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Enhancing Psychiatric Drug Safety: Lessons from Pharmacogenomic Studies of Hypersensitivity Reactions

Paolo Rinaldi[1], Marco De Luca[1], Federico Neri[1]*

[1]Department of Pharmacognosy, Faculty of Pharmacy, University of Pisa, Pisa, Italy.

***E-mail** ✉ federico.neri.pg@outlook.com

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ABSTRACT

Drug hypersensitivity reactions (DHRs) remain a significant hurdle in psychiatric treatment, frequently causing therapy discontinuation, reduced adherence, and suboptimal clinical outcomes. Pharmacogenomics offers a powerful approach to unravel the genetic underpinnings that influence drug metabolism, immune system activation, and individual vulnerability to adverse reactions. This review provides a comprehensive overview of the diverse mechanisms behind DHRs, focusing on immune-mediated pathways—particularly T cell-driven responses—reactive drug metabolite formation, and key genetic determinants. Variations in human leukocyte antigen (HLA) alleles and cytochrome P450 (CYP450) enzymes emerge as central factors in hypersensitivity risk. We examine pharmacogenomic links across commonly used psychiatric medications, including anticonvulsants like carbamazepine and lamotrigine, SSRIs, and newer therapeutics such as vortioxetine, psilocybin, and esketamine. Antipsychotic agents, including clozapine and newer drugs like aripiprazole, brexpiprazole, and cariprazine, are also discussed with regard to gene-drug interactions, highlighting risk alleles such as HLA-B15:02, HLA-A31:01, and CYP2D6 and CYP1A2 polymorphisms. The evidence underscores the potential of pharmacogenomic testing to anticipate and prevent severe reactions, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, agranulocytosis, and liver toxicity. The review also addresses clinical translation, exploring preemptive genetic screening, international guidelines (e.g., CPIC and DPWG), and practical challenges such as test accessibility, ethical considerations, and the absence of standardized protocols globally. Emerging technologies, including next-generation sequencing and integrative multiomic approaches, offer opportunities to refine prediction models and tailor psychiatric therapies more precisely. Finally, population-specific studies and international collaboration are crucial to bridging knowledge gaps, particularly in regions like the Middle East. Altogether, pharmacogenomics holds transformative promise for enhancing psychiatric drug safety and advancing personalized patient care.

Keywords: Personalized medicine, Psychiatric medications, Pharmacogenomics, Drug hypersensitivity, CYP450, HLA

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Introduction

Adverse immune reactions to psychiatric medications, known as drug hypersensitivity reactions (DHRs), remain a critical concern in mental health treatment, often causing treatment cessation, extended hospitalization, and in severe instances, life-threatening conditions such as Stevens-Johnson syndrome (SJS) or drug reaction with eosinophilia and systemic symptoms (DRESS) [1-3]. These reactions can occur with a broad spectrum of psychotropic agents, including anticonvulsants, antidepressants, and antipsychotics [4]. Their unpredictable nature, including occurrence after prior uneventful drug exposures and absence of dose dependence, presents a substantial clinical challenge [5]. As pharmacotherapy becomes increasingly central in psychiatric care, clarifying the biological and genetic factors behind DHRs is essential for safer, more effective treatment.

Pharmacogenomics has emerged as a key approach for uncovering genetic susceptibilities that influence drug metabolism and immune responses. Variants in human leukocyte antigen (HLA) genes and drug-metabolizing enzymes such as CYP2C19 and CYP2D6 have been strongly linked to hypersensitivity risk [1]. Notably, HLA-B15:02 and HLA-A31:01 are recognized predictors of severe cutaneous reactions to carbamazepine [6]. Integrating pharmacogenomic information into clinical decision-making allows clinicians to identify high-risk

patients before treatment, facilitating individualized drug choice and dose adjustments to reduce adverse outcomes.

