Deprescribing has been shown to Be Possible, not yet to be Beneficial: A Critical Review of the Trial Evidence

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Abstract

Background: Polypharmacy in older adults is near-universal and deprescribing has become a prominent response to it. The literature is frequently read as showing that deprescribing is beneficial. What most of it shows is that medicines can be withdrawn without an immediate deterioration in a surrogate marker, which is a different and weaker claim.

Objective. To examine what deprescribing trials have actually measured, to distinguish evidence of feasibility from evidence of benefit, and to set out what follows for practice.

Findings: The most rigorous trial in the field, OPTIMISE, randomised 569 primary care patients aged 80 years or older with systolic blood pressure below 150 mm Hg and taking two or more antihypertensives to withdrawal of one drug or usual care. Blood pressure remained below 150 mm Hg in 86.4 % of the reduction group and 87.7 % of usual care, meeting non-inferiority against a margin of 0.90 with an adjusted relative risk of 0.98. That is a demonstration that withdrawal was possible without losing blood-pressure control over 12 weeks; the trial was not powered for clinical outcomes, and its four-year follow-up was sized to detect a 58 % increase in hospitalisation or death rather than a benefit. Reduction was sustained in 66.3 % of the intervention group at 12 weeks and in 51 % of survivors at four years, so the intervention decays substantially. Across the field, trials measure whether the drug came off far more often than whether the patient was better off.

Conclusions: Feasibility and benefit are separate questions with separate evidence bases, and they are strongest for different drug classes. Deprescribing is best justified drug by drug, on the grounds that a specific medicine's harms now outweigh its remaining benefit for this patient, rather than by a general presumption that fewer medicines are better.

Keywords: Deprescribing; Polypharmacy, Older Adults, Potentially Inappropriate Medication, Antihypertensives, Evidence Appraisal.

1. INTRODUCTION

Older adults take many medicines, most of them started for a reason that was good at the time, by clinicians who have since moved on, for conditions that may have resolved or become irrelevant to how long the person now has to live. The accumulation is not irrational at any single step and is frequently irrational in total, and deprescribing — the planned withdrawal of medicines whose harms now outweigh their benefits — is the obvious corrective.

The idea is sound and the enthusiasm it has generated has outrun its evidence in a specific way. A substantial trial literature now exists, and it is commonly summarised as showing that deprescribing is safe and beneficial. Reading the trials closely gives a narrower result: that medicines can often be withdrawn without an immediate deterioration in the marker the drug was prescribed to control. That is worth knowing and it is not the same as showing that the patient is better off.

The distinction matters because the two claims license different actions. Evidence that a drug can be stopped supports stopping it where there is already a reason to — an adverse effect, a lapsed indication, a

change in goals. Evidence that stopping improves outcomes would support seeking out patients to deprescribe, which is what quality-improvement programmes built around pill counts actually do.

This review examines the gap. Three questions are addressed. What have the principal trials measured and found? Where does the evidence support benefit rather than feasibility? And what should a clinician do given a literature that is stronger on the first than on the second?

1.1 Scope and approach

This is a critical narrative review, not a systematic one. Trials and syntheses were identified through targeted searching and reference lists, and selected to represent the range of design quality and of drug classes rather than exhaustively. No protocol was registered, no formal appraisal instrument was applied, and the assessments in Figure 4 and Table 4 are the author's judgement. Quantitative findings are reported as published.

2. WHAT THE PRINCIPAL TRIALS FOUND

2.1 Optimise

OPTIMISE is the most rigorous trial in the field and repays close reading. It enrolled 569 participants from 69 English general practices, aged 80 years or older, with systolic blood pressure below 150 mm Hg and taking two or more antihypertensive medications, excluding those with previous myocardial infarction, heart failure or stroke. Mean age was 84.8 years, 48.5 % were women, and the median baseline count was two antihypertensives. Participants were randomised to removal of one antihypertensive or to usual care.

Table 1. OPTIMISE: design and findings as published

Feature	Value
Design	Open-label, randomised, non-inferiority trial in primary care
Participants	569 (intervention 282, control 287); 534 (93.8 %) completed
Population	Age ≥ 80 years, systolic BP < 150 mm Hg, ≥ 2 antihypertensives
Intervention	Removal of one antihypertensive
Primary outcome	Systolic BP below 150 mm Hg at 12 weeks
Non-inferiority margin	Relative risk 0.90
Result	86.4 % versus 87.7 %; adjusted RR 0.98 (97.5 % one-sided CI 0.92 to ∞)
Reduction sustained at 12 weeks	187 participants (66.3 %)
Secondary outcomes	Five of seven showed no significant difference
Long-term follow-up	Median 4.0 years; sized to detect a 58 % increase in hospitalisation or death
Reduction sustained at follow-up	109 participants, 51 % of those alive in the intervention group

