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Review Article

Therapeutic Drug Monitoring to Guide Precision Pharmacotherapy in Antipsychotic Treatment: A Systematic Review

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Abstract

Mental disorders have emerged as a significant global challenge in the field of public health, necessitating advanced therapeutic strategies. While antipsychotic agents remain the cornerstone of treatment strategy, conventional population-based drug treatment frequently fails to account for substantial inter-individual variability in pharmacokinetic (PK) and pharmacodynamic (PD) parameters. The emergence of precision medicine frameworks has catalyzed the development of therapeutic drug monitoring (TDM)-guided precision pharmacotherapeutic strategies, which are increasingly recognized as essential tools for optimizing treatment effects. This article synthesizes contemporary research advancements, with a focused analysis of the evolving role of TDM in personalizing antipsychotic regimens. Through critical evaluation of drug-effect relationships, this work elucidates evidence-based strategies to address current limitations in antipsychotic medication management, aiming to inform optimized clinical decision-making for heterogeneous patient populations.

Keywords: Therapeutic Drug Monitoring; Antipsychotics; Personalized Therapy.

INTRODUCTION

Antipsychotics constitute first-line treatment for managing severe psychiatric disorders, including schizophrenia spectrum disorders, bipolar affective illness, and treatment-resistant major depressive episodes [1]. While contemporary literature has yielded critical insights into their neuropharmacological mechanisms, persistent translational challenges remain in real-world clinical implementation. Of particular concern are critically ill patients manifesting profound cognitive impairment or suboptimal treatment adherence—populations systematically excluded from randomized controlled trials.,additional complexities include prolonged treatment durations and substantial interindividual heterogeneity in drug metabolism. Such multifactorial determinants perpetuate evidence gaps in psychopharmacology, underscoring the urgent need for personalized therapeutic strategies [2]. Therapeutic Drug Monitoring (TDM) utilizes high-precision bioanalytical methodologies to quantify the plasma concentrations of parent compounds and active metabolites, enabling rigorous characterization of exposure-response dynamics—a critical framework linking drug exposure thresholds to clinical endpoints including therapeutic efficacy and Adverse Drug Reactions (ADRs) [3]. TDM simultaneously optimizes therapeutic prognosis through exposure-guided dose titration while minimizing risks of concentration-dependent neurotoxicity and systemic ADRs, ultimately improving the prognosis of patients with psychiatric disorders. Thereby establishing a pharmacologically rational basis for individualized antipsychotic treatment. This review provides a critical appraisal of TDM's evolving applications in antipsychotic pharmacotherapy, focusing specifically on its integration with Pharmacometabolomic profiling and quantitative pharmacology models to enable precision dosing protocols. Furthermore, we evaluate emerging evidence on TDM-guided therapeutic algorithms in addressing psychiatric disorders, metabolic syndrome comorbidities, and polypharmacy challenges. The synthesized translational evidence seeks to establish an evidence-based framework for implementing TDM within hierarchical treatment guidelines, ultimately advancing the paradigm of mechanism-informed precision psychiatry.

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THE ROLE OF THERAPEUTIC DRUG MONITORING IN ANTIPSYCHOTIC PHARMACOTHERAPY

An Update on antipsychotic pharmacotherapy

The clinical management of psychiatric disorders includes psychopharmacological interventions, psychological interventions, physiotherapy, and management of metabolic syndrome, with antipsychotic pharmacotherapy constituting the therapeutic foundation [4]. First-generation antipsychotics (FGAs) exert their neuropharmacological effects via selective antagonism of central dopamine D2 receptors. While demonstrating robust efficacy in mitigating positive symptomatology, FGAs remain a poor response to clinical utility for negative syndrome and coexisting major depression [5]. Despite their substantial efficacy in alleviating clinical symptoms, the utility of FGAs remains substantially limited by a high incidence of ADRs, particularly Extrapyramidal Symptoms (EPS). Second-generation antipsychotics (SGAs) have now become the mainstay of antipsychotic treatment in clinical practice, superseding FGAs. SGAs exhibit dual mechanisms: potent antagonism of serotonin 5-HT_2A receptors and selective antagonism of dopamine receptors within mesolimbic and cortical regions [5]. SGAs exhibit superior therapeutic efficacy for both positive and negative symptoms with a reduced incidence of EPS [6]. Current international treatment guidelines designate SGAs as first-line pharmacotherapy in recommendations issued by psychiatric associations worldwide [4].

