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Polypharmacy in Chronic Diseases: A Mechanistic and Clinical Review of Drug–Drug Interactions in Elderly Patients

Swejal S. Await[1], Anuja D. Nirwane[2*], Nilesh B. Chougule[3]

[1,2,3]Department of Pharmacology, Ashokrao Mane Institute of Pharmacy Ambap, Wathar 416112, Maharashtra, India.

Corresponding Auther:- anujanirwane123@gmail.com

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ABSTRACT

The use of multiple drugs, often five or more, is a major global health concern, particularly among elderly individuals with multimorbidity. The frequency of polypharmacy varies from 45–96% in hospitalized patients to 4–39% in older people living in the community and 38–91% in residents of nursing homes. It is caused by things like self-medication with over-the-counter medications, poor medication histories, specialist prescribing, and chronic disease management. This intricacy increases the likelihood of drug-drug interactions (DDIs), adverse drug reactions, and prescribing cascades, which occur when side symptoms are mistaken as new conditions, leading to additional medication and less adherence. Age-related pharmacokinetic changes, such as reduced renal and hepatic clearance (e.g., CYP450 inhibition/induction affecting absorption, metabolism, or excretion) or pharmacodynamic effects (additive, synergistic, or antagonistic actions), exacerbate DDIs caused by pharmacokinetic mechanisms. Polypharmacy increases DDIs in chronic conditions: type 2 diabetes causes hypoglycemia from sulfonylureas-NSAIDs; COPD causes bronchospasm from beta-agonists with non-selective beta-blockers; neurodegenerative cases risk serotonin syndrome or bradyarrhythmias from cholinesterase inhibitors with anticholinergics; and cardiovascular patients experience hypotension from amlodipine-furosemide or bleeding from heparin-aspirin. Medication reconciliation, deprescribing unnecessary medications, multidisciplinary teams of doctors, pharmacists, and nurses, and tools like Micromedex or Lexicomp for identifying moderate-to-severe interactions are all key components of management methods. In an effort to balance therapeutic advantages against risks for better results and lower healthcare costs, routine clinical parameter monitoring, pharmacogenomics, and patient education further minimize harms.

Keywords: Polypharmacy, drug-drug interactions, elderly patients, multimorbidity, deprescribing, adverse drug reactions, CYP450, pharmacodynamics, chronic diseases, medication optimization.

1. Introduction

Globally, polypharmacy is a serious problem. It describes the administration of multiple medications at the same time. Examining the definition as it appears in a standard medical dictionary reveals that the word "poly" is derived from the Greek word for a quantity greater than one. In addition, "pharmacy" refers to "pharmacon," the Greek word for medicine. Regretfully, there isn't a universally

accepted threshold for the quantity of drugs that qualify as polypharmacy. Polypharmacy is usually defined using explicit criteria with different cut points. Although these stated criteria are valuable, they do not take into consideration the patient's wants or the prescribers' understanding of the patient. The use of more medications than are medically necessary is another definition of polypharmacy. According to this definition, drugs that are not recommended, ineffective, or a therapeutic duplication are identified using implicit criteria. Global demographic aging and the rising incidence of multimorbidity (the co-existence of multiple chronic conditions) are directly responsible for its high prevalence, which is frequently reported to be between 25% and 50% among older adults living in the community and even higher in institutional and complex care settings. The growing complexity frequently leads to problematic or improper polypharmacy, even if a mix of drugs may constitute suitable polypharmacy provided all medications are evidence-based, optimized, and required to fulfill therapeutic goals.[1]

Population and Polypharmacy Prevalence:

Table no.1 population and polypharmacy prevalence

Population	**Polypharmacy Prevalence**
Community-dwelling elderly	4–39% [2]
Hospitalized patients	45–96%[3]
Nursing home residents	38–91%[4]

Prevalence increases with age and multimorbidity. Socioeconomic deprivation also correlates with higher polypharmacy rates.[5]

Etiology of polypharmacy: Many circumstances lead to polypharmacy, which is mostly caused by the difficult burden of managing several medical diseases.[6] People who have several chronic or concurrent health conditions frequently require medication for each one, creating the complex scenario known as polypharmacy.[7] The issue is further exacerbated by the fact that many specialists may write prescriptions without fully understanding the patient's entire medication regimen.[8] The situation is made worse by an insufficient medication history, which leads to unintentional polypharmacy when medical personnel do not have a clear understanding of a patient's current drugs.[9,10] Other factors contributing to the widespread availability and use of pharmaceuticals include the practice of self-medication and the use of over-the-counter (OTC) pills without first contacting a physician.[11] The problem of polypharmacy might be exacerbated by changes or supplements to the prescription regimen brought on by medication adherence issues.[12] In order to create protocols that optimize medication distribution and minimize potential risks related to polypharmacy, healthcare professionals must comprehend and address these important features.[13] Regular medication evaluations, patient education, and interprofessional collaboration are all essential components for the effective management and prevention of polypharmacy.[14]

