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The Role of Pharmacology in Geriatric Medicine.

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Abstract

Pharmacology plays a pivotal role in geriatric medicine by addressing the complex needs of an aging population. Older adults often experience physiological changes, comorbidities, and polypharmacy, which significantly influence drug absorption, distribution, metabolism, and excretion. These factors increase their vulnerability to adverse drug reactions (ADRs), drug interactions, and therapeutic inefficacy. Geriatric pharmacology focuses on optimizing medication use through individualized therapy, careful dose adjustments, and comprehensive monitoring. This review highlights the principles of pharmacology in older adults, emphasizing the importance of personalized treatment plans, deprescribing, and interdisciplinary approaches to improve patient outcomes and safety.

Keywords-Geriatric pharmacology, aging, polypharmacy, adverse drug reactions, drug interactions, personalized medicine, deprescribing, medication safety, pharmacokinetics, pharmacodynamics

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Introduction

The aging population is growing rapidly worldwide, with older adults (aged 65 years and above) representing a significant proportion of healthcare consumers. Aging is accompanied by physiological changes that alter drug pharmacokinetics (PK) and pharmacodynamics (PD), leading to unique challenges in prescribing and managing medications for this population. Additionally, older adults often have multiple chronic conditions requiring multiple medications, making polypharmacy—a common phenomenon—both a necessity and a risk factor.

In geriatric pharmacology, optimizing medication therapy while minimizing harm is a priority. This involves understanding the interplay of age-related changes, comorbidities, and drug interactions to achieve the desired therapeutic outcomes. Adverse drug reactions (ADRs) and inappropriate prescribing are leading causes of morbidity and hospitalizations among older adults, emphasizing the need for careful medication management.

This discussion explores the role of pharmacology in geriatric medicine, focusing on age-related PK/PD changes, polypharmacy, ADRs, and strategies for safe and effective drug use in older adults. By integrating evidence-based practices and patient-centered approaches, geriatric pharmacology aims to enhance quality of life and ensure safety in the aging population.

1. Age-Related Physiological Changes and Pharmacokinetics

As individuals age, physiological changes in the body can significantly alter drug pharmacokinetics (PK)—the absorption, distribution, metabolism, and excretion of drugs. Understanding these changes is critical for adjusting medication regimens to ensure safety and efficacy in older adults.

1. Absorption

While drug absorption is generally not significantly impaired in older adults, certain age-related changes can affect this process:

- **Gastrointestinal (GI) Function:**
    - Slower gastric emptying and reduced splanchnic blood flow may delay the onset of drug action.
    - Reduced gastric acid secretion (*hypochlorhydria*) affects the solubility and absorption of certain medications:
        - Drugs requiring an acidic environment (e.g., calcium carbonate, ketoconazole) may have reduced bioavailability.

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- Changes in GI motility and enzyme activity can impact the absorption of nutrients and some drugs.

- **Clinical Relevance:**
  - Most orally administered drugs are not significantly affected by these changes.
  - Co-administration with acid-suppressing agents (e.g., proton pump inhibitors) can further reduce absorption of acid-dependent drugs.

2. Distribution

Drug distribution is influenced by age-related changes in body composition and protein binding:

- **Body Composition:**
  - **Increased Body Fat:**
    - Older adults have a higher proportion of body fat (~30% in men, ~40% in women) compared to younger adults.
    - Lipophilic (fat-soluble) drugs, such as benzodiazepines and diazepam, have a larger volume of distribution (Vd), resulting in:
      - Prolonged half-life.
      - Delayed drug clearance.
  - **Decreased Total Body Water:**
    - Total body water decreases (~10-15%), reducing the Vd of hydrophilic (water-soluble) drugs like aminoglycosides and digoxin.
    - This leads to higher plasma concentrations and an increased risk of toxicity.
  - **Reduced Lean Body Mass:**
    - Affects the distribution of certain drugs requiring lean tissue for distribution.
- **Plasma Protein Levels:**
  - **Reduced Albumin Levels:**
    - Albumin levels may decrease with age or in chronic illness, leading to reduced protein binding for drugs like warfarin and phenytoin.

