Establishing the worth of deprescribing inappropriate medications: are we there yet?

Ceasing unnecessary medications is a worthy act, but impacts on clinical outcomes are proving elusive

The burden and costs of potentially inappropriate medications (PIMs) and polypharmacy are major public health challenges. Medicines that are ineffective or no longer indicated, discordant with care goals or where harms outweigh benefits should be deprescribed.[1] However, despite the publication of numerous deprescribing studies and guidelines over the past decade, the effectiveness of deprescribing interventions in routine care remains unclear. In this Perspective, we describe the impacts of deprescribing on clinical outcomes, draw insights from recent trials, and discuss opportunities for designing future trials better able to demonstrate the patient-important effects of deprescribing.

Efficacy and safety of deprescribing interventions

Recent systematic reviews of deprescribing trials consistently show decreased prescribing of PIMs[2-4] with no safety concerns due to drug withdrawal. However, while animal studies show that deprescribing reduces frailty and functional impairment,[5] clinical studies in humans have failed to consistently show changes in clinical outcomes such as falls, hospitalisations, adverse drug events, and cognitive and physical function. This may be attributable to limitations in study design, such as:

- underpowered studies;
- residual confounding in uncontrolled trials;
- short term follow-up that fails to ascertain long term effects;
- infrequent use of quality-of-life measures sensitive to change with deprescribing;
- insufficient targeting of patients at highest risk of medication-related harm;
- suboptimal intensity and/or duration of deprescribing interventions; and
- limited use of potentially useful computerised decision support systems to assist deprescribing.[6]

Over the past 5 years, several multicentre randomised controlled trials (RCTs) have attempted to address some of these limitations. The SPPiRE (Supporting Prescribing in Older Adults with Multimorbidity in Irish Primary Care) cluster RCT involving 51 Irish general practices enrolled 404 multimorbid patients aged 65 years or over and receiving 15 or more regular medicines.[7] Intervention practices accessed a website for clinicians to complete an education module and use a template for a once-off patient medication review lasting 30–40 minutes. At the 6-month follow-up, there was a small but significant increase in PIMs reduction in the intervention group (incidence rate ratio, 0.95; 95%CI, 0.899–0.999; $P = 0.045$) but no change in self-reported patient outcomes.

In the SENATOR (Development and clinical trials of a new Software ENgine for the Assessment and optimization of drug and non-drug Therapy in Older peRsons) trial involving 1537 multimorbid older patients with polypharmacy admitted to six European hospitals, computer-generated medication optimisation advice for attending physicians was compared with standard care.[8] Uptake of advice was low (about 15%), and no between-group differences were seen for adverse drug events at 14 days or all-cause death or re-hospitalisations at 12 weeks after discharge.

Another cluster RCT of 3904 adults (aged ≥ 75 years; receiving eight or more regular medications) attending 359 general practices across four European countries evaluated an electronic decision support tool for deprescribing PIMs, incorporated into a comprehensive medication review, against standard care.[9] The composite of unplanned hospital admissions or death at 24 months was no different between groups.

The OPERAM (OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid older people) trial enrolled 2008 patients aged 70 years or over (three or more chronic conditions; five or more long term medications), and randomised 110 clusters of attending hospital physicians across four European countries to usual care or structured medication optimisation reviews performed jointly by a physician and a pharmacist, aided by a decision support system using the STOPP/START (Screening Tool of Older Person's Prescriptions and the Screening Tool to Alert to the Right Treatment) criteria.[10] Despite 61.3% of intervention patients having one or more predominantly PIM recommendations enacted at 2 months, at 12 months drug-related readmissions, all-cause mortality, falls, pain, and activities of daily living status were unchanged, although the quality of life was slightly better in the intervention group.

Most recently, a Canadian cluster RCT enrolled 5698 patients aged 65 years or over who were admitted to 11 hospitals and were taking five or more medications daily.[11] Personalised deprescribing suggestions were generated for the hospital physician, community pharmacist and usual attending doctor by a computerised decision tool (MedSafer). This tool integrated data about home medication lists and patient characteristics, including laboratory investigations and measures of prognosis and frailty, with prescribing guidelines and dosing rules. Even though deprescribing increased from 29.8% among control patients to 55.4% of intervention

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patients, at 30 days after discharge there was no difference in adverse drug events, falls, emergency department visits and/or hospitalisations, deaths, or quality of life, with no variations according to sex, palliative designation, frailty, or residence in a care facility.

Insights for future research

While all these studies confirm deprescribing as being safe, patient-important measures of medication-related harm did not improve. Several possible explanations deserve consideration in designing future deprescribing trials.

Small reductions in harmful medications: Absolute reductions in PIMs were ≤ 1.0 additional medication ceased per intervention patient, and those most frequently deprescribed, such as proton pump inhibitors and vitamin/mineral supplements, infrequently cause measurable harm.

Low uptake of advice: Reported acceptance of deprescribing advice was less than 50%, for various reasons,[12] including delays in clinicians receiving advice, prescriber inertia and lack of self-efficacy in deprescribing medications (especially those outside their specialty or initiated by other clinicians), recommendations of low clinical relevance to individuals, and divergence of opinion among doctors, pharmacists, patients, and family members.

Low intervention intensity: One-off medication reviews performed by a single person may not provide clinicians and patients with adequate time, encounters, information and incentive to formulate, agree, initiate and monitor deprescribing decisions over the long term.