This review aims to consolidate current knowledge on the pharmacogenomic basis of psychiatric DHRs, highlighting genetic risk factors, immune-mediated mechanisms, and clinical translation. We focus on both HLA and non-HLA genetic associations across major psychotropic drug classes, explore the role of genetic testing in preventing hypersensitivity, and discuss implementation challenges. Additionally, we consider future opportunities, including next-generation sequencing technologies and international collaborations, to advance precision psychiatry. By bridging mechanistic insights with clinical application, pharmacogenomics promises to enhance medication safety and therapeutic effectiveness in mental health care.

Mechanisms of drug hypersensitivity reactions

Immune-mediated pathways

Hypersensitivity to psychiatric medications represents a complex spectrum of immune-driven adverse events, often resulting in significant morbidity. Based on the Gell and Coombs classification, these reactions are divided into four principal types [7].

- Type I (Immediate, IgE-mediated): Triggered by allergen-specific IgE antibodies binding to mast cells and basophils, this pathway results in degranulation and release of mediators including histamine, prostaglandins, leukotrienes, and Th2 cytokines (IL-4, IL-5, IL-13). The downstream effects include vasodilation, bronchial constriction, and eosinophil recruitment [8].
- Type II (Antibody-dependent cytotoxicity): Occurs when IgG or IgM antibodies target drug-altered host cells, activating complement and initiating antibody-dependent cellular cytotoxicity (ADCC), leading to cell lysis and tissue injury [9]. circulating antigen-antibody complexes in tissues, which trigger complement activation and recruit neutrophils, causing local inflammation via pro-inflammatory cytokines like TNF-α and IL-1β [10].
- Type IV (Delayed-type, T cell-mediated): This mechanism underlies most psychiatric DHRs. Drug-modified peptides presented on MHC class I or II molecules activate CD8+ cytotoxic or CD4+ helper T cells, respectively. Activated T cells release pro-inflammatory cytokines (IFN-γ, TNF-α, IL-2, IL-17), driving immune cell recruitment and clonal expansion. Clinical presentations include morbilliform rashes, DRESS, and severe cutaneous adverse reactions (SCARs) such as SJS [11, 12].

Re-exposure in sensitized patients can trigger rapid Type I reactions, as preformed drug-specific antibodies activate mast cells, potentially causing urticaria, angioedema, or anaphylaxis. **Table 1** summarizes common cutaneous manifestations associated with psychiatric drug hypersensitivity.

Table 1. An outline of the principal cutaneous adverse drug reactions resulting from hypersensitivity to psychiatric medications

Condition	Definition	Drug-to-skin reaction interval	General symptoms	Skin features	BSA involved	Systemic involvement	Severity	Mortality rate	References
Stevens-Johnson Syndrome (SJS)	Rare, life-threatening immune-mediated reaction with erythematous eruptions and extensive detachment of epidermis and mucous membranes	7–21 days	Fever ≥38 °C, influenza-like symptoms	Initially morbilliform or urticarial rash progressing to dusky/red-violaceous atypical targetoid lesions, flaccid blisters, and full-thickness epidermal necrosis; painful lesions	<10%	Mucous membranes (oral, ocular, genital, pharyngeal, esophageal, GI, upper respiratory tract); possible liver, kidney, lung, bone marrow, or joint involvement	Severe (SCAR)	1–5%	Roujeau, 2005[13]; Del Pozzo-Magaña & Liy-Wong, 2024[14]; Graudins *et al.*, 2018[15]; Mockenhaupt, 2017[16]; Harr & French, 2010[17]

