Annals of Pharmacy Practice and Pharmacotherapy
ISSN: 3062-4436
2023, Volume 3, Issue 2, Page No: 11-21
Copyright CC BY-NC-SA 4.0
Available online at: www.galaxypub.co/page/journals

Galaxy Publication

The Prescribed Dose Is Not the Biologically Received Dose When Inflammation, Organ Dysfunction, Drug Interactions, and Phenoconversion Destabilize Exposure

Thomas Weber[1]*, Priya Nair[2], Ahmed El-Sayed[3]

[1]Department of Clinical Pharmacology and Pharmacokinetics, Faculty of Medicine, LMU Munich, Munich, Germany.
[2]Department of Pharmacy Practice and Precision Dosing, Faculty of Pharmacy, Indian Institute of Technology Bombay, Mumbai, India.
[3]Department of Clinical Pharmacy and Therapeutic Drug Monitoring, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt.

***E-mail** ✉ thomas.weber@lmu.de

Received: 08 April 2023; **Revised:** 18 July 2023; **Accepted:** 23 July 2023

ABSTRACT

A prescribed dose specifies the amount of drug administered, but it does not necessarily specify the exposure that a patient experiences. The distinction becomes clinically consequential when biological or treatment-related states change the processes connecting dose to systemic concentration. Inflammation can alter drug-metabolizing enzymes and transporters over time; kidney disease can modify active secretion as well as selected nonrenal pathways; hepatic dysfunction can affect metabolism, uptake, and extraction unevenly; and interacting drugs can shift functional metabolic phenotype away from that predicted by genotype. These mechanisms can converge on similar changes in exposure without being mechanistically interchangeable. The same measured concentration can therefore arise from different combinations of clearance, transport, adherence, interaction, disease, and phenotypic effects, while the same prescribed dose can produce different concentrations within the same patient as clinical state changes. This Perspective argues for separating the causal layers that generate exposure from the measurements used to observe it. Genotype, functional phenotype, organ function, interacting medicines, administered dose, measured concentration, and clinical response each answer different questions and should not be collapsed into a universal weighting scheme. Monitoring is most informative when the drug has a validated exposure target, clinically important consequences of misexposure, and a plausible mechanism that can be investigated or modified. The practical implication is conditional: prescribed dose becomes an unreliable proxy for biologically received exposure when a drug depends materially on pathways that are both clinically variable and dynamically altered in the patient being treated.

Keywords: Drug exposure, Inflammation, Phenoconversion, Drug–drug interactions, Organ dysfunction, Therapeutic drug monitoring

How to Cite This Article: Weber T, Nair P, El-Sayed A. The Prescribed Dose Is Not the Biologically Received Dose When Inflammation, Organ Dysfunction, Drug Interactions, and Phenoconversion Destabilize Exposure. Ann Pharm Pract Pharmacother. 2023;3(2):11-21. https://doi.org/10.51847/CCVLDNxp4S

Introduction

The prescribed dose is a treatment instruction, not a direct measurement of pharmacological exposure. For many medicines the distinction is modest because absorption, distribution, metabolism, and elimination remain sufficiently stable for a standard dose to predict an acceptable range of systemic exposure. That assumption becomes less secure when the biological state controlling disposition changes during treatment. Inflammation is one important example because cytokine-mediated regulation can alter drug-metabolizing enzymes and transporters and thereby change the relationship between the amount administered and the concentration subsequently achieved [1].

© 2023 Annals of Pharmacy Practice and Pharmacotherapy

The same problem extends beyond inflammatory biology. Drug-transporter abundance and function can differ in renal impairment, hepatic impairment, cancer, and other clinically important states, with consequences that depend on the transporter, tissue, substrate, and disease setting [2]. Regulatory experience with hepatic impairment similarly shows that the pharmacokinetic consequence of organ dysfunction cannot be inferred reliably from a diagnostic label alone; drug properties, clearance routes, study design, and the severity and nature of impairment determine whether a dosing modification is justified [3]. These established approaches already address important components of dose individualization. The unresolved issue is how to interpret situations in which several dynamic modifiers act simultaneously yet influence different causal layers.

Pharmacogenetics provides a particularly clear illustration of the distinction between an inherited prediction and a current biological state. A CYP2D6 genotype may predict an expected metabolic phenotype, but concomitant enzyme inhibition can convert that expected phenotype into a functionally slower one. Clinical pharmacogenetic interpretation therefore requires attention to phenoconversion rather than assuming that genotype remains an invariant representation of drug-metabolizing capacity throughout therapy [4]. Genotype is consequently neither irrelevant nor sufficient: it describes one determinant of capacity, whereas current phenotype reflects the combined effect of genotype and modifying conditions.

Measuring exposure can reduce uncertainty, but measurement introduces another distinction. Model-informed precision dosing can combine concentrations, covariates, prior pharmacokinetic information, and Bayesian updating to generate individualized dose predictions [5]. Yet a concentration is an observation of exposure, not necessarily an explanation for why that exposure occurred. This matters especially when clearance itself changes with disease trajectory. In therapeutic-antibody development, time-dependent clearance can generate apparent exposure–response relationships because patients who improve may clear drug more slowly, making higher subsequent exposure partly a consequence of response rather than its cause [6]. Dose, functional phenotype, organ clearance, adherence, concentration, and clinical response therefore occupy different causal or measurement layers. The central question is not whether any one layer is superior, but when the mapping from prescribed dose to biologically received exposure becomes unstable enough that interpretation or monitoring must change.