The clinical implementation of SGAs remains constrained. A meta-analysis by Leucht et al. [6], reveals that superior therapeutic efficacy for certain SGAs (e.g., amisulpride, clozapine, olanzapine, risperidone) requires plasma concentrations within therapeutic-range concentrations. Despite the lower risk of EPS, SGAs provoke significant ADRs including hyperprolactinemia and metabolic syndromes-notably obesity, lipid metabolism disorder, and hyperglycemia- requiring vigilant monitoring [6]. Such constraints and pharmacological limitations of antipsychotic therapies amplify clinical management difficulties, resulting in poor medication compliance, increased recurrence rate, and compromised long-term therapeutic efficacy in patients with psychotic disorders [7,8].

Current Analytical Methodologies in Therapeutic Drug Monitoring for Antipsychotics

TDM primarily relies on two principal analytical methodologies: immunoassays and chromatographic techniques. Enzyme-linked Immunosorbent Assay (ELISA) remains the most prevalent clinical implementation among immunoanalytical techniques, owing to its convenient operation, rapid analytical processing, high automation, and sensitivity [9]. The foundational methodology of ELISA developed immunoanalytical platforms, such as radioimmunoassay, chemiluminescent immunoassay, and fluorescent enzyme immunoassay [10,11]. Intrinsic technical constraints of immunoassays restrict clinical methodological utility: (1) a narrow linear range(approximately ~ 10^2); (2) extended method development cycles; (3) analytical interference from cross-reactivity; (4); nonspecific binding-induced analytical errors(false-positive/false-negative results) [12,13]. Analysis of antipsychotics generally involves the simultaneous quantification of the parent drug and its metabolite compounds. Given the inherent complexity of the biological matrix, the low concentrations of target analytes, and the high binding affinity of the parent drug, TDM of antipsychotics increasingly relies on highly sensitive analytical methodologies, particularly for low-concentration specimens. Moreover, automation, high throughput, durability, and cost-effectiveness are key considerations for selecting an appropriate analytical platform [11]. Advancements in analytical instrumentation have facilitated the extension of chromatographic techniques to become increasingly viable for macromolecular pharmaceutical analysis [14,15]. The analytical methods for antipsychotic determination increasingly rely on liquid chromatography combined with high-sensitivity detection. Owing to the intrinsic ultraviolet-absorbing properties present in most antipsychotics and their metabolites, high-performance chromatography with ultraviolet detection methods has been extensively developed and implemented as an advanced technique [16]. Furthermore, chromatographic analytical techniques encompass liquid chromatography-tandem mass spectrometry (LC-MS/MS), ultra-performance liquid chromatography, liquid-mass spectrometry technology, high-performance chromatography with electrochemical detection techniques and gas chromatography-mass spectrometry [14,15]. LC-MS/MS synergistically integrates high-efficiency chromatographic separation with high-resolution mass spectrometry detection, making it particularly suitable for complex mixture characterization, achieving dual analytical functions: (1)chromatographic peak identification with target compound quantification (minimizing co-elution effects on peak areas and eliminating nonspecific interference), and (2) multi-stage fragmentation of analytes to generate diagnostic fragment ions for structural characterization [17]. LC-MS/MS reveal significant advantages over immunoassays: a broader linear dynamic range (3-5 orders of magnitude), lower detection limits (pg/mL to μg/mL), accelerated method development, and matrix interference elimination through multi-reaction monitoring [12-18]. LC-MS/MS represents the definitive gold-standard methodology for TDM applications, providing robust quantification with minimal matrix interference [19]. The utility of chromatographic techniques in TDM continues to expand beyond plasma specimens to encompass alternative biological matrices—including dried blood spots, saliva, hair, and amniotic fluid [19] —as an indispensable analytical platform in contemporary TDM implementation. Persistent constraints hinder clinical impediments of these techniques: operational complexity, elevated consumable expenses of single detection, lengthy analytical processing, and expensive instrumentation/reagent burdens. Consequently, these factors collectively restrict large-scale clinical implementation of TDM analytical methodologies [20].