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        - This increases the free (active) fraction of the drug in the bloodstream, heightening therapeutic and toxic effects.
    - **Increased α1-Acid Glycoprotein:**
        - Levels of α1-acid glycoprotein, a plasma protein binding basic drugs (e.g., propranolol), may increase in response to inflammation or illness.

3. Metabolism

Drug metabolism occurs primarily in the liver, and age-related changes can significantly alter this process:

- **Phase I Reactions (Oxidation, Reduction, Hydrolysis):**
    - These reactions, mediated by the cytochrome P450 enzyme system, tend to decline with age.
    - Drugs metabolized through Phase I pathways, such as diazepam, theophylline, and propranolol, may exhibit:
        - Prolonged half-life.
        - Accumulation, leading to toxicity.
- **Phase II Reactions (Conjugation, Sulfation, Acetylation):**
    - These pathways, responsible for metabolizing drugs like lorazepam, oxazepam, and temazepam, are largely unaffected by aging.
    - Drugs undergoing Phase II metabolism are often preferred in older adults.
- **Hepatic Blood Flow:**
    - Reduced hepatic blood flow (~40% decrease) in older adults decreases the metabolism of high-extraction-ratio drugs (e.g., propranolol, verapamil).
- **Liver Size:**
    - Liver mass declines with age, further reducing the liver's metabolic capacity.

4. Excretion

Renal excretion is the primary route of elimination for many drugs, and renal function declines significantly with age:

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- **Glomerular Filtration Rate (GFR):**
  - GFR decreases by approximately 1% per year after the age of 40, leading to reduced clearance of renally excreted drugs like digoxin, aminoglycosides, and lithium.
  - Serum creatinine levels may appear normal due to reduced muscle mass, masking renal impairment.
- **Tubular Function:**
  - Declines in tubular secretion and reabsorption reduce the kidney's ability to handle drugs like diuretics and adjust to electrolyte imbalances.
- **Clinical Implications:**
  - Renally excreted drugs require dose adjustments based on creatinine clearance or estimated GFR (eGFR).
  - Failure to adjust doses can lead to drug accumulation and toxicity (e.g., nephrotoxicity from aminoglycosides or metformin-induced lactic acidosis).

Key Pharmacokinetic Adjustments

To account for age-related physiological changes:

1. **Absorption:**
   - Monitor for drug-nutrient interactions or altered absorption due to GI changes or co-medications.
2. **Distribution:**
   - Be cautious with lipophilic and hydrophilic drugs to avoid prolonged effects or toxicity.
3. **Metabolism:**
   - Prefer drugs undergoing Phase II metabolism when possible.
   - Monitor closely for drugs with reduced clearance via hepatic pathways.
4. **Excretion:**
   - Adjust dosages of renally excreted drugs based on renal function tests.

Conclusion

Understanding age-related changes in pharmacokinetics is essential for optimizing medication use in older adults. These physiological alterations highlight the importance of

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individualized therapy, careful dose adjustments, and vigilant monitoring to minimize adverse effects and ensure therapeutic efficacy.

2. Pharmacodynamics in Older Adults

Pharmacodynamics (PD) refers to the effects of drugs on the body, including their mechanisms of action, therapeutic effects, and side effects. In older adults, age-related physiological changes and alterations in receptor sensitivity can influence how drugs interact with the body. These changes often lead to increased sensitivity to certain medications and reduced effectiveness of others, necessitating careful consideration when prescribing and monitoring therapy.

Key Changes in Pharmacodynamics in Older Adults

1. **Altered Receptor Sensitivity**

Age-related changes in receptor number, binding affinity, and signal transduction pathways affect the response to medications:

- **Increased Sensitivity:**
  - Older adults exhibit heightened sensitivity to central nervous system (CNS) depressants such as benzodiazepines, opioids, and anesthetics. This is due to changes in receptor function and reduced homeostatic reserves, increasing risks of sedation, respiratory depression, and falls.
  - Enhanced response to anticoagulants (e.g., warfarin) due to altered vitamin K metabolism and reduced hepatic synthesis of clotting factors increases the risk of bleeding.
- **Decreased Sensitivity:**
  - β-adrenergic receptor function declines with age, leading to reduced responsiveness to β-blockers (e.g., propranolol) and potentially diminishing their effectiveness in managing hypertension or heart failure.

