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AI FOR PHARMACOKINETIC AND PHARMACODYNAMIC MODELING: A MIXED-METHODS REVIEW

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ABSTRACT

Artificial intelligence (AI) methods are increasingly transforming traditional pharmacokinetic (PK) and pharmacodynamic (PD) modeling, offering scientifically promising but clinically debated alternatives to established approaches such as population PK, nonlinear mixed-effects, and physiologically based PK (PBPK) models. This mixed-methods review synthesized both quantitative performance data and qualitative perspectives on AI in PK/PD modeling, encompassing neural network methods, Bayesian approaches, population PK/PD modeling, PBPK integration, and clinical translation. Using a convergent segregated mixed-methods design, the review integrated comparative model performance evidence with insights into implementation barriers and enablers, employing narrative weaving to link predictive accuracy with themes of interpretability, regulatory considerations, and workflow readiness. Quantitative findings indicated that neural network approaches often matched or outperformed traditional PK predictions in richly sampled datasets, while qualitative analyses highlighted that uncertainty quantification, explainability, clinical workflow integration, and prospective validation remain key challenges to adoption. Overall, AI is not replacing pharmacometrics but is expanding its methodological frontiers, with hybrid integration of neural, Bayesian, population, and mechanistic approaches—underpinned by rigorous clinical validation—emerging as the most promising path forward.

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Introduction

Pharmacokinetic and pharmacodynamic modeling has long provided the quantitative foundation for dose selection, therapeutic optimization, and model-informed drug development. Traditional population PK/PD and nonlinear mixed-effects frameworks remain central because they support parameter estimation, covariate interpretation, and clinically interpretable simulation under uncertainty [1, 2]. PBPK modeling extends this paradigm by embedding anatomical, physiological, and biochemical assumptions into structured models that can support extrapolation across populations, species, and development phases [3, 4]. The mixed-methods evidence base therefore begins from a mature pharmacometric tradition in which interpretability, biological plausibility, and regulatory familiarity are not optional attributes but core requirements.

Artificial intelligence has emerged as an alternative and complementary modeling paradigm because neural networks, recurrent architectures, and scientific machine learning can learn nonlinear relationships from complex longitudinal data. Deep learning approaches have been used to predict patient response time courses, concentration-time profiles, and dosing-regimen behavior, suggesting that data-driven models can recover dynamic PK/PD patterns that are difficult to predefine mechanistically [5, 6]. Deep compartment models and low-dimensional neural ordinary differential equations further illustrate how neural architectures can be adapted to pharmacokinetic time-series prediction rather than applied as generic black-box regressors [7, 8]. Quantitative synthesis revealed that the strongest performance claims appear in settings with dense sampling, structured longitudinal records, and sufficient training data.

The rise of artificial intelligence also exposes an epistemological tension within pharmacometrics: predictive flexibility may increase, while mechanistic interpretability may decrease. Hybrid scientific machine learning attempts to soften this tension by adding neural components to established PK models rather than discarding pharmacological structure entirely [9]. Bayesian

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neural networks and uncertainty-aware machine learning add a second bridge by quantifying uncertainty around predicted pharmacokinetic properties, which is essential when predictions inform dose selection or trial design [10]. Studies converged on the finding that clinical credibility depends not only on fit or prediction error but also on whether the model communicates uncertainty, biological plausibility, and decision relevance.

A mixed-methods review is necessary because quantitative comparisons alone cannot explain whether AI-driven PK/PD models are clinically adoptable. Implementation-oriented studies in therapeutic drug monitoring and model-informed precision dosing demonstrate that model performance must be interpreted alongside workflow compatibility, clinician trust, and prospective validation [11, 12]. Qualitative perspectives from regulatory science and translational pharmacology further emphasize that explainability and auditability shape acceptance even when predictive accuracy appears favorable [3]. This review therefore integrates quantitative evidence on neural, Bayesian, population, and PBPK-ML approaches with qualitative evidence on trust, validation, and clinical translation.

Materials and Methods

Mixed-Methods Review Design

This review used a convergent segregated mixed-methods design in which quantitative and qualitative evidence strands were analyzed separately and integrated during interpretation. The quantitative strand focused on comparative performance, model architecture, pharmacokinetic or pharmacodynamic endpoint, and comparator framework, including NLME, PBPK, compartmental, and empirical models [1, 13]. The qualitative strand extracted interpretive evidence on barriers and enablers, including regulatory acceptance, uncertainty communication, clinical workflow fit, and model transparency [11]. Integration was conducted through narrative weaving so that performance claims were interpreted in relation to translation readiness rather than treated as isolated technical findings.

