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How Should a Regimen Be Optimized When Improving One Medicine Destabilizes Another? Competing Therapeutic Objectives in Multimorbidity and Frailty

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ABSTRACT

Medication optimization in multimorbidity is frequently described as a search for inappropriate prescribing, unnecessary medicines, or opportunities for deprescribing. These approaches are valuable but incompletely represent a more difficult clinical problem: changing one component of a regimen can improve one therapeutic objective while worsening another. The competing consequences may involve disease control, adverse effects, drug interactions, prescribing cascades, functional reserve, treatment workload, patient priorities, or benefits that occur on different time horizons. Frailty further alters the consequences of therapeutic perturbation because modest physiological changes may have greater functional significance and because prognosis can change whether delayed preventive benefit remains clinically relevant. Evidence from medication-review trials also shows that improvement in prescribing indicators does not consistently translate into improvement in patient-level outcomes. Regimen optimization should therefore make competing objectives explicit, distinguish medication-level signals from patient-level consequences, and preserve uncertainty instead of collapsing it into a universal score. Patient priorities determine which compromises are acceptable, while reversibility and decision horizon determine how uncertain choices can be tested. The clinically defensible target is not maximal treatment of every condition independently, but a regimen whose expected benefits, harms, workload, feasibility, and temporal consequences remain acceptable for the individual patient and are reassessed as circumstances change.

Keywords: Multimorbidity, Frailty, Polypharmacy, Medication optimization, Deprescribing, Therapeutic conflict

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Introduction

Multimorbidity and polypharmacy are common in adult and older populations, although their reported prevalence varies substantially according to definitions, populations, and settings [1]. This epidemiological overlap creates a practical prescribing problem that is qualitatively different from managing several independent diseases. Each medicine may have a reasonable disease-specific indication, yet the resulting regimen can contain therapeutic objectives that interact, compete, or become incompatible as health status changes.

Patient-centred multimorbidity care already challenges the assumption that success can be inferred from disease-specific targets alone. In the pragmatic 3D trial, a structured approach integrating disease dimensions, medicines, depression, and patient priorities improved some aspects of patient-centred care without producing uniform

improvement across all clinical outcomes [2]. The lesson is not that disease-specific treatment should be abandoned. It is that the clinical value of a treatment cannot always be determined independently of the rest of the patient's illness and treatment context.

This problem becomes more pronounced in older people. Clinical practice guidelines often derive their recommendations from populations and endpoints that incompletely represent frailty, competing risks, multimorbidity, or limited physiological reserve [3]. A recommendation that is appropriate when considered against one disease endpoint may therefore require reinterpretation when another condition, treatment, or patient goal is introduced.

Medication number itself is also an inadequate summary of therapeutic quality. Polypharmacy can be appropriate when each treatment contributes sufficient expected value, while a smaller regimen may still contain an avoidable interaction, an untreated indication, an unacceptable adverse effect, or a medicine whose delayed benefit no longer fits the patient's prognosis [4]. In frail populations, polypharmacy and hyperpolypharmacy are associated with adverse outcomes, but these associations are heterogeneous and should not be interpreted as proof that medicine count alone causes those outcomes [5].

The clinically difficult question is consequently narrower than whether a medicine is "appropriate" in isolation. It is how to optimize a regimen when improving one therapeutic objective plausibly destabilizes another. Here, therapeutic conflict refers to a situation in which a regimen change expected to improve one clinically relevant objective may worsen another relevant outcome, risk, burden, or dimension of physiological reserve. The task is to recognize these conflicts, determine which are meaningful for the individual patient, and decide whether uncertainty should lead to continuation, modification, withdrawal, substitution, or a monitored therapeutic trial.

Appropriateness signals do not determine regimen-level success

Explicit prescribing criteria provide valuable signals about medication-related risk. The 2023 AGS Beers Criteria identify medicines that may be inappropriate under specified circumstances in older adults, while also emphasizing that such criteria should support clinical judgment and shared decision-making [6]. A criterion therefore identifies a reason to examine a medicine; it does not establish that discontinuation will improve the patient's overall regimen.