The Case for Implementing Therapeutic Drug Monitoring in Psychiatry

Inappropriate psychopharmacological prescribing remains substantially prevalent worldwide. Antipsychotics related-ADRs incidence among inpatients persists at concerning levels, with approximately 200,000 inpatient cases reported annually [21]. Conventional pharmacotherapy for psychiatric disorders adheres to population-based dosing regimens and experiential clinical therapeutic strategies [4]. While clinicians select medications based on clinical diagnostics, auxiliary examinations, and psychiatrist's judgment, this approach fails to account for patient-specific Pharmacokinetic (PK)/Pharmacodynamic (PD) heterogeneity governing antipsychotic drug disposition.

Clinically significant characteristics of SGAs include: substantial Pharmacokinetic (PK) heterogeneity, narrow therapeutic windows, a high incidence of ADRs, elevated treatment discontinuation rates due to poor adherence, and significant risk of Drug-Drug Interactions (DDIs) [22]. These constraints prevent conventional administration strategies from maximizing efficacy while minimizing toxicity, lacking quantitative biomarkers to guide precision pharmacotherapy. By accounting for patient-specific PK/PD heterogeneity, TDM dynamically adjusts dosing and determines target therapeutic-range concentrations. TDM formulates individualized dosing protocols (encompassing drug dosage, route of administration, and treatment time) to optimize the clinical efficacy of antipsychotics [23,24]. Consequently, implementing TDM in antipsychotics represents a clinically indispensable strategy in contemporary psychiatric practice.

APPLICATION OF THERAPEUTIC DRUG MONITORING TO GUIDE PERSONALIZED ANTIPSYCHOTIC PHARMACOTHERAPY

Significant interindividual PK heterogeneity is clinically revealed in psychiatric populations under standardized dosing, where population pharmacokinetic (PPK) studies demonstrate up to 45-fold fluctuations in plasma drug concentrations [25]. TDM constitutes an essential precision pharmacotherapy administration in psychiatry. The TDM consensus guidelines issued by the Arbeitsgemeinschaft fürNeuropsychopharmakologie und Pharmakopsychiatrie (AGNP) explicitly recommend TDM for populations with distinctive PK profiles, including but not limited to growth children, perinatal women, and elderly patients [26]. Quantitative assessment of antipsychotic drug exposure through TDM facilitates evidence-based dose management, assessment of DDI risk in polypharmacy, prevention of exposure-dependent ADRs, and ultimately optimizing individualized treatment of patients with psychiatric disorders.

Optimizing Clinical Outcomes in Antipsychotic Therapy: The Role of Therapeutic Drug Monitoring

