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Title: **A narrative review of the safety concerns of deprescribing in older adults and strategies to mitigate potential harms**

Abstract

Introduction: As with prescribing or continuing medications, deprescribing brings with it the potential for harm as well as benefit. Uncertainty and avoidance of harm has been reported as a barrier to deprescribing in practice and may contribute to continuation of inappropriate medications.

Areas covered: This narrative review covers four main safety concerns/potential harms of deprescribing in older adults: adverse drug withdrawal events, return of medical condition(s), reversal of drug-drug interactions and damage to the doctor-patient relationship. These are discussed in relation to medications in general, with some examples of medication classes used to illustrate the potential safety concerns. The majority of these harms can be minimized or even prevented by using a patient-centered, structured deprescribing process with planning, tapering and close monitoring during, and after medication withdrawal.

Expert opinion: More research is needed into the safety concerns of deprescribing, however, avenues exist during drug development and post-marketing surveillance to gain knowledge on this topic. Questions remain about when it is suitable to discontinue certain medications/medication classes and there is uncertainty about the harms and benefits of both medication continuation and discontinuation in complex older adults.

Keywords: adverse drug withdrawal reactions, deprescribing, doctor-patient relationship, drug-drug interactions, drug safety, older adults, risk management

Article highlights

- Overall, the chance of serious harm from adverse drug withdrawal events (ADWEs) appears to be rare, especially if tapering is conducted. However, there is a need for larger randomized

controlled trials to accurately estimate the prevalence and potential severity of ADWEs from deprescribing as well as determining the best strategy for reducing the risk of ADWEs.

- Mitigating the risks associated with return of condition involves close monitoring, tailored to the individual and medication in question with re-initiation of the medication (or initiation of alternative drug or non-drug treatment) where a return in condition is suspected or confirmed.
- Several predictors have been found to increase the risk of return of condition after medication withdrawal including previous indication for use and characteristics of the individual. The predictors appear to be specific to the medication/medication class.
- Little research is available to guide the management of reversal of drug-drug interactions upon deprescribing, however, general principles of management of drug-drug interactions (i.e. monitoring based on known pharmacokinetic and pharmacodynamic properties) can be employed.
- Both prescribers and patients/caregivers believe that a pre-existing good relationship coupled with clear and open communication to achieve shared-decision making are beneficial for positive deprescribing interactions.

1. Introduction

Appropriate use of medications involves the prescription of medications where the likely benefits outweigh the potential harms in that individual. Other considerations include whether there is a more suitable alternative (e.g. safer or less expensive) and whether it aligns with the individual's goals of care, preferences and values [1,2]. Benefits and harms of medication use are not static – both can change over time in an individual. For example, likely benefit may reduce if the medication is continued beyond the recommended course of treatment (i.e. no longer needed), no longer effective or if there are changes in care goals. Potential for harm from medication use can increase due to new medical conditions and medications (leading to drug-disease and drug-drug interactions), reduced physiological reserve and changes in pharmacokinetics and pharmacodynamics with ageing or other conditions [3,4]. Use of inappropriate medications (i.e. where the harms outweigh the benefits) has been associated with negative health outcomes such as adverse drug reactions, reduced quality of life and mortality [5–8].

Deprescribing is the process of withdrawal (and/or dose reduction) of inappropriate medications supervised by a health care professional [9,10]. High levels of inappropriate medication use in older adults across a variety of settings and countries [11–14] suggest that there are currently unrealized opportunities to conduct deprescribing. Medications may be initiated for an appropriate reason (indication), but insufficient monitoring and follow-up, transfer between providers and care settings and devolving responsibility may contribute to these medications being continued indefinitely and inappropriately.

The potential benefits of deprescribing may include improved adherence and quality of life, and reduced adverse drug reactions, falls and mortality [15–18]. Recent systematic reviews have concluded that deprescribing appears to be feasible and safe [16,18]. However, as with initial prescribing or continued prescribing, deprescribing brings with it the potential for harm as well as benefit. Uncertainty and avoidance of harm has been reported as a barrier to deprescribing in practice and may contribute to continuation of inappropriate medications [19–21]. The aim of this manuscript, therefore, was to review the potential safety concerns about deprescribing and discuss how these harms can be avoided or minimized.