Maculopapular (Morbilliform) Rash	Acute Generalized Exanthematous Pustulosis (AGEP)	DRESS Syndrome	Toxic Epidermal Necrolysis (TEN)
Common benign exanthem resembling measles, consisting of widespread macules and papules	Acute cutaneous reaction featuring numerous small, sterile, non-follicular pustules on erythematous background	Rare, potentially fatal delayed hypersensitivity reaction with widespread rash and internal organ involvement	Severe immune-mediated reaction causing widespread blistering and detachment of skin and mucous membranes (more extensive than SJS)
7–14 days (may be earlier if previously sensitized)	24 hours to 4 days	2–6 weeks	7–21 days
Low-grade fever, malaise	Fever ≥38 °C	Fever ≥38 °C	Fever ≥38 °C, influenza-like symptoms
Pink to red-brown macules and papules starting in axillae/groin, spreading symmetrically; often spares face and mucous membranes; may be pruritic	Rapid onset of tiny non-follicular sterile pustules on erythematous/edematous skin; pruritus or burning sensation; subsequent desquamation	Pink to red-brown macules and papules, often beginning in axillae/groin and spreading symmetrically; facial edema, follicular accentuation common; usually spares mucous membranes; may be pruritic	Initially morbilliform/urticarial rash progressing to dusky/red-violaceous targetoid lesions, flaccid blisters, and full-thickness skin sloughing; painful lesions
Usually <30%	Variable (often >10%, up to >30% in severe cases)	Usually >50%	≥30%
Rare (occasional lymphadenopathy); can be prodrome of more severe SCAR	Rare: hepatomegaly, lymphadenopathy, renal/hepatic injury, hypocalcemia, pleural effusion, respiratory distress, agranulocytosis	Lymphadenopathy, hepatitis, nephritis, pneumonitis, myocarditis, arthritis/arthralgia, eosinophilia, atypical lymphocytes	Mucous membranes (oral, ocular, genital, pharyngeal, esophageal, GI, upper respiratory tract); possible liver, kidney, lung, bone marrow, or joint involvement in severe cases
Usually mild (can progress to SCAR)	Severe (SCAR)	Severe (SCAR)	Severe (SCAR)
Very low	<5%	~10%	25–35%
Chowdhury *et al*., 2025[18]; Del Pozzo-Magaña & Liy-Wong, 2024[14]; Muzumdar *et al*., 2019[20]	Moore *et al*., 2023[19]; Del Pozzo-Magaña & Liy-Wong, 2024[14]; Mockenhaupt, 2017[16]	Del Pozzo-Magaña & Liy-Wong, 2024[14]; Mockenhaupt, 2017[16]; Chowdhury *et al*., 2025[18]	Del Pozzo-Magaña & Liy-Wong, 2024[14]; Roujeau, 2005[13]; Mockenhaupt, 2017[16]; Harr & French, 2010[17]

Urticarial Toxidermia (Drug-induced Urticaria)	Common histamine-mediated reaction producing transient wheals (“ hives”)	Hours to days (usually 1–48 h; delayed possible)	Possible angioedema, risk of anaphylaxis	Intensely pruritic, migratory wheals of variable size; may include burning sensation	Variable (10% to >30% in severe cases)	Rare unless associated with anaphylaxis	Mild to severe	Very low	Verheyden *et al.*, 2020[21]
Fixed Pigmented Erythema (Fixed Drug Eruption)	Recurrent localized hyperpigmented macule(s) that reappear at the same site upon re-exposure to the culprit drug	24 hours to several days	Usually none	One or several round/oval, sharply demarcated red-to-brown macules/plaques; may blister in active phase; residual hyperpigmentation	Variable (typically localized)	Very rare	Mild	Negligible	Del Pozzo-Magaña & Liy-Wong, 2024[14]; Mockenhaupt, 2017[16]

Abbreviations: SCAR = severe cutaneous adverse reaction; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; DRESS = drug reaction with eosinophilia and systemic symptoms; AGEP = acute generalized exanthematous pustulosis; BSA = body surface area.

Molecular mechanisms underlying drug hypersensitivity

Hypersensitivity reactions triggered by psychiatric medications involve intricate immune processes, and multiple models have been proposed to explain how small chemical compounds can activate the immune system.

Hapten/Pro-hapten mechanism

In this classical explanation, drugs or their reactive metabolites are typically too small to stimulate immunity on their own. When they covalently attach to endogenous proteins, they form novel conjugates that the immune system recognizes as foreign. These modified proteins are processed by antigen-presenting cells (APCs) and displayed on MHC class I or II molecules to naïve T cells, which may initiate an adaptive immune response upon recognition of these neo-antigens [22].