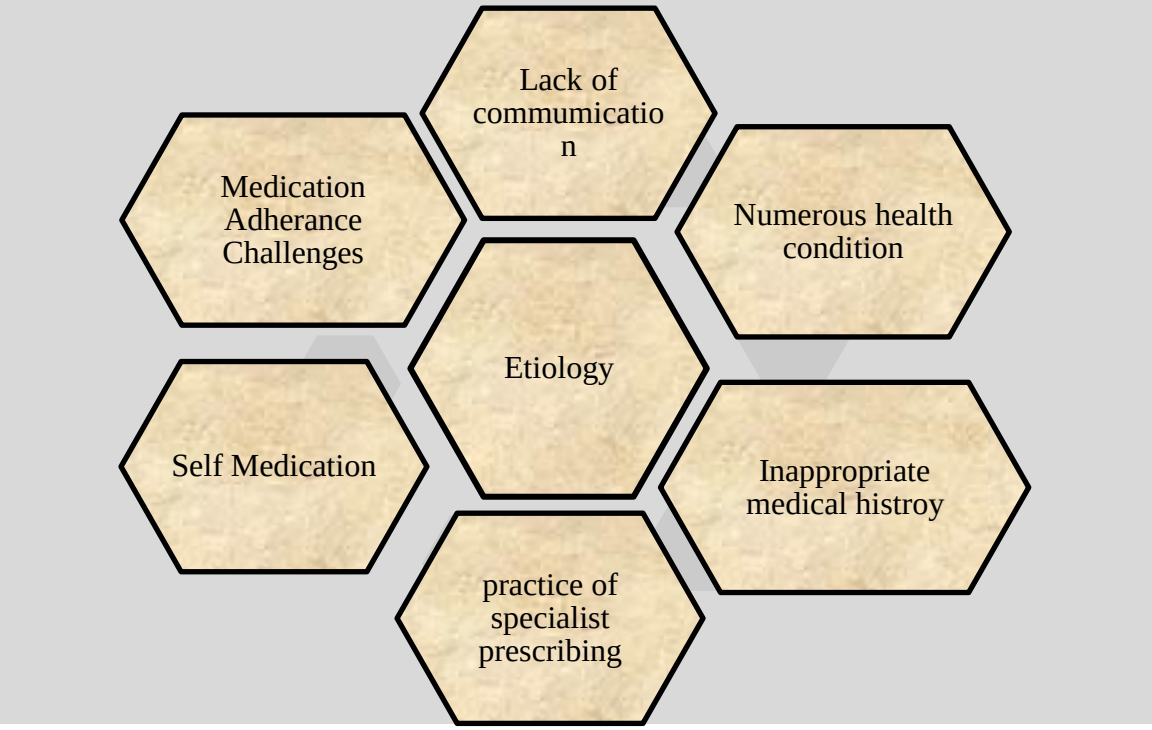

Fig no.1 Etiology of polypharmacy

Mechanism of harm and consequences: Through a number of interrelated processes, inappropriate polypharmacy significantly contributes to catastrophic clinical consequences.[15] First, the risk of drug-drug interactions (DDIs) and adverse drug reactions (ADRs) rises exponentially with each additional prescription, accounting for 5–28% of acute geriatric hospital admissions.[16,17] Second, the prescribing cascade is a frequent process that exacerbates the burden of polypharmacy by misdiagnosing an unpleasant drug effect as a new medical problem, which prompts the prescription of a new medication to address the "symptom."[18,19] Lastly, complicated regimens and a heavy pill load significantly lower medication adherence, endangering patient health and resulting in therapeutic failure.[20]

Addressing problematic polypharmacy: Due to the significant hazards, current efforts are now concentrated on medication optimization and deprescribing, which is the methodical process of stopping or cutting back on unnecessary prescriptions in order to improve results.[21,22] The use of explicit prescribing tools and multidisciplinary team approaches comprising doctors, pharmacists, and nurses are essential components of effective management regimens.[23] The STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert to Right Treatment) criteria, for example, offer evidence-based recommendations for identifying possibly improper prescriptions and missing acceptable ones, respectively.[24]