TDM enhances precision medicine by adjusting patient-specific dosage, targeting therapeutic concentration ranges, monitoring medication adherence, and reducing healthcare expenditures [26]. Standard TDM practice utilizes steady-state trough concentrations as reference standards, where the plasma concentration-time curve flattens during the terminal β-elimination phase. The concentration decay rate (dC/dt) diminishes significantly at this stage, minimizing optimal sampling time deviations [27]. SGAs characterized by dual antagonism of dopamine D2 receptor and 5-HT2A receptor constitute first-line pharmacotherapy for diverse psychiatric disorders, including treatment-resistant schizophrenia (TRS). Liu et al. [8], analyzed TDM data from TRS patients(n=61), revealing a significant correlation between clozapine concentrations within the 300-700 ng/mL window and improvements in Positive and Negative Syndrome Scale scores (χ^2=7.89, P<0.01). Drug efficacy depended on concentrations within the lower limit of the therapeutic range, while concentrations exceeding the upper limit of the therapeutic range were associated with elevated toxicity risk without improving efficacy [26]. Analysis of TDM data from 64 aripiprazole-treated patients revealed a significant association between plasma concentrations and clinical efficacy. The mean plasma concentration was significantly higher in the clinically improved group (494 ± 273 ng/mL) than in the non-improved group (286 ± 219 ng/mL). Furthermore, a significant elevation in Clinical Global Impression-Severity scale scores was observed specifically within the patient cohort achieving plasma concentrations exceeding 300 ng/mL [28]. This underscores the necessity for rigorous TDM of risperidone during clinical treatment. Kirschbaum et al. [29], reported, based on a clinical study in patients with aripiprazole (20 ± 8 mg/day), that maintaining steady-state plasma concentrations of 150–300 ng/mL resulted in a 37.2% higher improvement rate of positive symptoms. Targeting concentrations of 110–249 ng/mL reduced the incidence of EPS to less than 12% (P<0.05). Additionally, a significant increase in the improvement rate of Positive and Negative Syndrome Scale score was linked to steady-state trough concentrations exceeding 350 ng/mL [30]. This finding is corroborated by a prospective cohort study conducted by Li et al. [31], whose analysis of the receiver operating characteristic curve determined that the therapeutic window for effective aripiprazole plasma concentrations in patients with schizophrenia is 350–540 ng/mL, associated with a clinical response rate of 61.9%. Despite moderately broad therapeutic windows, SGAs exhibit substantial interindividual PK heterogeneity. Clozapine demonstrates plasma concentration fluctuations of up to 52% [32], while plasma concentrations vary 10-fold for risperidone [25]. Pharmacogenetic polymorphisms determine metabolism phenotypes. Genetic polymorphisms modulate key PK parameters—including bioavailability and elimination rate—ultimately altering the plasma concentration of antipsychotics and the incidence of ADRs [33]. Phase I reaction of the metabolic pathways for psychotropics primarily involves cytochrome P450 (CYP450) enzymes, notably CYP2D6 and CYP2C19 metabolizing approximately 25% of these agents [34]. Serving as critical membrane-spanning efflux systems, the ABC transporters superfamily provides defense against exogenous compounds. Specifically, P-glycoprotein (P-gp)-encoded by the ABCB1 gene-is highly expressed at the blood-brain barrier and intestinal epithelium. As a key efflux transporter, P-gp mediates the transportation of psychotherapeutic agents at biological targets, critically modulating their pharmacological distribution through barrier-specific efflux mechanisms [35]. Non-synonymous polymorphisms within the ABCB1 gene alter P-gp trafficking and substrate affinity, driving PD alterations in antipsychotics through single nucleotide polymorphism (SNP)-dependent efflux pathway regulation. The AGNP has issued guidelines that classify TDM applications into four levels of recommendation: "strongly recommended," "recommended," "useful," and "possibly useful." TDM is routinely implemented for medications, with a definitive therapeutic reference range and a narrow therapeutic index, such as clozapine, olanzapine, and risperidone [26]. AGNP recommends targeted TDM for antipsychotics categorized as "useful" or "possibly useful" in defined clinical circumstances. Based on evidence-based medicine, AGNP Consensus Guidelines recommend therapeutic reference ranges of 20-60 ng/mL for risperidone and 150-500 ng/mL for aripiprazole [26]. Notably, therapeutic windows of consensus show ethnic-regional divergence, potentially reflecting CYP2D6*10 allele prevalence in Asian populations causing altered metabolic phenotypes [26]. Administration of standard drug doses poses distinct risks based on CYP2D6 metabolizer status: Poor metabolizers (PMs) exhibit elevated plasma drug concentrations at standard doses, increasing their susceptibility to toxicity. Conversely, ultrarapid metabolizers (UMs) are prone to treatment failure due to subtherapeutic concentrations. The Dutch Pharmacogenetics Working Group recommends reducing the risperidone dose to 67% of the standard dose for PMs [36]. The recommended dosage should not exceed 10 mg/D or 300 mg/M for aripiprazole in PMs, equating to 67-75% of the maximum standard dosage. Should dose-related ADRs persist in PMs following the initial dosage reduction of aripiprazole, a further decrease to 50% of the standard dosage is warranted. For UMs, selecting alternative antipsychotics not primarily metabolized by CYP2D6—such as amisulpride, quetiapine, olanzapine, or clozapine—is recommended.