2. **Impaired Homeostatic Mechanisms**

Aging impairs the body's ability to maintain physiological equilibrium, which can exacerbate drug effects:

- **Orthostatic Hypotension:**
  - Reduced baroreceptor sensitivity and autonomic function make older adults more prone to orthostatic hypotension caused by antihypertensives, diuretics, or nitrates.

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- **Electrolyte Imbalances:**
  - Decreased renal and hormonal compensatory mechanisms increase susceptibility to imbalances (e.g., hypokalemia from diuretics, hyponatremia from SSRIs or antipsychotics).
- **Thermoregulatory Impairment:**
  - Drugs affecting thermoregulation, such as anticholinergics, may predispose older adults to hyperthermia or hypothermia.

3. **Changes in Drug Response by System**
   - **Central Nervous System (CNS):**
     - Greater sensitivity to CNS drugs (e.g., antipsychotics, sedatives) increases the risk of cognitive impairment, delirium, and falls.
     - Reduced dopaminergic function contributes to an increased susceptibility to extrapyramidal side effects from antipsychotic medications.
   - **Cardiovascular System:**
     - Reduced cardiac output and vascular compliance alter responses to cardiovascular drugs.
     - Increased risk of bradycardia and hypotension with calcium channel blockers, digoxin, and β-blockers.
   - **Musculoskeletal System:**
     - Drugs like corticosteroids and certain anticonvulsants accelerate bone loss, heightening the risk of osteoporosis and fractures.
4. **Drug-Drug and Drug-Disease Interactions**
   - Older adults are more vulnerable to adverse effects from drug-drug interactions due to polypharmacy.
   - Pre-existing conditions, such as renal or hepatic impairment, exacerbate the effects of medications like NSAIDs, increasing risks of nephrotoxicity or gastrointestinal bleeding.

Clinical Implications for Pharmacodynamics

Given these changes, clinicians should adopt strategies to ensure safe and effective drug use in older adults:

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1. **Start Low, Go Slow:**
    - Begin with the lowest effective dose and titrate slowly to minimize the risk of adverse drug reactions (ADRs).
2. **Monitor Therapeutic Responses and Side Effects:**
    - Regularly evaluate the therapeutic effects and potential toxicities of medications, especially those with narrow therapeutic windows (e.g., digoxin, warfarin).
3. **Minimize Polypharmacy:**
    - Limit the use of unnecessary medications to reduce the risk of drug-drug interactions and compounded side effects.
4. **Adjust for Comorbidities:**
    - Consider pre-existing conditions (e.g., cardiovascular disease, diabetes, or dementia) when prescribing, as these can influence drug efficacy and safety.
5. **Use Alternative Therapies Where Appropriate:**
    - Opt for non-pharmacological interventions when possible, such as lifestyle modifications for hypertension or physical therapy for musculoskeletal pain.

Conclusion

Pharmacodynamic changes in older adults significantly influence drug safety and efficacy. Heightened sensitivity to certain medications and impaired homeostatic mechanisms increase the risk of adverse effects, requiring a tailored approach to prescribing. Clinicians must consider these changes, monitor therapy closely, and prioritize patient-centered care to optimize therapeutic outcomes and enhance quality of life in the aging population.

3. Polypharmacy and Drug Interactions

Polypharmacy and drug interactions are significant concerns in geriatric medicine due to the prevalence of multiple chronic conditions requiring complex medication regimens. While necessary in many cases, polypharmacy increases the risk of adverse drug reactions (ADRs), drug interactions, and nonadherence, posing a significant challenge for healthcare providers.

Polypharmacy

Definition

Polypharmacy generally refers to the concurrent use of five or more medications. However, it is also characterized by the inappropriate use of medications, including unnecessary duplication, prescribing cascades, and drugs with no clear indication.