Polypharmacy and the Higher Risk of Drug-Drug Interactions: Particularly in older adults with several chronic comorbidities, polypharmacy is a serious public health concern. It is typically described as the concurrent use of five or more medications (though definitions vary, with "excessive polypharmacy" frequently involving 10 or more).[25]A DDI is an alteration in the effects of one medication brought about by the contemporaneous use of another medication or a non-prescription item, such as a herbal supplement. Age-related physiological changes that impact medication processing, such as decreased renal and hepatic clearance, decreased body water, and increased fat stores, all of which can vary drug concentrations and sensitivity, exacerbate this elevated risk.[26]

Polypharmacy in drug drug interaction: Because the likelihood of unwanted pharmacological interactions increases with the number of medications a patient takes, polypharmacy dramatically raises the likelihood of DDIs. The risk is significantly elevated in older people due to changed pharmacokinetics, which include slower metabolism, decreased renal clearance, and greater drug sensitivity. Up to 52% of patients on polypharmacy may have possible DDIs, many of which are of moderate clinical significance, according to research.[27]

Mechanisms of Drug-Drug Interactions: Pharmacokinetic and Pharmacodynamic: Pharmacokinetic (PK) interactions happen when a medication modifies another medication's Absorption, Distribution, Metabolism, or Excretion (ADME), which modifies the

drug's concentration at the site of action. The most frequent and clinically significant PK interactions are related to metabolism, namely the liver's Cytochrome P450 (CYP450) enzyme system.[28] A medication may be an inducer of a particular CYP450 isoenzyme (e.g., CYP3A4, CYP2D6) (speeding up metabolism, resulting in lower-than-expected levels and possible therapeutic failure) or an inhibitor (slowing down metabolism, resulting in higher-than-expected levels and potential toxicity). Increased plasma concentrations result from excretion interactions, which frequently entail competition for renal tubular secretion (e.g., Probenecid reducing Penicillin excretion).[29]

Pharmacodynamic (PD) interactions: occur when medications have additive, synergistic, or antagonistic effects by acting on the same physiological system or receptor location. Changes in the concentration of the drug in plasma have no effect on these interactions.[30] PD interactions include, for example: Synergistic effects, such as the increased risk of bleeding when anticoagulants (like Warfarin) and antiplatelet agents (like Aspirin) are combined; antagonistic effects, where one drug lessens the effect of another (e.g., SAIDs attenuating the antihypertensive effects of certain blood pressure medications); and additive effects, where two CNS depressants (like opioids and benzodiazepines) cause excessive sedation and an increased fall risk. Predicting and controlling DDIs requires an understanding of both PK and PD processes.[31]

Strategies for Detection, Prevention, and Management of Drug-Drug Interactions: Effective management of DDIs in polypharmacy requires a multimodal approach involving patients, pharmacists, and prescribers. The first step in prevention is a comprehensive medication reconciliation with every change in care, including prescription, over-the-counter, and herbal drugs. The deprescribing method, which attempts to lower the overall number of agents and the resulting DDI risk, is a crucial component of managing polypharmacy.[32] The deliberate practice of stopping or reducing medication when the hazards outweigh the advantages is known as deprescribing. Drug interaction databases (like Micromedex and Lexicomp) and validated clinical decision support technologies should be used by medical professionals for identification. These databases provide management recommendations and classify potential DDIs according to severity (mild, moderate, and severe). Crucially, the approach must include age, comorbidities, and physiological function in addition to identifying potential interactions and evaluating their clinical importance for each patient. Hepatic and renal function monitoring, as well as therapeutic drug monitoring for drugs with a narrow therapeutic index (such Digoxin and Warfarin), are examples of routine clinical and laboratory assessments. The clinical pharmacist is essential in identifying, treating, and preventing harmful DDIs through comprehensive drug reviews and patient education.[33]

Clinical Significance: Adverse drug responses (ADRs), treatment failure, readmissions to hospitals, and higher healthcare expenses are all repercussions of polypharmacy-related DDIs. Gastrointestinal bleeding, hypotension, renal failure, and cognitive disorders such delirium are common side effects of DDIs.[34]

Diseases in polypharmacy: The concurrent use of several medications, usually five or more, is known as polypharmacy, and it is a well-known public health concern that is frequently seen in patients with chronic illnesses, particularly in older persons. The phenomena results from the necessity to treat several comorbidities, including heart failure, diabetes, hypertension, and chronic obstructive pulmonary disease (COPD), which necessitates complicated medication regimens. In the past, the term "polypharmacy" has been used to describe both therapy combinations for rational complex disorders and excessive or unneeded medication.

