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From Infancy to Frailty: Age and Disease-Linked Modulation of Drug Metabolism

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Abstract

Drug metabolism is a central component of pharmacokinetics and plays a critical role in determining drug efficacy, safety, and therapeutic outcomes. This review examines how age and various health conditions influence drug metabolism, with particular emphasis on vulnerable populations such as neonates, children, the elderly, and individuals with hepatic, renal, cardiovascular, endocrine, or nutritional disorders. The three phases of drug metabolism modification (Phase I), conjugation (Phase II), and excretion (Phase III) are discussed in detail, highlighting how age-related physiological changes and disease states modulate these processes. Neonates and infants exhibit immature enzyme systems and altered hepatic blood flow, while elderly patients demonstrate declining liver and renal function, requiring careful dosage adjustments. Additionally, chronic diseases such as cirrhosis, chronic kidney disease, and diabetes significantly impact drug clearance by altering enzyme activity, protein binding, and organ perfusion. The review also explores the impact of genetic polymorphisms and malnutrition on drug biotransformation, emphasizing the need for personalized pharmacotherapy. Collectively, this work underscores the importance of integrating age, genetic variability, disease states, and nutritional status into pharmacological planning to enhance therapeutic precision and minimize adverse drug reactions.

Keywords: Drug Metabolism; Pharmacokinetics; Therapeutic Outcomes; Neonates and Infants; Elderly Patients; Phase I Metabolism; Enzyme Activity; Polymorphisms; Pharmacotherapy; Drug Clearance; Dosage Adjustments

Introduction

Drug metabolism, a critical determinant of pharmacokinetics and therapeutic efficacy, is significantly influenced by individual physiological variables such as age and health status. As the body ages, several biochemical and physiological processes including liver enzyme activity, organ perfusion, and plasma protein levels undergo modifications, all of which can alter drug disposition. Notably, the cytochrome P450 (CYP) enzyme system, responsible for metabolizing a vast number of therapeutic agents, shows age-dependent expression and activity, with reduced clearance observed in the elderly population [1,2]. Similarly, neonates and infants often possess immature hepatic and renal systems, leading to delayed drug clearance and increased drug half-life [3].

The influence of age on metabolism is not linear and varies across different metabolic pathways. Phase I reactions (oxidation, reduction, and hydrolysis), primarily mediated by CYP enzymes, are more affected by aging compared to Phase II conjugation reactions such as glucuronidation and sulfation [4,5]. This differential impact means that elderly individuals may be at higher risk for accumulation of drugs metabolized through Phase I pathways, potentially leading to toxicity or exaggerated pharmacologic responses. Conversely, certain pediatric populations, especially preterm neonates, may require adjusted dosages to account for underdeveloped metabolic capacity [6].

Health conditions particularly those affecting major metabolic organs like the liver, kidneys, and heart further complicate the prediction of drug metabolism. Liver diseases such as cirrhosis or hepatitis can drastically impair both Phase I and Phase II enzymatic functions, altering the bioavailability and clearance of hepatically metabolized drugs [7]. Similarly, chronic kidney disease affects renal clearance and may indirectly alter hepatic drug metabolism due to the accumulation of uremic toxins that downregulate CYP enzymes [8]. Cardiovascular disorders may also influence drug metabolism by compromising hepatic blood flow, thereby reducing the rate of first-pass metabolism and systemic clearance [9].

Considering both age and pathological conditions is essential in clinical pharmacology, especially in vulnerable populations such as geriatrics and patients with chronic illnesses. Failure to account for these factors may result in suboptimal therapeutic responses or increased adverse drug reactions. For this reason, it is important to understand relationship between patient specific variables and drug metabolism remains a key concern in drug development and personalized medicine [10,11]. Integrating pharmacokinetic modeling with clinical assessments can guide safer and more effective dosing strategies for patients across all age groups and health states.