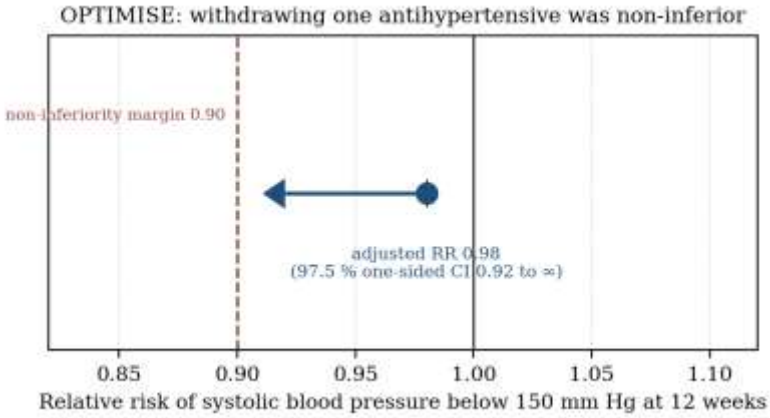

Figure 1. The OPTIMISE primary result against its non-inferiority margin.

The result is clean and the conclusion the investigators drew is the correct one: in this carefully selected group, withdrawing one antihypertensive did not meaningfully worsen blood-pressure control over twelve weeks. Three features of the design bound what else can be inferred from it.

The population was selected for the absence of a compelling indication, excluding previous myocardial infarction, heart failure and stroke. The finding therefore applies to patients in whom a clinician was already in equipoise, not to older patients on antihypertensives generally.

The outcome was a surrogate, and a lenient one. Maintaining systolic pressure below 150 mm Hg is not the same as maintaining cardiovascular protection, and the trial reported a modest rise in blood pressure in the intervention group alongside non-inferiority on the dichotomised outcome.

And the design was non-inferiority, which as a matter of logic can establish the absence of a large harm and can never establish a benefit. The long-term follow-up was powered to detect a 58 % increase in hospitalisation or death, which is a large harm; it was not powered to detect a benefit of any size, and reporting it as showing that deprescribing was safe over four years is the strongest reading its design supports.

2.2 Deprescribing decays

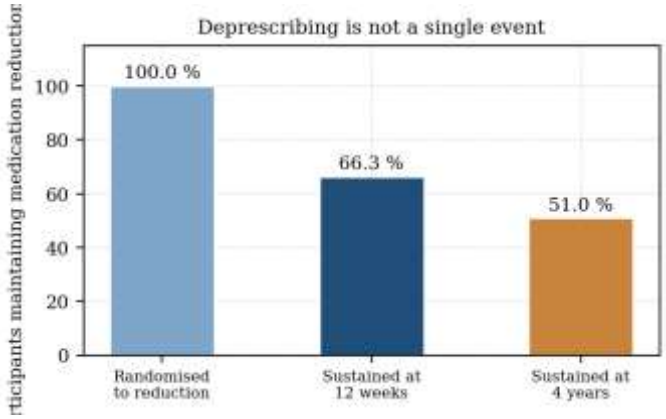

Figure 2. Proportion of the OPTIMISE intervention group maintaining medication reduction over time.

A third of the intervention group had medication reinstated within twelve weeks, and by four years only half of surviving participants were still on the reduced regimen. This is among the most practically useful findings in the field and it is rarely emphasised.

It means that deprescribing is not an event but a state requiring maintenance, and that the effect of any single deprescribing intervention on the medication burden a patient carries is roughly half what the immediate post-intervention count suggests. It also means that trials reporting only the medication count at the end of the intervention period systematically overstate what they achieved, and that quality metrics built on such counts will do the same.

3. WHAT THE FIELD MEASURES

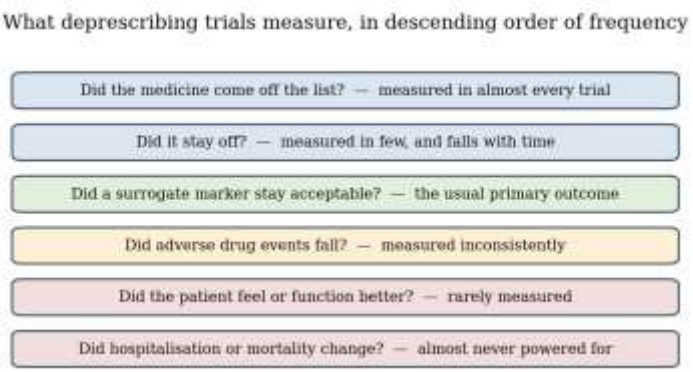

Figure 3. Outcomes of deprescribing trials, ordered by how often they are measured.