Pharmacological interaction with immune receptors (p-i) mechanism

This model posits that some drugs can interact directly and reversibly with immune receptors such as T cell receptors (TCRs) or HLA molecules, without requiring covalent binding or conventional antigen processing. Such interactions are sufficient to stimulate T cells in a manner independent of peptide presentation, bypassing the classical antigen recognition pathway [23].

Altered self-peptide repertoire

A notable example is abacavir hypersensitivity in individuals carrying HLA-B*57:01. In this scenario, the drug lodges within the peptide-binding groove of the HLA molecule, altering the set of self-peptides that are presented to T cells. These new peptide-HLA combinations may be mistakenly identified as foreign, provoking an immune response against the body’s own tissues [24, 25].

Cross-reactive memory t cells (heterologous immunity)

This hypothesis emphasizes the role of pre-existing memory T cells that were primed by past infections. If a drug generates peptide-HLA complexes structurally similar to pathogen-derived antigens, these memory T cells can

become reactivated. Individuals with susceptible HLA alleles and prior infectious exposure may therefore experience immune cross-reactivity, leading to hypersensitivity [23, 26, 27].

Danger signal model

According to the danger theory, immune activation relies not only on antigen recognition but also on cellular stress or tissue damage. Endogenous signals, known as damage-associated molecular patterns (DAMPs), released during injury or infection can heighten APC activation and provoke an immune response against drug-related antigens that might otherwise be ignored [28, 29].

Figure 1 schematically illustrates T cell activation pathways involved in drug-induced hypersensitivity reactions.

