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Safe Deprescribing Requires More Than Medication Withdrawal: A Clinical Pharmacy Framework for Sequencing, Monitoring, Therapeutic Substitution, and Restart Decisions in Complex Polypharmacy

Kenji Tanaka[1]*, Yui Kobayashi[1], Takeshi Nakamura[2]

[1] Department of Deprescribing and Polypharmacy Management, Faculty of Pharmacy, University of Tokyo, Tokyo, Japan.
[2] Department of Clinical Pharmacy and Medication Safety, Faculty of Pharmacy, Kyoto University, Kyoto, Japan.

***E-mail** ✉ tanaka.kenji@mol.f.u-tokyo.ac.jp

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ABSTRACT

Deprescribing is often described as the planned reduction or discontinuation of medicines whose harms, treatment burden, or limited expected benefit no longer justify continued use. That definition is necessary but incomplete for complex polypharmacy because a safe medication change does not end when a prescription is stopped. The clinical consequences of withdrawal depend on which medicine is changed first, what other medicines and conditions remain, whether symptoms represent withdrawal or recurrence, whether the original treatment need persists, and whether a stopped medicine should later be replaced or restarted. This Comment develops a proposed clinical-pharmacy framework that treats deprescribing as a reversible, monitored process rather than a one-way medication-removal task. It integrates four decision functions: sequencing medication changes under interacting risks; monitoring for withdrawal, recurrence, and effects of treatment substitution; reassessing whether an indication still requires therapy and, if so, whether a safer substitute is appropriate; and explicitly adjudicating restart decisions. The framework distinguishes medication-level change from patient-level benefit, appropriateness flags from individualized treatment plans, and restart from automatic evidence of deprescribing failure. Its purpose is to make the post-withdrawal treatment state clinically visible and to clarify where pharmacists can contribute regimen-level reasoning, follow-up design, communication, and continuity. The framework is conceptual, not prospectively validated. Drug class, frailty, cognition, care transitions, monitoring capacity, patient priorities, and health-system resources remain important boundaries. Evaluation should therefore test both clinical outcomes and whether the proposed decision states can be implemented, measured, and revised safely across settings.

Keywords: Deprescribing, Polypharmacy, Clinical pharmacy, Medication safety, Therapeutic substitution, Medication restart

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Introduction

Deprescribing has become an important component of medication optimisation in older adults with polypharmacy, particularly when treatment burden, adverse effects, changing goals, or diminishing expected benefit alter the balance of continued therapy. Contemporary clinical guidance emphasizes structured reassessment rather than indiscriminate medication reduction [1]. This distinction matters because polypharmacy is not intrinsically inappropriate: the same medication count may represent coherent multimorbidity treatment in one patient and avoidable burden or harm in another. Clinical appropriateness therefore cannot be inferred from the number of medicines alone [2].

Recent evidence reinforces the need to separate medication-level outcomes from broader patient outcomes. Umbrella and systematic-review evidence indicates that deprescribing interventions can reduce medication burden or potentially inappropriate medication exposure, while effects on mortality, quality of life, falls, hospitalization, and other patient-level outcomes remain heterogeneous across populations and interventions [3, 4]. That heterogeneity should not be read as evidence that deprescribing lacks value. Rather, it shows that a stopped medicine is an intermediate treatment event whose meaning depends on what happens next: symptoms may improve, a withdrawal syndrome may appear, the treated condition may recur, another medicine may become unnecessary, or a different therapy may be required.

This Comment therefore argues that safe deprescribing in complex polypharmacy should be understood as a longitudinal, reversible process. The central proposed contribution is a decision architecture linking four functions that are often handled separately: sequence choice, monitoring, therapeutic substitution, and restart adjudication. The framework does not assume that these functions are required in identical form for every medicine or patient. Instead, it asks clinicians to make explicit which dependencies matter, what post-change signals would alter the plan, and who will act on those signals. It also separates three decisions that are easily collapsed in practice: whether a medicine is a reasonable candidate for change, whether the patient is currently ready for that change, and whether the resulting treatment state remains acceptable after the change. These decisions may diverge when symptoms are unstable, monitoring is weak, or several medicines are pharmacologically or clinically interdependent.

