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Perspective

Polypharmacy in Multimorbidity: Toward an Integrated, Patient-Centered Pharmacotherapy

Soroush Mohammadi Jouabadi[1], **Sanaz Mokhtari**[2*]

[1] Division of Vascular Diseases and Pharmacology, Department of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands.

[2] Department of Pharmacotherapy, School of Pharmacy. Mazandaran University of Medical Sciences, Iran.

***Corresponding author:** Sanaz Mokhtari, Department of Pharmacotherapy, School of Pharmacy. Mazandaran University of Medical Sciences, Iran. E-mail: Sanaz.mo1375@gmail.com

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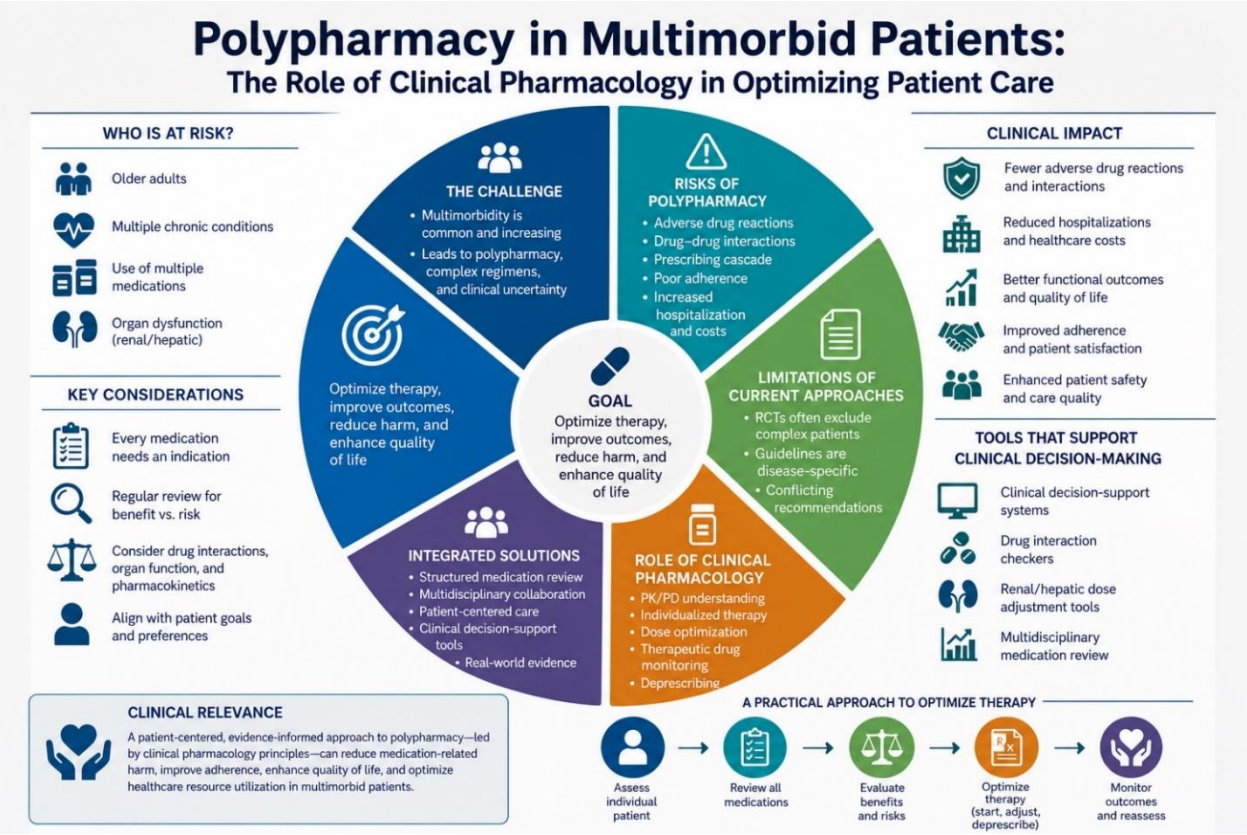
Abstract