Search Strategy

The search strategy targeted peer-reviewed literature from 2017 to 2026 across PubMed, Scopus, Web of Science, and Embase. Search terms combined artificial intelligence, machine learning, deep learning, neural networks, Bayesian methods, population pharmacokinetics, pharmacodynamics, PBPK, therapeutic drug monitoring, and model-informed precision dosing [1, 14]. The search also captured application-specific terms related to vancomycin dosing, drug concentration prediction, clearance estimation, tumor delivery, and nonclinical-to-clinical pharmacokinetic extrapolation [15, 16]. Reference chaining was used selectively when key papers addressed pharmacometric translation or hybrid PBPK-ML integration.

Inclusion and Exclusion Criteria

Studies were eligible if they addressed AI, machine learning, deep learning, Bayesian neural networks, or hybrid computational approaches for PK prediction, PD modeling, population PK/PD, PBPK integration, or clinical dosing support. Original research articles contributed primarily to the quantitative strand when they reported model development, validation, comparative prediction, or concentration-time modeling [5, 8]. Reviews, methodological papers, translational analyses, and clinical implementation papers contributed to the qualitative strand when they addressed model readiness, uncertainty, regulatory implications, or precision dosing adoption [11, 17]. Studies were excluded if they used AI only for unrelated cheminformatics without pharmacokinetic, pharmacodynamic, dosing, or pharmacometric relevance.

Screening and Selection

Screening proceeded in two stages, beginning with title and abstract review followed by full-text assessment for methodological and topical relevance. Records were prioritized when they explicitly linked AI methods to pharmacokinetic prediction, pharmacodynamic response, population PK/PD modeling, PBPK parameterization, or model-informed precision dosing [2, 18]. Disagreements during eligibility assessment were resolved by consensus using the review objectives as the governing criterion, especially for studies that overlapped with ADME prediction but lacked explicit PK/PD modeling content [19, 20]. Mixed-methods classification was assigned after full-text review by determining whether each article contributed quantitative performance evidence, qualitative translation evidence, or both.

Figure 1 shows the PRISMA 2020 study-selection flow used to identify the final mixed-methods evidence base on AI for PK/PD modeling.