Clinical pharmacy is a particularly relevant setting for this reasoning because pharmacists routinely work across whole-regimen medication problems, prescriber communication, patient education, and follow-up. The argument, however, is not that pharmacists uniquely own deprescribing or that the proposed architecture is validated. It is that complex medication withdrawal becomes safer to reason about when the treatment state after withdrawal is treated as an active clinical object rather than an unexamined endpoint. This framing also preserves reversibility: an initial stop can be appropriate even if later information justifies modification, substitution, or restart. The relevant quality question is therefore whether the process detects and responds to clinically meaningful change, not whether discontinuation remains permanent at all costs.

Why medication withdrawal is not a complete deprescribing strategy

A medicine can be successfully discontinued without the overall therapeutic problem being successfully resolved. Contemporary reviews of deprescribing and medication review in older people show a recurring pattern: prescribing-related outcomes may improve even when hard clinical outcomes are inconsistent, uncertain, or incompletely changed [5, 6]. This distinction is clinically important. A reduction in potentially inappropriate medication exposure may be valuable, yet it does not by itself show that symptoms remain controlled, that no withdrawal effects occurred, that treatment burden actually fell, or that another medicine was not subsequently required.

The incompleteness of withdrawal is also practical. Deprescribing interventions operate through patients, clinicians, care teams, workflows, and health systems. A technically correct medication decision can fail longitudinally if the patient does not understand the change, if symptoms are not linked back to the medication decision, or if different care settings reconstruct the regimen differently. A scoping review of implementation considerations identified barriers and facilitators across these levels, including communication, knowledge, time, roles, resources, and patient engagement [7]. A recommendation to stop a medicine may therefore be clinically reasonable but operationally unsafe if no one owns tapering instructions, symptom surveillance, communication across settings, or the response to deterioration.

Recent primary-care evidence further illustrates why individual medication changes and whole-regimen outcomes should be kept separate. In older patients with hyperpolypharmacy, a structured medication-review intervention produced more medication reductions or discontinuations without a simple one-to-one change in overall medication burden or broader health outcomes [8]. Such findings are compatible with several explanations, including persistent treatment needs, addition of alternative therapies, competing morbidity, and limited sensitivity of global outcomes to a targeted change.

The proposed implication is that completion should be defined more carefully. A deprescribing episode is not complete merely because a prescription disappears from the active list. It is clinically complete only when the post-change state has been assessed sufficiently to decide whether the new regimen remains acceptable, requires substitution, or warrants reversal. That proposed criterion shifts attention from permanence of withdrawal to

quality of transition: the intended benefit, foreseeable risks, observation plan, and response to deterioration should be coherent even when the final regimen differs from the original deprescribing plan. That standard is intentionally conceptual and should be tested rather than assumed.

Sequencing deprescribing under interacting risks

Complex polypharmacy creates dependencies that make the order of changes clinically meaningful. Prescribing cascades are a clear example: an adverse effect from one medicine may be interpreted as a new condition and treated with another medicine, creating a sequence in which the apparent "downstream" treatment is partly dependent on the upstream exposure [9]. If the downstream medicine is removed first while the precipitating exposure remains, the original problem may persist or become harder to interpret. Sequence choice should therefore begin with a regimen-level question: which planned change would most improve the interpretability of what follows?

Patient heterogeneity further limits generic priority rules. National evidence on the gabapentinoid–loop diuretic cascade shows that susceptibility to a particular prescribing cascade differs across older adults [10]. The lesson is not that a specific observed association determines an individual patient's sequence, but that medication interactions are filtered through patient vulnerability, indication, comorbidity, and competing explanations. Priority should consequently reflect both the plausibility of the dependency and the consequence of being wrong.

Drug-class evidence also argues for bounded sequencing. Long-term follow-up of selective antihypertensive deprescribing supports interpretation within the eligibility, treatment, and follow-up conditions in which reduction was studied [11]. The original OPTiMISE trial similarly evaluated removal of one antihypertensive medicine against a defined short-term physiological outcome in selected adults aged 80 years or older [12]. These studies do not establish a universal "one medicine at a time" rule, but they illustrate the value of making a discrete change when the resulting signal is clinically observable.