Overview of Drug Metabolism

Most therapeutic agents are classified as xenobiotics, meaning they are foreign chemical substances not endogenously produced by the human body. Once administered, these compounds undergo metabolic biotransformation—a series of enzymatic processes aimed at detoxifying and converting them into more water-soluble forms for excretion [12,13].

Drug metabolism primarily transforms active compounds into metabolites, which can be categorized as active, inactive, or toxic. Active metabolites retain pharmacological activity and can contribute to or prolong the therapeutic effects of the parent drug. In contrast, inactive metabolites are devoid of any biological effect, while toxic metabolites can produce adverse or harmful physiological responses [14].

A significant portion of drug metabolism occurs during first-pass metabolism, a process wherein orally administered drugs are substantially metabolized in the liver and to a lesser extent in the gastrointestinal tract—before reaching systemic circulation. This markedly reduces the bioavailability of many drugs, influencing dosing strategies and therapeutic outcomes [13,14].

Although the liver is the principal site of drug metabolism, metabolic enzymes are also expressed in various tissues, including the kidneys, lungs, and intestines, allowing for extrahepatic metabolism of certain agents [14]. Understanding the pathways and consequences of these metabolic changes is critical for optimizing therapeutic regimens and minimizing adverse effects, especially for clinicians and researchers focused on drug efficacy and safety

[12-15].

Phases of Drug Metabolism

Drug metabolism, an essential component of pharmacokinetics and detoxification, is typically divided into three interconnected phases: Phase I (modification), Phase II (conjugation), and Phase III (excretion). These metabolic stages work sequentially to transform lipophilic xenobiotics including pharmaceutical compounds and natural products into hydrophilic derivatives that can be more easily eliminated from the body.

Phase I – Modification: Phase I reactions involve the biochemical transformation of xenobiotics through the introduction or unmasking of functional groups (e.g., hydroxyl, amino, or carboxyl groups), thereby increasing their polarity. These nonsynthetic modifications are predominantly carried out by mixed-function oxidases, particularly the cytochrome P450 monooxygenase (CYP450) system, alongside cofactors such as NADPH and molecular oxygen (O_2) [16,17].

The catalytic cycle of CYP450 enzymes incorporates one atom of molecular oxygen into a substrate (RH), yielding a hydroxylated product (ROH), $NADP^+$, and water as byproducts:

$O_2 + NADPH + H^+ + RH \rightarrow NADP^+ + H_2O + ROH$ [17].

This hydroxylation process is vital for activating prodrugs and transforming pharmacologically inactive substances into active agents. However, it can also convert nontoxic molecules into harmful metabolites a process termed *toxification*. A case in point is the metabolic transformation of acetonitrile into hydroxyacetonitrile ($HOCH_2CN$), which rapidly decomposes to release formaldehyde and hydrogen cyanide, both of which are toxic [18].

Aside from oxidation, other Phase I reactions include reduction, hydrolysis, cyclization, and decyclization. These reactions may involve several enzyme systems including flavin-containing monooxygenases, alcohol dehydrogenase, aldehyde dehydrogenase, and monoamine oxidase. Reductive transformations often employ NADPH-cytochrome P450 reductase, a key component of electron transfer within the microsomal enzyme system, transferring electrons from NADPH via FAD and FMN cofactors to P450 enzymes [17].

Hydrolytic reactions, facilitated by esterases, amidases, and epoxide hydrolases, are also crucial in breaking down ester or amide bonds, thereby yielding more polar products for subsequent Phase II conjugation.

Phase I reactions are frequently simulated in vitro using biomimetic catalysts to assess the potential metabolites of new drug candidates. For instance, trimebutine can be oxidized to its major metabolite, desmethyltrimebutine, through hydroxylation followed by demethylation—a process that mimics human oxidative metabolism [19].

Phase II – Conjugation: Following functionalization, Phase II metabolism involves the conjugation of the reactive metabolites from Phase I with endogenous polar molecules such as glucuronic acid, glutathione (GSH), sulfate, glycine, or acetyl groups. These conjugation reactions increase water solubility and molecular weight, reducing the pharmacological activity and toxicity of the parent compound.

