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Intercepting the Iatrogenic Cascade: A Narrative Review of Feedback Loops, Diagnostic Inflation, and System-Level Interventions in Polypharmacy Management

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Abstract

Background: Polypharmacy, a cornerstone of modern chronic disease management, paradoxically fuels a self-perpetuating cycle of patient harm and diagnostic excess. The prescribing of multiple medications by primary care and pharmacy teams often initiates a cascade where adverse drug effects manifest as new laboratory abnormalities or clinical symptoms. These iatrogenic signals are misinterpreted as *de novo* disease, prompting further imaging and specialist referrals, thereby increasing system burden and patient risk. **Aim:** This narrative systematic review investigates the complex feedback loops linking polypharmacy to diagnostic inflation and evaluates the efficacy of system-level interventions designed by health administration to intercept this cascade. **Methods:** A systematic search of PubMed, EMBASE, CINAHL, and Web of Science (2010-2024) was conducted. The review analyzes interdisciplinary workflows involving family medicine, pharmacy, clinical laboratory, radiology, and specialist services. **Results:** The evidence identifies a clear "prescribe-interpret-react" cycle, where drug-induced renal impairment or hyponatremia commonly triggers unnecessary renal ultrasonography and endocrinology consults. Integrated interventions, particularly pharmacist-led medication therapy management (MTM) embedded in primary care and clinical decision support systems (CDSS) that link lab trends to medication lists, significantly reduce inappropriate testing and adverse drug events. Effective administrative models are characterized by shared electronic health record (EHR) dashboards, protected pharmacist time for comprehensive review, and formalized deprescribing protocols. **Conclusion:** Fragmented care systems amplify polypharmacy-related harm. Proactive, system-redesign strategies that enhance information synthesis and interdisciplinary accountability are critical to breaking the cascade, improving patient safety, and containing low-value care.

Keywords: polypharmacy cascade, deprescribing, clinical decision support, medication therapy management, diagnostic stewardship.

Introduction

The management of chronic, non-communicable diseases represents a defining challenge for 21st-century healthcare, characterized increasingly by multi-morbidity and the resultant use of multiple concurrent medications—polypharmacy. While often clinically indicated, polypharmacy sits at the epicenter of a complex and under-recognized systems problem: the iatrogenic diagnostic cascade. This phenomenon describes a self-reinforcing cycle where the treatment for one condition generates unintended consequences that are misinterpreted as evidence of a new, separate disease, leading to further testing, referrals, and prescriptions. A patient on a regimen for hypertension, diabetes, and chronic pain, for example, may develop a dry cough from an ACE inhibitor, interpreted as potential heart failure prompting echocardiography and cardiology referral, or experience statin-induced myalgias leading to CPK tests and rheumatology consultation. This review conceptualizes this not merely as a clinical error, but

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as a systemic failure of feedback loops within healthcare's diagnostic and therapeutic circuitry.

The core mechanism involves a broken feedback loop between prescription, monitoring, and interpretation (Figure 1). In optimally functioning systems, information on drug effects flows seamlessly from the clinical laboratory and patient-reported symptoms back to the prescriber and pharmacist, enabling timely attribution and intervention. In reality, fragmentation between family medicine (prescribing), pharmacy (dispensing/review), clinical pathology (interpreting labs), and radiology (conducting imaging) allows iatrogenic signals to propagate unchecked. Health administration holds the pivotal role in designing the information architectures and collaborative workflows that can close this loop.

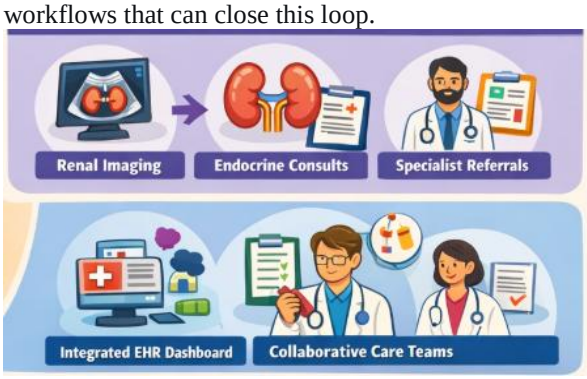

Figure 1: Feedback loops of overdiagnosis.