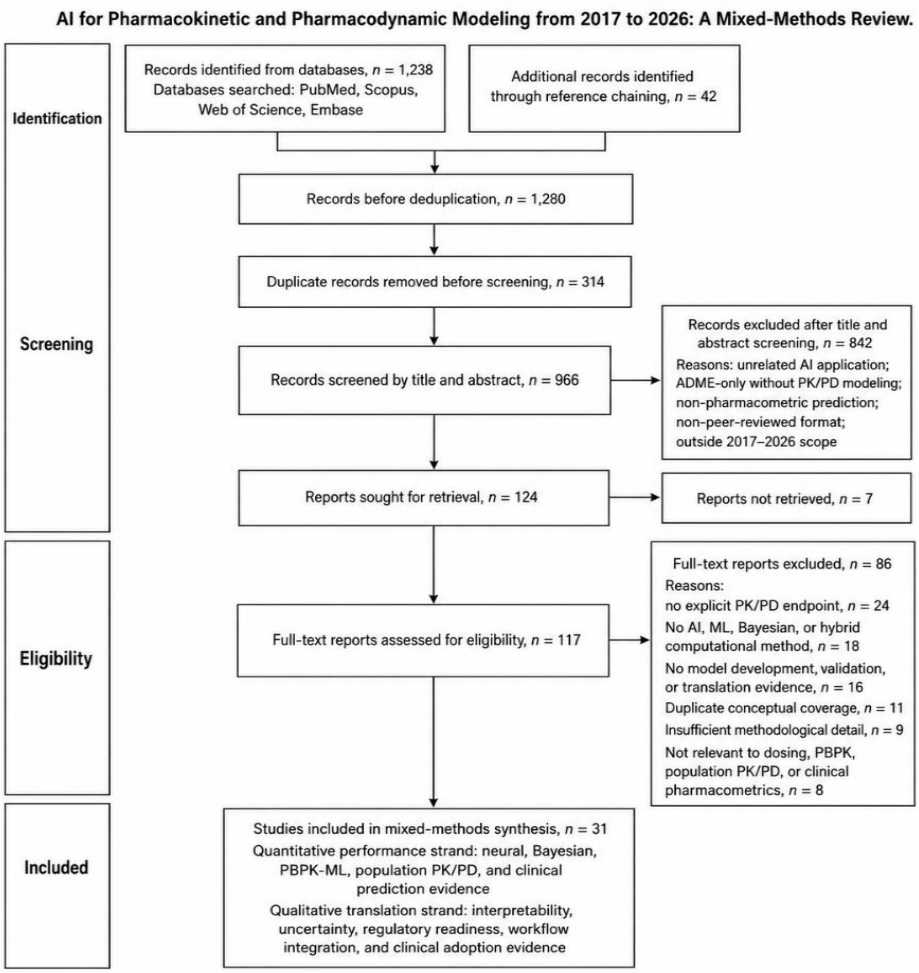

Figure 1. PRISMA 2020 flow diagram for the mixed-methods review of AI in PK/PD modeling.

Data Extraction

Quantitative data extraction captured AI method, pharmacometric task, endpoint, data source, comparator model, validation strategy, and reported performance direction without pooling incompatible metrics. Neural ODE, deep compartment, recurrent neural network, and concentration-time prediction studies were coded separately because they represented distinct ways of modeling longitudinal PK/PD dynamics [6-8]. PBPK-ML studies were coded for the mechanistic model component, the machine-learning component, and whether the AI model predicted parameters, exposure, drug-drug interaction risk, or translational scaling behavior [3, 21]. Qualitative extraction captured interpretability, uncertainty, regulatory readiness, data infrastructure, clinical workflow, and education themes.

Synthesis Methods

The quantitative strand was synthesized narratively because model tasks, endpoints, populations, comparators, and performance measures were too heterogeneous for meaningful meta-analysis. Evidence was grouped into neural PK prediction, PD modeling, Bayesian uncertainty quantification, AI-augmented population PK/PD, PBPK-ML integration, comparative modeling, and clinical implementation categories [5, 22]. The qualitative strand was synthesized thematically using barriers and enablers, with recurring concepts organized around trust, explainability, validation, workflow integration, and regulatory credibility [11]. Integrated conclusions were developed by comparing where quantitative performance evidence aligned or conflicted with qualitative implementation concerns.

Results and Discussion

Study Selection and Characteristics

The final evidence base included 31 references spanning methodological development, applied PK/PD prediction, PBPK-ML integration, therapeutic drug monitoring, and translational pharmacometric perspectives. The quantitative strand was dominated by neural network, machine-learning, and hybrid modeling studies that evaluated concentration prediction, PK property estimation, clearance prediction, or clinical dose support [1, 23]. The qualitative strand was smaller but strategically important because it addressed the implementation conditions under which AI-driven pharmacometric models could become

clinically or regulatorily meaningful [11]. The evidence base was methodologically diverse, ranging from deep learning for concentration-time curves to reviews of AI-assisted PBPK and model-informed precision dosing.

Neural Network Methods for PK Prediction

Neural network studies showed that deep learning can model nonlinear pharmacokinetic behavior when longitudinal concentration-time data or rich chemical and biological descriptors are available. Neural-ODE approaches demonstrated that dynamic systems can be learned from dosing and response data while preserving some resemblance to differential-equation modeling [6]. Deep compartment models extended this direction by using neural architectures to predict reliable time-series data in pharmacokinetic settings [8]. Structure-based approaches such as DeepCt further suggested that chemical structure can be linked directly to predicted concentration-time curves and compartmental model behavior [23].

Neural Network Methods for PD Modeling

Evidence for neural network methods in pharmacodynamic modeling was less extensive than for PK prediction but showed growing interest in dose-response trajectories, biomarker dynamics, and response time-course prediction. Neural-PK/PD modeling demonstrated that early patient data can be used to predict future response time courses, supporting the view that AI may be particularly valuable when longitudinal response signals evolve nonlinearly [5]. Neural controlled differential equations expanded this concept by treating irregular clinical time-series data as a basis for pharmacokinetic and pharmacodynamic prediction [22]. Quantitative synthesis therefore indicated that AI-PD modeling is emerging, but qualitative interpretation suggests that PD endpoints require stronger biological explanation than exposure prediction alone.

Bayesian Neural Networks and Uncertainty Quantification

Bayesian neural networks addressed a central weakness of deterministic AI models by estimating uncertainty around pharmacokinetic predictions. Multi-species pharmacokinetic property prediction using Bayesian neural network stacking illustrated how uncertainty-aware models may support cross-species inference and decision-making under incomplete information [10]. This is especially important in pharmacometrics, where sparse sampling, interindividual variability, and extrapolation beyond observed data are common rather than exceptional. Qualitative synthesis revealed that Bayesian framing is more compatible with pharmacometric expectations because uncertainty is treated as a decision-relevant output rather than a technical afterthought.