Sites for conjugation include functional groups such as -OH, $-NH_2$, -COOH, and -SH. Among the critical enzymes involved are UDP-glucuronosyltransferases, sulfotransferases, and glutathione S-transferases (GSTs)—the latter being particularly important in detoxifying electrophilic compounds by forming stable thioether conjugates [20].

Phase III – Excretion: In Phase III, the conjugated metabolites undergo further modifications such as cleavage or acetylation. For example, glutathione conjugates are sequentially converted to mercapturic acids through enzymatic cleavage of glycine and γ-glutamyl residues followed by acetylation of the cysteine moiety [21]. These modified conjugates are actively transported out of cells via ATP-binding cassette (ABC) transporters, notably the multidrug resistance protein (MRP) family [22,23].

These transporters utilize ATP hydrolysis to export hydrophilic anionic conjugates across cellular membranes, facilitating their ultimate excretion via bile or urine [24].

Factors Influencing Drug Metabolism

The metabolism of drugs particularly lipophilic agents plays a pivotal role in determining their pharmacological activity and duration in the body. A range of physiological, pathological, genetic, and environmental factors influence this process, largely via modulation of enzyme systems such as the cytochrome P450 monooxygenase family.

Enzyme Activity: The rate at which drugs are metabolized is critically dependent on the activity of drug-metabolizing enzymes. Enzyme induction can accelerate the breakdown of active drugs, thereby reducing their effectiveness, while enzyme inhibition can prolong drug activity by slowing clearance. However, in prodrugs, where metabolic activation is needed, enzyme induction can increase the levels of the active compound and potentially lead to toxicity.

Genetic Variation: Inherited differences in drug-metabolizing enzymes significantly affect individual responses to drugs. For instance, polymorphisms in *N-acetyltransferase 2 (NAT2)* divide individuals into slow and rapid acetylators. Slow acetylators are at a higher risk for dose-dependent toxicity, especially when treated with isoniazid, hydralazine, procainamide, or phenelzine [25,26]. Similar variability has been observed in enzymes like *CYP2D6*, *CYP3A4*, *DPYD*, and *UGT1A1*. Genetic testing for *DPYD* and *UGT1A1* is now recommended before administering drugs like 5-fluorouracil, capecitabine, or irinotecan, to prevent severe adverse reactions [27].

Age: Drug metabolism is generally slower in neonates, fetuses, and the elderly due to reduced enzyme activity or organ function, necessitating dosage adjustments across age groups.

Sex and Hormonal Status: Sex-based differences can influence enzyme expression and drug metabolism rates, although this varies with the specific compound and metabolic pathway involved.

Nutrition and Microbiota: Diet and gut microbiota significantly modulate drug metabolism. Microorganisms can degrade or biotransform drugs, potentially reducing their efficacy or altering their toxicity. For example, *Eggerthella lenta* in the gut microbiota has been shown to inactivate digoxin, thus impacting therapeutic outcomes [28].

Route of Administration and Dosage: The frequency, dosage, and route through which a drug is administered oral, intravenous, or otherwise affects how quickly it reaches metabolizing organs like the liver and its subsequent metabolic fate.

Disease States: Pathological conditions such as liver, kidney, and cardiac diseases can compromise the metabolic capacity of these organs, reducing clearance rates and increasing the risk of drug accumulation and toxicity.

Predictive Tools (In Silico Modeling): Advances in computational pharmacokinetics allow for in silico simulation of drug metabolism in virtual populations. These models are increasingly used to predict interindividual variability and identify patients at risk for adverse drug reactions before clinical trials commence [29].