The proposed sequencing principle is therefore interpretability before accumulation: when feasible, order changes so that clinically important effects can be attributed, monitored, and acted upon before additional changes obscure them. **Table 1** translates that principle into a sequence-dependency register without assigning universal priorities or time thresholds.

Table 1. When order changes meaning: a deprescribing sequence-dependency register

Candidate medication-change step	Reason for priority	Interaction with later changes	Withdrawal/ recurrence risk	Monitoring window	Condition to delay
Remove a plausible cascade-initiating medicine	May resolve a downstream treatment driver	Later withdrawal of the downstream medicine becomes easier to interpret	Drug- and disease-specific	Through the expected post-change risk period	Causal link too uncertain or acute instability present
Make one change with a directly observable clinical target	Improves attribution	Additional changes may obscure the target response	Depends on class and indication	Until the target is sufficiently reassessed	No reliable target or follow-up mechanism
Defer a medicine with substantial withdrawal or rebound concern	Prevents overlapping syndromes	Safer after other changes stabilize	Potentially high	Requires class-specific surveillance	Monitoring or tapering support unavailable
Reassess a medicine whose indication remains uncertain	Avoids creating untreated need	Later substitution may depend on this decision	Recurrence may mimic withdrawal	Until indication and trajectory are clarified	Treatment need cannot yet be adjudicated

Note: Entries are a proposed synthesis of the manuscript's sequencing logic. They are not validated priority rules, universal taper schedules, or quantitative thresholds.

Monitoring for withdrawal, recurrence, and substitution effects

Monitoring is the mechanism that converts medication withdrawal from an irreversible act into an adaptive clinical trial. Yet post-withdrawal outcomes are not measured consistently. A systematic review of deprescribing trials found substantial variation in how adverse drug withdrawal events were defined and reported [13]. This measurement problem creates an important interpretive boundary: absence of a reported withdrawal event cannot automatically be treated as evidence that no clinically relevant event occurred.

The same distinction applies to decision support. In the MedSafer cluster randomized trial, electronic decision support increased deprescribing activity in hospitalized older adults, but a medication action and a patient-level safety outcome remained analytically distinct [14]. For a longitudinal framework, detection and discontinuation are therefore only early steps. The clinically important question is whether the subsequent state is stable, improving, deteriorating, or indeterminate.

Monitoring must also persist across care transitions. Medication-related harm after hospital discharge is well documented in older adults, although such harm cannot be attributed specifically to deprescribing [15]. A medicine stopped in hospital may be interpreted differently by the patient, community pharmacist, general practitioner, specialist, or post-acute facility. Responsibility for surveillance can therefore become fragmented precisely when the regimen is changing. A safe plan should specify who receives the signal, who judges its significance, and who can modify the treatment.

Finally, post-withdrawal symptoms require differential interpretation. Evidence from chronic-medication discontinuation trials shows that consequences vary by medicine and condition [16]. Symptoms may reflect pharmacological withdrawal, rebound, recurrence of the treated disease, progression unrelated to withdrawal, or effects of another regimen change. The proposed monitoring task is thus not simply to ask whether the patient feels worse. It is to compare timing, trajectory, expected pharmacology, disease features, and concurrent changes sufficiently to decide whether observation, substitution, or restart is the most defensible next step. Universal monitoring intervals would be inappropriate; the relevant window must remain drug-, indication-, and patient-specific. Before the change, the team should therefore identify the observable baseline against which deterioration or improvement will be judged. After the change, documentation should capture direction and timing rather than a binary "tolerated/not tolerated" label. Where several changes occur close together, interpretive confidence should be downgraded because attribution becomes progressively less secure.

Therapeutic substitution when stopping does not resolve the treatment need

Deprescribing is appropriate when continued use of a particular medicine no longer fits the patient's benefit–harm balance, but that judgment does not automatically answer whether the underlying condition still requires treatment. Current deprescribing guidance emphasizes structured assessment, reduction or cessation where appropriate, and subsequent monitoring [17]. The additional distinction proposed here is explicit treatment-need reassessment: after deciding that a medicine is unsuitable, clinicians should separately decide whether the indication has resolved, whether non-pharmacological management is sufficient, or whether a safer or more acceptable therapy is still needed.