The same distinction applies to STOPP/START version 3. Its inclusion of potentially inappropriate medicines and potential prescribing omissions is particularly important in multimorbidity because optimization can fail through both excess treatment and undertreatment [7]. Removing a medicine may reduce adverse-effect exposure while simultaneously weakening control of another clinically important condition. Conversely, avoiding a potentially risky treatment may leave an untreated indication whose consequences are more important to the patient.

Intervention evidence reinforces the separation between medication-level and patient-level success. A systematic review and meta-analysis of medication review and deprescribing in older inpatients found that prescribing-related outcomes can improve even when effects on mortality and other major clinical endpoints are inconsistent [8]. This discordance matters because an intervention can be technically successful in identifying or withdrawing medicines without demonstrating that the net patient experience has improved.

The SPPiRE cluster trial similarly evaluated medication review in older people with multimorbidity and substantial polypharmacy while incorporating deprescribing and patient priorities [9]. Such interventions demonstrate that whole-regimen review is feasible, but their effects do not justify treating every reduction in medication exposure as equivalent to therapeutic improvement.

The OPTICA trial provides a related caution. Structured pharmacotherapy optimization can generate recommendations and alter prescribing processes, yet the clinical meaning of those recommendations depends on implementation and on which outcomes are subsequently examined [10]. Identifying a medication-related problem is therefore an intermediate clinical act. It remains necessary to determine whether correcting that problem improves the outcomes that matter in the particular patient.

OPERAM makes the distinction especially clear. In multimorbid older adults, structured optimization reduced inappropriate prescribing, but improvement in prescribing quality did not translate into a statistically significant reduction in the primary outcome of drug-related hospital admissions [11]. Medication-level appropriateness and patient-level benefit should consequently remain separate domains of evaluation. Neither can safely substitute for the other.

This distinction changes the central question of regimen review. Instead of asking only whether each medicine satisfies an appropriateness criterion, clinicians must ask what happens to the whole therapeutic configuration

when the regimen is changed. That question requires attention to the mechanisms through which one treatment can alter the value, safety, or feasibility of another.

When therapeutic objectives collide: Benefit, harm, interaction, and physiological reserve

Drug–drug interactions are one obvious route through which therapeutic objectives become coupled. A systematic review and meta-analysis found substantial prevalence of potential drug–drug interactions among community-dwelling older adults, with considerable heterogeneity according to populations and interaction-detection methods [12]. A potential interaction is not synonymous with clinical harm, but it identifies a situation in which the benefit expected from one medicine may depend on the presence, dose, timing, or pharmacological consequences of another.

Prescribing cascades expose a different form of regimen instability. A systematic review identified numerous situations in which an adverse drug effect could be interpreted as a new medical problem and followed by additional prescribing [13]. The resulting medicine may treat the manifestation while preserving the original cause, increasing regimen complexity and sometimes generating additional adverse effects. Recognizing a possible cascade therefore requires more than identifying two temporally associated medicines; alternative disease explanations, dose relationships, therapeutic necessity, and the feasibility of modifying the initiating treatment must also be considered.

Frailty introduces another dimension because physiological reserve changes the consequences of therapeutic perturbation. In the STOPPFrail randomized trial, structured deprescribing reduced medication exposure in selected older people with advanced frailty and limited life expectancy [14]. The relevance of this evidence lies less in a general instruction to deprescribe than in what it reveals about changing therapeutic objectives. When prognosis shortens or reserve becomes limited, preventing a distant outcome can lose relative importance compared with immediate symptom burden, adverse effects, function, or treatment workload.

Some conflicts can be explored through reversible changes. In the OPTIMISE randomized trial, withdrawal of one antihypertensive medicine in selected adults aged 80 years or older preserved short-term blood-pressure control in most participants [15]. Such evidence supports the clinical usefulness of reversibility: the practical possibility of modifying a treatment and observing its consequences while retaining an option to restore or further adjust therapy. Reversibility should not be assumed for every medicine, disease state, or adverse consequence.