This narrative review was informed by a literature search conducted in May 2017. We proposed four main safety concerns/harms based on prior literature and the authors' expertise: adverse drug withdrawal events (ADWEs), return of medical condition(s), reversal of drug-drug interactions and damage to the doctor-patient relationship. We conducted searches into each of these four topics using PubMed and Google Scholar where necessary to identify previously published systematic reviews and original studies (where no review existed). From these articles we also extracted potential risk mitigation strategies. Reference lists, citation checking and personal reference libraries were also utilized. This manuscript is not a systematic review, instead it aimed to give an overview of the principles of this broad topic and provide practical insights into mitigating potential harms. As such, medications in general are discussed while examples of medication classes are provided to illustrate the potential safety concerns.

2. Safety considerations

2.1 Adverse Drug Withdrawal Events

An ADWE is defined as a "clinically significant set of symptoms or signs caused by the removal of a drug" [22]. ADWEs can be caused by return of the medical condition which the drug was being used to treat (indicating that the medication was having a benefit) or due to a physiological alteration caused by the medication (withdrawal reaction/physiological ADWE). These two types of ADWEs can be difficult to differentiate in practice. For the purpose of this review we discuss ADWEs as a physiological reactions to withdrawal of medications in this section (e.g. rebound phenomena due to alterations in receptor binding or down or up-regulation of co-factors) and symptoms due to the return of the medical condition in the next section. Physiological ADWEs can manifest as similar symptoms to those that the drug is indicated for (e.g. rebound hypertension on discontinuation of an alpha-antagonist) or as completely new symptoms (e.g. nausea and weakness on discontinuation of corticosteroids) [22,23]. In a recent systematic review and meta-analysis on the feasibility and effect on mortality and other health outcomes of deprescribing medications in older adults, the most frequent ADWEs reported were exacerbations of the underlying condition for which the medication was originally prescribed, or known physiological withdrawal effects [18]. Although their meta-analysis demonstrated no statistically

significant increase in ADWEs [18], the potential consequences of ADWEs in an individual needs to be carefully considered when deprescribing [24].

An example of a physiological reaction to withdrawal is rebound acid hypersecretion after discontinuation of long term use of proton pump inhibitors (PPIs). Long term suppression of gastric acid release is thought to lead to up-regulation of receptors and increased production of acid stimulating factors. Decreased stomach pH, return of gastrointestinal reflux symptoms and new presentation of reflux symptoms in healthy volunteers have all been described in studies of abrupt PPI discontinuation [25–28].

There are several medication classes which are known to cause ADWEs. Corticosteroids are considered at high risk of causing discontinuation syndromes as long term use can lead to suppression of the hypothalamic-pituitary adrenal axis [29,30]. Abruptly ceasing corticosteroid therapy can result in adrenal insufficiency and can be highly dangerous with manifestations such as nausea, fever, anorexia, lethargy, arthralgias, postural hypotension, hyponatremia and hyperkalemia [31]. Other medications frequently associated with ADWEs include those acting on the central nervous system (CNS), such as antidepressants, anti-parkinsonian agents, antipsychotics, benzodiazepines and narcotic analgesics, and those acting on the gastrointestinal system, such as anti-reflux medications [23,32,33].

ADWEs are not uncommon in older adults. In a study observing the prevalence of medication discontinuation in ambulatory older adults enrolled in a 1-year health service intervention trial, 26% of participants experienced an ADWE. Forty-two percent of the ADWEs were due to cardiovascular medications and 18% were associated with CNS medications [22]. In a retrospective study of 175 nursing home residents and 190 drug discontinuations, 62 individuals experienced 94 ADWEs over an 18-month period. Again, the most common drug classes were cardiovascular and CNS medications, as well as gastrointestinal drugs [34]. In this study, an increased number of diagnoses, increased number of medications, longer nursing home stays and hospitalization were risk factors associated with ADWEs [22]. In a retrospective cohort study that aimed to describe the prevalence of unplanned hospitalizations caused by therapeutic failures and ADWEs in community-dwelling older adults in the USA, 1% of unplanned admissions were caused by ADWEs [35]. In this study, eight cases were identified as ADWE-related hospitalizations, where five cases were associated with cardiovascular medications and three cases were associated with CNS medications [35].