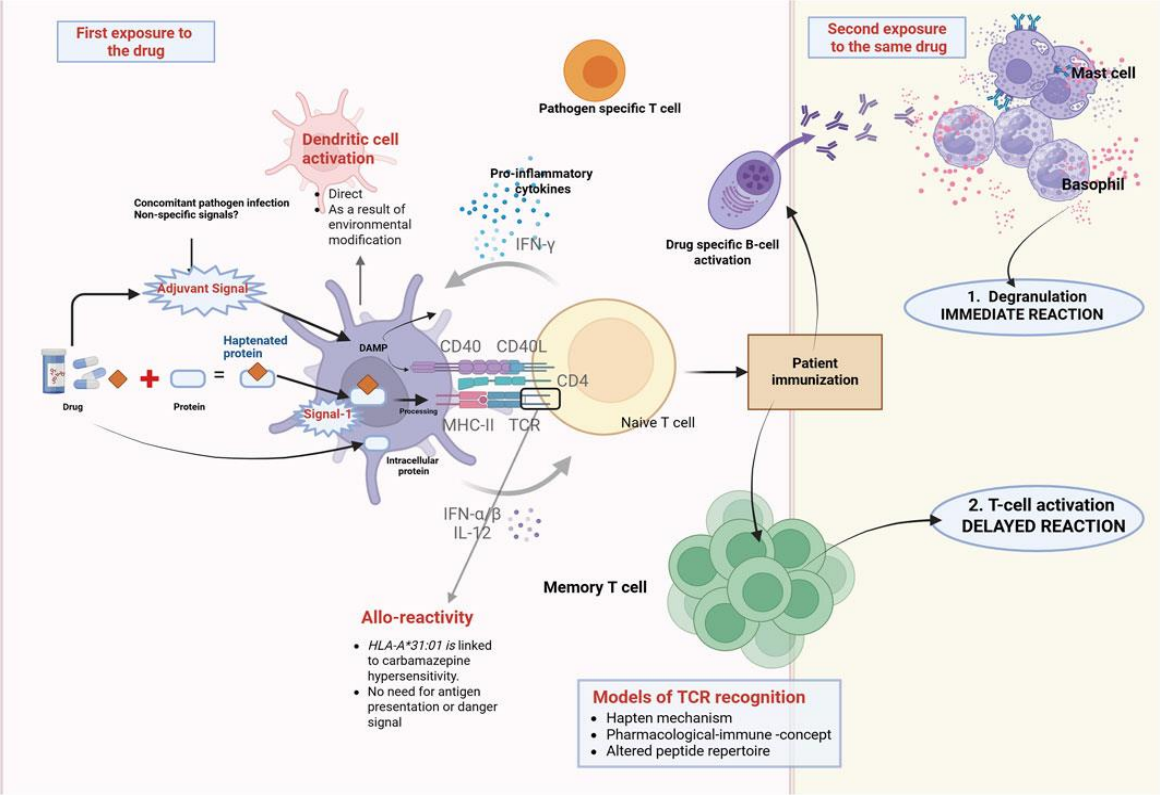

Figure 1. Immunological Pathways in Drug-Induced Hypersensitivity. T cells are central players in drug-induced immune reactions, serving as key mediators in virtually all hypersensitivity events. Chemically reactive drugs or their metabolites can interact with the immune system through multiple pathways. One well-known mechanism, the hapten model, involves drugs binding covalently to host proteins to create new antigens. Recognition of these modified peptides by the T cell receptor (TCR) via MHC molecules is referred to as Signal 1. However, full T cell activation requires an additional co-stimulatory input, Signal 2; in its absence, immune tolerance is maintained. Re-exposure to the drug can trigger hypersensitivity responses, ranging from mild manifestations like hives and angioedema to severe reactions such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN).

Other mechanisms contributing to T cell memory formation include direct drug interactions with immune receptors (p-i concept) and modifications of peptide presentation within the HLA groove (adapted from Azoury *et al*., 2018 [30]).

Genetic determinants of psychiatric drug hypersensitivity

The human leukocyte antigen (HLA) system, located on chromosome 6 (6p21.3), is essential for immune surveillance, allowing the body to distinguish self from non-self. HLA molecules coordinate both cellular and humoral immunity by presenting antigens to T cells, supporting complement activation, and guiding cytotoxic responses [31]. While critical for defense against pathogens, HLA variants also contribute to autoimmune diseases, inflammatory disorders, and drug-induced hypersensitivity.

HLA genes are grouped into three classes: Class I (HLA-A, -B, -C) presents intracellular peptides to CD8+ cytotoxic T cells; Class II (HLA-DR, -DQ, -DP) presents extracellular antigens to CD4+ helper T cells; and Class III encodes immune-related proteins, including complement components [31]. This genomic region is highly polymorphic, with thousands of alleles, and variations within peptide-binding regions influence how antigens are displayed and how T cells respond [32].

Some drugs can activate T cells by directly interacting with HLA molecules or HLA-bound peptides, bypassing conventional antigen processing, as described in the pharmacological interaction (p-i) hypothesis [33].

HLA allele frequencies vary across populations, affecting individual susceptibility to drug hypersensitivity and highlighting the need for population-specific pharmacogenomics. In the MENA region, including the UAE, alleles linked to severe cutaneous adverse reactions (SCARs) such as SJS and TEN differ in prevalence [34].

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has identified HLA alleles relevant to psychiatric and antiepileptic drug reactions:

- HLA-B*15:02 – Strongly linked to carbamazepine- and phenytoin-induced SJS/TEN; rare in Near Eastern populations (0.0002) but associated with severe outcomes [35].
- HLA-B*57:01 – Connected to bupropion hypersensitivity, more frequent in the regional population (0.0234) [36].
- HLA-A*31:01 – Also associated with carbamazepine hypersensitivity, with a frequency of 0.0111 locally [37].

Despite these data, fine-grained, ethnicity-specific mapping is lacking, emphasizing the need for country-level studies to inform personalized prescribing. In the UAE, limited resources and data on HLA-associated drug reactions hinder widespread implementation of pharmacogenomic testing. Projects such as the Emirati Genome Program are expected to provide critical data for advancing precision medicine in the region.

Table 2 provides an overview of HLA allele-drug associations for psychiatric and antiepileptic medications, offering guidance for identifying high-risk patients and supporting genotype-informed prescribing to improve drug safety [38].

Table 2. HLA Alleles Associated with Psychiatric Drug Hypersensitivity Reactions. This table outlines notable correlations between specific HLA gene variants and adverse hypersensitivity outcomes related to psychiatric and antiepileptic medications.