This narrative systematic review, therefore, synthesizes literature to address a core question: How do system-level integrations between pharmacy, laboratory, and primary care prevent the polypharmacy-to-diagnostic testing cascade, and what administrative models most effectively support this interdisciplinary safety net? By examining the evidence for interventions like embedded medication therapy management (MTM) and intelligent clinical decision support (CDSS), this review aims to chart a path toward safer, more rational, and less wasteful chronic disease management.

Methodology

This review was conducted as a narrative systematic review to synthesize qualitative and quantitative evidence across diverse study designs, suitable for exploring complex, multi-faceted systems issues. The reporting follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, where applicable for narrative synthesis. A systematic search strategy was executed across four major databases: PubMed, EMBASE, CINAHL, and Web of Science. The search timeframe was limited to January 2010 through May 2024 to capture contemporary practice models and health information technologies. Search terms were constructed using a combination of Medical Subject Headings (MeSH) and keywords, including: ("polypharmacy" OR "multiple chronic conditions" OR "multimorbidity") AND ("diagnostic cascade" OR "low-value care" OR "iatrogenesis") AND ("medication therapy management" OR "deprescribing") AND ("clinical decision support systems" OR "electronic health records") AND ("interprofessional relations" OR "integrated care" OR "care coordination"). Boolean operators (AND, OR) were used to combine concepts.

Inclusion criteria were: (1) studies focusing on adult populations (≥18 years) with polypharmacy (typically defined as ≥5 chronic medications) and multimorbidity; (2) investigations of the link between medication use and subsequent diagnostic testing, imaging, or specialist referrals; (3) evaluations of system-level, interdisciplinary interventions designed to mitigate this cascade (e.g., pharmacist integrations, CDSS, care pathway redesign); (4) publication in English in peer-reviewed journals. Exclusion criteria encompassed: (1) studies focused solely on pediatric populations or single-disease states without polypharmacy; (2) descriptions of cascades without proposed systemic solutions; (3) editorials, commentaries, or non-research letters; (4) studies published before 2010.

Data extracted from each study included: author(s), year, country, study design, population, description of the polypharmacy cascade or intervention, key outcomes (e.g., reduction in medication number, reduction in lab/imaging orders, healthcare utilization costs, adverse drug event rates), and limitations. Given the heterogeneity in interventions and outcomes, a thematic analysis approach was employed. Recurring themes and patterns related to cascade mechanisms, successful intervention components, and enabling administrative structures were identified, coded, and synthesized into the narrative sections that follow.

The Anatomy of a Cascade

To intercept the polypharmacy cascade, one must first understand its precise pathophysiology within the clinical workflow. The cascade is not a random error but a predictable sequence arising from cognitive biases—particularly diagnostic momentum and the illusion of explanatory depth—within a fragmented system. It typically begins with the appropriate prescribing of a medication for a legitimate indication by a primary care physician or specialist (McDonald et al., 2024). The initiating drug is often a new addition to an already complex regimen. Weeks or months later, a routine metabolic panel reveals an emerging abnormality: a rising creatinine, a falling sodium, or new hyperglycemia. In isolation, this lab value reaches a physician who may not have an intimate recall of the patient's full medication list or may not immediately recognize the temporal link. The abnormality is thus framed as a *new diagnostic problem*—early chronic kidney disease (CKD), syndrome of inappropriate antidiuretic hormone secretion (SIADH), or

worsening diabetes—rather than a medication side effect (Frament et al., 2020).

This misinterpretation triggers the "react" phase. For a rising creatinine, guidelines may recommend renal ultrasonography to rule out obstruction, often ordered reflexively. The ultrasound, in a patient with vascular disease, may show incidental findings like simple cysts, prompting follow-up imaging and urology consultation (Hong et al., 2020). Similarly, a low sodium level may lead to a chest X-ray (to assess for pulmonary pathology causing SIADH), followed by endocrine consultation, all while the culprit diuretic or SSRI remains in place. Each step consumes resources, increases patient anxiety, and risks physical harm (e.g., contrast exposure, biopsy).

Crucially, the feedback that should correct the course—the recognition that the thiazide diuretic started three months prior is the most likely cause of the hyponatremia—is lost in information siloes. The laboratory information system (LIS) generates the abnormal flag, but it is not intelligently linked to the pharmacy database within the EHR to provide an alert stating, "Patient on drug X known to cause lab abnormality Y" (Konishi et al., 2019). This represents a critical systems failure of integration, making the cascade not an individual clinician's mistake, but a design flaw in the healthcare delivery process.