ADWEs may be prevented by tapering (slowing reducing the dose prior to discontinuation) the medication, rather than abrupt discontinuation [23,36–38]. However, it is possible for a withdrawal reaction to occur even with tapering [22]. A recent systematic review of interventions to deprescribe benzodiazepines and other hypnotics among older people examined seven publications and concluded that tapering appeared to be an effective strategy to minimize ADWEs. However, they noted that there was scarce information on the best way to conduct tapering in practice [39]. This is true for many medication classes; that is, tapering is recommended but optimal tapering regimens are understudied [23,37]. To address this issue as a barrier to deprescribing in practice, a number of medication-specific evidence based guidelines on deprescribing (proton pump inhibitors, benzodiazepines, antipsychotics

and anti-hyperglycemics) include practical recommendations on how to conduct tapering [40]. Information about the duration of use, cumulative dose and pharmacokinetic and pharmacodynamic properties of the medication may be used to inform the tapering regimen [23,41]. For example, a slower tapering regimen with small dose reductions is recommended in individuals who have been taking a corticosteroid for a long period of time and at high doses [29,30]. Medications with longer half-lives require longer monitoring for ADWEs after discontinuation. For example, in a randomized controlled trial of deprescribing medications in frail older people, where the intervention included an individualized medication review followed by the planned discontinuatio of non-beneficial medications, two participants in the intervention group experienced significant ADWEs [32]. One individual experienced increased agitation from the discontinuation of oxazepam whilst the other was diagnosed with symptomatic rapid atrial fibrillation requiring hospitalization following discontinuation of amiodarone five months prior [32]. The tapering regimen may also need to be tailored to the individual and their circumstances such as whether they use a dose administration aid or have a carer involved in medication administration [36].

Tapering to prevent withdrawal reactions is desired not only to prevent patient discomfort but also to attempt to distinguish a physiological withdrawal reaction from return of the medical condition (which necessitates re-initiation of the medication and/or other management strategies). As symptoms of rebound phenomena can mimic the original condition, tapering may increase confidence of the health care professional that the symptoms reflect a true return of medical condition (i.e. that the medication was having a beneficial effect). In addition to prevention of ADWEs, tapering of medications prior to discontinuation may increase patient willingness to try deprescribing, and where there is a return of the condition, minimize the impact of the return of symptoms and assist in identifying the lowest effective dose [36].

Depending on individual circumstances, it may be possible for multiple medications to be discontinued simultaneously [23]. In a recent randomized controlled trial involving deprescribing medications in frail older people living in residential aged care facilities, up to three medications could be withdrawn concurrently, with consideration on the likelihood of the medications causing ADWEs when withdrawn. The study investigators only withdrew more than one medication in cases where either ADWEs were unlikely, or if the ADWEs were predictable, thus allowing the discontinued medication to be restarted if the ADWE was observed [32].

Medications that may not require tapering when being discontinued include aspirin, statins and multivitamins (in people with an adequate nutritional intake). These medications, along with bisphosphonates, iron supplements and angiotensin II antagonists, were shown to have the highest success rates of discontinuation in a recent randomized controlled trial and have a low risk of a physiological ADWE [32].

Overall, the chance of serious harm from ADWEs appears to be rare, especially if tapering is conducted [22,35,42]. However, there is a need for larger randomized controlled trials to accurately estimate the

prevalence and potential severity of ADWEs from deprescribing as well as determining the best strategy for reducing the risk of ADWEs.

2.2 Return of medical condition

Upon discontinuation of a medication there is the potential for a return of the medical condition which the medication was being used to treat. As mentioned above, this occurrence of symptoms may not be clearly differentiated from ADWEs in deprescribing studies. Timing of the occurrence of symptoms may act as a differentiating factor, such as with return of insomnia after benzodiazepine discontinuation. Sleep problems have been found to be more common during the withdrawal phase but once tapering is complete, a return of insomnia symptoms appears less likely [43]. Insomnia during tapering and immediately after discontinuation is likely due to an ADWE, while return in the longer term may reflect a true return of condition. Systematic reviews have described the ability to withdraw benzodiazepine use in approximately 25 to 85% of older adult users without return of condition (often with tapering regimens to minimize ADWEs) [39,42].

The prevalence of return of condition following deprescribing as determined by need to restart the medication may vary between 2 and 80% [44–46]. This large variability is due to many factors including differences in population, in medications that were stopped, in the process of deprescribing employed and the follow-up period. Below we discuss the reported rates of return of condition of several of the most commonly used (and commonly studied) medications used both to treat symptoms and as preventative medications. The populations in the discussed articles vary significantly as do the methods of determining whether the medication is appropriate to stop. We also outline possible predicting factors for return of condition and discuss mitigation strategies.