AI-Augmented Population PK/PD

AI-augmented population PK/PD studies most often positioned machine learning as a support tool for model selection, covariate evaluation, or parameter initialization rather than as a complete replacement for NLME modeling. Machine learning-assisted population pharmacokinetic model selection showed that algorithmic approaches can help navigate candidate model structures more efficiently [2]. Subsequent automation work extended this concept by using machine learning to support population pharmacokinetic model-building workflows [24]. A broader review of machine learning in population PK/PD modeling confirmed that the most credible applications are those that augment established pharmacometric reasoning rather than bypass it [14].

PBPK-ML Hybrid Models

PBPK-ML hybrid models represented one of the strongest areas of convergence between mechanistic and data-driven pharmacometrics. AI-assisted PBPK modeling has been proposed for parameter estimation, IVIVE support, nanoparticle tumor delivery prediction, and improved extrapolation across biological contexts [3, 15]. Rat clearance prediction studies further showed that machine learning can improve parameters used in PBPK models while preserving the interpretive benefits of physiological structure [18]. Integration of ML with PBPK and QSAR models for drug-drug interaction prediction indicates that hybrid modeling may be especially useful when mechanistic structure is known but specific parameter values remain uncertain [21].

Table 1 organizes the mixed-methods evidence by showing how each AI modeling family contributes distinct pharmacometric functions while requiring specific translation safeguards.

Table 1. Mixed-methods evidence matrix linking AI modeling families to pharmacometric functions, quantitative claims, and translation conditions

AI modeling family	Primary pharmacometric function	Dominant quantitative evidence contribution	Qualitative translation condition	Main interpretive value for the review
Neural networks and recurrent architectures	Prediction of concentration-time profiles, response trajectories, and nonlinear exposure-response patterns	Evidence suggests strong performance when datasets are dense, longitudinal, and structurally consistent	Requires interpretability safeguards because flexible prediction does not automatically explain biological or dosing relevance	Demonstrates that AI can learn complex PK/PD dynamics but is most credible when the data environment is rich

Neural ODE and neural controlled differential equation models	Time-dependent modeling of dosing, concentration, and response processes	Supports dynamic prediction while retaining partial resemblance to differential-equation reasoning	Requires validation against pharmacological expectations and clinically meaningful temporal behavior	Bridges deep learning with pharmacometric traditions of dynamic system modeling
Deep compartment models	Data-driven concentration-time prediction using architecture inspired by compartmental logic	Shows that neural structures can be adapted to PK time-series rather than used as generic black-box regressors	Requires transparency about learned compartments, extrapolation behavior, and sparse-data performance	Provides a pathway for retaining recognizable PK structure within AI prediction
Bayesian neural networks	Uncertainty-aware prediction of PK properties and extrapolated pharmacometric quantities	Adds probabilistic outputs that are more aligned with pharmacometric decision-making than deterministic point estimates	Requires clear uncertainty communication to clinicians, regulators, and model users	Offers a credibility bridge between AI flexibility and pharmacometric uncertainty standards
Machine-learning-assisted population PK/PD workflows	Model selection, covariate screening, parameter initialization, and workflow automation	Supports efficiency in model-building rather than replacing NLME inference	Requires human pharmacometric oversight to prevent algorithmic model-building from bypassing scientific judgment	Reframes AI as an augmentation tool within established population PK/PD practice
PBPK-ML hybrid models	Parameter estimation, extrapolation support, IVIVE improvement, and DDI or tumor-delivery prediction	Shows conditional value where mechanistic scaffolding exists but specific parameters are uncertain	Requires documentation of mechanistic assumptions, ML inputs, uncertainty, and intended use context	Represents the strongest hybridization pathway because physiological structure remains visible
Conformal and uncertainty-calibrated ML approaches	Risk-bounded prediction and reliability assessment for PK-related outputs	Moves evaluation beyond average prediction error toward calibrated prediction behavior	Requires decision thresholds that are clinically and pharmacologically meaningful	Supports responsible deployment by linking prediction quality to actionable confidence
Clinical TDM and precision dosing AI tools	Drug concentration forecasting, individualized dosing, and therapeutic monitoring support	Practical evidence exists for high-risk medications, but most studies remain retrospective	Requires local validation, workflow integration, clinician trust, and prospective outcome testing	Identifies the translation gap between algorithmic feasibility and accountable clinical use