Figure 3 states the structural problem. The outcome measured in almost every trial is whether the medicine came off the list, which is a measure of the intervention rather than of its consequence. Outcomes closer to what a patient would recognise as benefit — feeling better, functioning better, being admitted to hospital less often — are measured least.

This ordering is not a failure of investigators so much as a consequence of what is affordable. A trial powered to detect a difference in hospitalisation from withdrawing one medicine in a population whose annual hospitalisation risk is moderate would require several thousand participants followed for years. A trial that counts pills requires a few hundred for a few months. The literature has been shaped by that arithmetic, and it is worth stating plainly rather than treating the resulting evidence as though the harder studies had been done.

Table 2. Principal trial designs in the field and what each can establish

Design	Typical primary outcome	What it can establish	What it cannot
Non-inferiority withdrawal trial	Surrogate marker maintained	That withdrawal does not cause a large deterioration	Any benefit; small harms; long-term effects
Educational or pharmacist-led intervention trial	Proportion of target drugs discontinued	That prescribing behaviour can be changed	Whether patients gained anything
Cluster-randomised implementation trial	Medication counts or appropriateness scores	That a programme is deliverable at scale	Clinical consequence
Observational cohort with deprescribing exposure	Mortality or hospitalisation	Association only	Causation; confounding by indication is severe here

The last row deserves particular caution. Observational comparisons of patients who were and were not deprescribed are confounded in a direction that is difficult to reason about: clinicians stop medicines both in patients who are doing well enough not to need them and in patients who are dying, and those two groups have opposite prognoses. Studies reporting that deprescribing is associated with better or worse outcomes are largely reporting which of those motivations dominated in their setting.

3.1 Where benefit has been shown, and where it has not

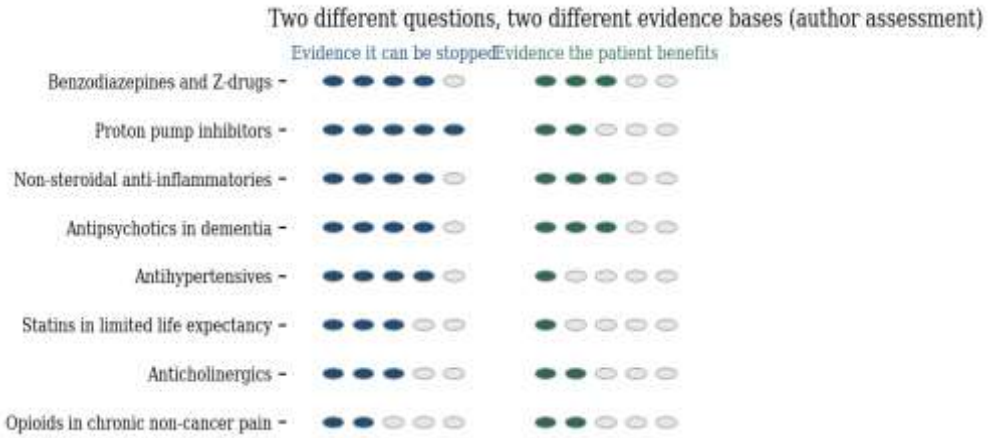

Figure 4. Evidence that a class can be withdrawn against evidence that patients benefit. Assessments are the author's judgement.

Table 3. Drug classes and the basis for deprescribing

Class	Basis for withdrawal	Strength of the benefit case
Benzodiazepines and Z-drugs	Falls, fractures, cognitive impairment, dependence; efficacy for insomnia is short-lived	Reasonable: harms are well characterised and continuing benefit is doubtful
Proton pump inhibitors beyond indication	Prolonged use without indication; infection and fracture associations	Moderate: withdrawal is easy and continuing benefit is often absent
Non-steroidal anti-inflammatories	Gastrointestinal, renal and cardiovascular harm	Reasonable, where an alternative analgesic exists
Antipsychotics in dementia	Mortality and cerebrovascular risk; limited efficacy for most symptoms	Reasonable, though withdrawal can precipitate relapse in some patients
Antihypertensives	Hypotension, syncope, acute kidney injury, electrolyte disturbance in frailty	Weak: feasibility shown in selected patients, benefit not demonstrated
Statins in limited life expectancy	Time to benefit exceeds prognosis	Weak: reasoning is sound, trial evidence scarce
Opioids in chronic non-cancer pain	Limited long-term efficacy; dependence and overdose risk	Weak, and abrupt withdrawal carries its own documented harms

The two columns of Figure 4 come apart most sharply for antihypertensives, which is instructive because that is where the strongest trial sits. OPTIMISE established feasibility convincingly and benefit not at all, and a recent systematic review of economic evaluations reported that deprescribing was most consistently cost-saving for sedatives, non-steroidal anti-inflammatories and prolonged proton pump inhibitor use, while evidence for antihypertensive deprescribing was limited and context-dependent, with one model suggesting potential long-term harm under specific assumptions.