2.2.1 Medications for symptomatic conditions

Among individuals taking long-term PPIs for Gastro-Esophageal Reflux Disease (GERD), dyspepsia, or unknown indication, recurrence of symptoms that requires resumption of therapy occurs in approximately 30-70% of individuals over a 12 month period following deprescribing [47,48]. Intermittent use of alternative treatments may halve the number of individuals requiring PPIs to be recommenced [49]. By comparison, approximately 20% of trial participants who continued their PPI have recurrence of symptoms [50]. Symptoms return most often within four weeks of deprescribing (some of which may reflect a physiological ADWE, discussed in the previous section) while recurrence may be more likely in males and those taking PPIs for GERD [50,51].

Among people with coronary artery disease who were previously angina-free, deprescribing of nitrates resulted in symptoms returning in 10% compared to 2.5% of those continuing during 3 month follow-up. In all cases this occurred within one month and restarting nitrate treatment resulted in improvement in individuals' symptoms [52].

Fear of symptom return may also be a concern when stopping antipsychotics for behavioral and psychological symptoms of dementia (BPSD). Studies report a worsening of symptoms in 13-25% of participants following deprescribing [53–55]. However, BPSD symptoms are known to fluctuate and a Cochrane review conducted in 2012 found no significant difference in neuropsychiatric or behavioral symptoms between individuals deprescribed and those who continue based on randomized, placebo-controlled trial data [56]. Worsening of symptoms may be more likely in individuals with agitation and psychosis who had responded well to treatment and those with more severe symptoms at baseline [56].

Clinicians may also consider deprescribing long term cholinesterase inhibitors in people with Alzheimer's disease. Evidence is unclear on which individuals are suitable to discontinue these medications without deterioration of cognition [57], though deterioration may be more likely in individuals with delusions or hallucinations [58]. Concerns about harm (worsening of cognitive scores) that cannot be reversed upon re-initiation of cholinesterase inhibitors has been reported [59,60]. However, there are significant limitations to these studies and these claims have not been substantiated in other studies [61,62].

For stable participants taking diuretics, return of clinical signs required diuretic therapy to be resumed in 0-60% of individuals within six months of deprescribing [46,63–65]. Signs of heart failure, hypertension, respiratory symptoms, weight gain, and ankle edema were more common in these individuals compared to those continuing diuretics. Women and individuals where the initial indication was heart failure as opposed to hypertension or ankle edema were more likely to have symptom recurrence [65]. With regular monitoring, most of these cases can be identified routinely to minimize consequences for individuals [63], and symptoms reverted to baseline levels after treatment was restarted [66].

2.2.2 Preventative medications

As opposed to symptomatic treatments where individuals can identify and report symptoms that recur, preventative treatments, such as many cardiovascular medications, may require more vigilant monitoring to detect signs of a condition/risk factor returning. While it is not possible to truly detect a 'return of condition' for preventative medications (as these medications reduce/treat risk factors with the aim of preventing future events), it may be possible to monitor the same surrogate markers that are used during treatment initiation following discontinuation (for example, blood pressure).

In studies of antihypertensive deprescribing, 20-85% of participants remained normotensive for 4-260 weeks [46]. A systematic review of antihypertensive withdrawal trials found that on average, 40% of participants at one year and 26% at two years were normotensive, however, studies were generally small and heterogeneous, and more recently published studies tended to show greater return of hypertension [67]. Recurrence was less likely in participants with lower blood pressure and in those on monotherapy before deprescribing [67]. Other predictors differed across studies; there may be a lower risk of return of hypertension in individuals who are younger, diagnosed more recently, or with no history of cardiovascular disease [68,69]. Although beta blockers have been linked to ADWEs, they were not associated with symptoms after withdrawal completion in one study [70]. Hypertension returns most often in the first 3-4 months therefore increased monitoring during this period may be appropriate

[69,71,72]. Regarding the long term preventive role of antihypertensives, cardiovascular event rates were not significantly different before withdrawal, during/after withdrawal, and after resumption of antihypertensive treatment in one study [73], while another found those deprescribed had an equal mortality risk and fewer cardiovascular events than those resuming treatment [74]. Participants in these studies were selected as suitable for deprescribing (i.e. were taking antihypertensives inappropriately). Studies of digoxin deprescribing in older adults in sinus rhythm have found that 9-25% of individuals have worsening clinical condition or symptoms [75–78], generally within the first six weeks [76,77], whereas return of condition was more common following deprescribing in individuals with atrial fibrillation [75].