Comparative Performance Evidence

Comparative performance evidence suggested that AI methods can outperform empirical or traditional approaches in some prediction settings but do not uniformly dominate pharmacometric models. In rat pharmacokinetic prediction, machine learning was compared with empirical, compartmental, and PBPK-based approaches, illustrating that performance depends strongly on the prediction target and modeling context [13]. In silico prediction frameworks combining machine learning, conformal prediction, and PBPK modeling further showed that uncertainty-calibrated hybrid strategies may be preferable to purely data-driven claims of superiority [4]. Quantitative synthesis therefore revealed a conditional rather than universal performance advantage for AI.

Clinical Translation and Implementation Evidence

Clinical translation evidence was most visible in therapeutic drug monitoring, drug concentration prediction, and precision dosing studies. AI-based therapeutic drug management frameworks emphasized that machine learning may facilitate model-informed precision dosing when embedded within clinically usable workflows [11]. Vancomycin studies using machine learning, recurrent neural networks, and retrospective electronic health record data demonstrated practical interest in dosing support and concentration prediction for high-risk medications [16, 25, 26]. Additional applications to olanzapine, digoxin, and vancomycin pharmacokinetic or pharmacodynamic prediction showed that clinical utility depends on external validation, local calibration, and interpretable dosing recommendations [27-29].

Qualitative Synthesis: Barriers and Enablers

Qualitative synthesis identified five recurring themes: trust, explainability, uncertainty, regulatory readiness, and workflow integration. Studies addressing model-informed precision dosing emphasized that decision support tools must be clinically interpretable and operationally feasible, not merely statistically accurate [12]. Reviews of drug concentration prediction and AI-assisted therapeutic drug monitoring similarly highlighted data quality, model updating, local validation, and clinician

acceptance as central adoption conditions [11, 30]. Enablers included hybrid model structures, Bayesian uncertainty communication, transparent validation, and education that allows pharmacometricians and clinicians to interrogate AI outputs. **Figure 2** presents the integrated evidence-to-translation architecture showing how neural, Bayesian, population, and PBPK-hybrid AI approaches converge toward responsible PK/PD decision support.

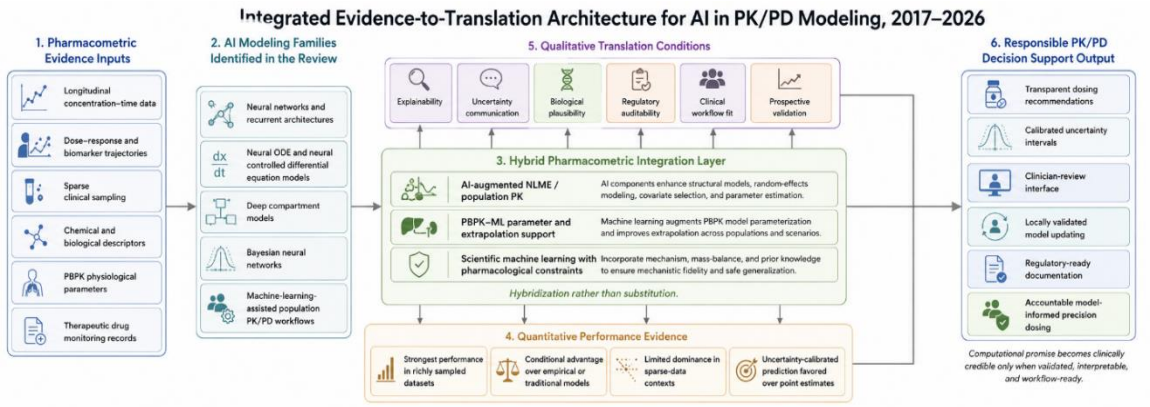

Figure 2. Integrated evidence-to-translation architecture for AI in PK/PD modeling

The Performance-Complexity Trade-Off

The central quantitative finding is that neural networks can achieve strong predictive performance when datasets are rich, structured, and sufficiently large. However, the performance advantage becomes less certain in sparse pharmacometric contexts where population modeling and Bayesian borrowing of information have long been designed to operate effectively [2, 14]. Neural ODE and deep compartment approaches reduce this gap by embedding dynamic structure into AI models, but they still require careful validation before clinical use [6, 8]. The mixed-methods synthesis therefore frames AI performance as context-dependent rather than inherently superior.