Inflammation creates a moving metabolic phenotype

Inflammation does not produce a single, uniform reduction in drug metabolism. Human phenotyping during acute SARS-CoV-2 infection demonstrated that the activities of different cytochrome P450 enzymes could move in different directions: CYP1A2, CYP2C19, and CYP3A activity decreased, whereas CYP2B6 and CYP2C9 activity increased and the observed change in CYP2D6 did not reach conventional statistical significance [7]. The important implication is methodological as well as biological. “Inflammation” cannot be converted into one global correction factor for drug exposure because its effect depends on the pathway through which a specific drug is handled.

The effect can nevertheless be substantial for a susceptible pathway. In critically ill patients with severe COVID-19, higher inflammatory burden was associated with reduced midazolam metabolism, consistent with suppression of CYP3A-mediated clearance [8, 9]. These findings help explain why an unchanged maintenance dose can yield a different systemic concentration as inflammatory state evolves. They do not establish that every critically ill patient requires the same adjustment, nor that C-reactive protein or interleukin-6 provides a universally transportable dosing threshold. The direct evidence concerns particular inflammatory states, probe substrates, and patient populations.

The clinical challenge becomes sharper when inflammation occurs in a patient already receiving an interacting medicine. Physiologically based pharmacokinetic analyses have shown that inflammatory modulation and perpetrator-drug effects can be represented simultaneously for CYP3A- and CYP2C19-mediated disposition [10]. Related modeling work has used inflammatory biomarkers such as C-reactive protein to improve prediction of selected CYP3A4 and CYP2C19 substrate pharmacokinetics [11]. These approaches demonstrate that more than one modifier can act on the same disposition pathway. They do not justify replacing those modifiers with a single “inflammation plus interaction” score. The contribution of each process remains drug-, pathway-, model-, and state-dependent.

A useful clinical distinction is therefore between *prescribed dose stability* and *metabolic phenotype stability*. A prescription may remain unchanged while the functional phenotype through which the dose is processed changes over hours or days. When this occurs in a drug with a narrow therapeutic index, steep exposure–toxicity

relationship, or limited capacity to tolerate underexposure, the nominal dose becomes progressively less informative unless the changing biological state is incorporated into interpretation.

Organ dysfunction alters more than organ clearance

Renal impairment is often treated conceptually as a reduction in renal drug elimination, yet chronic kidney disease can also modify selected nonrenal pathways. A systematic assessment of CYP- and transporter-mediated elimination found heterogeneous effects across CYP1A2, CYP2C8, CYP2C9, CYP2C19, and OATP-related pathways rather than a common reduction in metabolic capacity [12]. This is an important boundary on simple dose–organ-function reasoning. Estimated glomerular filtration rate can describe one important dimension of renal function, but it cannot automatically specify what happens to every metabolic or transporter pathway contributing to exposure.

Even within advanced renal disease, disposition can remain temporally dynamic. In patients with end-stage renal disease receiving hemodialysis, CYP3A activity varied across the dialysis interval, with evidence that dialysis transiently reduced the chronic inhibition of CYP3A observed between sessions [13]. A patient can therefore move through different functional states without any change in prescribed dose or genotype. Timing of administration, sampling, and dialysis can become part of the exposure interpretation.

At the same time, renal impairment does not uniformly alter all nonrenal drug handling. In a clinical microdose cocktail study, renal impairment increased exposure to several transporter substrates and modified some interaction effects, yet midazolam exposure was not materially altered [14]. The null result for the CYP3A probe is as informative as the positive findings for other substrates: renal impairment is not a pharmacokinetic multiplier that acts identically across medicines. Similar distinctions arise within renal transport itself. Physiologically based modeling of OAT1/3 substrates indicates that active tubular secretion can decline progressively as chronic kidney disease advances [15]. Separate modeling across metabolized drugs found that residual metabolic activity under renal impairment varied among CYP pathways, reinforcing the need for drug-specific rather than organ-label-based assumptions [16].

Hepatic dysfunction presents a parallel but mechanistically different problem. Phenotyping with the Basel cocktail showed that cirrhosis affected the pharmacokinetics of six CYP substrates differently rather than producing a uniform proportional loss of enzyme activity [17]. Hepatic impairment can also affect uptake transport independently of CYP-mediated metabolism; quantitative analyses of endogenous biomarkers and substrate drugs demonstrate that OATP1B function is itself a relevant component of altered hepatic disposition [18]. The conventional phrase “reduced hepatic clearance” can therefore conceal several distinct processes: reduced metabolic capacity, altered uptake, changes in hepatic blood flow or extraction, protein-binding changes, and disease-specific alterations in transporter expression or function.

Mechanistic modeling can improve prediction when these processes are represented explicitly. Physiologically based models incorporating hepatic-impairment-related physiological and CYP3A changes have reproduced the pharmacokinetics of several CYP3A substrates within clinically useful prediction ranges, while still showing considerable variation among drugs [19]. The underlying lesson is not that a single hepatic model solves dose individualization, but that the drug's actual extraction characteristics and pathway dependence matter.