Heterogeneity of treatment effects: Individual patient response to drugs can differ significantly from reported average treatment effects due to age, comorbidity burden and other factors, leading to variable response to deprescribing. At the population level, such heterogeneity may render deprescribing effects undetectable without large samples and subgroup analyses.

Insensitive outcome measures: While adverse drug events are important, other relevant outcomes such as medication burden may not be reliably measured, and multifactorial outcomes such as quality of life and falls may be insensitive to change by an intervention targeting only one of many contributors. Certain benefits may also take a long time to manifest, beyond the sometimes short term follow-up periods of existing trials.

Fragmented care: As patient care spans multiple clinical settings, disconnected information communication results in failure of propagation of, and adherence to, deprescribing decisions through the chain of multiple prescribers.[13]

Changing illness trajectories: Deprescribing is not a one-off activity but needs to be repeated when changes occur in patients' clinical status that alter benefit–harm estimates for specific medications.

Enhancing deprescribing intervention trials

Learnings from these and other studies generate opportunities for designing future trials with greatest potential to demonstrate patient benefit. First, researchers need to consider the barriers and enablers towards deprescribing that exist at multiple levels (Box).[14] Implementation science theories and frameworks[15] may support designing interventions that integrate with clinical workflows and seek to change both clinician and patient behaviour. An interdisciplinary approach to codesigning interventions with medical practitioners, pharmacists and other disciplines may enhance effectiveness through combining existing knowledge with consideration of local context.[16] Continuing patient and provider education tailored to their needs, patient-specific drug recommendations, close clinical follow-up with multiple visits, and reliable communication of deprescribing actions and advice between all participating clinicians are key areas for future work. While researchers can redesign local practice only so much, efforts to apply multiple strategies should be pursued as much as practicable.

Second, hybrid implementation efficacy trials can be used to identify deficiencies in intervention design and delivery while also measuring outcomes.[17] For example, process evaluations in one trial confirmed the utility of awareness-raising strategies for evidence-based prescribing, but in changing behaviour identified additional facilitators, such as academic outreach visits to prescribers, better targeting of high risk patients, more nuanced evidence on medication appropriateness, better integration of decision support tools into practice software, and patient information materials in tailored formats.[18] Adaptive trials with pre-specified interim analyses could identify ineffective interventions or implementation failures (eg, low enactment of deprescribing recommendations) while the trial is running and make adjustments as required. Alternative evidence sources, such as modelling techniques and expert consensus conferences, may need to be considered where the costs and logistical challenges of long term trials prove prohibitive.

Third, where evidence reveals factors predicting individuals more likely to benefit or be harmed by withdrawing problematic medications, such as anticonvulsant[19] and antihypertensive drugs,[20] these should be integrated into guidelines and decision support systems. Machine learning applied to large-scale clinical trial or pharmacovigilance data are identifying patient phenotypes at greater risk of medication-specific harm to whom deprescribing interventions could be targeted.[21,22]

Fourth, sensitive medication-related quality of life measures relevant to both medication class-specific effects and individual goals of care may be better able to detect subtle but important patient-centred outcomes.[23]

Finally, n-of-1 trials, in which patients act as their own control during randomised cycles of exposure to a drug or placebo, may provide more nuanced assessment of

Barriers and enablers to deprescribing: examples across different levels of the health care system[14]

	Barriers	Potential enablers
Individuals/public (including patients and their caregivers)	• Fear or ambivalence about ceasing medications • Belief that their medication is necessary and beneficial • Misperceptions of deprescribing motives (care rationing, or that the prescriber is "giving up") • Previous bad experiences with deprescribing	• Shared decision making that embraces discussion of care goals and treatment preferences • Consumer-facing websites and portals that provide education in medication effects • Decision aids and educational materials that inform and empower patients in shared decision making • Support for the process of deprescribing (eg, follow-up)
Health care professionals	• Lack of tools or resources to assist with deprescribing (or lack of awareness of such tools) • Clinical inertia • Lack of self-efficacy • Personal beliefs and attitudes towards deprescribing (eg, fear of withdrawal reactions) • Deference to professional etiquette/ hierarchies	• Easy to use, accessible tools and resources that account for the whole person with comorbid conditions and frailty • Data to inform nuanced medication-specific benefit–harm estimates of both continuation and discontinuation • Guidelines that use such data to provide nuanced recommendations about individuals most likely to benefit from deprescribing • Deprescribing viewed by all clinicians and disciplines as a normal and positive part of regular care
System of care (local health care organisations and the broader environment)	• Limited time and resources for deprescribing • Focus on acute/presenting problem and culture which drives prescribing • Lack of incentive or renumeration for deprescribing/deprescribing activities • Disconnected information and communication systems relating to medication use	• Organisational and financial support for multidisciplinary care and non-pharmacological alternatives • Protected and scheduled time, financial reimbursement and professional recognition (eg, CPD credits) for conducting regular deprescribing reviews • Fully connected electronic medical records for transferring medication-related information • Clinical decision support systems to trigger the deprescribing process

CPD = continuing professional development. ◆

deprescribing effects in individuals. In a systematic review that found only six deprescribing studies using the n-of-1 method, four were able to show between 44% and 64% of patients successfully ceasing the targeted medication due to non-significant treatment benefits.[24]

Although recent deprescribing trials do not conclude improvement in clinical outcomes, they have signalled areas of innovation and offered insights into designing future trials more likely to establish the worth of deprescribing inappropriate medications. We are not there yet but we are making progress. The members of the Australian Deprescribing Network, the first deprescribing network established internationally and which led the way with policy and practice recommendations,[1,25] are actively contributing to this challenging research agenda.

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