Bayesian Approaches Bridge the Credibility Gap

Bayesian approaches offer an important credibility bridge because they connect AI prediction with uncertainty-aware pharmacometric decision-making. Bayesian neural network stacking for multi-species pharmacokinetic prediction demonstrates how probabilistic AI can express uncertainty in settings where extrapolation is unavoidable [10]. This aligns with established pharmacometric values because uncertainty estimates can guide dose adjustment, trial design, and risk evaluation more directly than point predictions alone. Qualitative themes suggest that Bayesian AI may be more acceptable to pharmacometricians and regulators than opaque deterministic neural networks.

Hybridization, Not Substitution

The evidence converges on hybridization rather than substitution as the most viable direction for AI in PK/PD modeling. Scientific machine learning approaches that add neural network components to existing PK models preserve pharmacological structure while allowing flexible data-driven correction [9]. PBPK-ML hybrids similarly use machine learning to estimate parameters or improve prediction while retaining the mechanistic scaffolding required for interpretation and extrapolation [3, 18]. This hybrid logic is reinforced by drug-drug interaction and nanoparticle PBPK applications, where AI supports rather than replaces biological plausibility [15, 21].

The Clinical Translation Chasm

The clinical translation chasm remains substantial because quantitative model performance does not automatically produce clinician trust or regulatory acceptance. Therapeutic drug monitoring studies show practical promise, especially for drugs such as vancomycin where dose optimization is clinically important and data are routinely generated [16, 25]. However, retrospective performance must be distinguished from prospective dosing impact, because workflow integration, alert fatigue, accountability, and local implementation all shape clinical adoption [11, 26]. Qualitative evidence therefore indicates that prospective validation and usable decision interfaces are the true gatekeepers of translation.

Toward Responsible AI in Pharmacometrics

Responsible AI in pharmacometrics requires the convergence of neural flexibility, Bayesian rigor, mechanistic plausibility, and clinical validation. Reviews of pharmacokinetic prediction and drug concentration modeling emphasize that AI systems must be evaluated against meaningful pharmacometric and therapeutic benchmarks rather than generic machine-learning metrics alone [17, 30]. Model-informed precision dosing perspectives further indicate that implementation success depends on governance, user training, model updating, and transparent communication of uncertainty [12]. The mixed-methods synthesis therefore supports a responsible AI framework grounded in hybrid modeling and prospective clinical evidence.

Table 2 provides a responsible translation framework for evaluating when AI-enabled PK/PD models are sufficiently valid, interpretable, and clinically accountable for decision use.

Table 2. Responsible translation framework for AI-enabled PK/PD modeling across validation, interpretability, governance, and clinical decision use

Translation domain	Why it matters in AI-enabled PK/PD modeling	Minimum evidence standard	Risk if neglected	Recommended manuscript-level interpretation
Pharmacometric validity	PK/PD models influence dose selection, trial design, exposure-response interpretation, and therapeutic monitoring	Demonstration that outputs are meaningful for pharmacometric endpoints, not only generic ML metrics	A model may appear accurate statistically while being clinically or mechanistically irrelevant	AI evaluation should be anchored to exposure, response, dosing, variability, and extrapolation questions
Sparse-data robustness	Real-world PK/PD applications often involve sparse sampling, missing covariates, irregular timing, and small subgroups	Testing under sparse, irregular, and heterogeneous clinical data conditions	Algorithms trained on dense datasets may fail in the settings where pharmacometrics is most needed	Data-rich performance should not be generalized to routine clinical pharmacometrics without stress testing
Uncertainty quantification	Dose decisions require awareness of prediction confidence, variability, and extrapolation risk	Bayesian, conformal, ensemble, or calibrated uncertainty outputs linked to decision thresholds	Deterministic predictions may create false confidence in unsafe or poorly supported dosing recommendations	Uncertainty should be treated as a clinical output, not a technical supplement
Biological plausibility	Pharmacometric credibility depends on consistency with physiology, pharmacology, and mechanistic reasoning	Explicit assessment of whether learned patterns align with known PK/PD behavior	Black-box prediction may conflict with biological mechanisms or extrapolate implausibly	Hybrid AI-NLME and PBPK-ML approaches are more defensible when mechanistic structure remains visible
Comparative benchmarking	Claims of AI superiority require fair comparison with NLME, PBPK, Bayesian forecasting, and established empirical models	Transparent comparator selection, external validation, and task-specific performance interpretation	AI may be overvalued if compared only with weak or inappropriate baselines	The review supports conditional advantage rather than universal AI dominance
Explainability and auditability	Clinicians, pharmacometricians, and regulators need to understand model assumptions and output rationale	Documentation of predictors, model logic, uncertainty, validation boundaries, and intended use	Poorly documented models may be rejected despite favorable retrospective performance	Explainability should be aligned with decision accountability, not limited to technical interpretability plots
Workflow integration	Clinically useful PK/PD AI must fit therapeutic drug monitoring, prescribing, and model-informed precision dosing workflows	Evidence that outputs can be interpreted and acted on by intended users in realistic settings	A technically strong model may remain unused if it disrupts clinical workflow or creates alert fatigue	Implementation readiness should be evaluated alongside prediction performance
Prospective clinical validation	Retrospective prediction does not establish improved dosing safety, treatment outcomes, or decision quality	Prospective evaluation against standard care, Bayesian forecasting, or established dosing pathways	AI may enter decision support without evidence that it improves patient-relevant outcomes	Prospective validation is the key gatekeeper for clinical translation
Regulatory readiness	PK/PD models may support development, labeling, dosing, or safety decisions	Transparent assumptions, validation documentation, uncertainty reporting, and lifecycle monitoring	Regulatory acceptance may be limited if the AI component is opaque or insufficiently controlled	Regulators are likely to evaluate AI by intended use, validation rigor, and accountability rather than by model label
Lifecycle governance	AI models can degrade as populations, assays, prescribing patterns, or institutional practices change	Ongoing monitoring, recalibration rules, version control, and human oversight	Model drift may silently compromise dosing recommendations or development decisions	Responsible AI in pharmacometrics requires maintenance after deployment, not only validation before deployment