Drug modality places another boundary around organ-function reasoning. Therapeutic peptides and proteins do not necessarily respond to renal or hepatic dysfunction in the same way as conventional small molecules. Regulatory analyses show heterogeneous organ-impairment effects and substantial variation in whether clinically actionable dose modification is supported [20]. A dose–exposure argument that is valid for a predominantly CYP3A-cleared small molecule should therefore not be transferred automatically to a monoclonal antibody, peptide, or protein therapeutic.

Taken together, renal and hepatic dysfunction illustrate why biologically received exposure cannot be inferred from an organ-dysfunction label alone. Filtration, active secretion, uptake transport, enzyme activity, extraction, dialysis, modality, and disease severity are related but separable determinants. Their clinical importance depends on which of them materially contributes to the disposition of the drug actually being prescribed.

Drug interactions and phenoconversion reclassify the active metabolic state

Drug interactions provide an additional mechanism through which the patient's active disposition state can diverge from the assumptions embedded in a standard dose. Transport proteins are regulated through multiple transcriptional, post-transcriptional, trafficking, and signaling mechanisms, and their abundance or activity can change in response to disease, drugs, diet, and other exposures [21]. Biological regulation, however, should not

be equated automatically with a clinically important interaction. An International Transporter Consortium assessment concluded that systemic inhibition of P-glycoprotein or BCRP has limited clinical importance in a number of settings, emphasizing that transporter involvement, organ localization, substrate dependence, and inhibitor exposure must be considered before inferring a meaningful exposure change [22].

Genotype creates a different form of prior information. For CYP2D6, functional allelic variation modifies the degree to which an inhibitor can alter apparent phenotype and drug–drug interaction magnitude [23]. This is the basis for a drug–drug–gene interaction: inherited metabolic capacity and a concurrent pharmacological perturbation jointly determine the functional state observed during treatment. Clinical commentaries have therefore argued that drug–drug and drug–gene effects cannot always be interpreted independently when both converge on the same enzyme system [24].

The concept becomes operational through phenoconversion. Quantitative approaches to CYP-mediated drug–drug–gene interactions show that several existing schemes can be expressed as related models in which genotype-defined activity is altered by inhibition, while also exposing unresolved assumptions when those models are used outside the conditions from which they were derived [25]. Prospective evidence in CYP2C19-genotyped healthy volunteers further demonstrates that potent inhibitors can shift a large proportion of participants into a different measured metabolic phenotype [26]. Phenoconversion is therefore not merely a theoretical correction to genotype. It is an observable change in functional metabolic state. Its magnitude and clinical relevance remain dependent on the inhibitor, enzyme, genotype, substrate, exposure to the perpetrator, and timing of measurement.

These findings also show why the major modifiers considered in this Perspective should not be collapsed into one hierarchy. Inflammation can alter enzyme or transporter regulation; chronic kidney disease can change filtration, secretion, and selected nonrenal pathways; cirrhosis can alter metabolic and uptake processes; a perpetrator drug can inhibit or induce a specific pathway; and genotype can alter baseline capacity and susceptibility to phenoconversion. Each route may increase, decrease, or leave systemic exposure unchanged depending on the medicine. A similar concentration can therefore be generated by biologically different states, and the same prescribed dose can map to different exposures as those states change.

The clinically useful question is consequently drug-specific: which disposition processes contribute materially to exposure for this medicine, which of those processes are currently unstable in this patient, how quickly can they change, and which observations can reveal the resulting exposure state? **Table 1** separates these modifier classes without imposing a universal ranking or weighting.

Table 1. Drug-specific conditions that can destabilize the mapping between prescribed dose and systemic exposure

Modifier state	Pharmacokinetic process altered	Expected exposure direction	Characteristic time scale	What can make the change observable	When the prescribed dose becomes an unreliable exposure proxy
Acute systemic inflammation affecting a susceptible CYP pathway	Enzyme expression/activity and sometimes transporter regulation	Often increased exposure when metabolic clearance is suppressed; direction remains pathway-specific	Hours to days as inflammatory state evolves	Inflammatory biomarkers, phenotyping probes, drug concentrations, temporal clinical trajectory	When the drug depends materially on an inflammation-sensitive pathway and the inflammatory state changes during otherwise unchanged dosing
Chronic kidney disease affecting filtration and active secretion	Glomerular filtration, OAT-mediated secretion, renal handling of metabolites	Commonly increased exposure for drugs dependent on renal elimination; magnitude varies by pathway	Persistent across CKD stage, with superimposed acute changes possible	Renal-function measurements, concentration data, knowledge of renal secretion pathway	When total renal contribution cannot be represented adequately by nominal dose and a single filtration estimate
Hemodialysis-associated state change	Extracorporeal removal and temporary modification of uremic inhibition of nonrenal pathways	Drug- and timing-dependent	Within and between dialysis sessions	Dialysis timing, pre/post-dialysis concentrations, pathway-specific phenotyping	When exposure differs materially across the dialysis cycle despite an unchanged prescription