Effect of Age on Drug Metabolism

Drug Metabolism in Neonates and Infants: Drug metabolism in neonates and infants is an evolving process influenced by developmental stage, genetic variation, environment, and disease [31,33,34]. Phase I enzymes, especially cytochrome P450 (CYP) enzymes, and Phase II conjugation enzymes mediate drug metabolism [36]. CYP enzyme expression varies: CYP1A2 and CYP3A4 develop postnatally, while others like CYP2C9 and CYP2C19 are active in utero but reach adult levels only months or years after birth [34,38, 39, 40]. Genetic polymorphisms, such as those affecting CYP2D6, impact metabolism and drug toxicity, as seen in codeine and paroxetine exposure [37,41,42]. Some enzymes like CYP3A7 dominate in the fetal period and decline after birth, while others like CYP3A4 gradually increase to adult levels by around 3 years of age [31, 35, 40, 43].

Phase II enzymes, particularly UGT isoforms, are crucial for glucuronidation reactions that support drug detoxification and bilirubin metabolism. UGT1A1 development is influenced by age, illness, and maternal factors, while UGT2B7 matures rapidly within two weeks postnatally and continues to develop until two years [45, 46]. Sulphation pathways (SULT1A1) are functional at birth, while acetylation via NAT enzymes matures more slowly, complet-

ing development between 2–4 years [51,52]. Genetic polymorphisms complicate interpretation of metabolism in neonates since enzyme systems may not yet be fully expressed [30,31,51].

Beyond enzymes, physiological changes also impact hepatic drug metabolism. Hepatic blood flow increases after birth due to ductus venosus closure and portal circulation establishment, affecting drugs with high hepatic extraction like propranolol [32]. These changes, along with early gut colonization, stimulate hepatic enzyme induction and create variability in drug clearance. Thus, pharmacological models based on adult physiology are often unreliable in the early neonatal period and become valid only after ductus venosus closure, typically within the first week [44, 52].

Pediatric Drug Metabolism Differences: Pediatric drug metabolism differs markedly from that of adults due to age-related changes in liver size, enzyme expression, and overall metabolic capacity. Liver microsomal protein content increases from about 26 mg g^{-1} in neonates to approximately 40 mg g^{-1} in adults, impacting the rate at which drugs are metabolized [53]. While neonates typically receive lower mg kg^{-1} doses due to immature enzyme systems, infants and preschool-aged children may demonstrate higher hepatic clearance. This is largely due to a relatively larger liver-to-body mass ratio and increased liver blood flow in early life stages [54]. Therefore, simple weight-based dosing may not accurately predict drug metabolism in pediatric patients.

Ontogeny of metabolic pathways must be considered when administering drugs to children. The historical case of grey baby syndrome caused by chloramphenicol overdose in neonates highlights the danger of using adult data for pediatric dosing without accounting for developmental differences [55]. Additionally, differences in gut enzyme expression and microbial colonization affect the metabolism and bioavailability of drugs such as digoxin, whose inactivation in the gut increases with age [56,57]. Key metabolic enzymes like CYP3A4 and CYP3A5 show limited expression in infants under six months [58], underlining the importance of age-specific pharmacokinetic assessments to ensure safe and effective pediatric drug therapy.

Drug Metabolism in Adults: Drug metabolism in adults is influenced by various age-related physiological changes, even before reaching elderly status. Between the ages of 20 and 65, subtle yet significant alterations in hepatic function, enzyme activity, and body composition can impact pharmacokinetics.

As individuals age, hepatic blood flow and liver mass gradually decline, potentially reducing the liver's capacity to metabolize drugs, particularly those undergoing extensive first-pass metabolism. This reduction can lead to increased bioavailability of certain medications, necessitating dosage adjustments to avoid toxicity [59].

Additionally, the activity of cytochrome P450 enzymes, responsible for phase I metabolic reactions, may decrease with age. For example, studies have shown a decline in CYP3A4 activity, affecting the metabolism of drugs like midazolam and nifedipine [60]. Conversely, phase II reactions, such as glucuronidation, are generally preserved, maintaining the metabolism of drugs like lorazepam.