Multimorbidity, particularly among older adults, has become a defining challenge in contemporary clinical practice, strongly driving the prevalence of polypharmacy. While guideline-based, disease-specific treatment approaches remain central to modern therapeutics, their cumulative application in complex patients often leads to convoluted medication regimens that fail to reflect individual physiological needs. Current clinical evidence frequently relies on randomized controlled trials that exclude multimorbid populations, creating a significant translational gap that manifests as therapeutic duplication, drug–drug interactions, and an overwhelming treatment burden. Consequently, polypharmacy must be addressed not merely as a clinical burden, but through actionable, pharmacological solutions. This perspective advocates for a paradigm shift toward integrated prescribing models driven by clinical pharmacology. We emphasize the integration of Pharmacokinetics/Pharmacodynamics (PK/PD) modeling, which when combined with Artificial Intelligence (AI), Electronic Health Records (EHR), and pharmacogenomics provides a tangible, mechanistic framework to safely reduce medication counts and optimize individualized dosing. By simulating drug exposure and toxicity risks before treatment initiation, these models facilitate targeted deprescribing and the simplification of complex regimens. Furthermore, the role of clinical pharmacists is essential in translating these precision medicine tools into routine clinical workflows. Through structured medication reviews and multidisciplinary collaboration, this approach shifts the clinical focus from strict guideline adherence toward a balanced, holistic assessment of patient-specific risks and benefits. Ultimately, embedding predictive modeling into healthcare infrastructure is critical for bridging the gap between pharmacological theory and real-world clinical practice, ensuring that pharmacotherapy remains aligned with individual patient priorities, functional status, and treatment goals. This integrated strategy is vital for minimizing preventable adverse outcomes and improving the overall quality of care for patients with multimorbidity.

Keywords: Multimorbidity, Polypharmacy, Patient-centered care, Deprescribing, Clinical pharmacology



Graphical Abstract. Polypharmacy in Multimorbidity: A Clinical Pharmacology Approach. Polypharmacy in multimorbid patients reflects the limitations of disease-centered prescribing. Clinical pharmacology enables individualized, patient-centered therapy through medication review, PK/PD-informed decisions, and deprescribing, supported by multidisciplinary care and decision-support systems to improve safety and outcomes.

Introduction

With the evolving clinical landscape, multimorbidity, particularly among older adults, has become an increasingly important challenge in daily medical practice (1). In this context, polypharmacy has emerged as a frequent consequence, often driven by strict adherence to guideline-based, disease-specific treatment strategies (2). While essential for individual diseases, their cumulative application frequently fails to align with the physiological complexity of multimorbid patients.

Limitations of Disease-Centered Prescribing

Although the use of multiple medications may be clinically justified in certain cases, it is associated with significant risks, including adverse drug reactions, drug–drug interactions, and a heavy treatment burden (3). A key limitation lies in the structure of current clinical evidence, where randomized controlled trials predominantly focus on single diseases and frequently exclude complex, multimorbid patients. (4).

This creates a translational gap between evidence generation and real-world clinical populations (5). Inconsistencies across guidelines often lead to therapeutic duplication and excessive medication use (2). Thus, a strictly disease-

centered prescribing model is inherently insufficient (6). Disease-specific frameworks fail to capture systemic drug interactions, highlighting the urgent need for advanced clinical tools and integrated approaches (7).

The Proposed Solution: PK/PD Modeling and Precision Medicine

Moving beyond the mere recognition of polypharmacy as a systemic challenge, the critical next step requires the application of advanced clinical pharmacology to actively optimize and simplify therapeutic regimens (8). Pharmacokinetics/Pharmacodynamics (PK/PD) modeling serves as the cornerstone of this solution (9).