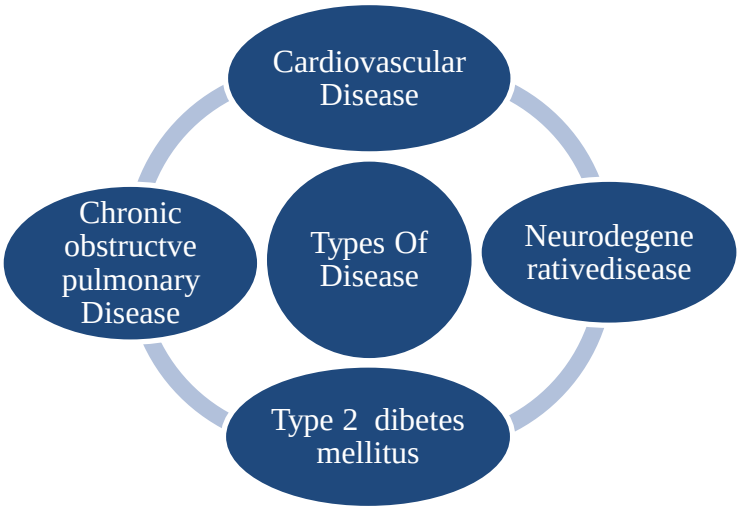

Fig.2.Types of Disease in polypharmacy

1. Cardiovascular Disease: Because patients with cardiovascular disease (CVD) frequently have severe polypharmacy, drug-drug interactions (DDIs) are widespread and clinically significant. Recent research (2024–2025) emphasize the most prevalent and harmful pairings, their causes, and measures to decrease risk.[35]

Common Interacting Cardiovascular Drugs: 64.2% of cardiovascular in-patients had at least one possible drug-drug interaction, with a median of eight per patient, according to a 2025 hospital-based study. The classes that were most commonly involved were as follows: 1. Diuretics (31.2%), including spironolactone and furosemide. 2. Antiplatelet and anticoagulants (23.8%), including heparin, aspirin, and clopidogrel.[36,37]

The top combinations and consequences identified included: 1. Amlodipine + Furosemide -> Moderate Hypotension 2. Heparin + Aspirin/Clopidogrel => Moderate–major increased risk of bleeding 3. Formoterol/Hydrocortisone + Furosemide => Moderate hypokalemia risk.[38]

Mechanisms and Clinical Implication: In cardiovascular medicine, a number of interaction mechanisms recur: 1] Pharmacodynamic synergy, in which medications have opposing or additive physiological effects (e.g., aspirin and clopidogrel, both raising bleeding risk).[39] 2] Pharmacokinetic interference, such as hepatic enzyme stimulation or inhibition; for example, PPIs (omeprazole, pantoprazole) reduce clopidogrel activation by inhibiting CYP2C19.3] Impact on renal function, particularly when ACE inhibitors and NSAIDs are taken together, as prostaglandin inhibition exacerbates renal perfusion and reduces the effects of antihypertensive medications.[40]

Management and Prevention Strategies: Recent research suggests a number of strategies to lower DDIs, including: Pharmacogenomics-guided therapy can help customize dosage and medication selection, especially for medications metabolized by CYP2C19 (such as clopidogrel). To identify negative effects early, clinical measures such blood pressure, electrolytes, renal function, and INR should be monitored. Lifestyle: frequent exercise, giving up smoking, eating a diet high in fruits and vegetables and low in sodium and saturated fats, managing weight.

Environmental: Reducing air pollution exposure also dramatically lowers the risk of cardiovascular disease screening: Regular monitoring of blood pressure, cholesterol, and glucose, especially in individuals with risk factors.[41,42]