Changes in body composition also play a role; increased body fat and decreased lean body mass can alter the volume of distribution for lipophilic and hydrophilic drugs, respectively. This can result in prolonged half-lives for lipophilic drugs and higher plasma concentrations for hydrophilic drugs, impacting both efficacy and safety [61].

Furthermore, renal function, which is crucial for the excretion of many drugs, begins to decline in middle age. The glomerular filtration rate decreases approximately 1% per year after the age of 40, affecting the clearance of renally excreted drugs and necessitating careful monitoring and potential dose adjustments [62].

Drug Metabolism in the Elderly: Age-related physiological decline significantly influences the pharmacokinetics and pharmacodynamics of drugs in elderly individuals. As the body ages, the efficiency of organ systems—particularly those involved in drug absorption, distribution, metabolism, and excretion (ADME)—diminishes. Although the liver function indexes may remain within normal ranges, hepatic drug metabolism becomes impaired due to reduced enzymatic activity, diminished liver blood flow, and a decline in functional parenchymal cells [63]. These

changes contribute to a prolonged drug half-life, increased drug accumulation, and heightened sensitivity to standard doses, predisposing elderly individuals to adverse drug reactions. The observed metabolic attenuation necessitates consideration in dosage form design, especially for drugs with narrow therapeutic indices.

Furthermore, renal excretion, a primary route for drug clearance, becomes increasingly compromised due to progressive decline in kidney function with age. This renal insufficiency plays a pivotal role in the toxic accumulation of drugs or their metabolites, making it the most critical factor in age-associated pharmacokinetic alterations [63]. In line with broader age-stratified drug development frameworks, understanding the pharmacological profile in the elderly provides crucial insights that inform pediatric drug metabolism research. Both populations exhibit altered enzyme activity and require individualized pharmacotherapeutic considerations. Therefore, elucidating the mechanisms of impaired drug clearance in older adults can guide age-specific drug design and dosage protocols, especially as the field progresses toward precision medicine for vulnerable age groups.

Effect of Health Conditions on Drug Metabolism

Liver Diseases: Health conditions, particularly hepatic impairment such as end-stage liver disease, profoundly affect drug metabolism by altering pharmacokinetic processes including absorption, distribution, and elimination. In cases of severe hepatic dysfunction, portosystemic shunting allows blood from the portal vein to bypass hepatic metabolism, resulting in higher systemic concentrations of drugs undergoing extensive first-pass metabolism [64]. This reduced hepatic perfusion compromises drug biotransformation, particularly in medications with significant hepatic first-pass effects, although drugs with low enzyme affinity such as diazepam and paroxetine remain relatively unaffected [64]. Moreover, liver cirrhosis reduces the synthesis of plasma proteins like albumin and alpha-1-acid glycoprotein, which increases the free fraction of highly protein-bound drugs such as fluoxetine, aripiprazole, and diazepam heightening the risk of toxicity [65,66,67]. This consideration is especially relevant in pediatric populations with co-existing hepatic pathologies, as immature enzyme systems and disease-induced impairments may synergistically amplify the pharmacological activity and adverse effects of such drugs.

Additionally, hepatic metabolism involves two critical phases. Phase I reactions, mediated by cytochrome P450 enzymes, are often impaired in liver disease, potentially leading to prolonged drug activity or formation of toxic metabolites [68]. Conversely, Phase II conjugation reactions, particularly glucuronidation, are generally preserved even in advanced hepatic dysfunction [69]. This makes drugs metabolized mainly via glucuronidation such as temazepam, lorazepam, oxazepam, and olanzapine safer therapeutic options in vulnerable populations [70, 71]. In pediatric pharmacotherapy, understanding these distinctions is crucial, as similar hepatic immaturity or disease states may necessitate selecting agents with limited reliance on Phase I metabolism to minimize risk and enhance therapeutic precision.