HLA Allele	Associated Drugs	Reported Clinical Reactions	Evidence Level	Guideline/Source	References
HLA-B*15:02	Carbamazepine, Phenytoin, Lamotrigine	Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Maculopapular Exanthema (MPE)	1A	Clinical guideline	Wang *et al.* (2011)[38]; Locharernkul *et al.* (2008)[35]; Koomdee *et al.* (2017)[39]
HLA-A*31:01	Carbamazepine	Maculopapular rash, Hypersensitivity Syndrome, SJS/TEN	1A	Clinical guideline	McCormack *et al.* (2011)[40]; Kim *et al.* (2011)[41]
HLA-B*35:08, HLA-B*39:01, HLA-B*44:03, HLA-A*02:07, HLA-A*33:03	Lamotrigine	Maculopapular Exanthema (MPE)	3	–	Koomdee *et al.* (2017)[39]
HLA-DRB1*07:01	Fluoxetine, Sertraline	Severe Cutaneous Adverse Reaction (SCAR)	Not Available	–	Ahmed *et al.* (2021) [42]
HLA-B*57:01	Bupropion	SJS, TEN	Not Available	–	Pavlos *et al.* (2012)[36]
HLA-DQB1*05:02	Clozapine	Agranulocytosis	3	–	Islam *et al.* (2022) [43]
HLA-B*59:01	Clozapine	Myocarditis	Not Available	–	Islam *et al.* (2022) [43]

Pharmacogenomics in psychiatric medication hypersensitivity

The susceptibility to hypersensitivity reactions varies widely among psychiatric drugs, with genetic factors shaping individual risk profiles [44, 45]. Deciphering these associations is essential for tailoring treatments and minimizing adverse events [46]. While extensive research has identified key genetic markers for anticonvulsants and clozapine, the mechanisms underlying hypersensitivity to newer antidepressants and certain antipsychotics remain poorly characterized. Innovative therapies, including rapid-acting antidepressants such as esketamine (a ketamine derivative) and psilocybin (a serotonergic psychedelic), have emerged for treatment-resistant depression; however, their pharmacogenomic implications and hypersensitivity risks are largely unexplored. Genetic variability in drug metabolism and receptor interactions may influence both therapeutic outcomes and adverse reactions in these cases.

Anticonvulsants

Carbamazepine and lamotrigine are among the anticonvulsants most frequently associated with severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The HLA-B15:02 allele is a major predictor of carbamazepine-induced SCARs in East and Southeast Asian populations, prompting guidelines for pre-treatment genetic testing in these groups. HLA-A31:01 is another variant linked to carbamazepine hypersensitivity across diverse ethnic backgrounds, though its predictive power differs between populations. For lamotrigine, HLA-B38:02 and HLA-B07:02 have been implicated in certain European and Hispanic populations, but the evidence is not as robust as for carbamazepine. Genetic variants in metabolizing enzymes, such as EPHX1 and UGT1A4, can also affect lamotrigine clearance and toxicity risk.

Antidepressants

While hypersensitivity is less prevalent for antidepressants compared to anticonvulsants, immune-mediated adverse events can still present significant clinical challenges. SSRIs like fluoxetine and sertraline have occasionally been associated with cutaneous reactions, with some studies suggesting links to HLA-DRB1*07:01 and CYP2D6 poor metabolizer status [42]. Pharmacogenomic insights may also help identify individuals at risk for rare but severe outcomes, such as antidepressant-related suicidality [47].

Depression pathophysiology involves disruptions in the hypothalamic-pituitary-adrenal (HPA) axis and alterations in neurotransmitter systems, particularly serotonergic signaling [48-51]. Hyperactivation of the HPA axis and elevated cortisol levels can impair neuroplasticity and contribute to depressive symptoms [52]. Serotonergic dysfunction affects emotional regulation, stress response, and cognitive processing, indicating that neuroendocrine and neurotransmitter mechanisms collectively contribute to disease development and persistence [51, 53].