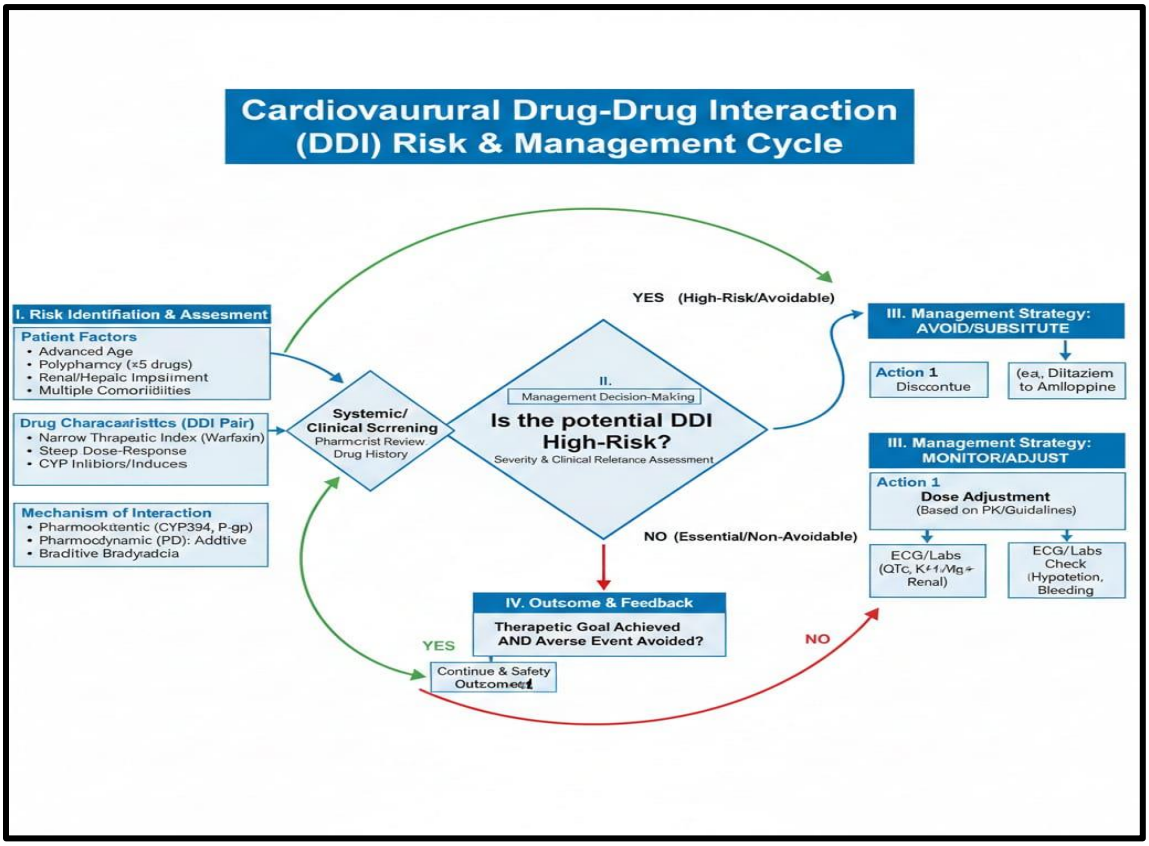

Fig no.3 Cardiovasular Disease

Neurodegenerative Disease: Due to polypharmacy in older individuals, drug–drug interactions (DDIs) are neurodegenerative diseases (NDDs) such Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, and amyotrophic lateral sclerosis (ALS). These interactions result from the brain and liver's intricate metabolic pathways and overlapping pharmacodynamic profiles.[43]

Key Drug–Drug Interactions in Neurodegenerative Disorders: Up to 50% of older persons with neurodegenerative disorders are exposed to potentially dangerous drug combinations, according to drug interaction studies. Cholinesterase inhibitors, NMDA antagonists, dopaminergic medications, and CNS depressants are among the pharmacological types that are frequently impacted.[44]

Alzheimer's disease (AD): Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) reduce cognitive benefits and worsen confusion when combined with anticholinergics (oxybutynin, diphenhydramine). Combining bradycardic drugs (beta-blockers, digoxin) may increase the risk of bradyarrhythmias and syncope. Combining NMDA antagonists (memantine) with other NMDA-active drugs (ketamine, dextromethorphan) increases the risk of neurotoxicity.[45]

Parkinson's disease (PD): Due to catecholamine buildup, levodopa used with non-selective MAO inhibitors (phenelzine, tranylcypromine) may result in a hypertensive crisis.Levodopa may exacerbate orthostatic hypotension when used with antihypertensives such as beta-blockers and diuretics. Additive hypotension and hallucinations can be brought on by COMT inhibitors (entacapone, tolcapone) and dopamine agonists (pramipexole, ropinirole). The risk of serotonin syndrome common in

is increased by serotonergic antidepressants combined with MAO-B inhibitors (rasagiline, selegiline).[46]

Pharmacological Basis of Interactions: Pharmacodynamic interference: Numerous NDD medications target the neurotransmitter systems (serotonin, acetylcholine, and dopamine), which can have antagonistic or additive effects when taken together.[47]