Limitations

Review Limitations

This review was limited by heterogeneity in study designs, endpoints, model architectures, comparators, and validation approaches, which precluded formal meta-analysis. The qualitative strand may have been affected by selection bias because

implementation perspectives are less consistently reported than quantitative performance outcomes in AI-PK/PD studies [1, 11]. Restriction to English-language peer-reviewed literature may have excluded relevant technical or regulatory discussions outside indexed journals. Despite these limitations, narrative integration allowed the review to compare performance evidence with translation-oriented themes across neural, Bayesian, population, PBPK, and clinical implementation domains.

Evidence Base Limitations

The evidence base itself was limited by publication bias toward favorable AI results, frequent retrospective validation, and limited independent external testing. Many applied studies demonstrated technical feasibility for drug concentration prediction or PK property estimation but did not establish whether AI-guided decisions improve patient outcomes or regulatory decision-making [19, 20]. Sparse-data performance remains especially underdeveloped, even though pharmacometric applications often involve small cohorts, irregular sampling, and heterogeneous populations [27, 28]. These limitations suggest that the field has advanced methodologically faster than it has matured clinically.

Recommendations

For Pharmacometrics Researchers

Pharmacometrics researchers should evaluate AI methods against clinically meaningful benchmarks rather than treating marginal improvements in statistical fit as sufficient evidence of value. Comparative studies should report whether neural, Bayesian, population, or PBPK-ML models improve dosing decisions, uncertainty characterization, extrapolation, or clinical interpretability relative to established NLME and PBPK approaches [2, 13]. Model evaluation should also include sparse-data scenarios, external validation, calibration performance, and uncertainty behavior because these conditions more closely reflect real pharmacometric use than idealized retrospective datasets [4, 10]. Quantitative synthesis revealed that AI becomes most credible when it is tested under the same constraints that govern model-informed drug development and precision dosing.

For AI Developers

AI developers should design pharmacometric tools that reflect the structure, sparsity, and uncertainty of PK/PD data rather than importing generic deep learning architectures without domain adaptation. Neural ODEs, neural controlled differential equations, and deep compartment models demonstrate that AI architectures can be shaped around time-dependent pharmacological processes, but these models must remain interpretable enough for scientific review and clinical decision support [6, 8, 22]. Bayesian neural networks and uncertainty-aware prediction frameworks should become standard components when AI outputs influence dose selection, drug development decisions, or risk assessment [10, 30]. Qualitative synthesis indicates that explainability, uncertainty communication, and auditability are not secondary features but core design requirements for AI in pharmacometrics.