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Prevalence

- Polypharmacy is common in older adults due to the need for managing chronic conditions such as diabetes, hypertension, cardiovascular disease, and arthritis.
- Approximately 50% of older adults take at least five prescription drugs, and 12% take ten or more.

Risks of Polypharmacy

1. **Adverse Drug Reactions (ADRs):**
    - Older adults are at an increased risk of ADRs due to age-related changes in pharmacokinetics and pharmacodynamics.
    - Common ADRs include cognitive impairment, falls, bleeding, and renal dysfunction.
2. **Drug-Drug Interactions:**
    - The risk of interactions increases exponentially with the number of medications.
    - For example:
        - Warfarin combined with NSAIDs or antibiotics increases bleeding risk.
        - ACE inhibitors with potassium supplements can lead to hyperkalemia.
3. **Drug-Disease Interactions:**
    - Some drugs exacerbate pre-existing conditions. For example:
        - NSAIDs can worsen heart failure or renal insufficiency.
        - Anticholinergics can aggravate dementia or glaucoma.
4. **Medication Nonadherence:**
    - Complex regimens increase the likelihood of missed doses, errors, or intentional discontinuation.
5. **Prescribing Cascade:**
    - Symptoms caused by one drug may be misinterpreted as a new medical condition, leading to the prescription of additional medications.

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Drug Interactions

Drug interactions occur when one medication affects the pharmacokinetics or pharmacodynamics of another, altering its effectiveness or increasing toxicity.

Types of Drug Interactions

1. **Pharmacokinetic Interactions:**
    - **Absorption:** Drugs like antacids or proton pump inhibitors can reduce the absorption of certain antibiotics (e.g., tetracyclines, fluoroquinolones).
    - **Distribution:** Competition for protein binding sites (e.g., warfarin and phenytoin) can increase the active concentration of one drug.
    - **Metabolism:** Enzyme inducers (e.g., rifampin, phenytoin) or inhibitors (e.g., macrolide antibiotics, azole antifungals) affect the metabolism of drugs like warfarin or statins.
    - **Excretion:** NSAIDs can reduce renal clearance of drugs like lithium or methotrexate, increasing toxicity.
2. **Pharmacodynamic Interactions:**
    - **Additive Effects:** Combining CNS depressants (e.g., benzodiazepines and opioids) increases the risk of sedation and respiratory depression.
    - **Antagonistic Effects:** β-blockers may counteract the effects of β-agonists used for asthma.
    - **Synergistic Toxicity:** Combining drugs like ACE inhibitors and NSAIDs may exacerbate renal dysfunction.

Common High-Risk Drug Classes in Older Adults

- **Anticoagulants (e.g., warfarin, DOACs):** High risk of bleeding when combined with antiplatelets, NSAIDs, or certain antibiotics.
- **Anticholinergics (e.g., diphenhydramine, oxybutynin):** Increased risk of cognitive impairment and falls when used with CNS depressants.
- **Psychotropic Drugs (e.g., SSRIs, benzodiazepines):** Increased risk of sedation, falls, and hyponatremia.
- **Opioids:** High risk of respiratory depression and constipation when combined with sedatives or anticholinergic agents.

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Addressing Polypharmacy and Drug Interactions

1. Comprehensive Medication Review

- Regularly review all medications, including over-the-counter (OTC) drugs and supplements.
- Use tools such as:
    - **Beers Criteria:** Identifies potentially inappropriate medications (PIMs) in older adults.
    - **STOPP/START Criteria:** Helps identify PIMs and underused medications.

2. Deprescribing

- Systematically discontinue unnecessary or harmful medications.
- Prioritize medications with minimal benefits or high risk of ADRs.
- Use shared decision-making to align deprescribing with patient goals and preferences.

3. Simplify Medication Regimens

- Reduce the number of medications where possible.
- Use combination drugs or long-acting formulations to improve adherence.

4. Monitor for Interactions

- Utilize electronic prescribing systems with drug interaction alerts.
- Educate patients and caregivers about potential signs of ADRs and interactions.