Kidney Impairment: Kidney impairment significantly alters drug metabolism and elimination, particularly for drugs primarily cleared through renal pathways. In chronic kidney disease (CKD), the reduction in glomerular filtration rate (GFR), tubular secretion, and renal blood flow leads to accumulation of renally-excreted drugs and their metabolites, increasing the risk of toxicity [72]. While the kidney is not a primary site for drug metabolism, it plays a vital role in the clearance of hydrophilic drugs such as aminoglycosides, lithium, and certain antiepileptics like gabapentin and topiramate [73].

Renal impairment can also affect hepatic drug metabolism indirectly. Studies indicate that uremic toxins can downregulate cytochrome P450 enzymes and impair hepatic phase I metabolism [74]. This dual burden of reduced renal clearance and compromised liver enzyme activity alters both pharmacokinetics and pharmacodynamics, making dose adjustment critical in patients with renal insufficiency [75]. Furthermore, protein binding of drugs is also altered due to decreased albumin levels and accumulation of uremic toxins, leading to an increased free fraction of drugs like phenytoin, which can potentiate their pharmacological effects [76].

In pediatric patients with kidney disease, develop-

mental immaturity of renal function complicates drug dosing even further, necessitating careful therapeutic monitoring. Drug selection in these populations must therefore consider both altered elimination and potential hepatic enzyme suppression to prevent adverse drug reactions [77].

Cardiovascular Disorders: Cardiovascular disorders (CVDs) significantly affect drug metabolism by altering physiological and biochemical processes. One key factor is the reduced cardiac output in heart failure, which diminishes hepatic blood flow, thereby impairing hepatic drug metabolism, especially for high-extraction-ratio drugs [78]. Drugs such as lidocaine, propranolol, and verapamil are notably affected due to their dependence on hepatic perfusion [79]. Furthermore, patients with CVDs often exhibit hepatic congestion, which reduces the liver's capacity to metabolize drugs efficiently [80].

Inflammation, common in chronic CVDs, can suppress the expression of cytochrome P450 enzymes, further impairing drug metabolism [81]. This leads to prolonged drug half-life and potential toxicity. For instance, reduced CYP3A4 activity has been reported in heart failure patients, resulting in altered metabolism of statins and calcium channel blockers [82]. Moreover, CVDs often require polypharmacy, increasing the risk of drug–drug interactions that complicate metabolism [83].

Renal perfusion is also compromised in CVDs, affecting the excretion and clearance of drugs and their metabolites, thus indirectly influencing systemic drug concentrations [84]. Consequently, personalized dosing regimens and therapeutic drug monitoring become essential in managing patients with cardiovascular disorders to prevent adverse effects and ensure therapeutic efficacy [85].

Endocrine Disorders: Endocrine disorders significantly influence drug metabolism by modulating the activity of drug-metabolizing enzymes and altering pharmacokinetics. For instance, hypothyroidism reduces the metabolic rate and downregulates cytochrome P450 enzymes, leading to decreased drug clearance and prolonged drug half-life [86]. In contrast, hyperthyroidism accelerates metabolism by enhancing hepatic enzyme activity, potentially reducing drug efficacy due to rapid clearance [87]. Diabetes mellitus, a prevalent endocrine disorder, also affects drug metabolism through hyperglycemia-induced changes in liver enzyme expression, particularly CYP2E1 and CYP3A4, which can alter the metabolism of various oral hypoglycemics and cardiovascular drugs [88]. Additionally, insulin resistance and chronic inflammation associated with diabetes contribute to hepatic dysfunction, modifying drug biotransformation [89]. Adrenal disorders like Cushing's syndrome increase cortisol levels, which can induce hepatic enzymes and impact the pharmacokinetics of glucocorticoids, anticoagulants, and anticonvulsants [90]. Furthermore, hormonal therapies used in endocrine disorders can affect liver enzyme expression and drug transporters, leading to drug–drug interactions and altered plasma concentrations [91]. These variations necessitate individualized dosing and close therapeutic monitoring in endocrine patients to avoid toxicity or therapeutic failure.