After deprescribing of bisphosphonates in postmenopausal women treated for 3-5 years, bone mineral density declined significantly, although levels remained better than pre-treatment levels [79,80]. With the exception of vertebral fractures, deprescribing does not appear to increase fracture risk [80,81]. Bisphosphonates, however, present a unique situation of sustained effect as the drug becomes incorporated into the bone. It is thought that there may be a residual effect due to re-release of the drug locally and systemically due to bone resorption [80].

Deprescribing of preventative medications may be more challenging where there is no surrogate measure that can be used to monitor potential event risk, for example aspirin for cardiovascular prevention or antiepileptics for prevention of seizures where a clinical event may have significant consequences for individuals. There is no way of monitoring whether this will occur or not following deprescribing (until the point of the cardiovascular event or seizure). When antiepileptics are withdrawn among individuals who have been seizure-free for ≥2 years, seizures recur in 34% at 3-4 years [82]. Few studies identifying predictors of recurrence have included older adults therefore limiting the utility of this evidence to inform antiepileptic deprescribing decisions in this age group [82].

As discussed throughout the above section, mitigating the risks associated with return of condition involves close monitoring, tailored to the individual and medication in question with re-initiation of the medication (or initiation of alternative drug or non-drug treatment) where a return in condition is suspected or confirmed. Several predictors have been found to increase the risk of return of condition. These may relate to the indication for use or characteristics of the individual and appear to be specific to the medication/medication class. Other factors that may be causing symptoms at the time of deprescribing should be considered (such as ADWEs) and change in condition should be considered against the overall disease trajectories where the condition is known to fluctuate (for example when deprescribing antipsychotics in people with dementia).

2.3 Reversal of drug-drug interactions

The prevalence of drug-drug interactions increases with increasing numbers of medications [83]. The overwhelming majority of literature considers drug-drug interactions in the context of initiating a new medication. However, there is limited research on the reversal of drug-drug interactions with

deprescribing [84]. Therefore first principles should guide clinical decisions, especially when a medication with a narrow therapeutic index is involved [85].

Drug-drug interactions can be the result of pharmacokinetic or pharmacodynamics interactions, with the most common pharmacokinetic interactions involving enzyme induction or inhibition [86]. While we did not identify any studies which reported clinical outcomes of reversal of enzyme induction/inhibition DDIs through deprescribing, this concept has been established in the literature on smoking cessation. The enzyme *CYP1A2* is induced by smoking, especially in people with the *CYP1A2*1F* polymorphism [87]. Clozapine, an antipsychotic medication with a narrow therapeutic index, is metabolized by *CYP1A2*. Clozapine toxicity has been reported in individuals who stop smoking owing to the reduction in *CYP1A2* activity [87]. Likewise, case reports were identified which described hospitalization for opioid and theophylline toxicity following smoking cessation (due to reversal of *CYP1A2* induction) [88,89]. In these cases, toxicity occurred shortly after the cessation of smoking, however, some studies suggest *CYP1A2* may take several months to return to normal levels [90]. Thus clinicians should be aware of the potential for reversal of drug-drug interactions during this time.

A medication's half-life and duration of action also impact the time required for pharmacokinetic and pharmacodynamics drug-drug interactions to reverse after deprescribing. For example, consider individuals who have a stable INR while concomitantly prescribed warfarin and either simvastatin or amiodarone. If simvastatin is deprescribed, a reduction in INR is likely to occur quickly in individuals with *CYP2C9*3* polymorphism [91]. Conversely, because of amiodarone's long half-life, the INR will take a few months to gradually reduce after deprescribing [92]. As such, monitoring needs to be tailored based on this knowledge.

Prescribing medications that both increase and decrease serum potassium is an example of a common pharmacodynamic drug-drug interaction. Guidelines recommend testing serum potassium levels when initiating medications that alter potassium levels, however, there are no recommendations for monitoring when they are deprescribed [93]. In a study where participants took both a potassium increasing and decreasing medication, over 90% of participants who had one of the medications deprescribed had changes to their serum potassium level [84]. Hyperkalaemia and hypokalaemia were reported in 3.2% and 17.2% of participants respectively, however, the clinical importance of this was not reported.