Pharmacokinetic interference: Antipsychotics, donepezil, and selegiline are metabolized by CYP450 enzymes, especially CYP2D6, CYP3A4, and CYP1A2. Co-administration of enzyme inhibitors (fluoxetine, erythromycin) or inducers (carbamazepine, phenytoin) modifies plasma levels and efficacy.[48]

Polypharmacology and combination therapy: Fixed-dose combinations must be clinically justified and closely watched for unfavorable pharmacokinetic overlap since multiple-target or "cocktail" techniques employed in NDDs enhance the likelihood of DDI.[49]

Clinical implication and Managemenat: Every patient visit should include a thorough medication evaluation to find possibly interfering medications and deprescribe unneeded CNS or autonomic treatments. Therapeutic drug monitoring (TDM) is used for medications including lithium, valproate, and several dopaminergic medicines that have narrow therapeutic indices. Pharmacogenomic data, particularly CYP2D6 and CYP3A4 genotypes, are used in personalized pharmacotherapy to predict altered metabolism in AD and PD treatments. The burden of polypharmacy and the danger of drug interactions may be decreased by non-pharmacological therapies like cognitive training or physical therapy.[50]

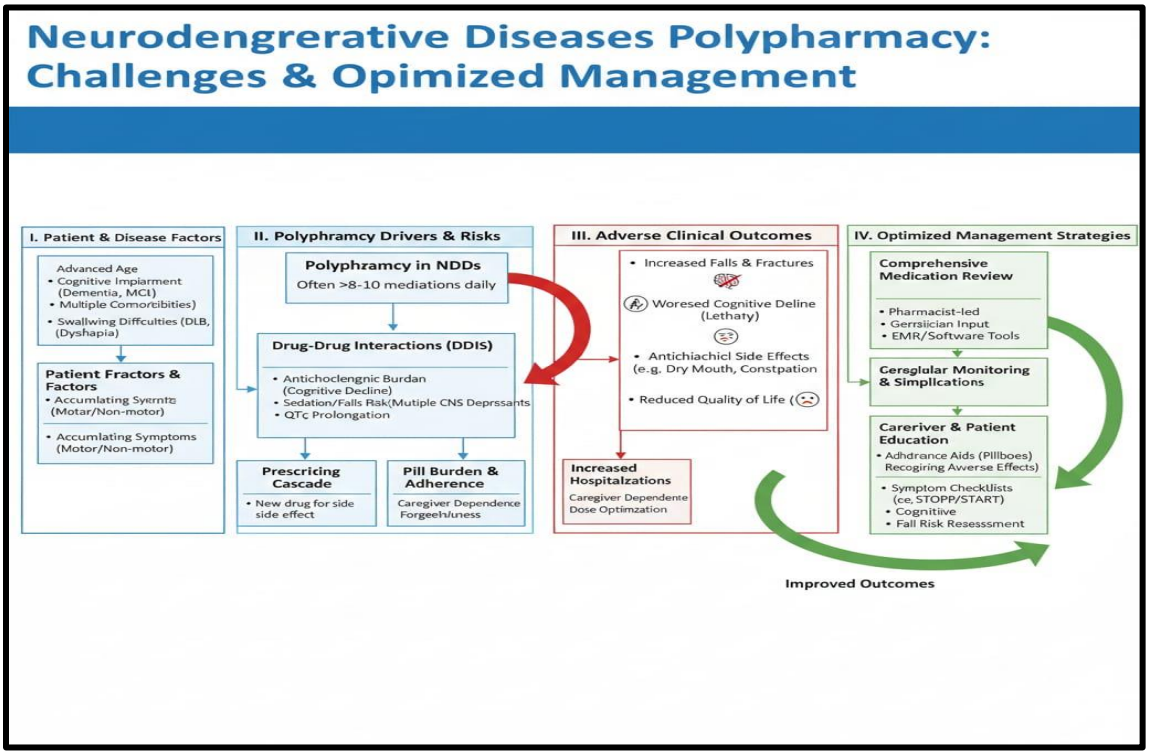

Fig no.4 Neurodegenerative Disease

Diabetes mellitus: Type 2 diabetes mellitus (T2DM) patients frequently experience drug-drug interactions (DDIs) as a result of polypharmacy for the treatment of concomitant conditions such hypertension, dyslipidemia, and cardiovascular disease. Hypo- or hyperglycemia and other negative systemic consequences may result from these interactions' alteration of glycemic regulation.[51]