Genetic variations in serotonergic pathways (e.g., SLC6A4), HPA axis modulators (e.g., FKBP5), and metabolizing enzymes (CYP2C19, CYP2D6) have been associated with increased susceptibility to suicidal ideation during antidepressant therapy [47, 54]. FKBP5 polymorphisms, for instance, influence glucocorticoid receptor regulation and HPA feedback. When combined with environmental stressors like childhood trauma, these variants can exacerbate stress sensitivity, predisposing individuals to depression or PTSD [55]. CYP2C19 poor metabolizers may accumulate higher plasma levels of antidepressants, potentially heightening emotional instability, while carriers of the short SLC6A4 allele may show increased sensitivity to SSRI effects. Although current pharmacogenomic guidelines do not yet integrate suicidality risk into standard recommendations, polygenic risk scores and integrated pharmacogenomic-pharmacodynamic models are promising tools for future personalized risk assessment.

Other antidepressants, including bupropion, have been linked to hypersensitivity, potentially mediated by HLA-B*57:01 [36]. Agomelatine metabolism, primarily via CYP1A2, may influence adverse reaction susceptibility in slow metabolizers. Limited data exist for novel antidepressants such as vortioxetine; however, case reports suggest potential immune-mediated responses, highlighting the need for research into the role of HLA variants and cytochrome P450 polymorphisms (e.g., CYP2D6, CYP3A4).

Esketamine, an NMDA receptor antagonist used for treatment-resistant depression, is mainly metabolized by CYP3A4, with CYP2B6 playing a secondary role [56, 57]. Genetic differences in these enzymes can alter how quickly the drug is cleared, impacting both effectiveness and safety. Individuals carrying the CYP3A4*22 variant, which reduces enzymatic activity, may experience prolonged drug exposure, increasing the likelihood of side effects such as dissociation, elevated blood pressure, or liver toxicity. Variants in CYP2B6, particularly the *6 haplotype, may further modify drug metabolism, affecting therapeutic outcomes. While no clear HLA associations with esketamine hypersensitivity have been documented, rare immune-like reactions—including hives and

angioedema—have been reported, suggesting a potential genetic component that requires more study, especially as esketamine use expands.

Psilocybin, a prodrug converted into psilocin, produces its effects primarily via 5-HT2A receptor activation. Its metabolism involves deamination by monoamine oxidase (MAO) and glucuronidation through UGT1A10. Genetic variation in these pathways may influence both drug response and adverse events. Polymorphisms in the 5-HT2A gene (HTR2A), such as T102C (rs6313), can modify the intensity of psychedelic experiences, though their role in hypersensitivity remains uncertain. Differences in MAOA activity (notably the high-activity VNTR 3.5/4-repeat) or UGT1A10 function could alter psilocin clearance, potentially affecting tolerability. Although no HLA variants have been conclusively linked to psilocybin hypersensitivity, structural similarities to serotonin and observed cases of mast cell activation point to possible immunogenetic mechanisms, meriting further investigation.

Antipsychotics

Hypersensitivity reactions differ widely across antipsychotic medications. Clozapine carries the highest documented risk, including agranulocytosis and myocarditis. HLA-DQB105:02 is strongly associated with clozapine-induced agranulocytosis, whereas HLA-B59:01 correlates with myocarditis, particularly in Asian populations [43, 58]. However, HLA screening is not widely implemented globally due to varying allele frequencies. Genetic differences in CYP1A2, clozapine's primary metabolizing enzyme, also influence drug levels, with slow metabolizers at higher risk for toxicity or treatment failure.

For second-generation antipsychotics, hypersensitivity is less frequent but can occur. Olanzapine has been linked anecdotally to skin reactions, possibly associated with HLA-B*38:02 [59]. Aripiprazole
, metabolized largely by CYP2D6, may accumulate in poor metabolizers, increasing the risk of immune-mediated adverse effects [60]. Newer agents such as brexpiprazole and cariprazine show similar pharmacogenomic considerations: brexpiprazole's clearance is affected by CYP2D6 variants, while cariprazine metabolism depends on CYP3A4, creating potential sensitivity in patients with impaired enzyme activity or concurrent CYP3A4 inhibitors [61-64].