Therapeutic Drug Monitoring for the Prevention and Management of Adverse Effects in Antipsychotic Pharmacotherapy

FGAs are high-affinity antagonists of dopamine D2 receptors and elicit dose-dependent neurotoxic reactions. Clinical data indicate that the incidence of EPS in patients treated with FGAs ranges from 15–30%, with an annual accumulated incidence of tardive dyskinesia approximating 5% [37]. In contrast, SGAs partially antagonize dopamine D2 receptors, reducing the incidence of EPS to 5–15%. SGAs also possess a high affinity for α-adrenergic, muscarinic, and histamine receptors, potentially inducing orthostatic hypotension, central sedation, reflex bradycardia, anticholinergic syndrome, and metabolic syndrome [38]. SGAs-related ARDs correlate positively with plasma concentrations. TDM provides a quantitative basis for ensuring neuroreceptor occupancy at the therapeutic thresholds and for defining ADR-related concentration thresholds. This approach offers critical guidance for implementing individualized pharmacotherapy in clinical practice. The study has shown that plasma concentrations of olanzapine exceeding 40 ng/mL are associated with a 2.3-fold increase in the risk of metabolic syndrome (95% CI 1.7–3.1) compared to concentrations within the therapeutic window (20–40 ng/mL) [39]. Similarly, the incidence of orthostatic hypotension rises from 14.2% to 38.6%, with the plasma concentrations of quetiapine exceeding 500 ng/ml [40]. The dosage of clozapine above 600 mg/day elevates seizure risk by 3.8-fold (P<0.001), and plasma concentrations exceeding 1000 ng/mL are associated with neurotoxicity occurring in 24.7% of cases, suggesting such concentrations inadvisable [41]. Amisulpride demonstrates a linear correlation between D2 receptor occupancy and plasma concentration (r=0.82) [42]. Maintaining plasma concentrations of amisulpride within the 320–600 ng/mL range was associated with a low EPS incidence of 8.2% in schizophrenia patients. In contrast, plasma concentrations exceeding 600 ng/mL elevated the risk of QTc prolongation to 18.5% (RR = 2.4) [43]. Emerging

evidence reveals genetic susceptibility mechanisms underlying ADRs in neuropsychopharmacology. Key regulators of HTR2C, MC4R, NPY, and CNR1 contribute to antipsychotic-induced metabolic syndrome [44]. Alteration in dopamine receptor signaling pathways via RGS2 [45] and HTR2A [46] polymorphisms contribute to drug-induced dystonia or tardive dyskinesia, while HTR1A polymorphisms robustly modulate therapeutic response to negative symptoms in schizophrenia [47].

TDM-Based Prevention Strategies for Antipsychotic-Induced Adverse Events

Combination therapy with antidepressants, anxiolytics, antiepileptics, and antimanic drugs, is common in psychiatric treatment for managing severe complications. Multiple clinical studies have recently systematically characterized the PK profiles of SGAs and their potential for DDIs [48-51]. The metabolism of most SGAs is principally catalyzed by drug-induced hepatic drug enzymes, particularly the CYP450 enzyme system. Combined medication can inhibit or induce cytochrome isoenzymes, reducing the clearance of SGAs, and leading to elevated plasma concentration and an increased incidence of drug-related ADRs, resulting in drug-relevant DDIs [48]. Accordingly, when formulating treatment regimens, particularly for elderly patients receiving multiple medications the AGNP consensus guidelines for TDM recommend selecting SGAs with a low risk of DDIs and implementing personalized dosing adjustments [26]. A prospective study by Zhang et al. [49] revealed that the steady-state plasma concentrations of risperidone sustained an increase of 38.6% for four weeks co-administration of fluoxetine, while plasma concentrations of 9-hydroxyrisperidone were markedly decreased. Fluoxetine alters the metabolism of risperidone by potentially inhibiting CYP2D6. This study recommends co-administration of risperidone with fluoxetine to reduce the dosage of risperidone, thereby preventing the occurrence of EPS. Fluvoxamine exhibits a strong inhibitor of CYP1A2 and CYP2C19, with moderate inhibition of CYP3A4. Co-administration of fluvoxamine with olanzapine, as reported by Wang et al. [50], significantly increased the peak plasma concentration of olanzapine from 19.5 μg/L to 29.1 μg/L ($P<0.01$) and prolonged its elimination half-life from 32.2 hours to 46.1 hours ($P<0.05$), inducing or exacerbating symptoms of EPS. A retrospective analysis of 255 patients demonstrated that compared with the single-agent group, fluoxetine, fluvoxamine, and paroxetine co-administered with clozapine increased plasma concentrations of clozapine by 42%, 263%, and 30%, respectively ($P<0.05$), whereas sodium phenobarbital combined with clozapine reduced concentrations by 28% ($P<0.01$) [51]. Existing literature on DDIs of antipsychotics requires further validation, and the potential mechanisms of DDIs are not fully characterized. Advancing this field necessitates multicenter cohort studies to establish the clinical value of TDM in DDI management, develop a systematic early-warning system for SGA-related DDIs, and optimize the therapeutic effects of SGAs.