Prevalence and Risk Factors: A 2024 multi-center study found that 92% of hospitalized T2DM patients had at least one possible DDI, with the majority being classified as moderate in severity (category C). The incidence of DDI was significantly increased by comorbidities, polypharmacy (more than eight prescriptions), and the use of cardiovascular or antimicrobial medications. Similarly, a 2025 hospital study that was published in the International Journal of Advanced Life Science Research found that 68% of T2DM outpatients had at least one suspected DDI, primarily compromising glycemic control.[52]

Common Drug–Drug Interactions in T2DM: Oral hypoglycemic medications, particularly metformin and sulfonylureas, and frequently co-prescribed medications are the most common DDIs: 1) Metformin + Corticosteroids (budesonide, hydrocortisone): Metformin's effectiveness is reduced, resulting in hyperglycemia. 2) NSAIDs (diclofenac, aspirin) and sulfonylureas (glibenclamide, glimepiride): The hypoglycemia effects are enhanced by protein-binding displacement. 3) Insulin + beta-blockers (metoprolol): These drugs conceal hypoglycemia symptoms and increase the risk that serious events will go unnoticed.[53]

Mechanisms of Interaction: Pharmacodynamic: Additive or antagonistic effects on the metabolism of glucose (e.g., sulfonylureas diminish glucose production, corticosteroids increase it).[54] Pharmacokinetic: changed metabolism or absorption through CYP enzymes. For instance, azole antifungals suppress these enzymes and may result in hypoglycemia, whereas rifampin and phenytoin increase CYP3A4 and CYP2C9, decreasing the effectiveness of sulfonylureas. Renal competition: Metformin plasma levels and the risk of lactic acidosis are increased when medications like cimetidine and metformin compete for renal tubular secretion.[55]

Management and Clinical Guidance: Every diabetic patient should have a routine medication review utilizing DDI-checking software (Lexi-Interact, Micromedex), particularly when starting a new therapy.monitoring blood sugar levels following co-prescription medication changes, and modifying antidiabetic therapy as necessary. minimizing polypharmacy by deprescribing unnecessary medications, especially in older people with numerous comorbidities.[57]

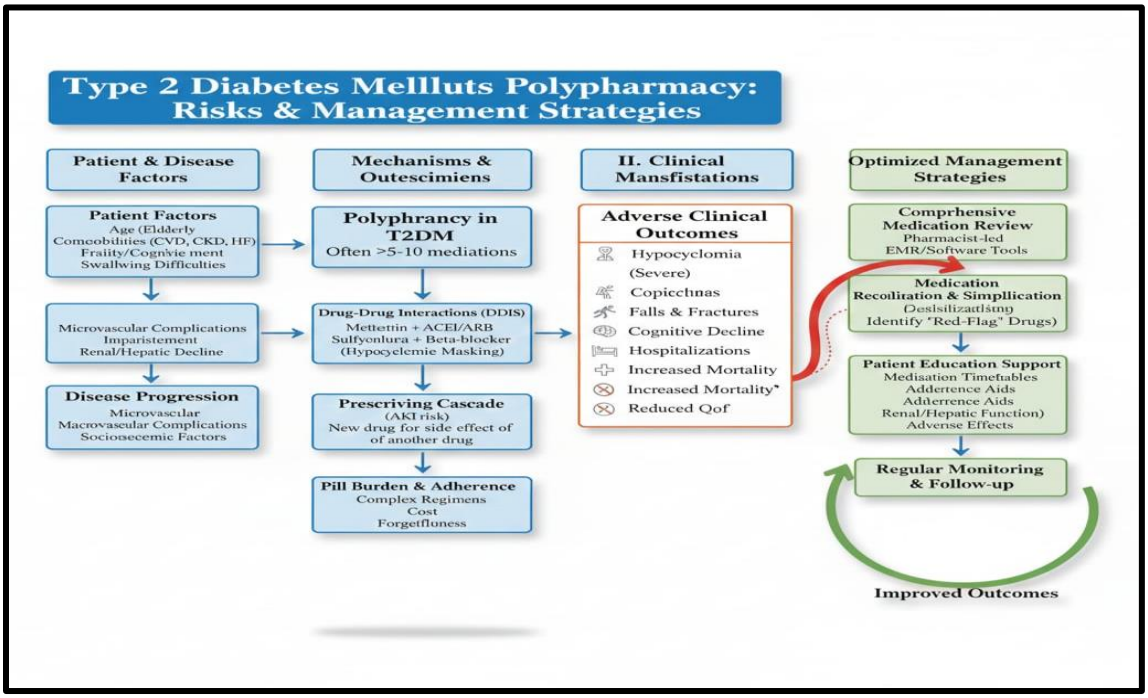

Fig no. Type 2 Diabetic Mellitus

Chronic obstructive pulmonary disease: Due to the extensive use of inhaled treatments, corticosteroids, bronchodilators, and medications for concomitant illnesses such depression, diabetes, and cardiovascular disease, drug-drug interactions (DDIs) in chronic obstructive pulmonary disease (COPD) are clinically relevant. To maximize treatment and reduce negative effects, it is essential to comprehend these relationships.