This separation avoids therapeutic nihilism. Pharmacist-led deprescribing can be achieved through patient education and prescriber engagement rather than unilateral medication removal; the D-PRESCRIBE randomized trial demonstrated medication-specific change through such a collaborative process [18]. The present framework extends that logic conceptually by asking the team to make the replacement question visible whenever treatment need persists. This is not a claim that substitution is always required, nor that pharmacists alone should select it.

The distinction is particularly important in older adults, for whom medication harms coexist with genuine therapeutic benefits. Contemporary clinical scholarship emphasizes that pharmacotherapy can continue to support healthy aging when benefits, burdens, function, and goals are appropriately balanced [19]. A medicine may therefore be wrong while its indication remains right. Conversely, an indication may no longer justify treatment even if an alternative exists.

Explicit appropriateness tools illustrate the same boundary. The AGS Beers Criteria identify medicines and situations that warrant avoidance or caution in older adults, but such criteria are decision supports rather than individualized replacement plans [20]. They cannot determine, on their own, the optimal sequence, substitute, or future restart decision. In the proposed framework, substitution is therefore conditional: it follows reassessment of the continuing treatment need, available alternatives, patient priorities, feasibility, and the expected monitoring burden. Its success should be judged not by whether another prescription was issued, but by whether the revised treatment better fits the patient's current clinical state without introducing an unrecognized new risk. A substitute can itself create adverse effects, interactions, adherence burden, cost, or monitoring demands; replacement is therefore a new therapeutic decision, not the administrative completion of deprescribing.

Restart decisions and the logic of reversibility

Deprescribing is often evaluated as though persistence of discontinuation were the desired endpoint. That assumption is too rigid for longitudinal care. In adults discharged from hospital to skilled nursing, medication restart after deprescribing is an observable and clinically important trajectory [21]. A restart event alone, however, cannot reveal whether the original stop was inappropriate, whether the indication recurred, whether withdrawal became unacceptable, whether a new clinical state emerged, or whether care-transition discontinuity simply reconstructed the earlier regimen. Permanence and quality are therefore different outcomes.

Frailty makes this distinction especially important because physiological reserve, treatment goals, competing risks, and tolerance of symptoms differ substantially among patients. Evidence on deprescribing in frail older people is heterogeneous and does not support a universal stop-or-restart threshold [22]. Reversibility should consequently be planned before withdrawal, particularly when deterioration could be clinically consequential or difficult to distinguish from the patient's underlying disease.

The Opti-med trial provides a useful precedent: protocolized deprescribing in frail older adults could accommodate restarting a medicine or introducing a suitable alternative when clinically important withdrawal effects or treatment needs emerged [23]. This does not validate a general restart algorithm. It does show that reversal need not contradict deprescribing when it is a reasoned response to new post-withdrawal information.

Restart decisions also need a counterfactual question: what would happen if the medicine were not restarted? A symptom temporally associated with withdrawal may still be self-limited, treatable by another route, or outweighed by the harms that motivated deprescribing. Conversely, waiting for unequivocal deterioration can be unsafe when recurrence has serious consequences. The proposed approach therefore favors pre-specified clinical signals and explicit responsibility for reassessment over retrospective judgments based only on whether a prescription reappeared.

The proposed logic is therefore asymmetric. Continued discontinuation requires an acceptable post-withdrawal state; substitution requires persistent treatment need with a preferable alternative; restart requires evidence that resuming the previous therapy is more defensible than continued withdrawal or substitution. **Table 2** makes those competing post-withdrawal states explicit.

Table 2. Reading post-withdrawal signals before deciding to continue, substitute, or restart

Post-withdrawal signal	Competing explanation	Severity/ trajectory	Substitute option	Restart threshold logic	Follow-up action
Stable or improving state	Natural fluctuation	Non-progressive	Usually unnecessary	No restart signal	Continue planned surveillance
New symptoms soon after change	Withdrawal, rebound, unrelated illness	Timing and progression matter	Consider if treatment need persists	Restart if clinically important deterioration plausibly relates to withdrawal and alternatives are inferior	Reassess promptly
Return of treated condition	Disease recurrence or undertreatment	Persistent or worsening	Consider safer/effective alternative	Restart if prior therapy remains the best acceptable option	Re-evaluate indication and goals
Problem after substitution	New adverse effect, interaction, inadequate response	Depends on consequence	Modify or stop substitute	Restart only after comparing prior and replacement risks	Reassess whole regimen

Note: Decision logic is proposed and intentionally non-quantitative. Drug-specific guidance, patient preferences, urgency, and monitoring capacity remain controlling considerations.