Harmful outcomes from drug-drug interactions at the initiation of therapy are assessed in pharmacoepidemiological studies [94]. We were unable to identify any pharmacoepidemiological studies investigating harmful outcomes from drug-drug interaction reversal as a result of deprescribing. This remains an area for future research.

2.4 Harm to the doctor-patient relationship

The final harm to be discussed in this narrative review is the potential for deprescribing to damage the doctor-patient relationship. A good doctor-patient relationship is important for delivering patient-centered care and achieving the best health outcomes for individuals [19,95–97].

Two systematic reviews exploring General Practitioner (GP) and prescriber attitudes reported concern about this harm as barriers to reducing polypharmacy and inappropriate medication use [19,20]. Anderson and colleagues reported that a fear of 'unknown or negative consequences of change' including damage to the therapeutic relationship, acted as a barrier to deprescribing contributing to the theme of 'inertia'. Additionally, under the theme of 'feasibility', included studies reported that patients were perceived to be resistant to change and not accepting of alternatives [20]. Bokhof and Junius-Walker reported a similar sub-theme of 'GPs' assumptions about patient reactions' which arose from their synthesis of qualitative studies. GPs reported that their patients would be resistant to deprescribing as the expectation is to prescribe [19]. As deprescribing goes against the status quo [98,99], this could be interpreted as a sign of being given up on which in turn could damage the doctor-patient relationship [19]. Deprescribing of preventative medications, particularly in the end of life setting, is seen by prescribers as problematic as they fear that this could be interpreted as withdrawal of care, being no longer worth treating, being 'given up on' or even hastening death. This could be severely damaging to the doctor-patient relationship [100–103]. In a focus group study examining views about use of benzodiazepines in older adults, potential negative outcomes of prescriber initiation of deprescribing included the patient questioning their doctor's authority and competence and even finding an alternative doctor who would prescribe the medication (thus ending the therapeutic relationship) [104].

While these qualitative studies report that prescribers are concerned about potential damage to the doctor-patient relationship through attempted deprescribing, studies capturing patient views do not necessarily echo this concern. The Patients' Attitudes Towards Deprescribing (PATD) questionnaire was developed and validated to explore how individuals feel about this topic [105]. In six separate studies conducted in Australia (n=3 studies) [106–108], Italy [109], Canada [110] and Singapore [111] approximately 70-90% of participants reported that they would be willing to discontinue a medication if their doctor said it was possible. Tjia and colleagues investigated how individuals with a life-limiting illness felt about statin discontinuation (a preventative medication) [112]. Among 297 participants, less than 5% felt that statin deprescribing represented abandonment from their doctor. Many participants even reported anticipating benefits of deprescribing including reduced medication costs (63%) and improved quality of life (25%) [112]. Another study which interviewed individuals who had recently had a medication discontinued found that 73% were satisfied or very satisfied with the decision to discontinue the medication [113]. The results of these studies are in stark contrast to the concerns reported by GPs in qualitative studies. A revised version of the PATD has recently been published [114], as has a questionnaire titled 'Patient Perceptions of Deprescribing' [115], highlighting the ongoing interest in this topic.

Qualitative studies with older adults and caregivers reveal complex and competing views towards medication use and deprescribing, lending some support to the concerns expressed by prescribers.

Fears related to medication discontinuation – both specific (i.e. fear of adverse drug withdrawal reactions and fear of return of condition) and non-specific (unsure how they will cope without their medications) have been reported. Additionally, believing that the medication is appropriate or still needed may be a barrier to deprescribing. These views conflict with feelings of wanting to minimize medication use, fear about adverse effects and preferring non-pharmacological treatments [19,116–119]. Individuals recognize that there are often competing interests with medication use – that they can have both the potential for benefit and harm [97,118]. In a recent mixed methods study, quantitative data found that a majority of participants (total n=196) held a high belief in the necessity of their medications, however, qualitative data from a sub-set of participants (n=11) revealed a complex interplay of positive and negative attitudes about their medications [120]. Similar to the quantitative study by Tjia and colleagues [112], a qualitative study with 12 individuals with a life-limiting illness and 12 caregivers of this population revealed an understanding of the change in appropriateness of medication use at this life stage [121]. Some participants, however, reported being surprised when deprescribing of a medication was recommended as they had been previously told that they needed to take this medication 'for the rest of their life' [121].

In a reverse scenario, patients may be worried about voicing concerns about their medications to their doctor out of fear of damaging the doctor-patient relationship [5]. In a study looking at patient satisfaction and medication appropriateness, four out of every five participants reported satisfaction with their medications while only half felt able to handle their medication regimens, indicating that patient concerns may go unvoiced [5].