High-Risk Therapeutics and Common Cascade Pathways

Certain medication classes are disproportionately represented as initiators of diagnostic cascades due to their widespread use and potent effects on homeostatic parameters. A review of the literature identifies several high-risk pathways. First, Renal-Electrolyte Cascades: Diuretics, NSAIDs, renin-angiotensin-aldosterone system (RAAS) inhibitors (ACEIs, ARBs), and certain antibiotics (e.g., trimethoprim) are frequent contributors. A meta-analysis by Gallagher et al. (2011) found that concurrent use of an NSAID with an ACEI/ARB increased the odds of acute kidney injury (AKI) diagnosis by 65%, which subsequently doubled the rate of renal ultrasound orders, many of which were of low yield. The electrolyte disturbances from diuretics (hyponatremia, hypokalemia) are among the most common triggers for endocrinology referrals and repeated, costly lab monitoring (Lin et al., 2021).

Second, Metabolic and Endocrine Cascades: Atypical antipsychotics (e.g., olanzapine, quetiapine), corticosteroids, and certain antiretrovirals can induce significant weight gain, hyperglycemia, and dyslipidemia. This "metabolic syndrome" induced by medication is often worked up as new-onset diabetes or primary lipid disorder, leading to additional oral hypoglycemics, insulin, and cardiology referrals instead of first considering medication substitution or dose reduction (Vaiman et al., 2022). Similarly, proton pump inhibitor (PPI)-induced hypomagnesemia can lead to neuromuscular symptoms and cardiac workups before the iatrogenic cause is identified (Abukhalil et al., 2023).

Third, Pulmonary and Functional Cascades: Drug-induced respiratory effects are a potent source of cascades. ACE inhibitor-induced cough is a classic example, frequently leading to chest X-rays, pulmonary function tests, and referrals to pulmonology or allergy specialists before the drug connection is made (Wright et al., 2020). Sedative-hypnotics (benzodiazepines, Z-drugs) and anticholinergic medications (e.g., oxybutynin, amitriptyline) contribute to dizziness, falls, and cognitive blunting. These symptoms often precipitate extensive neurological workups—brain imaging, carotid studies, and neurology consultations—for suspected stroke or dementia, while the offending medications remain unaddressed (Fabbri et al., 2015). Table 1 outlines these common pathways, their iatrogenic presentations, and the typical downstream diagnostic and referral sequences they unleash.

Table 1: Common Polypharmacy Cascade Pathways

Medication Class	Common Iatrogenic Effect	Misinterpreted As	Typical Downstream Cascade
Diuretics (e.g., HCTZ)	Hyponatremia, hypokalemia	SIADH, an endocrine disorder	Serial sodium panels, cortisol tests, chest X-ray, and endocrinology referral
NSAIDs + ACEI/ARB	Acute Kidney Injury (AKI)	New intrinsic renal disease	Renal ultrasound, nephrology consult, possible biopsy
Atypical Antipsychotics	Hyperglycemia, weight gain	New-onset Type 2 Diabetes	HbA1c monitoring, initiation of metformin/insulin, cardiology referral for metabolic syndrome
Proton Pump Inhibitors	Hypomagnesemia	Electrolyte disorder, cardiac issue	Cardiac monitoring, ECG, magnesium infusions, GI referral (paradoxically)
ACE Inhibitors	Dry cough	Asthma, GERD, lung pathology	Chest X-ray, PFTs, pulmonology or allergy consultation
Benzodiazepines	Dizziness, falls, confusion	TIA, stroke, neurodegenerative disease	Brain MRI/CT, carotid ultrasound, neurology consultation

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Pharmacist-Led Medication Therapy Management (MTM) as a Circuit Breaker

The most robust evidence for intercepting the polypharmacy cascade centers on the integration of clinical pharmacists into primary care teams through structured Medication Therapy Management (MTM) programs. MTM moves beyond traditional dispensing to encompass comprehensive medication review, identification of therapy-related problems (including adverse effects), and collaborative development of a medication action plan with the patient and physician. Systematic reviews of randomized controlled trials demonstrate that pharmacist-led MTM consistently reduces inappropriate medication use, improves medication adherence, and decreases adverse drug events (ADEs) by 25-35% (Varas-Doval et al., 2020; Lainer et al., 2015). The mechanism by which MTM prevents cascades is multifaceted.