The proposed safe-deprescribing decision framework

The framework proposed here treats deprescribing as repeated movement between medication states rather than a single transition from “taking” to “stopped.” It begins with whole-regimen assessment, identifies a candidate change, chooses a sequence that preserves interpretability, and specifies what must be monitored before the change is made. Patient and care-partner priorities belong inside this process rather than after it. A pharmacist-led telehealth pilot in people living with dementia illustrates the feasibility of integrating medication review, care-partner engagement, and communication with primary care, while not establishing clinical effectiveness [24].

Digital tools can support candidate identification and clinician action, but they occupy only one part of the architecture. A randomized EHR intervention in older adults increased deprescribing behavior [25]. The proposed framework therefore places decision support upstream of clinical adjudication: an electronic prompt may identify an opportunity, but it does not determine sequence, distinguish withdrawal from recurrence, select a substitute, or judge a later restart.

Comprehensive medication review provides another relevant practice mechanism. In Medicare beneficiaries, comprehensive medication review was associated with potentially inappropriate medication discontinuation in routine care [26]. Because that evidence is observational, the association should not be treated as proof that medication review alone causes better clinical outcomes. Within the proposed architecture, review instead functions as a recurring checkpoint at which medication dependencies, treatment need, patient priorities, and new clinical information can be reconciled.

At the patient level, the framework tracks symptoms, goals, function, treatment burden, and willingness to continue the trial. At the drug/regimen level, it tracks indication, interactions, withdrawal liability, and whether another medication depends on the changed exposure. At the clinician and care-team level, it assigns monitoring and response ownership. At the system level, it asks whether information can cross settings quickly enough for the planned feedback loop to function. These levels should remain separable because failure at one level can mimic failure at another.

The resulting model has four linked decision functions—sequence, monitor, substitute, and restart—connected by feedback rather than a fixed pathway. Evidence supports the component problems and practices separately; their integration into one decision architecture is the original proposal of this Comment and requires prospective evaluation. **Figure 1** visualizes that adaptive structure and makes the distinction between evidence-supported clinical observations and proposed decision links explicit.

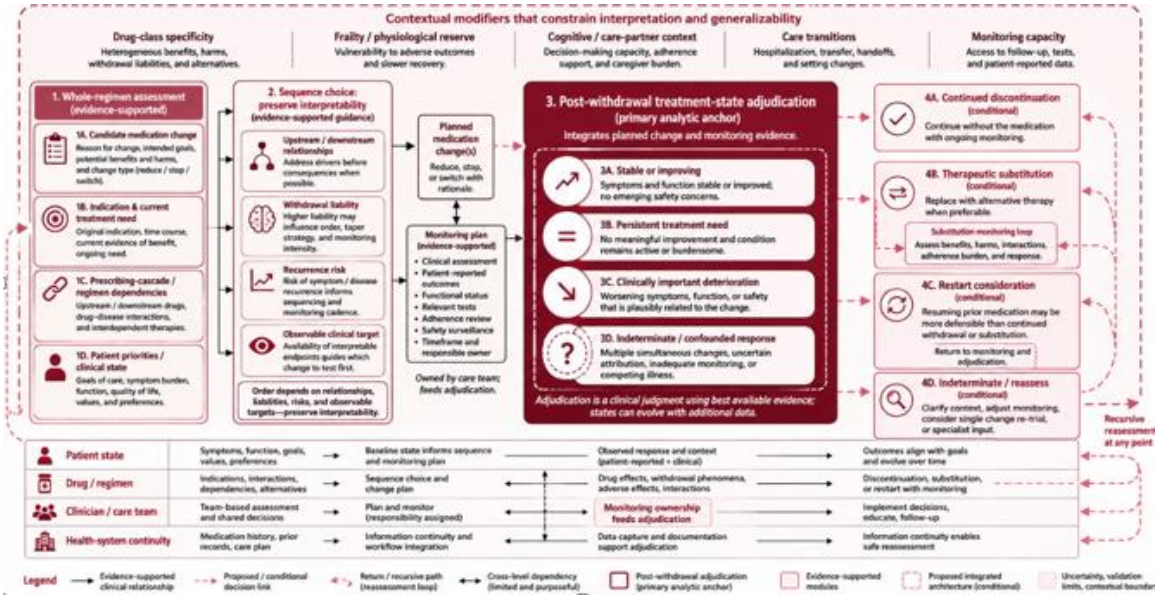

Figure 1. Safe deprescribing remains provisional until the post-withdrawal treatment state is adjudicated