Validated tools have been developed to capture the quality of the doctor-patient relationship. These may focus on concepts such as loyalty, communication style, patient trust in their physician or satisfaction with treatment [95]. No studies were identified that quantitatively captured the quality of the doctor-patient relationship before and after a deprescribing intervention. The concept of trust in physician has been discussed in the literature in relation to patient willingness to have a medication deprescribed. In several qualitative studies patients and doctors have emphasized the importance of trust and a good relationship for conducting deprescribing of inappropriate medications as well as enabling overall medication management. Where there is trust, doctors can be a strong influence towards or against deprescribing [19,33,97,116,118,119]. Quantitatively, increased willingness to deprescribe (as measured by the PATD) has been correlated with increased trust in physician (Wake Forest Trust in Physician Scale) in two separate studies [106,111]. Medication adherence has been found to be associated with the quality of the doctor-patient relationship [96,122]. Deprescribing has been reported to potentially lead to increased medication adherence, although there is limited evidence to support this [15,16,123].

While the evidence is sparse, there does not appear to be an overall measurable harm to the doctor-patient relationship. However, this picture is obscured by the way the deprescribing studies are conducted in the research setting (where the GP may or may not be involved in deprescribing decisions).

Qualitative studies revealed strategies to preserve the doctor-patient relationship throughout deprescribing (**Box 1**). Both prescribers and patients/caregivers believed that a pre-existing good relationship coupled with clear and open communication to achieve shared-decision making are beneficial for positive deprescribing interactions.

Box 1: Factors which may support preservation of the doctor-patient relationship throughout deprescribing [20,101–103,120,124–129]

Previously established relationship

- positive past experiences which lead to patient confidence
- long standing relationship with continuity of care
- previous time investment

Where the relationship is new (e.g. patient transferred from another prescriber)

- transparency about medication concerns
- focus on current situation and benefits rather than placing blame

Prescriber characteristics

- supportive
- empathetic
- patient
- perseverant

Patient trust in the prescriber

Adequate discussion/open communication about the decision to deprescribe

- discussion of risks and benefits (in the context of uncertainty)
- place risks and benefits in the context of the individuals goals of care, prognosis values and preferences
- discover and reconcile both parties agendas to find common ground
- use of clear and straightforward language – ensure and check patient understanding
- where there is resistance – determine the reason for the resistance (might be an appropriate reason to continue medication or alter deprescribing process)
- encourage patients/family to voice concerns

Patient-centeredness

- focus on the person, not the disease/conditions
- know the patient, e.g. living situation, family dynamics
- promote patient-empowerment through education
- consider all dimensions: bio-psycho-social

Use of shared decision making

Adequate time for consultation

- discussion may occur over multiple consultations
- with opportunity for follow-up consultations

Tailor deprescribing process to patient needs and potential for immediate harm from the medication

Where necessary, gain a second clinical opinion , e.g. geriatrician, psychiatrist, other specialist or pharmacist

3. Conclusion

The potential harms from deprescribing include ADWEs, return of condition, reversal of drug-drug interactions and damage to the doctor-patient relationship. However, the majority of these harms can be minimized or even prevented by using a patient-centered, structured deprescribing process with planning, tapering and close monitoring during, and after medication withdrawal.

4. Expert Opinion

More research is needed to address the safety concerns of deprescribing. Questions remain about when it is suitable to discontinue certain medications/medication classes. For example, the potential for harm on discontinuation of preventative medications in older adults is not clear for many medication classes. Of note, Kutner and colleagues conducted a randomized controlled trial on discontinuation of statins in individuals with a life expectancy of less than 12 months. They found no difference in mortality or cardiovascular outcomes between the two groups [130]. However, studies like this are rare and as such there is a dearth of information of when and in whom it is suitable to discontinue specific medications. Conducting randomized controlled trials for all medications commonly used in geriatric medicine in all potential situations is, however, not practical and unlikely to be realized.

Another area which is lacking in evidence is information on the potential harms through reversal of drug-drug interactions upon deprescribing. Although it should be noted that information on the clinical significance and management of drug-drug interactions in older adults with polypharmacy is also scarce [86].