The decision horizon must also extend beyond the first apparently successful change. Long-term follow-up of the OPTiMISE population examined hospitalization and mortality after the original antihypertensive-reduction strategy [16]. Short-term tolerability and longer-term clinical consequences are different questions. A treatment change that appears acceptable over weeks may remain uncertain over years, particularly when the treatment is intended to prevent infrequent but serious future events.

Time to benefit provides the complementary perspective. A meta-analysis of statins for primary prevention estimated that meaningful cardiovascular benefit can require years of treatment in the populations studied [17]. Such estimates are therapy- and population-specific, but the underlying principle is broadly important: delayed expected benefit should be interpreted against prognosis, competing risks, time to potential harm, and the outcomes the patient actually values.

These judgments are additionally constrained by the evidence base itself. Older adults with multimorbidity, frailty, altered physiology, and complex treatment regimens remain incompletely represented in many drug-development programs, limiting confidence when trial evidence is transferred to patients whose risk structure differs substantially from the source population [18]. Evidence uncertainty is therefore part of the treatment problem. It should not be converted into false numerical precision.

The therapeutic conflicts described above vary in mechanism and in how safely they can be tested. A pharmacokinetic interaction, a prescribing cascade, limited physiological reserve, delayed preventive benefit, and weak external validity are not interchangeable reasons for changing treatment. Their differences become clinically useful when the expected improvement, possible destabilization, reversibility, and relevant observation horizon are examined together.

Table 1 compares the principal forms of therapeutic conflict according to what a regimen change is intended to improve, what it may destabilize, and how reversibility and time alter the clinical interpretation.

Table 1. Regimen conflicts in which improvement of one therapeutic objective can destabilize another

Therapeutic-conflict pattern	Objective being improved	Objective or outcome potentially destabilized	Regimen-level mechanism	Reversibility of an initial change	Clinically relevant decision horizon	What should prompt renewed evaluation
Interaction-sensitive treatment	Control of the target condition	Toxicity, reduced efficacy of another medicine, or altered exposure	Pharmacokinetic or pharmacodynamic interaction between regimen components	Often modifiable through dose, timing, substitution, or withdrawal, but not uniformly	Depends on onset and persistence of interaction effects	New symptoms, exposure change, organ-function change, addition or removal of an interacting medicine
Possible prescribing cascade	Relief of a newly recognized symptom or condition	Persistence of the initiating adverse drug effect, greater regimen complexity, additional adverse effects	A medicine-related effect is treated as a new disorder without resolving the initiating cause	Potentially reversible when the initiating drug or added treatment can be safely modified	From immediate symptom evolution to longer-term accumulation of treatment burden	Recognition of temporal linkage, dose dependence, atypical symptom pattern, or an alternative explanation
Frailty- or prognosis-sensitive preventive therapy	Prevention of future disease events	Current function, symptom burden, adverse effects, or treatment workload	Delayed benefit competes with reduced reserve, limited prognosis, or immediate burdens	Highly treatment- and condition-specific	Determined by prognosis, expected time to benefit, and time to harm	Declining function, advancing frailty, shortened prognosis, new care goals, or changing adverse-effect burden
Monitored medication reduction	Lower adverse-effect exposure, regimen burden, or physiological stress	Loss of control of the treated condition	Withdrawal or dose reduction tests whether the treatment remains necessary at its current intensity	Relatively high only when the underlying condition can be monitored and therapy can be restored safely	Must include both an early response window and any important delayed consequences	Target deterioration, withdrawal effects, symptom recurrence, or new evidence of preventive benefit
Delayed-benefit preventive treatment	Reduction of future morbidity	Immediate adverse effects, workload, interactions, or opportunity cost	Benefit accumulates later than treatment burden or toxicity	Variable; withdrawal may remove future protection even when immediate effects are absent	Long enough to encompass expected preventive benefit	Major change in prognosis, baseline risk, competing disease, treatment tolerance, or patient priorities
Evidence-transfer conflict	Application of evidence-based disease treatment	Uncertain benefit–harm balance in a patient unlike the source population	Trial estimates may not transport directly across frailty, comorbidity, physiology, or regimen complexity	Depends on treatment and clinical observability	Determined by the uncertainty being tested and seriousness of possible harm	New patient-specific response data, emerging evidence, physiological change, or failure of expected treatment effect