High-risk polypharmacy scenarios and boundary conditions

The framework should be applied most cautiously when the consequence of misclassification is high or the evidence does not transfer cleanly. Drug class, care setting, and cognitive context are major examples. Contemporary evidence on antihypertensive deprescribing, medication review in long-term care, and deprescribing in dementia each demonstrates context dependence rather than a universal stopping rule [27-29]. These sources address different populations and outcomes; their shared contribution is to show why a single generic threshold cannot substitute for medication- and setting-specific judgment.

Frailty further alters vulnerability and competing priorities, while care transitions can weaken continuity of monitoring. Restart after hospital-to-skilled-nursing transfer may reflect recurrent treatment need, but it may also reflect communication failure or reversion to a prior medication list [21]. A restart should therefore be interpreted as a new decision point, not merely counted as loss of deprescribing persistence.

Pharmacology creates another boundary. Withdrawal, rebound, disease recurrence, and the consequences of delayed treatment are not interchangeable, and their timing varies across medicines [16]. Current practice guidance accordingly requires class- and patient-sensitive monitoring rather than a universal observation period [17]. The framework is therefore a meta-architecture for organizing decisions, not a substitute for drug-specific tapering or disease-specific treatment guidance.

Boundary conditions also become more restrictive when several medicines change simultaneously. The more exposures altered within the same observation period, the harder it becomes to attribute improvement or deterioration to a particular change. Sometimes simultaneous changes are clinically necessary, but the resulting uncertainty should be documented rather than hidden. In those circumstances, the framework calls for tighter follow-up and lower confidence in causal attribution, not a forced reconstruction of a single explanation.

Finally, feasibility is itself a safety boundary. Staffing, pharmacist access, communication channels, patient or care-partner capacity, EHR interoperability, and responsibility for follow-up can determine whether a theoretically sound plan remains actionable. **Figure 2** separates these interacting risk lanes so that reduced monitoring capacity visibly narrows the margin for complex or rapidly sequenced changes.