Despite the current gap in evidence on the harms of deprescribing Gnjidic and colleagues [131] describe that there are plenty of opportunities for measuring outcomes of deprescribing within current drug development processes. Throughout phase I-V studies participants stop the drug treatment, either as part of the design or due to adverse reactions. Systemic follow-up and recording of outcomes of these participants would greatly add to knowledge on how to best prescribe (and deprescribe) these medications. The 2007 Institute of Medicine future of drug safety report stated that actively pursuing

and collecting new knowledge of the benefits and harms of medication use should continue after approval [132]. Avenues exist for collecting this knowledge related to deprescribing in practice. For example, analysis of large electronic pharmaceutical/medical databases may contain information about deprescribing practices and outcomes in the real world setting. Novel methodologies used for detecting adverse drug reactions and other negative outcomes in pharmacoepidemiology could be applied to studying the potential harms of deprescribing [62,133], although a more systematic approach in recording of outcomes is still needed.

The concern about harm from potential return of symptoms or lack of protection resulting in an event (e.g. cardiovascular prevention) is intrinsically linked with the difficulty in determining if a medication is truly inappropriate for an individual. Older adults are a complex heterogeneous population. Chronological age may not be representative of biological age and the many combinations of medical conditions, medications and social conditions make it impossible for clinicians and researchers to describe the 'typical' older adult. Prescribers have reported this complexity as a barrier to deprescribing, citing a lack of evidence and a lack of generalizability of the evidence to the individual that they are treating [19,20]. Many implicit and explicit tools have been developed to help health care professionals in the identification of inappropriate medications; while they are widely used in research, they have not yet been adopted into routine practice [1].

When applying the principles of risk assessment to the deprescribing process, the occurrence likelihood varies depending on characteristics of the patient and the medication deprescribed, from improbable to expected. The effect of the impact is usually insignificant or minor. Therefore, based on existing evidence, on a risk matrix, deprescribing is considered low or moderate risk. Risk controls for deprescribing can be considered within the hierarchy of controls framework [134]. The current controls are predominantly administrative, through education to health care practitioners and consumers. While such controls are considered relatively weak in risk management, the strongest controls such as elimination or substitution of deprescribing, would result in perpetuation of the hazards of inappropriate polypharmacy.

Overall, there may be considerable uncertainty in the determination of appropriateness of a medication and the potential resulting benefit or harm of deprescribing in an individual. The concept of uncertainty is inherent in almost all clinical decisions, the challenge for both health care professionals and consumers is moving forward in the face of the uncertainty [135]. This uncertainty in the safety of deprescribing arises from multiple concepts including uncertainty in probability of future events, uncertainty about the strength of effects (and conflicting results from studies), unstudied questions (lack of data) and difficulties translating population level finding to individuals and those not represented in the studies (especially within the complex older population) [136]. Complicating this uncertainty is the knowledge that many high impact clinical studies boasting large effects are later contradicted by other studies [137]. Clinicians may be uncomfortable discussing uncertainty with their patients [135,136]. Anderson and colleagues conducted focus groups with clinicians which revealed the uncertainties confronting them when managing inappropriate polypharmacy in older adults [138]. Their analysis indicated that management of uncertainty was reliant on their framing of risk [138]. Clinicians with

previous negative experiences of discontinuing medication may be hesitant to proactively deprescribe as they may prioritize avoiding harm from deprescribing [138,139]. Potential harm resulting from continuing medications may be a familiar and acceptable risk for clinicians, while potential harm from discontinuation may be measured against this with consequences more strongly weighted than the 'accepted' harms of continuation [138,140,141]. GPs may deal with uncertainty by pursuing an acceptable therapeutic regimen, even if this is not 'ideal' [100].

One of the main recommendations for dealing with uncertainty is to acknowledge it, that is, to discuss it with patients and communicate the source of the uncertainty [132,135]. This discussion can be incorporated into shared-decision making [135,136]. As discussed above, shared-decision making may be essential in maintaining the doctor-patient relationship throughout deprescribing. The process of deprescribing has been described by several authors [4,36]. The proposed processes have similar steps which include taking a comprehensive medication and medical history, identification of inappropriate medications, determination of suitability for discontinuation, planning withdrawal, monitoring, and follow-up and documentation/communication. They also emphasize the need for the individual to be involved throughout the process and participate in shared-decision making. A process such as this integrates the strategies discussed above to mitigate many of the potential harms of deprescribing. Further research is needed into the implementation of deprescribing processes, including development of tools, guidelines and algorithms to assist clinicians and consumers throughout the process.

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