Treatment workload can become a competing therapeutic outcome

A regimen can remain pharmacologically defensible and still become difficult to live with. Treatment burden in multimorbidity extends beyond medication count to the work of taking medicines, monitoring disease, attending services, navigating administrative requirements, coordinating care, and integrating these demands into everyday life [19]. These activities consume time, attention, physical capacity, financial resources, and support from patients or caregivers. When this workload approaches or exceeds available capacity, the regimen itself can become a source of clinical strain.

Treatment burden can be measured, but measurement is context dependent. Cross-cultural adaptation and validation of the Arabic Multimorbidity Treatment Burden Questionnaire illustrates that patient-reported burden is not a context-free construct whose scores can automatically be transferred between populations [20]. Language, health-system organization, expectations of care, family involvement, and access to services can change how treatment work is experienced and reported.

The clinical relevance of this burden is supported by observational evidence linking greater treatment burden with poorer health-related quality of life in people with multimorbidity [21]. Cross-sectional associations cannot establish direction of causation: worsening health may simultaneously increase treatment workload and reduce quality of life. Even so, treatment workload should not disappear from regimen evaluation merely because it is harder to quantify than blood pressure, glycaemia, or another disease-specific endpoint.

These considerations make shared decision-making particularly important in complex care. A scoping review of shared decision-making in patients with complex care needs found that decisions frequently occur within multiple interacting health, social, and organizational circumstances [22]. The relevant choice may therefore be whether a marginal disease-specific benefit warrants additional monitoring, another medicine, a higher risk of interaction, or a greater demand on limited patient capacity. Different patients can reasonably make different choices from the same clinical evidence.

Outcome selection must reflect this complexity. Work to develop a core outcome set for hospital deprescribing trials in older people demonstrates that evaluation of medication change requires multiple outcomes rather than a single measure such as medicine count [23]. The same principle applies more broadly to therapeutic optimization. A change can reduce inappropriate prescribing yet worsen symptoms; reduce cardiovascular risk yet increase falls or fatigue; simplify the regimen yet sacrifice a benefit the patient considers essential. These are not measurement inconveniences. They are competing therapeutic outcomes.

Treatment workload should therefore be considered alongside pharmacological benefit and harm when a regimen is optimized. It should not be assigned a universal weight, because the same workload may be acceptable to one patient and intolerable to another. Determining which burden is justified therefore requires identifying the outcomes the patient prioritizes and the compromises they are willing to accept.

Patient priorities determine which trade-offs are acceptable

Competing therapeutic objectives cannot be resolved solely by ranking medicines according to pharmacological appropriateness. Older adults with multiple chronic conditions express heterogeneous outcome goals and medication preferences, including different judgments about which medicines are helpful or burdensome [24]. A regimen-level decision therefore requires an explicit account of what the patient is trying to preserve, improve, or avoid.

Such priorities can be elicited through structured clinical processes rather than assumed from diagnosis or age. A clinically feasible approach to identifying health priorities has shown that patients can articulate valued activities, health goals, and treatment preferences when these are deliberately incorporated into encounters [25]. These priorities should guide trade-offs without being converted into a universal numerical weighting scheme.

Implementation remains demanding. Patient Priorities Care has been shown to be feasible in older adults with multiple chronic conditions, but its incorporation into routine practice requires time, workflow adaptation, and coordination between professionals [26]. The implication is that priority-sensitive prescribing is an organizational task as well as a communication task.

When clinicians align decisions with expressed patient priorities, the result may be less burdensome and more goal-directed care. Observational trial evidence has associated priorities-aligned decision-making with changes in care consistent with those objectives, although residual confounding prevents a causal interpretation of every observed difference [27].