Cirrhosis affecting CYP-mediated metabolism	Enzyme-specific metabolic capacity, hepatic physiology and extraction	Frequently increased exposure for clearance-sensitive substrates, but not proportionally across CYP pathways	Chronic with progression or decompensation	Liver-disease severity, drug concentrations, pathway-specific probes	When the medicine relies heavily on a pathway disproportionately altered by the patient's hepatic disease
Hepatic impairment affecting uptake transport	Hepatic uptake before metabolism or biliary disposition	Substrate-dependent; reduced uptake may alter both systemic exposure and intrahepatic availability	Chronic or disease-state dependent	Endogenous transporter biomarkers, substrate PK, organ-function assessment	When uptake transport is a major determinant of disposition but dose adjustment assumes metabolism alone
CYP inhibitor or inducer	Enzyme activity	Increased exposure with inhibition; decreased exposure with induction for susceptible substrates	Can emerge or resolve as perpetrator exposure changes	Medication reconciliation, perpetrator concentration/exposure, victim-drug concentration	When interacting treatment changes while the victim-drug dose remains fixed
Drug–gene interaction with phenoconversion	Current functional metabolic phenotype relative to genotype-predicted phenotype	Direction follows the functional shift produced by the perpetrator and baseline genotype	Dynamic over perpetrator initiation, discontinuation, or dose change	Genotype plus current medication profile, phenotyping, concentration measurement	When genotype-predicted phenotype no longer represents current enzymatic activity
Systemic P-gp/BCRP inhibition	Efflux transport	Variable and often modest in settings where systemic inhibition has limited contribution	During inhibitor exposure	Substrate-specific DDI data and measured exposure where justified	Only when the relevant transporter materially constrains disposition; transporter inhibition alone is insufficient evidence

The resulting dose–exposure relationship is better represented as a deformable pharmacokinetic surface than as a fixed arrow from dose to concentration. **Figure 1** depicts how the same nominal dose can enter different exposure regions as inflammation, organ function, interacting drugs, and functional phenotype change, while preserving the distinction between processes that alter clearance, transport, or metabolic capacity.

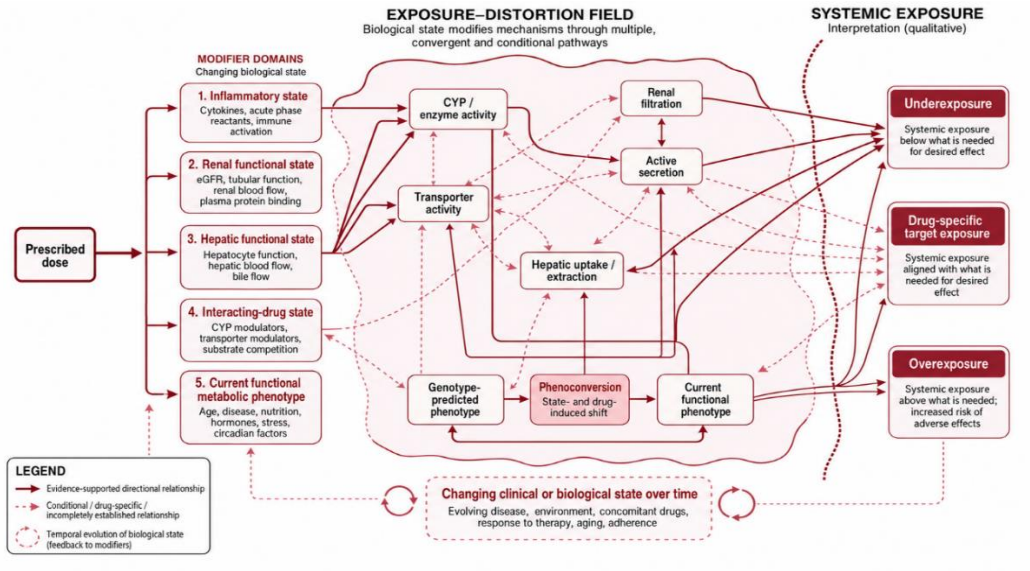

Figure 1. Dynamic distortion of the prescribed-dose–exposure relationship by changing biological and treatment states

Dose, concentration, and clinical response can disagree for different reasons

Once systemic exposure is measured, the interpretive problem changes but does not disappear. A concentration measurement characterizes drug concentration at a particular sampling time; it does not by itself establish the full

exposure profile, the process that produced it, or whether exposure caused the subsequent clinical outcome. This distinction is especially important when clearance changes with disease trajectory. For nivolumab, time-varying clearance was associated with disease dynamics, so patients who improved could subsequently show lower clearance and greater exposure [27]. Broader analyses of therapeutic monoclonal antibodies show how such bidirectional relationships can generate apparently strong exposure–response associations unless baseline prognosis, disease evolution, clearance, and exposure are separated analytically [28]. Thus, a high concentration may sometimes contribute to response, sometimes reflect slower clearance in a responder, and sometimes represent both processes.

A low concentration is equally ambiguous. Prospective therapeutic drug monitoring of oral targeted anticancer therapies illustrates why measurement should initiate causal investigation rather than automatic dose escalation. Concentrations below drug-specific targets were managed through interventions that could include assessment of adherence, food requirements, interacting medicines, treatment interruption, or dose modification [29]. The measured concentration identified an exposure problem; it did not identify its mechanism.

This separation produces several clinically distinct discordance patterns. A patient may be prescribed the intended dose but achieve low exposure because of induction, poor adherence, impaired absorption, or unusually rapid clearance. Another patient may receive the same dose and develop high exposure because inflammation suppresses metabolism, renal secretion declines, cirrhosis alters hepatic disposition, or an inhibitor produces phenoconversion. A third patient may show an apparently favorable exposure–response association primarily because improving disease lowers clearance. **Table 2** therefore compares discordance configurations without treating dose, phenotype, concentration, and response as interchangeable indicators of one underlying state.

