to manage pain), the discontinuation of medicines should be on trial basis (with appropriate warnings about potential ADWEs) and recommencement of the medicine at a lower dose or an alternative medicine if symptoms recur.[27]

DEPRESCRIBING IN SPECIFIC AREAS

Deprescribing of proton pump inhibitors (PPIs)

PPIs which are recommended as a first-line treatment for gastro-oesophageal reflux disease (GORD) and other acid-related disorders, are amongst the most frequently prescribed medicines in primary care.[48,49] Although PPIs are highly effective, long-term use of PPIs is associated with increased risks of ADRs (e.g. diarrhoea, vitamin B12 deficiency, *C difficile* infection, increased risk of fractures and community-acquired pneumonia).[48,49] **It is recognised that there is a need to optimise prescribing of PPIs, as evidence suggests that PPIs are frequently overprescribed.[48]** Long-term potentially inappropriate use of PPIs also contributes to polypharmacy and increased healthcare expenditure.[6]

The goals of deprescribing or discontinuing PPIs are to reduce medication burden and possible harm of continued therapy. As with any deprescribing intervention, it is important that the patient is involved in the decision to deprescribe and that the patient is aware of the need to undertake lifestyle measures e.g. avoidance of alcohol or specific foods which may precipitate symptoms.[49,50] *The Medicines Management Programme's Preferred Drug document for PPIs and Prescribing Tips and Tools for PPIs for the treatment of GORD contains useful information including an algorithm for the deprescribing of PPIs.*[50]

As some patients experience withdrawal symptoms (e.g. dyspepsia symptoms) following deprescribing of PPIs, lowering the daily dose of a PPI is often the first step in stopping PPI therapy.[49] The tapering of PPI treatment rather than abrupt cessation, has been suggested to minimise withdrawal symptoms, especially in patients who have been treated for longer duration and in those who have experienced symptom recurrence after PPI withdrawal.[49] The use of an alginate may reduce the risk of dyspepsia symptoms.[50] The evidence suggests that the success rate of deprescribing among patients with GORD increases when a step-down approach to on-demand use is taken rather than an abrupt discontinuation.[49]

It should be noted however, that long-term PPI use can be appropriate, where there is a clear indication that the benefits outweigh the risks, such as in patients with conditions including Barrett's oesophagus, severe oesophagitis, documented history of bleeding gastrointestinal ulcers and NSAID use with bleeding risk factors (e.g. concomitant use of anticoagulants or antiplatelets).[49-51]

Deprescribing of benzodiazepine receptor agonists

While the use of benzodiazepine receptor agonists (BZRAs) can be effective for the short-term management of acute severe anxiety or insomnia, **long-term use of BZRAs is associated with problems including tolerance, dependence and withdrawal symptoms.[4,52,53]** The use of BZRAs is especially of concern in the older population as they are associated with an increased risk of adverse effects including falls, drowsiness, cognitive impairment, hypotension and hip fractures.[53] **Therefore these medications should be prescribed with caution, at the lowest effective dose and for the shortest possible duration for the above indications.[4,53]** Regular medication reviews are recommended for those who are prescribed long-term BZRAs.[4,33,53] Analysis of Irish pharmacy claims on the General Medical Services (GMS) scheme data from 2019 indicated that of those patients who were dispensed BZRAs, approximately 15% of benzodiazepines and 27% of z-drugs (e.g. zopiclone and zolpidem) were dispensed for >3 months during the 12-month period.[53] The four most commonly dispensed BZRAs on the General Medical Services (GMS) Scheme in 2019 were zopiclone, zolpidem, diazepam and alprazolam.[53] *The Medicines Management Programme's Guidance on the appropriate prescribing of BZRAs for the treatment of anxiety and insomnia contains useful information including an algorithm for the deprescribing of BZRAs*.[53]

Appropriate patients should be invited to withdraw from long-term BZRA use, and provided with information regarding the harms associated with long-term use and the process of deprescribing.[53] Evidence suggests that the deprescribing of benzodiazepines and other hypnotics is possible in many patients, however patient engagement is important.[24,25,37]

Short-term users of BZRAs (up to 4 weeks) can usually have their dose tapered within 2 to 4 weeks, long-term users however will need to have the BZRA withdrawn over a much longer period of several months or more.[53] **Abrupt withdrawal of BZRAs can result in confusion, toxic psychosis and convulsions, therefore it is important that withdrawal is managed correctly, with gradual tapering of doses**.

There are two approaches to facilitate dose reduction: (i) patients may have their current BZRA slowly withdrawn or (ii) patients may be switched to an equivalent dose of a long-acting slowly-metabolised benzodiazepine such as **diazepam** which is slowly tapered down. Box 1 summarises a suggested approach for managing patients who are suitable to stop BZRAs.