PROGRESS IN PRECISION DOSING STRATEGIES FOR ANTIPSYCHOTIC THERAPY

Advances in precision medicine have catalyzed diverse individualized therapeutic technologies, providing clinical assessment tools for antipsychotic treatment strategies. These methodologies transcend the limitations of population PK through the integration of individual and metabolic information, enabling accurate prediction of target drug effects. Given the complementary functions of diverse individualized therapeutic technologies in antipsychotic pharmacotherapy, this chapter reviews progress in pharmacometabolomics and quantitative pharmacology for personalized antipsychotic dosing strategies. This synthesis offers a multidimensional perspective on emerging research directions and facilitates novel insights into the integrated application of individualized therapeutic techniques, including TDM.

Pharmacometabolomic Analysis

Following antipsychotic administration, parent drugs are primarily biotransformed into pharmacologically active or inactive metabolites by CYP450 isozymes and intestinal microflora.

Parent drugs and their metabolic compounds initiate endogenous cascade reactions of metabolic pathways via transport systems, resulting in dynamic fluctuations of metabolites within biofluids (blood, cerebrospinal fluid, etc). Clayton et al. conceptualized pharmacometabolomics in 2006 [52]. Operating through metabolomic analytical platforms, pharmacometabolomics compares longitudinally metabolic fingerprints before and after drug treatment, identifying novel biomarkers that predict drug response, and recognizing molecular mechanisms underlying interindividual therapeutic heterogeneity in psychiatric disorders. Psychotropic medication induces dynamic changes in metabolic phenotypes in patients with psychiatric diseases. The imaging data of magnetic resonance spectroscopy reveals partial normalization of the prefrontal cortex N-acetyl aspartate/creatine (NAA/Cr) ratio following 6 months of atypical antipsychotic treatment, correlating significantly with cognitive improvement ($P<0.01$). Yamamori et al. [53] demonstrated significantly elevated plasma D-serine concentrations and D-/L-serine ratios in schizophrenia patients receiving clozapine treatment compared to pre-treatment baselines, with no significant changes observed in the control group. These findings suggest metabolite fluctuations serve dual purposes: as predictive biomarkers of therapeutic efficacy and potentially involved in molecular pathways underlying clinical improvement. The drug metabolism of antipsychotics contributes to molecular mechanisms underlying drug-related ADRs. Compared to pretreatment baselines, olanzapine-treated cohorts exhibit tricarboxylic acid cycle disorder, triggering suppression of AMP-activated protein kinase (AMPK) signaling. This AMPK down-regulation drives olanzapine-induced adverse effects, including weight gain and insulin resistance [54]. A distinct technical advantage of pharmacometabonomics is its capacity to elucidate the synergistic effects of gene expression regulatory networks and environmental exposure factors on disease at the metabolic level. Critically, integrating metabolomic fingerprints with genomic and proteomic data reveals novel insights into pharmacotherapy mechanisms in psychiatric disorders. The synergistic combination of pharmacometabolomic technology with TDM, constructing multidimensional clinical medication decision-making, represents a frontier research and development direction in personalized therapeutics for antipsychotic drugs [27].