Table 2. Distinct discordance configurations between prescribed dose, functional phenotype, measured exposure, and clinical response

Observed configuration	Plausible causal layer	What the concentration establishes	What it does not establish	Appropriate interpretive next step
Standard dose with unexpectedly low exposure	Nonadherence, absorption limitation, induction, high intrinsic clearance, altered administration conditions	Underexposure occurred at the sampled time	Which mechanism caused it	Verify administration, adherence, interacting drugs, food requirements, sampling validity, and drug-specific clearance determinants
Standard dose with unexpectedly high exposure	Enzyme inhibition, inflammatory suppression, reduced renal secretion, hepatic dysfunction, phenoconversion	Exposure exceeds the expected drug-specific range	Whether the cause is genetic, inflammatory, organ-related, or pharmacological	Identify the dominant disposition pathway and current modifiers before changing dose
Genotype-predicted normal metabolism with high exposure	Drug-induced or disease-associated phenoconversion	Current exposure is inconsistent with genotype-only expectation	That the genotype result was incorrect	Reassess current functional phenotype and interacting or inflammatory conditions
Reduced organ function with unchanged exposure	Pathway not materially involved, compensating clearance, insufficient severity, or drug-specific resilience	Exposure is not detectably altered under the observed condition	That organ dysfunction is pharmacokinetically irrelevant for all drugs or future states	Preserve the null finding and avoid extrapolation across substrates
High exposure with favorable response	Pharmacological benefit, response-driven fall in clearance, or both	Exposure and response coexist	Direction of causality	Use longitudinal exposure and disease-state information before inferring dose–response causality
Low exposure without treatment failure	Wide therapeutic margin, insensitive endpoint, delayed pharmacodynamics, or measurement timing	Sampled exposure was low relative to expectation	That treatment is ineffective	Interpret against drug-specific exposure–response evidence and sampling context

Toxicity at apparently conventional exposure	Pharmacodynamic sensitivity, active metabolite, tissue exposure, measurement limitation, or unrelated toxicity	Conventional systemic concentration was observed	That exposure is harmless or causally unrelated	Reassess the relevant exposure metric, susceptibility factors, metabolites, and temporal relationship

The practical consequence is that "biologically received dose" should not become another single score. What can be observed directly is administered dose, concentrations at particular times, biomarkers, organ-function measures, concomitant treatment, phenotype-related information, and clinical response. The causal interpretation linking these observations remains drug- and state-specific.

Monitoring should follow the drug, mechanism, and consequence of error

Therapeutic monitoring is most valuable when three conditions coincide: exposure varies enough to matter, a credible exposure target or model exists, and the clinical consequences of missing that target justify intervention. Antibiotic precision-dosing literature illustrates how therapeutic drug monitoring can be extended through pharmacokinetic models and Bayesian updating when rapidly changing physiology makes standard dosing unreliable [30]. The relevant principle is not that every dynamically altered drug requires monitoring, but that measurement has greater value when it resolves uncertainty that can change a clinically consequential decision.

Implementation infrastructure can make this process faster without resolving the underlying biological question. Electronic health record-integrated precision-dosing systems can combine patient data, concentration measurements, and pharmacokinetic models at the point of care [31]. However, widespread adoption of model-informed precision dosing has been limited by model qualification, prospective clinical evidence, implementation burden, usability, and uncertainty about when a prediction meaningfully improves care [32]. Digital availability of a dosing recommendation therefore does not make that recommendation biologically valid.

Model choice adds another layer of uncertainty. Precision-dosing software requires models that are appropriate for the patient population, sampling design, drug, endpoint, and intended clinical use [33]. External evaluations show that alternative pharmacokinetic models and model-ensembling strategies can materially change predicted target attainment [34]. A concentration interpreted through an unsuitable model can therefore produce apparent precision without reliable individualization.

These considerations argue for a monitoring response that begins with mechanism and therapeutic consequence rather than with a universal escalation algorithm. A concentration may be the preferred observation for one drug, functional phenotyping for another, repeated renal-function assessment for a third, and medication reconciliation for a fourth. Even when several data streams are available, the actionable combination remains drug-specific because the relative importance of inflammation, organ dysfunction, interacting medicines, and functional phenotype differs across substrates. Concentration measurement, a validated pharmacokinetic model, and a clinically meaningful target are most informative when used together rather than treated as substitutes for one another [5, 29, 33].

Table 3. Matching modifiable exposure drivers to measurements and clinical responses

Exposure driver or uncertainty	Feasible observation	What the observation can clarify	Decision consequence when therapeutic margin is narrow	Decision consequence when therapeutic margin is broad
Rapidly changing inflammatory state	Serial clinical state, inflammatory biomarkers, drug concentration where validated	Whether a susceptible metabolic pathway may be changing during treatment	Earlier reassessment of exposure and dosing may be justified	Observation may be sufficient unless exposure or response changes materially
Declining renal filtration	Serial renal-function measurements plus concentration where useful	Change in renal elimination capacity	Recalculate or measure exposure for drugs strongly dependent on renal clearance	Routine organ-function-based adjustment may remain adequate
Change in active renal secretion or nonrenal metabolism during CKD	Drug-specific pathway knowledge, concentration, model-supported assessment	Whether eGFR alone incompletely explains exposure	Consider pathway-aware monitoring when consequences of accumulation are serious	Avoid adding complex monitoring without evidence of meaningful exposure sensitivity