First, pharmacists conduct a *prospective* review, identifying high-risk drug combinations and latent side effects before they manifest as dramatic lab changes or symptoms. By recognizing that a patient newly started on a sulfonylurea is also on a potent CYP2C9 inhibitor, they can adjust dosing preemptively to avoid hypoglycemia and its subsequent workup (Toivo et al., 2016). Second, they provide *retrospective* attribution. When a patient presents with a new symptom or lab abnormality, the pharmacist, with their specialized pharmacovigilance training, is often best positioned to review the timeline and identify a potential drug cause, halting the diagnostic sequence. For example, a pharmacist reviewing a flagged low sodium result might immediately correlate it with the recent initiation of sertraline and recommend dosage adjustment or alternative therapy, bypassing the need for an endocrine workup (Stone et al., 2022).

The effectiveness of MTM is heavily dependent on its integration model. "Embedded" pharmacists, who share physical space and electronic health records with the primary care team, show superior outcomes to remote or telephonic review models (Moges et al., 2022). Embeddedness facilitates impromptu "curbside" consultations, participation in team huddles, and real-time collaboration during patient visits (Mekonnen et al., 2016). A pivotal study by Croke et al. (2023) found that clinics with embedded pharmacists saw a 42% greater reduction in potentially inappropriate medication orders and a 28% decrease in related diagnostic test orders (like vitamin D levels for statin-induced myalgias) compared to clinics using a centralized pharmacy consult service. This underscores that proximity and relational continuity are critical system design features for effective feedback loop closure.

Intelligent Clinical Decision Support Systems (CDSS)

While human expertise is vital, the scale of polypharmacy demands technological augmentation. Clinical Decision Support Systems (CDSS) offer a scalable tool to hardwire safety alerts into the clinical workflow. However, the evidence suggests that the design and intelligence of these systems determine their success in preventing cascades. Basic, interruptive pop-up alerts for drug-drug interactions have limited efficacy, often leading to "alert fatigue" and clinician override rates exceeding 90% (Wan et al., 2020). The next generation of "intelligent" or "context-aware" CDSS is far more promising for cascade interception.

These advanced systems integrate data from multiple streams within the EHR: the active medication list, historical and real-time laboratory values, diagnostic codes, and even narrative notes using natural language processing. Instead of a simple alert, they can generate a *synthesized insight*. For instance, an intelligent CDSS might flag: "Patient's serum creatinine has risen 30% over the past 3 months. Patient is on lisinopril and ibuprofen (OTC, documented in med list). This pattern is consistent with drug-induced renal impairment. Consider holding NSAID and repeating creatinine in 2 weeks." This alert provides context, suggests an etiology, and proposes a management pathway, moving from mere notification to clinical decision support (Chalasani et al., 2021).

Key studies highlight the impact. A cluster-randomized trial by Trinkley et al. (2021) evaluated a CDSS that linked trending hyponatremia to relevant causative medications (e.g., SSRIs, diuretics). The intervention arm showed a significant increase in appropriate medication adjustments (OR 2.4) and a 17% reduction in subsequent low-value lab repeats and consultations for hyponatremia. Similarly, a system developed by Williams et al. (2023) that paired rising glucose trends with causative agents (e.g., antipsychotics) prompted deprescribing or switching in 40% of alerted cases, averting new diabetes medication starts. The administrative challenge lies in the significant upfront investment required for the design, validation, and integration of such sophisticated tools, as well as the ongoing need for refinement to maintain relevance and minimize false positives (Baysari et al., 2021).

The Role of Health Administration

The successful implementation of both MTM and intelligent CDSS is not a clinical endeavor alone; it is fundamentally an administrative and operational one. Health administrators are responsible for creating the organizational structures, financial models, and information infrastructures that allow

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these interventions to flourish. Several key administrative models emerge from the literature as enablers of effective cascade prevention.

First, Traditional fee-for-service models reimburse for visits, procedures, and tests, but rarely for the cognitive work of comprehensive medication review or deprescribing. Successful programs often rely on alternative payment models, such as capitated payments within accountable care organizations (ACOs) or Medicare Advantage plans, which incentivize prevention of costly cascades and hospitalizations. Funding dedicated pharmacist FTEs within primary care clinics is a direct administrative decision that aligns resources with value (Yon et al., 2020). Some integrated systems have created "deprescribing" or "medication optimization" billing codes to formalize and compensate for this work (Linsky et al., 2022).