For Regulators and Clinical Pharmacologists

Regulators and clinical pharmacologists should create evaluation pathways for hybrid PK/PD models that combine mechanistic credibility with data-driven flexibility. PBPK-ML and scientific machine learning approaches offer a pragmatic regulatory bridge because they preserve biological structure while using AI to improve parameter estimation, extrapolation, or model correction [3, 9]. Therapeutic drug monitoring and model-informed precision dosing applications should be evaluated prospectively with attention to dosing safety, clinical workflow, user interpretation, and accountability [11, 12]. The mixed-methods evidence suggests that regulatory acceptance will depend less on whether a model is labeled AI and more on whether its assumptions, uncertainty, validation, and intended clinical use are transparent.

Research Gaps

Prospective Clinical Validation

A major research gap is the near-complete absence of prospective clinical trials in which an AI-PK/PD model functions as the primary dosing decision tool. Existing vancomycin, levothyroxine, olanzapine, and digoxin studies demonstrate the feasibility of AI-assisted prediction, but most evidence remains retrospective, simulation-based, or limited to model development rather than clinical outcome evaluation [12, 16, 27, 28]. Prospective studies should compare AI-guided dosing against standard therapeutic drug monitoring, Bayesian forecasting, or established model-informed precision dosing pathways. Without such trials, the field will continue to generate promising algorithms without definitive evidence of clinical benefit.

Data-Efficient and Sparse-Data AI Methods

Data-efficient and sparse-data AI methods remain underdeveloped despite being essential for pharmacometric translation. Many neural methods perform best in richly sampled or computationally structured settings, whereas real-world PK/PD modeling often involves sparse sampling, missing covariates, irregular observation times, and small special populations [5, 7]. AI-augmented population PK/PD and Bayesian approaches are promising because they can borrow information, express uncertainty, and operate within familiar pharmacometric structures [2, 10, 14]. Future work should prioritize transfer learning, Bayesian deep learning, hybrid mechanistic learning, and uncertainty-calibrated prediction for small heterogeneous datasets.

Implications

For Pharmacometric Science

AI is compelling pharmacometric science to re-examine assumptions about model structure, covariate discovery, parameter variability, and the relationship between prediction and explanation. Machine learning-assisted model selection and population PK/PD automation suggest that algorithmic tools can support parts of the modeling workflow while leaving scientific judgment and mechanistic interpretation intact [2, 24]. PBPK-ML integration also shows that mechanistic and data-driven reasoning can be complementary rather than competing paradigms [18, 21]. The implication is not a replacement of pharmacometrics but an expansion of its methodological toolkit.

For Drug Development and Precision Dosing

AI-augmented PK/PD models could accelerate drug development and precision dosing by improving early PK prediction, concentration forecasting, parameter estimation, and therapeutic monitoring. Computational pharmacokinetic prediction studies demonstrate potential value during drug design, especially when machine learning is used to estimate nonclinical or human PK properties before extensive clinical data are available [19, 20]. In clinical settings, concentration prediction and TDM applications suggest that AI may help individualize therapy when validated against real dosing outcomes and embedded in usable clinical workflows [11, 25, 26]. The practical implication is that prediction accuracy must be paired with transparent validation, clinical governance, and decision accountability.

For Education and Workforce

The next generation of pharmacometricians will need fluency in both mechanistic modeling and machine learning. Educational programs should include NLME modeling, PBPK principles, Bayesian inference, neural networks, uncertainty quantification, model evaluation, and implementation science as connected competencies rather than separate technical silos [1, 3]. Clinical pharmacologists and AI developers also need shared language for explaining model assumptions, uncertainty, decision thresholds, and clinical consequences. Qualitative synthesis indicates that workforce readiness will be a decisive enabler of responsible AI adoption in PK/PD modeling.

Conclusion

AI methods, particularly neural networks and Bayesian machine learning, have demonstrated compelling PK/PD predictive performance in data-rich settings. Their superiority over traditional population approaches narrows substantially in realistic, sparse clinical datasets where uncertainty, interpretability, and biological plausibility remain essential.

The most promising and pragmatically viable path forward is hybridization. Embedding machine learning within, or alongside, mechanistic PBPK and NLME frameworks is more credible than seeking wholesale replacement of established pharmacometric methods.

Clinical translation remains the critical bottleneck. Qualitative evidence reveals that model trust, interpretability, workflow integration, and prospective validation in therapeutic decision-making are far more important determinants of adoption than marginal gains in prediction error metrics.

The integration of neural, Bayesian, and mechanistic approaches, underpinned by rigorous prospective clinical evidence, will define the next era of pharmacometric modeling. The future of AI in PK/PD modeling will depend on whether the field can convert computational promise into transparent, validated, and clinically accountable decision support.

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