5. Individualized Therapy

- Adjust doses based on renal and hepatic function.
- Consider patient-specific factors such as comorbidities, cognitive status, and functional ability.

6. Interdisciplinary Care

- Collaborate with pharmacists, nurses, and other healthcare providers to optimize medication use and monitor for interactions.

Conclusion

Polypharmacy and drug interactions are critical concerns in geriatric pharmacology, requiring proactive strategies to mitigate risks. Regular medication reviews, careful prescribing practices, and patient-centered care are essential for improving therapeutic outcomes and

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reducing medication-related harm in older adults. By prioritizing safety and efficacy, healthcare providers can enhance the quality of life for this vulnerable population.

4. Adverse Drug Reactions (ADRs)

Adverse Drug Reactions (ADRs) are harmful or unintended effects of medications that occur at normal doses. In older adults, ADRs are of particular concern due to age-related physiological changes, polypharmacy, and the high prevalence of chronic conditions requiring pharmacologic treatment. These reactions can lead to significant morbidity, mortality, and functional decline in this population.

1. Prevalence and Significance of ADRs in Older Adults

Older adults are more susceptible to ADRs for several reasons:

- **Polypharmacy:** The more medications a person takes, the higher the risk of drug-drug interactions and cumulative side effects.
- **Age-related Physiological Changes:** Reduced renal and hepatic function, altered receptor sensitivity, and changes in drug absorption, distribution, and metabolism can affect how drugs act in the body.
- **Comorbidities:** Chronic diseases like heart disease, diabetes, and kidney disease can influence the body's response to medications.

Approximately 20-30% of hospital admissions in older adults are due to ADRs, and ADRs are responsible for 10-20% of all hospital-related deaths in this population.

2. Common Types of ADRs in Older Adults

ADRs in older adults can vary depending on the type of medication, its mechanism of action, and the individual’s physiological status. Common types include:

1. Central Nervous System (CNS) ADRs:

- **Sedation and Cognitive Impairment:** Medications such as benzodiazepines, anticholinergics, and opioids can cause excessive sedation, confusion, and delirium, which are particularly dangerous for older adults who may already have cognitive decline.
- **Falls and Fractures:** CNS depressants (e.g., sedatives, antipsychotics) increase the risk of falls and fractures, especially when combined with other sedating drugs.
- **Extrapyramidal Symptoms:** Antipsychotic medications may cause movement disorders such as tremors, rigidity, and tardive dyskinesia.

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2. Cardiovascular ADRs:

- **Hypotension and Orthostatic Hypotension:** Medications like antihypertensives, diuretics, and nitrates can cause low blood pressure, leading to dizziness, fainting, and falls.
- **Bradycardia:** β-blockers and calcium channel blockers can cause slow heart rates, leading to dizziness, syncope, and, in severe cases, heart block.
- **Electrolyte Imbalances:** Diuretics can lead to potassium, sodium, and magnesium imbalances, resulting in arrhythmias or muscle weakness.

3. Renal ADRs:

- **Nephrotoxicity:** Nonsteroidal anti-inflammatory drugs (NSAIDs), ACE inhibitors, and certain antibiotics (e.g., aminoglycosides) can cause kidney damage, especially in older adults with pre-existing renal insufficiency.
- **Fluid and Electrolyte Disturbances:** Diuretics and ACE inhibitors can cause dehydration, hyponatremia, or hyperkalemia, particularly in older adults with poor renal function.

4. Gastrointestinal ADRs:

- **Gastrointestinal Bleeding:** NSAIDs and anticoagulants (e.g., warfarin) increase the risk of bleeding, especially in those with peptic ulcer disease or gastritis.
- **Constipation:** Opioids, anticholinergics, and calcium channel blockers often cause constipation, which can lead to discomfort, fecal impaction, or bowel obstruction.
- **Nausea and Vomiting:** Chemotherapy, antibiotics, and some cardiovascular drugs (e.g., digoxin) can cause nausea and vomiting, especially when taken over extended periods.