The pattern that emerges is that the benefit case is strongest where a class has well-characterised harms and doubtful continuing efficacy, and weakest where the drug is genuinely effective and the argument for stopping rests on frailty or prognosis. That is intuitive and it has a consequence: deprescribing programmes that target medication counts rather than specific classes will spend most of their effort in the region where the case is weakest.

3.2 Time to benefit

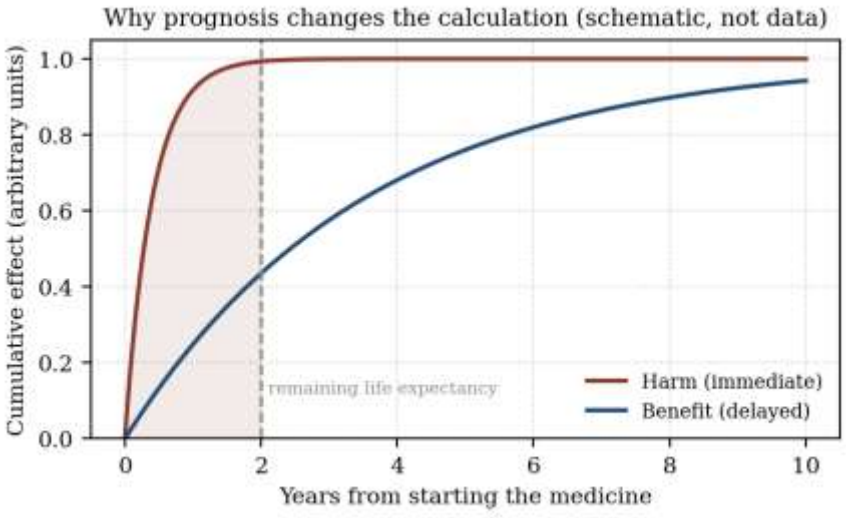

Figure 5. Why prognosis changes the calculation: harms accrue immediately while benefits accrue over years. Schematic, not data.

The most defensible general argument for deprescribing is not that fewer medicines are better but that many preventive medicines have a time to benefit measured in years while their harms begin immediately. A patient whose remaining life expectancy is shorter than the time to benefit is exposed to the whole of the harm and to a fraction of the benefit, and the arithmetic favours stopping regardless of how effective the drug is in a population with longer to live.

This reasoning is sound, quantifiable in principle, and rests on two estimates that are usually unavailable: the time to benefit of the specific drug in this patient's risk group, and the patient's remaining life expectancy. Neither is recorded in a typical consultation, and prognostic estimation in older adults is imprecise. The argument therefore justifies deprescribing in principle more clearly than it identifies who to deprescribe in practice.

4. WHAT FOLLOWS FOR PRACTICE

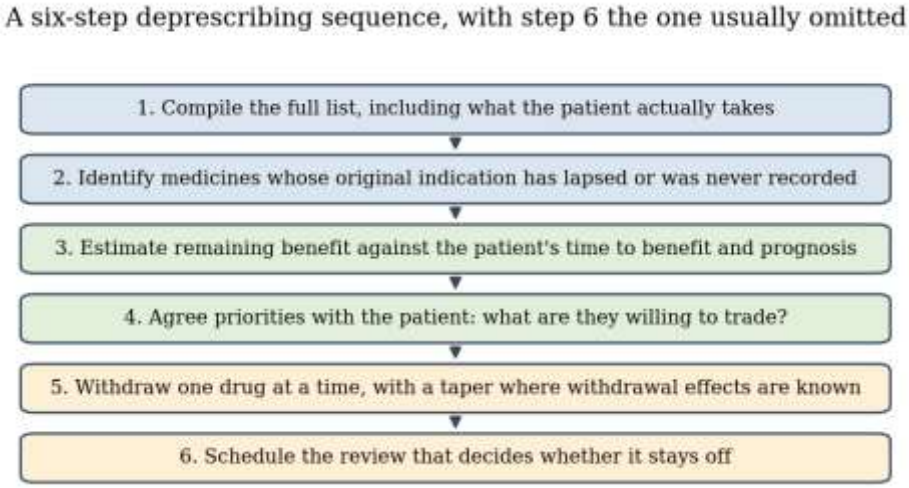

Figure 6. A six-step deprescribing sequence.