Nutritional Status and Malnutrition: Nutritional status plays a critical role in modulating drug metabolism by influencing the activity of drug-metabolizing enzymes, drug transporters, and organ function. Malnutrition, including both undernutrition and specific micronutrient deficiencies, can significantly impair hepatic enzyme systems such as the cytochrome P450 family [92]. Protein-energy malnutrition is known to decrease hepatic enzyme activity, leading to reduced metabolism and prolonged half-life of drugs such as phenytoin and theophylline [93]. This effect is partly due to a decrease in liver microsomal proteins and cofactors like NADPH, which are essential for phase I metabolic reactions [94]. Additionally, hypoalbuminemia in malnourished individuals reduces plasma protein binding of drugs, increasing the free, pharmacologically active drug fraction and the risk of toxicity [95].

Micronutrient deficiencies, such as those of zinc, iron, and vitamin A, can impair specific metabolic pathways. For instance, zinc is crucial for the structural integrity and function of numerous enzymes, and its deficiency may alter the metabolism of retinoids and other drugs [96]. Conversely, obesity, a form of overnutrition, can increase the expression of some CYP enzymes (e.g., CYP2E1), potentially leading to enhanced metabolism of certain drugs and reduced therapeutic efficacy [97]. Furthermore, changes in body fat composition and liver lipid content in obese individuals may affect the volume of distribution and hepatic

clearance of lipophilic drugs [98]. Therefore, both malnutrition and overnutrition demand individualized pharmacotherapy to ensure optimal drug efficacy and minimize adverse reactions.

Genetic Disorders Affecting Metabolism: Genetic disorders significantly influence pediatric drug metabolism, often resulting in life-threatening consequences if not identified early. A striking example is the tragic case of Michael Adams-Conroy, a nine-year-old who died from a grand mal seizure due to toxic accumulation of Prozac in his system a result of a mutation in the *CYP2D6* gene that impaired the drug's metabolism [99]. *CYP2D6* belongs to the cytochrome P450 enzyme family, responsible for metabolizing approximately 25% of all prescribed drugs, including pediatric antidepressants and cancer therapeutics [99]. In pediatric patients, the immaturity of enzyme systems already influences drug kinetics; a compounding genetic defect exacerbates variability in drug response. Children with poor or intermediate *CYP2D6* metabolizer status may either accumulate toxic drug levels or fail to activate prodrugs into therapeutic forms, leading to therapeutic failure or adverse effects. The implications are particularly severe with drugs like tamoxifen, where poor metabolizers cannot generate sufficient levels of the active metabolite endoxifen, diminishing the drug's efficacy [99].

More than 90% of individuals carry at least one variant allele in CYP genes, such as *CYP2D6*, *CYP2C9*, and *CYP3A5*, which play essential roles in pediatric pharmacokinetics [100]. These variants categorize patients into poor, intermediate, extensive, or ultra-rapid metabolizers, each requiring tailored dosing strategies. In children, whose metabolic pathways are still developing, the impact of these genetic variations is even more pronounced. For instance, poor pediatric metabolizers of *CYP2D6*-dependent drugs may present with increased side effects or toxicity due to drug accumulation, while ultra-rapid metabolizers may eliminate drugs too quickly for therapeutic benefit. Personalized pharmacogenetic screening still underutilized in pediatrics can guide safer and more effective dosing, particularly in psychiatric and oncological pediatric therapies. As Laika et al. [101] notes, integrating genetic testing into early clinical trial designs and pediatric practice can reduce adverse events and optimize outcomes in children with genetic metabolic disorders.