Box 1: A suggested approach for managing patients who want to stop BZRAs*[53,54]

Decide if the patient can reduce the dose and stop their current BZRA without switching to diazepam.

- Switching to diazepam should be considered for:
  - patients on short-acting potent benzodiazepines (alprazolam and lorazepam)
  - patients using preparations that do not easily allow for small reductions in dose (alprazolam, flurazepam, lormetazepam)
  - patients 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).
- Switch the patient to an equivalent dose of diazepam *(equivalent doses outlined in Medicines Management Programme Guidance on appropriate prescribing of BZRA for the treatment of anxiety and insomnia.)*
  - Seek specialist advice before switching to diazepam in patients with hepatic dysfunction as diazepam may accumulate to toxic levels in these individuals
- If switching patient to diazepam, carry out gradually in a stepwise manner. Consider making the first switch in the night-time dose to avoid day time sedation
- Start dose withdrawal when conversion to diazepam is complete
- Upon dose reduction of the patient's current BZRA or diazepam, negotiate a gradual withdrawal schedule which is flexible. Be guided by the patient in making adjustments so that they remain comfortable with the withdrawal process
- Dose tapering such as a 5 - 10% reduction every 1 - 2 weeks, or an eighth of the dose fortnightly, with a slower reduction at lower doses. The rate of reduction should take into account the drug, dose and duration of treatment, as well as personal circumstances
  - Titrate dose according to severity of withdrawal symptoms. If the patient experiences difficulties with a dose reduction, encourage them to persevere and suggest delaying the next reduction. Do not revert to a higher dose. Make future dose reductions in smaller steps if necessary
  - Review frequently to detect and manage problems, and to provide advice and encouragement

summarised from Medicines Management Programme guidance on appropriate prescribing of BZRAs for the treatment of anxiety and insomnia and the NICE CKS Benzodiazepine and z-drug withdrawal

Deprescribing of non-steroidal anti-inflammatory drugs

NSAIDs are associated with gastrointestinal, cardiac and renal adverse effects; older adults are at particular risk.[55-57] There are circumstances where the use of NSAIDs is associated with significant risk, and should be avoided where possible (see table 2).[33] An Irish study of PIP prevalence in primary care has found that the use of NSAIDs in patients with moderate-severe hypertension to be the most frequent potentially inappropriate drug, as per the STOPP criteria.[58]

Where an NSAID is deemed necessary, it should be prescribed with caution and for the shortest time and lowest effective dose possible.[56,57] The discontinuation of NSAIDs, particularly in chronic pain or inflammatory disorders can be particularly challenging in primary care. There is evidence for the benefit of non-pharmacological interventions, such as physical activity, for the management of chronic pain.[55] From a pharmacological perspective, alternatives (if necessary) include the use of topical NSAID preparations and non-NSAID oral analgesics.[55-57] Consultation with the patient is of vital importance, and it may be that a shared decision is made to continue with an NSAID, after the patient has been made aware of the potential risks.[33]

Table 2: High risk use of NSAIDs[33]

Adverse Drug Reaction	Risk factors include
Gastrointestinal	Age >75 years History of gastrointestinal ulcer Use with antiplatelets and anticoagulants, steroids and selective serotonin reuptake inhibitors Heavy alcohol use *If NSAIDs are essential: Consider gastro-protection with a PPI*
Cardiovascular	CVD risk >20% Previous CVD events Heart Failure
Renal	Age >65 years On angiotensin converting enzyme inhibitor, angiotensin II receptor antagonist and/or diuretics Chronic kidney disease or heart failure *If NSAIDs are essential: Monitor eGFR; stop during intercurrent illness*

NSAID – non-steroidal anti-inflammatory drug; PPI – proton pump inhibitor; CVD cardiovascular disease; eGFR – estimated glomerular filtration rate

SUMMARY

Deprescribing is an effective intervention to reduce PIP and the risk of ADRs. It is a patient centred process, requires shared decision making and monitoring for adverse effects. There are multiple barriers to deprescribing in primary care, however a structured medication review process can identify therapeutic agents for deprescribing. Long-term use of PPIs, BZRA medications and NSAIDs are recognised as common indicators of PIP in the elderly, and are highlighted as specific areas for deprescribing.

USEFUL RESOURCES FOR DEPRESCRIBING

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 Guidance Realistic Prescribing 3rd Edition 2018	https://www.therapeutics.scot.nhs.uk/wp-content/uploads/2018/04/Polypharmacy-Guidance-2018.pdf *(important to check for further updated guidance)*
Canadian Deprescribing Network	https://www.deprescribingnetwork.ca/
Australian Deprescribing Network	https://www.australiandeprescribingnetwork.com.au/
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