Progressive or decompensated hepatic dysfunction	Clinical liver assessment, concentration, relevant biomarkers or validated model	Whether metabolism, uptake, or extraction may have changed	Reassess drug-specific exposure before assuming a standard impairment adjustment remains valid	Conservative clinical observation may suffice when exposure tolerance is wide
New inhibitor or inducer	Medication reconciliation, interaction assessment, concentration or phenotype where justified	Whether current disposition differs from baseline	Prompt evaluation when interaction magnitude could produce toxicity or therapeutic failure	Manage according to established DDI evidence without unnecessary testing
Suspected phenoconversion	Genotype plus current medication/inflammation context; functional phenotype where available	Whether genotype-predicted capacity still represents current enzyme activity	Current phenotype may deserve greater weight than genotype-only interpretation	Genotype may remain adequate when the drug is insensitive to the affected pathway
Unexplained low concentration	Repeat/validated concentration, adherence and administration review	Whether underexposure is persistent and potentially modifiable	Investigate cause before automatic escalation	Repeat measurement may be unnecessary if clinical consequences are minimal
Model-dependent dose recommendation	Model-validation information and patient-data compatibility	Whether the prediction is applicable to the current patient	Use only sufficiently validated models when dosing errors carry major harm	Simpler dosing may be preferable when model complexity adds little clinical value

The measurement-to-action relationship is summarized in **Figure 2**. It deliberately separates causal modifiers from proxies and outcomes: inflammation, organ dysfunction, interacting drugs, and functional phenotype sit upstream; concentrations, biomarkers, adverse effects, and response are observations downstream. Clinical action branches according to the drug's therapeutic margin, validated exposure–response information, and whether the suspected modifier is measurable or modifiable.

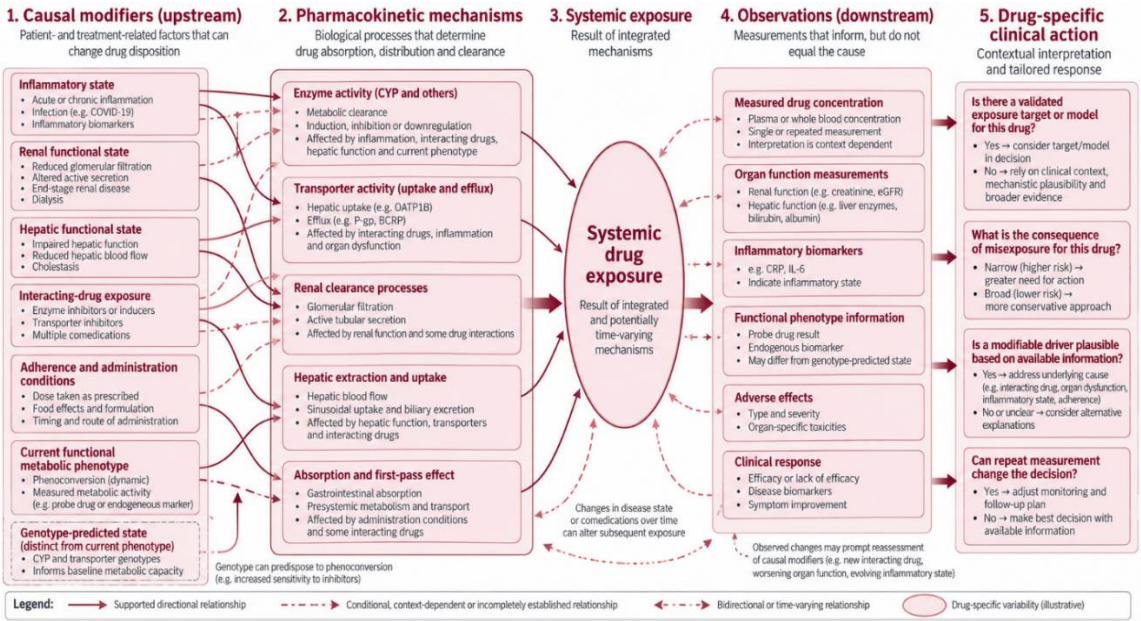

Figure 2. Separating causes of exposure instability from the measurements used to act on it

Conclusion

A prescribed dose is an adequate practical proxy for exposure only while the processes connecting administration to systemic concentration remain sufficiently stable for the drug being administered. That condition can fail when inflammation changes enzyme or transporter activity, kidney or liver disease alters relevant clearance pathways, interacting medicines modify disposition, or current metabolic phenotype diverges from genotype-predicted capacity. These modifiers can converge on similar exposure changes while remaining mechanistically distinct.

The resulting clinical problem cannot be solved by replacing prescribed dose with another universal index. Dose, genotype, functional phenotype, organ function, interacting medicines, adherence, concentration, and response describe different layers of the treatment process. Their value depends on the drug's disposition pathways, the rate at which the patient's state is changing, the validity of available exposure targets or models, and the consequence of under- or overexposure.

Two propositions follow from this synthesis. First, when a medicine depends materially on a dynamically modifiable pathway, within-patient exposure should become more predictable from the current functional state of that pathway than from prescribed dose alone as the state changes. Second, when different modifiers produce similar concentration changes, identifying the correct causal modifier should improve subsequent exposure prediction more than applying a common adjustment for dose–exposure discordance. These propositions are testable and deliberately drug-specific.