More recent controlled evidence also cautions against assuming that a priorities-based model automatically improves all measurable outcomes. In a nonrandomized controlled trial, Patient Priorities-Aligned Care did not produce statistically significant differences across the main measured outcomes despite potentially favorable point estimates [28]. Priority alignment should therefore be treated as a decision principle, not as a guarantee of superior clinical outcomes.

How a treatment change is discussed can itself influence acceptability. In a national study of older adults, deprescribing framed around avoidance of side effects was generally preferred, but substantial individual variability remained [29]. Communication should consequently reveal the trade-off rather than steer the patient toward a predetermined choice.

Willingness to reduce treatment must also be distinguished from medication-taking behavior. Older adults in an OPTICA substudy could be highly adherent while also expressing willingness to deprescribe, with no evidence that willingness itself was simply a marker of poor adherence [30]. Preference, behavior, and therapeutic necessity are distinct variables.

Table 2 summarizes the types of evidence that should be kept separate when judging whether a regimen-level compromise is acceptable.

Table 2. Evidence domains for judging a competing-objective regimen

Evidence domain	Regimen-level question	What supports continuation or intensification	What supports reduction or modification	Major interpretive caution
Additive therapeutic benefit	Does each component contribute meaningful benefit beyond the rest of the regimen?	Clear complementary benefit on outcomes relevant to the patient	Marginal, duplicated, or no longer relevant expected benefit	Disease-specific efficacy does not establish whole-regimen value
Antagonistic risk	Does one component increase toxicity or reduce the effectiveness of another?	Interaction is clinically negligible, avoidable, or monitorable	Interaction materially alters exposure, safety, or efficacy	Potential interactions are not equivalent to realized harm
Treatment workload	Is the regimen feasible within the patient's available capacity?	Required work is acceptable and sustainable	Monitoring, administration, appointments, or self-management exceed capacity	Workload is broader than medicine count
Priority conflict	Does expected benefit address an outcome the patient values enough to justify the trade-off?	Benefit aligns with patient-defined goals	Burden or risk affects outcomes the patient places higher	Preferences are individual and can change
Temporal fit	Does the likely time to benefit fit prognosis and competing risks?	Expected benefit occurs within a clinically relevant horizon	Benefit is substantially delayed relative to burden or harm	Time-to-benefit estimates are treatment- and population-specific
Evidence uncertainty	How confidently can trial evidence be transferred to this patient?	Patient resembles studied populations and response is observable	Frailty, multimorbidity, physiology, or regimen complexity create important uncertainty	Uncertainty should not be hidden inside a false precision score

The interaction among these domains is best represented as a constrained landscape rather than as a single hierarchy. **Figure 1** depicts regimen optimization as movement within patient-specific feasibility boundaries, where improving one therapeutic objective may narrow the acceptable range of another.