PK/PD modeling can directly help reduce polypharmacy by predicting how multiple drugs interact within the body, thereby optimizing individualized dosing based on patient-specific characteristics such as age, kidney function, genetics, and comorbidities (10). Crucially, these models allow clinicians to identify medications that provide little additional therapeutic benefit but significantly increase the risk of toxicity (11). By simulating drug exposure, efficacy, and adverse effects prior to the initiation of treatment, PK/PD models provide a quantifiable basis for safer prescribing, targeted deprescribing, and the overall simplification of complex medication regimens particularly in elderly and multimorbid patients (12). In routine clinical practice, however, the implementation of PK/PD-guided therapy does not necessarily require intensive blood sampling. Advances in population PK models, Bayesian forecasting, and model-informed precision dosing enable individualized dose optimization using limited sampling strategies together with routinely available clinical data, thereby improving the feasibility of PK/PD applications in real-world polypharmacy management. Furthermore, when combined with Electronic Health Record (EHR) data, Artificial Intelligence (AI), and pharmacogenomics, these models enable robust precision medicine approaches (13). This integration not only improves therapeutic efficacy but also systematically reduces adverse drug reactions and eliminates unnecessary medication use.

Translating Pharmacology into Clinical Practice

To successfully implement these model-informed dosing approaches, the clinical infrastructure must evolve (14). In the context of polypharmacy, dose optimization extends beyond adjusting individual drug doses; rather, it aims to manage the cumulative effects of multiple concomitant medications. By integrating patient-specific pharmacokinetics with potential drug–drug interactions, model-informed PK/PD approaches help optimize the overall therapeutic regimen, maximizing efficacy while minimizing toxicity across the entire treatment plan. This shift is optimally driven by the expanding role of clinical pharmacists in routine care (15). Clinical pharmacists can integrate clinical pharmacology tools, including PK/PD-informed approaches, to support individualized therapeutic decision-making based on patient-specific pharmacological characteristic (16).

Through structured medication reviews and proactive deprescribing strategies, multidisciplinary teams can optimize therapeutic regimens, reduce inappropriate polypharmacy, and improve the benefit–risk balance of pharmacotherapy through individualized, patient-centered care (17). In patients receiving multiple concomitant medications, individualized PK/PD-guided dosing complements medication review by optimizing the exposure of essential therapies while facilitating deprescribing of unnecessary or potentially harmful medications, thereby

improving the overall management of polypharmacy.

Conclusion

Addressing polypharmacy in multimorbidity requires a definitive shift beyond traditional disease-centered prescribing. The integration of PK/PD modeling, AI, and precision medicine offers a clear, mechanistic pathway to safely reduce unnecessary medications and optimize therapeutic regimens. Translating these pharmacological principles into real-world patient benefit relies on strengthening multidisciplinary collaboration particularly empowering clinical pharmacists and embedding these predictive tools into routine clinical workflows.

Implications for Patient Care

In routine clinical practice, this integrated approach fundamentally changes the management of patients receiving multiple concomitant medications by shifting the focus from optimizing individual drugs to optimizing the overall therapeutic regimen. For example, in an older patient with chronic kidney disease receiving an anticoagulant, an antibiotic, and antihypertensive therapy, PK/PD-informed modeling can predict altered drug exposure resulting from impaired renal function and drug–drug interactions. These predictions enable clinicians to individualize the doses of essential medications while identifying drugs that provide limited additional benefit and may be safely deprescribed, thereby reducing treatment burden without compromising therapeutic efficacy. Accordingly, prescribing decisions extend beyond disease-specific targets to include therapeutic necessity, cumulative medication burden, and patient-specific PK/PD interactions. Deprescribing therefore becomes a proactive, data-driven strategy integrated with precision dosing rather than a reactive response to adverse drug events, particularly in older adults with multimorbidity and functional decline. By combining objective pharmacological modeling with patient preferences, functional status, and individualized treatment goals, this approach supports safer, more effective, and patient-centered management of polypharmacy.

Conflict of Interests

The authors declare that there is no conflict of interest.

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Author Contributions

All authors contributed to the conception and design of the study, literature search, data interpretation, drafting of the manuscript, and critical revision of the article. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Ethics Statement

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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