This relationship is conditional rather than universal. The prescribed dose ceases to be a reliable representation of biologically received exposure when clinically important disposition pathways are unstable enough that the same dose no longer predicts an acceptably consistent exposure state. In those circumstances, mechanism-aware interpretation and appropriately validated measurement can provide information that the prescription itself cannot.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Dunvald ACD, Järvinen E, Mortensen C, Stage TB. Clinical and molecular perspectives on inflammation-mediated regulation of drug metabolism and transport. Clin Pharmacol Ther. 2022;112(2):277-90. doi:10.1002/cpt.2432
2. Chu X, Prasad B, Neuhoff S, Yoshida K, Leeder JS, Mukherjee D, et al. Clinical implications of altered drug transporter abundance/function and PBPK modeling in specific populations: An ITC perspective. Clin Pharmacol Ther. 2022;112(3):501-26. doi:10.1002/cpt.2643
3. Yang DZ, Alhadab A, Parivar K, Wang DD, Elmeliegy M. Analysis of US Food and Drug Administration oncology approvals on the characterization of hepatic impairment effect and dosing recommendations. Clin Pharmacol Ther. 2022;112(4):782-90. doi:10.1002/cpt.2505
4. Cicali EJ, Elchynski AL, Cook KJ, Houder JT, Thomas CD, Smith DM, et al. How to integrate CYP2D6 phenoconversion into clinical pharmacogenetics: A tutorial. Clin Pharmacol Ther. 2021;110(3):677-87. doi:10.1002/cpt.2354
5. Minichmayr IK, Dreesen E, Centanni M, Wang Z, Hoffert Y, Friberg LE, et al. Model-informed precision dosing: State of the art and future perspectives. Adv Drug Deliv Rev. 2024;215:115421. doi:10.1016/j.addr.2024.115421
6. Proctor JR, Wong H. Time-dependent clearance can confound exposure-response analysis of therapeutic antibodies: A comprehensive review of the current literature. Clin Transl Sci. 2024;17(1):e13676. doi:10.1111/cts.13676
7. Lenoir C, Terrier J, Gloor Y, Curtin F, Rollason V, Desmeules JA, et al. Impact of SARS-CoV-2 infection (COVID-19) on cytochromes P450 activity assessed by the Geneva cocktail. Clin Pharmacol Ther. 2021;110(5):1358-67. doi:10.1002/cpt.2412
8. Le Carpentier EC, Canet E, Masson D, Martin M, Deslandes G, Gaultier A, et al. Impact of inflammation on midazolam metabolism in severe COVID-19 patients. Clin Pharmacol Ther. 2022;112(5):1033-9. doi:10.1002/cpt.2698
9. Smeets TJL, Valkenburg AJ, van der Jagt M, Koch BCP, Endeman H, Gommers DAMPJ, et al. Hyperinflammation reduces midazolam metabolism in critically ill adults with COVID-19. Clin Pharmacokinet. 2022;61(7):973-83. doi:10.1007/s40262-022-01122-5