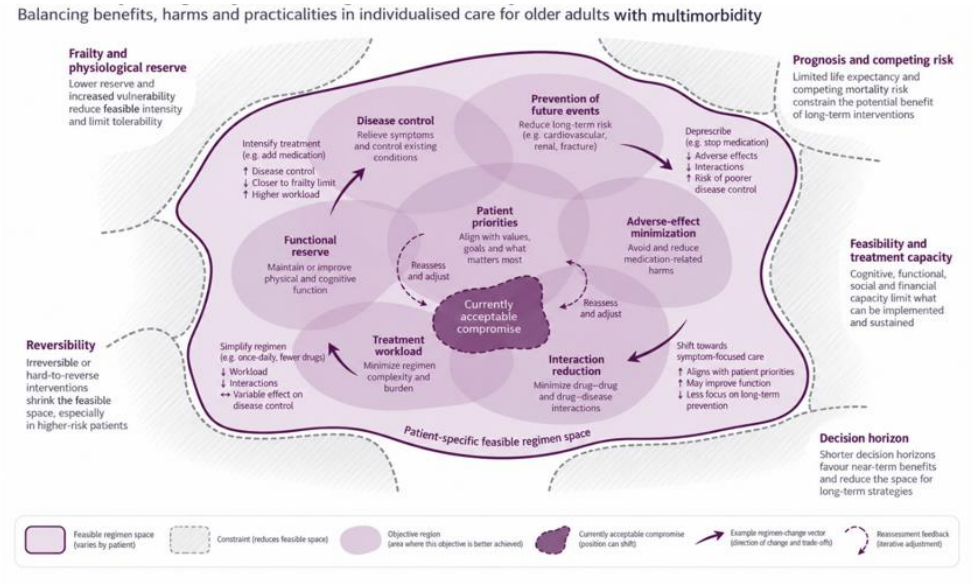

Figure 1. Competing-objective regimen landscape in multimorbidity and frailty

Optimization requires reversible trials and scheduled reassessment

When no option clearly dominates, regimen optimization can be treated as a sequence of monitored, revisable decisions. Qualitative work on priorities-aligned decision-making describes strategies such as identifying one actionable priority and using serial trials of starting, stopping, continuing, or modifying treatment while observing effects on patient-important outcomes [31].

This approach is particularly useful when a change is reasonably reversible. Selected antihypertensive reduction in OPTIMISE showed that one medicine could be withdrawn while short-term blood-pressure control was preserved in most participants [15]. Longer-term follow-up illustrates why an initially acceptable result should not terminate evaluation when clinically important consequences may emerge over a different horizon [16].

Reassessment should also be multidimensional. Deprescribing outcome-set development has identified medication changes, adverse events, quality of life, mortality, and hospital use as distinct outcomes worth considering [23]. A successful regimen change should therefore not be defined by medication count alone.

Finally, neither patient priorities nor treatment acceptability should be regarded as static. The absence of clear benefit across all outcomes in a priorities-aligned care trial argues against treating any one decision model as self-validating [28]. Similarly, willingness to deprescribe should not be assumed to remain constant or to represent adherence behavior [30]. The regimen should be reopened when the clinical or personal conditions that justified the previous compromise materially change.

Table 3 identifies practical reassessment triggers that can convert an initially acceptable compromise into a new optimization problem.

Table 3. Reassessment triggers after a competing-objective regimen decision

Reassessment trigger	Why the previous compromise may no longer hold	Principal domains to reconsider
New symptom, adverse effect, fall, or functional decline	A previously tolerated regimen may now exceed physiological or functional reserve	Harm, function, interaction burden, reversibility
Loss of disease control after reduction	The benefit sacrificed by modification may be greater than initially estimated	Disease control, rescue options, monitoring interval
Major change in prognosis or frailty	Time to benefit and competing risks may have shifted	Preventive benefit, immediate burden, decision horizon
New medicine or discontinuation elsewhere in the regimen	Interaction structure and prescribing-cascade risk may change	Exposure, efficacy, toxicity, regimen complexity
Increased treatment workload or reduced patient capacity	A feasible regimen may become unsustainable	Workload, adherence feasibility, caregiver demands
Change in patient goals or priorities	The acceptable trade-off is preference dependent	Goal concordance, symptoms, function, burden
New evidence or unexpected treatment response	Initial uncertainty may have been reduced or redirected	Benefit–harm estimate, transferability, next reversible trial

Conclusion

Regimen optimization in multimorbidity and frailty is not equivalent to maximizing the appropriateness of each medicine independently. The more difficult problem arises when a change expected to improve one therapeutic objective plausibly worsens another. Disease control, adverse effects, interactions, prescribing cascades, functional reserve, treatment workload, prognosis, patient priorities, and time to benefit can all compete within the same regimen.

The appropriate response is not a universal score or fixed hierarchy. Clinicians should identify the specific therapeutic conflict, determine which outcomes matter most to the patient, assess whether the proposed change is reversible, and define the horizon over which benefit and harm will be judged. When uncertainty remains and a change is sufficiently reversible, a monitored therapeutic trial with scheduled reassessment can help determine whether the proposed compromise remains acceptable. The aim is a regimen that remains acceptably aligned with the individual patient's objectives and capacity as both treatment effects and clinical circumstances evolve.

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