Clinical Implications and Pharmacological Considerations

Drug Dosing Adjustments Based on Age and Health Status

Drug dosing must be tailored to individual characteristics such as age, renal and hepatic function, and comorbidities. In pediatric and geriatric populations, physiological changes significantly alter pharmacokinetics. For instance, neonates have immature liver enzyme systems and reduced glomerular filtration rates, requiring lower doses or extended dosing intervals [102]. Conversely, the elderly experience decreased renal and hepatic function, affecting both drug metabolism and clearance [103]. This is particularly important for drugs with narrow therapeutic windows like digoxin and aminoglycosides, which can easily reach toxic levels if not adjusted properly [104]. Furthermore, in patients with hepatic or renal impairment, dose adjustments are essential to prevent accumulation of drugs or their metabolites, which may exacerbate toxicity [105]. Clinical guidelines increasingly recommend therapeutic drug monitoring and individualized dosing to optimize efficacy and minimize adverse outcomes.

Risk of Adverse Drug Reactions

The risk of adverse drug reactions (ADRs) is heightened in patients at both ends of the age spectrum and in those with multiple comorbidities. ADRs account for significant morbidity and are a leading cause of hospitalization among the elderly [106]. Age-related pharmacodynamic changes, such as altered receptor sensitivity and impaired homeostatic mechanisms, further increase susceptibility [103]. Children, particularly neonates and infants, are also vulnerable due to underdeveloped drug elimination systems and blood–brain barrier permeability [102]. For example, chloramphenicol toxicity in neonates, known as “gray baby syndrome,” exemplifies the importance of considering developmental pharmacology in pediatric dosing (Weiss et al., 1960). In addition, pharmacogenomic variability, such as polymorphisms in CYP enzymes, can increase ADR risks by influencing drug metabolism [108]. Therefore, accurate risk assessment and vigilance are necessary in vulnerable popula-

tions to prevent life-threatening drug reactions.

Polypharmacy in the Elderly and Chronically Ill

Polypharmacy, commonly defined as the use of five or more medications, is prevalent among elderly and chronically ill patients, posing a major challenge in clinical pharmacology [109]. It increases the likelihood of drug–-drug interactions, medication errors, and non-adherence, thereby complicating treatment outcomes [110]. For example, simultaneous administration of anticoagulants, antihypertensives, and antidiabetic agents may result in unpredictable pharmacodynamic responses and a higher risk of bleeding, hypotension, or hypoglycemia. Moreover, many elderly individuals are treated by multiple specialists, often leading to duplicated therapies or unnecessary medications [111]. Clinical pharmacists play a vital role in medication reconciliation and deprescribing, particularly in geriatric care settings. Strategies such as comprehensive medication reviews, use of screening tools like the Beers Criteria, and patient education are essential to minimize the risks of polypharmacy [112].

Conclusion

Age and health status are powerful determinants of drug metabolism, influencing not only how drugs are processed in the body but also their therapeutic and toxicological profiles. In neonates and infants, immature liver and renal functions significantly delay drug clearance, while in older adults, reduced hepatic perfusion and enzyme activity necessitate dosage recalibration. Similarly, chronic health conditions—including hepatic, renal, and endocrine disorders—exert a multifaceted impact on drug metabolism by altering enzymatic pathways, transport systems, and excretion mechanisms. These variations increase the likelihood of drug toxicity or therapeutic failure if not properly accounted for. Therefore, clinicians and researchers must adopt individualized treatment approaches grounded in developmental pharmacology, organ function, and genetic background to ensure drug safety and efficacy across diverse patient populations.

Future Perspective

As medicine advances toward a more personalized and precision-based paradigm, the integration of pharmacogenetics, developmental biology, and real-time clinical monitoring will become indispensable in optimizing drug metabolism. Future research should focus on developing predictive models such as in silico simulations and population-based pharmacokinetic algorithms that incorporate variables like age, organ maturity, comorbidity, and genetic polymorphisms. In pediatrics, more targeted investigations into enzyme ontogeny and gut microbiota influence are needed to guide age-appropriate formulations and dosing. In geriatrics, emphasis should be placed on managing polypharmacy and comorbidities that affect metabolism. Ultimately, investing in comprehensive, stratified drug development protocols will ensure safer and more effective treatments tailored to the metabolic capacity of each individual, particularly in medically fragile or developmentally unique populations.

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