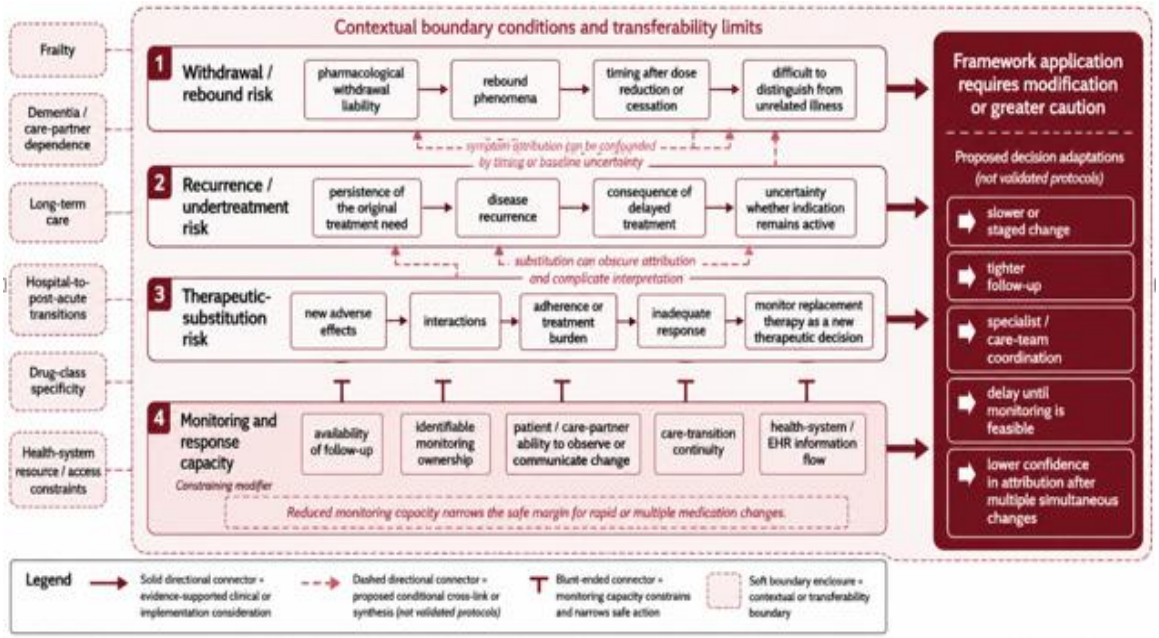

Figure 2. Withdrawal, recurrence, replacement risk, and monitoring capacity define where deprescribing decisions require modification

Implications for clinical pharmacy practice

For clinical pharmacists, the practical implication is not to add another deprescribing checklist, but to change the unit of work from "a medicine to stop" to "a treatment state to manage." Implementation evidence shows that deprescribing depends on patient engagement, professional roles, communication, time, and organizational resources [7]. A pharmacist review should therefore make explicit the candidate medicine, sequence rationale, expected post-change signal, monitoring owner, unresolved treatment need, and conditions under which the plan will be reconsidered.

Guideline-based medication reduction and monitoring remain the clinical foundation [17]. The proposed addition is a deliberate handoff from the stopping decision to post-withdrawal adjudication. In cognitively vulnerable patients, pharmacist involvement may also require care-partner communication and shared interpretation of symptoms; pilot evidence in dementia shows that such integrated workflows are feasible in at least some primary-care settings [24].

EHR prompts may increase deprescribing activity [25], but pharmacists can help prevent actionability from being confused with completeness by checking drug interactions, competing indications, feasibility of monitoring, and the downstream consequences of substitutions. Real-world comprehensive medication review is associated with potentially inappropriate medication discontinuation [26], yet access to such services and their implementation vary across health systems.

For practice evaluation, medication discontinuation should therefore be reported alongside the downstream state. Useful process outcomes would include whether a monitoring plan was documented, whether follow-up occurred, whether a substitute was introduced, whether a restart occurred, and whether the reason for that restart was clinically adjudicated. These measures should complement rather than replace patient outcomes. They would allow future studies to test whether a reversible workflow improves continuity and interpretability even when the final medication count changes little.

The framework therefore suggests a documentation standard rather than a new scoring system: record why this medicine is changing now, what must remain clinically stable, what signal would trigger substitution or restart, and who will act. Prospective evaluation should test whether this structure improves interpretability, continuity, patient experience, and medication safety without increasing workload or undertreatment. Comparative implementation studies should also establish where pharmacist-led coordination adds value and where other team configurations are equally effective.

Conclusion

Safe deprescribing in complex polypharmacy is better understood as a reversible clinical process than as successful medication withdrawal alone. The central contribution of this Comment is a proposed architecture that links four decisions usually considered separately: which medicine should change first, how the resulting state should be monitored, whether an unresolved indication requires therapeutic substitution, and when restarting a previously withdrawn medicine becomes reasonable.

This framing changes the meaning of success. A permanent stop is not necessarily successful if it produces untreated disease, unacceptable withdrawal, or an unsafe replacement; a restart is not necessarily failure if new information makes reversal the better treatment decision. The relevant endpoint is a defensible and monitored treatment state that remains aligned with clinical need and patient priorities.

The proposal has important limits. It is not a validated algorithm, does not supply universal tapering schedules or restart thresholds, and should not override medicine-specific guidance. Evidence is particularly context dependent in frailty, dementia, long-term care, care transitions, and medication classes with clinically important withdrawal, rebound, or recurrence risks. Monitoring capacity, communication, professional scope, digital infrastructure, and access to pharmacy services may further determine whether the approach is feasible.

Future evaluation should therefore test the framework prospectively across drugs, populations, and health systems, including adverse withdrawal events, recurrence, substitution outcomes, restart appropriateness, treatment burden, patient-reported outcomes, utilization, continuity, and implementation demands. Until such evidence exists, its value is as a disciplined way to make reversibility, uncertainty, and post-withdrawal responsibility explicit.

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