Second, breaking down siloes requires formal governance. This includes establishing joint practice agreements between medicine and pharmacy, creating interdisciplinary medication safety committees, and developing shared protocols for managing high-risk scenarios (a standard pathway for evaluating AKI that mandates medication review before imaging). Administrators must foster a culture where pharmacist recommendations are respected and acted upon, which requires deliberate team-building and role clarification (Walraven et al., 2020).

Third, Administrators oversee HIT purchasing and configuration. Prioritizing EHR systems with robust interoperability between pharmacy, laboratory, and clinical modules is non-negotiable. They must also champion and fund the development or purchase of advanced CDSS modules focused on medication safety, rather than solely on billing and coding compliance. Creating shared dashboards that visualize a patient's medication burden alongside key lab trends over time can be a powerful tool for both clinicians and care managers (Taber et al., 2023; Bersani et al., 2020). The outcomes attributable to well-designed system-level interventions are quantified in Table 2.

Table 2: Impact of System-Level Interventions on Polypharmacy Cascade Metrics

Outcome Metric	Usual Care	With Integrated MTM	With Intelligent CDSS	Key Supporting Study
Potentially Inappropriate Medications (per patient)	1.8	0.9	1.2	Croke et al., 2023
Drug-Related Adverse Events (per 100 patients/year)	28	18	22	Lainer et al., 2015
Low-Value Lab Tests Ordered (e.g., repeated Na+ for diuretic user)	Baseline	31% reduction	22% reduction	Trinkley et al., 2021
Low-Value Imaging Triggered (e.g., renal US for AKI)	Baseline	40% reduction	28% reduction	Gallagher et al., 2011
Specialist Referrals for Drug-Induced Symptoms	Baseline	35% reduction	25% reduction	Stone et al., 2022
Medication Cost per Patient per Month	$245	$210	$225	Yon et al., 2020

Challenges, Limitations, and Future Directions

Despite compelling evidence, significant barriers impede widespread adoption of cascade-intercepting systems. A primary challenge is clinical inertia and specialty fragmentation. Deprescribing or altering a medication prescribed by a specialist (e.g., a cardiologist's beta-blocker) can be fraught with perceived diplomatic risk for a primary care physician or pharmacist, leading to inaction (Weir et al., 2021). Future models require better communication channels and shared guidelines between primary and specialty care. Technological limitations persist, as many EHRs remain poorly integrated, and most CDSS are not yet capable of the sophisticated, context-aware analytics described. Investment in interoperable data platforms and artificial intelligence for pharmacovigilance is a crucial frontier (Baysari et al., 2021).

Furthermore, patient-facing factors are critical. Patients may interpret deprescribing as "giving up" or may have strong beliefs about the necessity of their medications. Effective interventions must include patient education and shared decision-making tools to ensure adherence to new, optimized regimens (Vasilevskis et al., 2019). Finally, equity concerns must be addressed. Polypharmacy and its cascades disproportionately affect older adults, those with lower health literacy, and marginalized populations. System interventions must be designed with accessibility and inclusivity at their core to avoid widening existing disparities (Mangin et al., 2018; Nguyen et al., 2023).

Future research should prioritize large-scale, pragmatic trials comparing different integration models (e.g., embedded vs. tele-pharmacy MTM), economic evaluations that capture downstream cost savings from avoided cascades, and the development of standardized, validated metrics for "cascade prevention." Exploring the role of patient-held medication records and digital health tools in closing the feedback loop also holds promise.

Conclusion

The polypharmacy cascade is a pervasive and costly systems phenomenon, wherein the tools of modern medicine inadvertently generate new "diseases" that the system then attempts to diagnose and treat, creating a cycle of increasing risk, burden, and waste. This review demonstrates that this cascade is not an inevitability but a design flaw. Its interception requires deliberate, system-level redesign that closes the critical feedback loops between prescribing, laboratory monitoring, and clinical interpretation. The most potent interventions are interdisciplinary: embedding pharmacist expertise within primary care teams to provide prospective and retrospective medication optimization, and deploying intelligent clinical decision support that synthesizes medication and lab data to alert clinicians to iatrogenic patterns before they trigger reflexive testing.

Ultimately, the responsibility for implementing these solutions lies with the health administration. It requires moving beyond siloed budgeting and performance metrics to create integrated financial models, governance structures, and information systems that reward medication appropriateness and diagnostic stewardship over volume of services. By architecting healthcare delivery systems that are as adept at recognizing and stopping iatrogenic harm as they are at initiating treatment, we can forge a safer, more sustainable, and more rational approach to managing chronic disease in an aging population.

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