Quantitative Pharmacology Analysis

Building upon traditional PK, quantitative pharmacology is an emerging interdisciplinary discipline by integrating fundamental mathematical theories and artificial intelligence computational techniques. Leveraging mathematical modeling and computer simulation technology, quantitative pharmacology integrates comprehensive parametric modeling of PK, PD, physiological functions, and disease progression. This methodology enables the construction of multi-level dynamic PK-PD models that are designed to optimize personalized medication strategies and support clinical decision-making. Leveraging the principles of nonlinear mixed-effects modeling to integrate genetic and non-genetic covariates, PPK modeling stands as the most developed and extensively utilized methodology in contemporary quantitative

pharmacology [55]. Empirical studies have validated PPK models for numerous antipsychotic drugs, consistently identifying age, sex, ethnicity, and dosage regimen as critical covariates significantly influencing both therapeutic efficacy and the incidence of adverse effects [55-57]. Driven by the widespread advancement of computer-based artificial intelligence technology, machine learning (ML) algorithms-based models now enable the development of antipsychotic drug concentration prediction models. These models analyze nonlinear relationships within drug-time curves, while ensemble learning strategies enhance their performance of extrapolation prediction. ML models demonstrate substantially superior predictive performance compared to PPK models. Masychev et al. [58], extracted characteristic electroencephalogram spectral features from patients with TRS. They constructed an ML algorithms-based model to predict therapeutic response to clozapine therapy, achieving an overall prediction accuracy of 89.90%. Based on brain morphometric measurement parameters of MRI scans from baseline and first-week quetiapine treatment, Lei et al. [59], constructed a multilayer feedforward neural network and support vector machine for predictive modeling. The resulting models demonstrated a mean predictive accuracy of 83.2%, with an AUC of 0.93 ($P < 0.001$). Except for developing medication-specific predictive modeling, researchers have also engineered ML models for forecasting overall therapeutic outcomes across the antipsychotic drug spectrum. Genome-wide association analysis (GWAS) conducted in a multi-center clinical cohort of schizophrenia patients revealed significant associations between five SNP locus (MEGF10, SLC1A1, PCDH7, CNTNAP5, and TNIK) and antipsychotic treatment efficacy [60]. A pharmacogenetic efficacy prediction model developed by Sainz et al. [61], based on SNP locus (SLC9A3, HMOX1, SLC22A16, LOC284581), demonstrated robust performance with an AUC of 0.833 through 10-fold cross-validation. Based on the XGBoost algorithm, Wang et al. [62], developed a predictive model for antipsychotic treatment response by combining polygenic risk scores with the image data of magnetic resonance imaging (MRI). The model manifested robust performance with an overall predictive accuracy of 86% (sensitivity: 85%, specificity: 86%), validated by leave-one-out cross-validation. Quantitative pharmacology integrates PK/PD parameters with genetic/non-genetic factors to construct predictive models for guiding clinical precision medicine and establishing personalized dosing regimens. This approach combined with TDM offers the distinct clinical advantage of predicting drug efficacy during the initial treatment stages, thereby serving as a vital technological foundation for optimizing pharmacotherapy [63].