The sequence in Figure 6 is conventional in its first five steps and differs from most published frameworks in the emphasis it places on the sixth. Given that a third of OPTIMISE withdrawals were reversed within twelve weeks and half within four years, the review that decides whether a drug stays off is not an administrative afterthought but part of the intervention, and a deprescribing decision made without scheduling it is substantially less likely to persist.

Table 4. Implications

Finding	Implication	Practice
Trials measure withdrawal, not benefit	The literature supports feasibility more than advantage	Deprescribe for a specific reason, not to reduce a count
Non-inferiority designs cannot show benefit	A null result is not a positive one	Read "non-inferior" as "no large harm detected"
OPTIMISE excluded compelling indications	Findings apply to patients already in equipoise	Do not generalise to patients with established cardiovascular disease
A third of withdrawals reversed by 12 weeks	Deprescribing decays	Schedule the review that decides whether it stays off
Benefit case strongest for sedatives, PPIs, NSAIDs	Class matters more than number	Target classes with known harm and doubtful benefit
Benefit case weakest for antihypertensives	The best trial is in the weakest class	Treat antihypertensive deprescribing as individualised, not routine

Observational comparisons severely confounded	Associations run in both directions	Discount cohort studies of deprescribing exposure

The first row is the review's central practical claim. A count of medicines is a poor target because it treats an unnecessary sedative and a necessary anticoagulant as interchangeable units, and because it creates pressure to stop whatever is easiest rather than whatever is least justified. The question that should drive a deprescribing decision is whether this particular medicine is still earning its place for this particular patient, and that question has an answer even where the trial literature does not.

4.1 What would strengthen the evidence

Three studies would move the field further than another feasibility trial. A withdrawal trial powered for a patient-reported outcome — function, symptom burden, or days at home — rather than a surrogate would test the claim that patients feel better, which is the claim usually made and never measured. A trial with a maintenance component, comparing deprescribing with and without scheduled review, would establish how much of the decay documented here is preventable. And a study reporting time to benefit alongside prognosis for the commonest preventive medicines would convert the argument in Section 3.2 from a principle into a decision rule.

4.2 Limitations of this review

This is a narrative review by a single author, without a registered protocol, systematic search, duplicate screening or formal risk-of-bias appraisal, and it concentrates on a small number of prominent trials chosen to illustrate the argument. A systematic review would identify substantially more studies, particularly in classes treated briefly here, and might place several of the assessments in Figure 4 and Table 3 differently. The judgements of evidence strength are exactly that. Readers who weigh the pharmacist-led intervention literature more heavily, or who regard reductions in potentially inappropriate prescribing as a benefit in itself, will reach a more favourable assessment than the one offered here, and that disagreement is substantive rather than factual.

The review addresses adults and does not cover deprescribing at the end of life, in care homes specifically, or in people with severe cognitive impairment, each of which has its own literature and different considerations. It also does not address the practical and relational obstacles — patient reluctance, clinician discomfort at stopping a colleague's prescription, fragmented responsibility across specialties — which are frequently the binding constraint and which no trial evidence resolves.

Finally, nothing here should be read as an argument against deprescribing. The claim is about what the evidence currently supports, not about what is likely to be true, and it is entirely possible that adequately powered trials would demonstrate the benefits that are presently assumed.

5. CONCLUSION

The strongest trial in the deprescribing literature withdrew one antihypertensive from 282 carefully selected patients over 80 and found that blood pressure stayed below 150 mm Hg in 86.4 % of them against 87.7 % on usual care, meeting a non-inferiority margin. That is a demonstration that the drug could come off, in patients chosen because their clinician already thought it might. It is not a demonstration that they were better for it, and the design could not have shown that.

Two things follow. Deprescribing should be justified drug by drug, on the grounds that a specific medicine's harms now exceed its remaining benefit for this patient, and not by a general presumption that a shorter list is better — a presumption that directs effort toward whatever is easiest to stop rather than whatever is least defensible to continue. And because a third of withdrawals were reversed within twelve weeks and half within four years, the decision to stop a medicine should be accompanied by the appointment at which someone decides whether it stays stopped. On present evidence that scheduled review may be the more consequential half of the intervention.

Declarations

Ethical approval: Not applicable.

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Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions:

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Dr. Priyadharshini P.	✓	✓	✓			✓		✓	✓	✓	✓	✓		

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

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