5. Hematologic ADRs:

- **Bleeding:** Warfarin, direct oral anticoagulants (DOACs), and antiplatelet drugs (e.g., aspirin) increase the risk of bleeding, particularly when combined with other anticoagulants or in those with poor nutritional status.
- **Anemia:** Chemotherapy, some antihypertensives (e.g., ACE inhibitors), and drugs that affect bone marrow function (e.g., methotrexate, chloramphenicol) can lead to anemia in older adults.

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6. Endocrine and Metabolic ADRs:

- **Hyperglycemia:** Medications such as corticosteroids, atypical antipsychotics, and diuretics may cause elevated blood sugar levels, which is especially problematic for older adults with diabetes or those at risk for developing diabetes.
- **Hypoglycemia:** Insulin and sulfonylureas may cause low blood sugar levels, which can lead to confusion, dizziness, or falls.

3. Risk Factors for ADRs in Older Adults

Several factors make older adults particularly vulnerable to ADRs:

- **Polypharmacy:** The concurrent use of multiple medications increases the likelihood of drug-drug interactions, cumulative toxic effects, and adverse events.
- **Changes in Physiology:**
    - Decreased renal and hepatic function slows the elimination of drugs, leading to drug accumulation and increased risk of toxicity.
    - Alterations in body composition, such as increased fat mass and reduced lean body mass, change the distribution of drugs, affecting their pharmacokinetics.
- **Impaired Homeostatic Mechanisms:**
    - Reduced ability to compensate for fluid loss, temperature changes, or hypotension increases the risk of ADRs such as dehydration, hyponatremia, and falls.
- **Comorbid Conditions:** Chronic conditions like heart disease, diabetes, and dementia increase vulnerability to ADRs, particularly when medications interact with the underlying disease process.

4. Preventing and Managing ADRs in Older Adults

To minimize the risk and impact of ADRs, healthcare providers should:

1. Medication Review and Deprescribing:

- Regularly review the patient's medication regimen to identify unnecessary, inappropriate, or duplicative medications. Tools like the **Beers Criteria** and **STOPP/START criteria** can help identify potentially harmful drugs for older adults.
- Deprescribing involves reducing or stopping medications that are no longer needed or may be harmful.

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2. Individualized Dosing and Monitoring:

- Start medications at lower doses and titrate up slowly to minimize side effects.
- Regularly monitor drug levels (e.g., for warfarin, digoxin) and clinical parameters (e.g., renal function, electrolytes) to detect adverse effects early.
- For high-risk medications (e.g., anticoagulants, antipsychotics), use caution and adjust dosing as necessary.

3. Educate Patients and Caregivers:

- Teach patients and caregivers about the potential side effects of medications and how to recognize ADRs.
- Ensure that patients understand the importance of medication adherence and follow-up appointments.

4. Promote Non-Pharmacological Interventions:

- Where appropriate, recommend lifestyle changes (e.g., dietary modifications, exercise) as alternatives to medications for managing chronic conditions.

5. Interdisciplinary Care:

- Involve a team of healthcare professionals, including pharmacists, to assess and optimize medication regimens.

Conclusion

Adverse Drug Reactions (ADRs) in older adults present a significant challenge in geriatric medicine due to the complex interplay of age-related physiological changes, polypharmacy, and comorbid conditions. These reactions can lead to increased morbidity, hospital admissions, and even death, underscoring the need for careful medication management. Key factors contributing to ADRs in older adults include altered pharmacokinetics and pharmacodynamics, drug-drug and drug-disease interactions, and the heightened sensitivity of aging organs.

To mitigate these risks, healthcare providers must prioritize strategies such as regular medication reviews, deprescribing unnecessary medications, individualized dosing, and ongoing patient education. Collaborative care models, including the involvement of pharmacists, are essential in optimizing therapeutic outcomes and minimizing adverse effects. Ultimately, by adopting a cautious, patient-centered approach to prescribing and monitoring, healthcare professionals can improve the safety and quality of life for older adults, enhancing their ability to benefit from pharmacological therapies while reducing the incidence of harmful drug-related events.

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