DISCUSSION AND CONCLUSION

TDM has become a pivotal research domain in clinical pharmacology, integrating multidimensional knowledge systems including pharmaceutical analysis, drug metabolism, PD, and toxicology. Current research on TDM of antipsychotics remains insufficient in scope and methodological rigor. Firstly, there is no clear consensus on the standardized analytical methodologies for TDM of psychotropic drugs. This lack of consensus has compromised cross-study comparability, as demonstrated by a systematic deviation of 5-15% between high-performance liquid chromatography and immunoassay in psychotropic agent quantification [64]. Secondly, in vivo TDM is affected by physio-pathological factors, pharmaceutical interactions, genetic polymorphisms, and patient compliance [26]. These inherent limitations underscore the insufficiency of TDM-guided therapeutic regimen optimization, necessitating multimodal integration with clinical PK principles and pharmacogenomic profiling. PD focuses on the interactions between drugs—after reaching their target positions—and biological targets such as receptors, metabolizing enzymes, and transport systems (e.g. carrier proteins, structural proteins, and ion channels), ultimately exerting diverse pharmacological effects. Variability in PD among individuals receiving antipsychotics is predominantly driven by variations in drug-target engagement [27]. Such PD heterogeneity substantially modulates drug exposure levels, where genetic polymorphisms serve as critical determinants of PD variability. Recent advancements have positioned pharmacogenomics (PGx)-guided personalized therapy as transformative research in precision medicine. Multiple genomic loci implicated in the clinical treatment efficacy of antipsychotics—specifically CNTNAP5, GRID2, GRM7, KCNK9, PCDH7, SLC1A1, and TNIK—were screened through GWAS and subsequently replicated in independent cohorts [65]. In a GWAS of the Han Chinese schizophrenia cohort, Professor Yue's group independently confirmed significant associations between five SNP locus (MEGF10, SLC1A1, PCDH7, CNTNAP5, TNIK) and antipsychotic treatment efficacy [60]. Research on targeting candidate genes revealed that multiple SNPs in neurotransmitter receptor genes—including DRD2, HTR1A, and HTR2A—participate in regulating the PD processes of antipsychotics [46]. Utilizing genotyping and metabolism polymorphism technologies, metabolic phenotypes for SGAs can be stratified into ultrarapid metabolism, extensive metabolism, intermediate metabolism, and poor metabolism, primarily determined by polymorphisms in CYP450 isoforms (CYP2D6/CYP3A4). Compared with the post-treatment monitoring framework of conventional TDM, pharmacogenomic profiling enables a priori prediction of drug disposition characteristics prior to therapeutic initiation, making pharmacogenomics guidance for individualized dose optimization more prospective. Commercial PGx testing services are currently available for over 40 psychotropic medications, guiding personalized dosing strategies through analysis of polymorphisms in key pharmacogenes such as CYP2D6, CYP2C19, and HTR2A [66]. Patients with major depressive disorder managed through PGx testing exhibited significantly reduced drug interaction rates relative to conventionally treated patients in the investigation by Oslin et al., [67]. Clinical implementation of GeneSight® PGx testing doubled the symptom remission rates in treatment-refractory d pression cohorts compared to standard care, as reported by Winner and colleagues [68]. However, clinical validation studies reveal 18.3% discordance rates between predicted metabolic phenotypes and drug plasma exposure metrics [69]. TDM serves as an essential validation tool, thereby exploring genotype-phenotype discordances through concentration-time curve analysis, aiming to establish a translational bridge between SGA-metabolizing enzyme polymorphisms and critical PK parameters. Diverse precision medicine technologies play complementary yet distinct roles in psychotropic medication management. Personalized treatment optimization requires integrated methodologies beyond any single approach. The methodology establishes a PGx-based genetic susceptibility assessment system, integrating real-time TDM metrics with PD/PK parameters, ultimately constructing a longitudinal predictive model for antipsychotic treatment outcomes, enabling dynamic optimization of treatment regimens within an evidence-based medicine framework. Precision medicine of psychotropic medication facilitates continuous dose optimization through real-time biofeedback, enhancing treatment outcomes while reducing economic burdens in mental healthcare. Nevertheless, implementation challenges hinder the translation pathway from laboratory to bedside [27]. Future clinical medication is poised to implement precision dosing algorithms through integrated PK-PD modeling, merging genomic data, proteomic data, and TDM parameters. The development of a multidimensional therapeutic framework iteratively combines genotype-derived metabolic predictions with TDM-validated exposure parameters, thereby enabling adaptive

optimization of individualized antipsychotic treatment regimens through ML algorithms-based models. Scaling multidimensional cohort consortia through prospective multicenter is designed to validate novel PD biomarkers and to establish computationally optimized dosing regimens for neuropsychiatric therapeutics. There are critical steps toward resolving precision medicine challenges in psychiatric therapeutics.

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