Common Drug Classes and Interactions: LABA + Inhaled Corticosteroid (ICS): Exhibits potent synergy via β2-adrenergic receptor-induced cAMP signaling and glucocorticoid receptor activation. The bronchodilation and anti-inflammatory benefits are enhanced by this cross-talk.Similar to BUD/FF/GLY (budesonide/formoterol/glycopyrronium), triple treatment (ICS + LABA + LAMA) produces extremely synergistic bronchorelaxation through the convergence of cAMP–PKA pathways, offering superior control of airway blockage.

In contrast, combinations outside these classes can provoke adverse DDIs: The combination of β2-agonists and nonselective beta-blockers (propranolol) reduces the effectiveness of bronchodilation and causes bronchospasm. Protease inhibitors (ritonavir) used with corticosteroids significantly enhance corticosteroid exposure, increasing the risk of adrenal suppression and Cushing's syndrome.[58]

Mechanisms Underlying Interactions: ICS/LABA synergy: β2-agonists promote corticosteroid receptor activation, resulting in increased anti-inflammatory efficacy, whereas ICS upregulate β2-receptor expression and improve downstream cAMP production. Novel PDE inhibitors (PDE3/4 inhibitors + LABA or LAMA): These combinations necessitate cautious titration, yet they produce additive or synergistic bronchodilation by converging on cAMP signaling and calcium regulation pathways.[59]

Comorbid Conditions and Drug-Drug Interactions: Comorbid conditions that increase the risk of DDIs include diabetes, heart failure, and hypertension:

- β-agonists + Diuretics: The risk of hypokalemia is increased by more potassium loss.
- ICS + Warfarin: This amplifies the anticoagulant effect and raises the risk of bleeding.[60]

Management and Clinical Recommendations: Medication reconciliation should be done frequently, especially when there are many prescribers or comorbidities. Dose balancing in combination inhalers should follow the isoeffectiveness approach to ensure synergy without damage. Clinical surveillance for ECG abnormalities, serum potassium, and infection risk is recommended for patients receiving long-term polytherapy. By teaching patients when to use inhalers and steering clear of over-the-counter drugs that shouldn't be taken (such decongestants), interaction risks are reduced.[61]

Category	Drug combination	Mechanism	Main clinical risk	Practical management

COPD	Theophylline + **β-blockers** (especially non-selective)	Pharmacodynamic antagonism / additive cardiopulmonary effects	Bronchospasm, reduced bronchodilator response; risk of theophylline adverse effects	Prefer cardioselective β-blocker if needed; use lowest effective dose; monitor respiratory status closely.[62]
Cardiovascular disease	**DOACs (apixaban/rivaroxaban)** + strong **P-gp/CYP3A4 inhibitors** (ketoconazole, ritonavir).	↓ clearance → ↑ DOAC levels	Major bleeding.	Avoid combination if possible; if unavoidable follow product-specific dose reductions/monitoring.[63]
Type 2 diabetes mellitus	**Metformin + iodinated contrast** (IV contrast for CT/angiography).	Acute kidney injury → metformin accumulation.	Lactic acidosis (rare but serious).	Follow local guidance:withhold metformin in high-risk patients around contrast and check renal function (many guidelines allow continued use in low-risk pts).[64,65]
Neurodegenrative disease	**MAO-B inhibitors (selegiline/rasagiline) + SSRIs / SNRIs / tramadol.**	Excess serotonergic activity → serotonin syndrome (PD risk).	Agitation, hyperthermia, neuromuscular hyperactivity potentially life-threatening.	Avoid or use extreme caution; if combined, use lowest doses and monitor closely; allow appropriate washout per guidance.[66]

Conclusion:

Polypharmacy significantly raises the risk of drug-drug interactions, particularly in people with chronic illnesses like diabetes and hypertension. These interactions may lead to negative consequences, prolonged hospital stays, and higher healthcare costs. Effective medication management is essential to lowering risks and improving patient outcomes. Regular review and, if possible, deprescription are included in this. Organized programs that involve clinical pharmacologists and utilize drug interaction databases might enhance medication safety. In general, carefully balancing the benefits of polypharmacy against its risks is necessary to maximize treatment and patient quality of life.

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