10. Lenoir C, Niederer A, Rollason V, Desmeules JA, Daali Y, Samer CF. Prediction of cytochromes P450 3A and 2C19 modulation by both inflammation and drug interactions using physiologically based pharmacokinetics. CPT Pharmacometrics Syst Pharmacol. 2022;11(1):30-43. doi:10.1002/psp4.12730
11. Simon F, Gautier-Veyret E, Truffot A, Chenel M, Payen L, Stanke-Labesque F, et al. Modeling approach to predict the impact of inflammation on the pharmacokinetics of CYP2C19 and CYP3A4 substrates. Pharm Res. 2021;38(3):415-28. doi:10.1007/s11095-021-03019-7
12. Tan ML, Yoshida K, Zhao P, Zhang L, Nolin TD, Piquette-Miller M, et al. Effect of chronic kidney disease on nonrenal elimination pathways: A systematic assessment of CYP1A2, CYP2C8, CYP2C9, CYP2C19, and OATP. Clin Pharmacol Ther. 2018;103(5):854-67. doi:10.1002/cpt.807
13. Egeland EJ, Witczak BJ, Zaré HK, Christensen H, Åsberg A, Robertsen I. Chronic inhibition of CYP3A is temporarily reduced by each hemodialysis session in patients with end-stage renal disease. Clin Pharmacol Ther. 2020;108(4):866-73. doi:10.1002/cpt.1875
14. Tatosian DA, Yee KL, Zhang Z, Mostoller K, Paul E, Sutradhar S, et al. A microdose cocktail to evaluate drug interactions in patients with renal impairment. Clin Pharmacol Ther. 2021;109(2):403-15. doi:10.1002/cpt.1998
15. Dubinsky S, Malik P, Hajducek DM, Edginton A. Determining the effects of chronic kidney disease on organic anion transporter1/3 activity through physiologically based pharmacokinetic modeling. Clin Pharmacokinet. 2022;61(7):997-1012. doi:10.1007/s40262-022-01121-6
16. Tuloup V, Goutelle S, Tod M, Bourguignon L. Evaluation of renal impairment influence on metabolic drug clearance using a modelling approach. Clin Pharmacokinet. 2023;62(2):307-19. doi:10.1007/s40262-022-01205-3
17. Duthaler U, Bachmann F, Suenderhauf C, Grandinetti T, Pfefferkorn F, Haschke M, et al. Liver cirrhosis affects the pharmacokinetics of the six substrates of the Basel phenotyping cocktail differently. Clin Pharmacokinet. 2022;61(7):1039-55. doi:10.1007/s40262-022-01119-0
18. Lin J, Kimoto E, Yamazaki S, Vourvahis M, Bergman A, Rodrigues AD, et al. Effect of hepatic impairment on OATP1B activity: Quantitative pharmacokinetic analysis of endogenous biomarker and substrate drugs. Clin Pharmacol Ther. 2023;113(5):1058-69. doi:10.1002/cpt.2829
19. Ladumor MK, Storelli F, Liang X, Lai Y, Enogieru OJ, Chothe PP, et al. Predicting changes in the pharmacokinetics of CYP3A-metabolized drugs in hepatic impairment and insights into factors driving these changes. CPT Pharmacometrics Syst Pharmacol. 2023;12(2):261-73. doi:10.1002/psp4.12901
20. Fletcher EP, Sahre M, Hon YY, Balakrishnan A, Zhou L, Sun Q, et al. Impact of organ impairment on the pharmacokinetics of therapeutic peptides and proteins. AAPS J. 2023;25(4):54. doi:10.1208/s12248-023-00819-0
21. Brouwer KLR, Evers R, Hayden E, Hu S, Li CY, Meyer Zu Schwabedissen HE, et al. Regulation of drug transport proteins—from mechanisms to clinical impact: A white paper on behalf of the International Transporter Consortium. Clin Pharmacol Ther. 2022;112(3):461-84. doi:10.1002/cpt.2605
22. Taskar KS, Yang X, Neuhoff S, Patel M, Yoshida K, Paine MF, et al. Clinical relevance of hepatic and renal P-gp/BCRP inhibition of drugs: An International Transporter Consortium perspective. Clin Pharmacol Ther. 2022;112(3):573-92. doi:10.1002/cpt.2670
23. Storelli F, Matthey A, Lenglet S, Thomas A, Desmeules J, Daali Y. Impact of CYP2D6 functional allelic variations on phenoconversion and drug-drug interactions. Clin Pharmacol Ther. 2018;104(1):148-57. doi:10.1002/cpt.889
24. Bruckmueller H, Cascorbi I. Drug-drug-gene interactions: A call for clinical consideration. Clin Pharmacol Ther. 2021;110(3):549-51. doi:10.1002/cpt.2348
25. Viviani R, Berres J, Stingl JC. Phenotypic models of drug-drug-gene interactions mediated by cytochrome drug-metabolizing enzymes. Clin Pharmacol Ther. 2024;116(3):592-601. doi:10.1002/cpt.3188
26. Abouir K, Exquis N, Gloor Y, Daali Y, Samer CF. Phenoconversion due to drug-drug interactions in CYP2C19 genotyped healthy volunteers. Clin Pharmacol Ther. 2024;116(4):1121-9. doi:10.1002/cpt.3378
27. Liu C, Yu J, Li H, Liu J, Xu Y, Song P, et al. Association of time-varying clearance of nivolumab with disease dynamics and its implications on exposure response analysis. Clin Pharmacol Ther. 2017;101(5):657-66. doi:10.1002/cpt.656

28. Dai HI, Vugmeyster Y, Mangal N. Characterizing exposure-response relationship for therapeutic monoclonal antibodies in immuno-oncology and beyond: Challenges, perspectives, and prospects. Clin Pharmacol Ther. 2020;108(6):1156-70. doi:10.1002/cpt.1953
29. Groenland SL, van Eerden RAG, Westerdijk K, Meertens M, Koolen SLW, Moes DJAR, et al. Therapeutic drug monitoring-based precision dosing of oral targeted therapies in oncology: A prospective multicenter study. Ann Oncol. 2022;33(10):1071-82. doi:10.1016/j.annonc.2022.06.010
30. Wicha SG, Märtson AG, Nielsen EI, Koch BCP, Friberg LE, Alffenaar JW, et al. From therapeutic drug monitoring to model-informed precision dosing for antibiotics. Clin Pharmacol Ther. 2021;109(4):928-41. doi:10.1002/cpt.2202
31. Vinks AA, Peck RW, Neely M, Mould DR. Development and implementation of electronic health record-integrated model-informed clinical decision support tools for the precision dosing of drugs. Clin Pharmacol Ther. 2020;107(1):129-35. doi:10.1002/cpt.1679
32. Darwich AS, Ogungbenro K, Vinks AA, Powell JR, Reny JL, Marsousi N, et al. Why has model-informed precision dosing not yet become common clinical reality? Lessons from the past and a roadmap for the future. Clin Pharmacol Ther. 2017;101(5):646-56. doi:10.1002/cpt.659
33. Taylor ZL, Poweleit EA, Paice K, Somers KM, Pavia K, Vinks AA, et al. Tutorial on model selection and validation of model input into precision dosing software for model-informed precision dosing. CPT Pharmacometrics Syst Pharmacol. 2023;12(12):1827-45. doi:10.1002/psp4.13056
34. Agema BC, Kocher T, Öztürk AB, Giraud EL, van Erp NP, de Winter BCM, et al. Selecting the best pharmacokinetic models for a priori model-informed precision dosing with model ensembling. Clin Pharmacokinet. 2024;63(10):1449-61. doi:10.1007/s40262-024-01425-9