First-generation antipsychotics like haloperidol rarely trigger hypersensitivity, but CYP2D6 poor metabolizers may experience elevated drug levels and increased adverse effects [65]. Overall, these findings highlight the critical value of pharmacogenomic-guided therapy to enhance safety and optimize efficacy in psychiatric treatment, particularly for drugs with a high risk of immune-mediated reactions or in genetically susceptible populations.

Determinants of drug hypersensitivity beyond genetics

The likelihood and severity of drug hypersensitivity reactions (DHRs) are influenced by a combination of drug-specific and patient-specific factors beyond inherited genetic variants. Drug-related characteristics that contribute include the chemical reactivity of the compound, its ability to trigger cellular stress or "danger" signals, the presence of T cells capable of recognizing drug-modified antigens, and the route and frequency of administration [66].

Low-molecular-weight drugs may bind directly to proteins or become reactive through photochemical activation (e.g., UV-induced photosensitivity), forming hapten-protein complexes that can trigger immune responses [22, 67]. Notably, such complexes may be present in both allergic and non-allergic individuals. Some medications can also promote dendritic cell activation by upregulating co-stimulatory markers like CD40, while danger-associated molecules (DAMPs) such as HMGB1 serve as biomarkers of adverse drug reactions. Elevated HMGB1 is frequently observed in DRESS and SJS/TEN, whereas IL-33 increases in early stages of TEN [68-70]. The potential for HMGB1 levels to serve as a quantitative marker of reaction severity remains under investigation.

Experimental models using THP-1 cells or mature dendritic cells measuring IL-8 production have been developed to evaluate drug-induced hypersensitivity in vitro [71, 72]. Two key concepts emerge: first, the existence of pre-programmed T-cell repertoires capable of recognizing specific drug-peptide complexes—exemplified by benzylpenicillin, where immunodominant peptides activate peripheral blood mononuclear cells (PBMCs) from allergic individuals [30]. Second, intermittent or repeated drug exposure may promote sensitization more than continuous administration, with parenteral routes generally more likely to induce hypersensitivity than oral intake.

Patient-related factors also modulate DHR risk. Allergic individuals exhibit drug-specific T-cell responses, and ex vivo testing—including lymphocyte transformation assays—can help identify these reactions [73]. Advanced age, polypharmacy, and concurrent infections increase susceptibility [74, 75]. Moreover, individual differences

in regulatory T-cell populations and immune checkpoint expression, such as PD-1 and CTLA4, contribute to the variability in clinical presentation, even in the presence of established risk factors [76, 77].

Clinical implications of pharmacogenomic testing

Pharmacogenomic (PGx) screening is increasingly recognized as a valuable tool in psychiatry for minimizing adverse drug reactions (ADRs) and optimizing therapeutic outcomes. One major application is pre-emptive testing to identify patients at high risk of hypersensitivity before initiating psychotropic therapy.

Personalized drug selection

Genetic testing enables clinicians to tailor medication choices based on variants in drug-metabolizing enzymes, such as CYP2D6 and CYP2C19, which influence both efficacy and tolerability [78]. Evidence indicates that PGx-guided prescribing reduces the incidence of ADRs, including sedation, insomnia, restlessness, and extrapyramidal symptoms. For example, PGx-informed patients experienced a 33.3% ADR rate versus 44.3% in standard-care controls, alongside reduced polypharmacy and fewer psychiatric hospitalizations [78-81].

Real-world cases illustrate the clinical utility of PGx testing. A 75-year-old patient developed severe liver toxicity after starting agomelatine; subsequent genotyping revealed the CYP1A2 rs762551 AA genotype, linked to ultra-rapid metabolism and accumulation of hepatotoxic metabolites [82, 83]. Although CPIC guidelines for agomelatine are not established, these findings highlight the role of pharmacogenomic information in preventing serious ADRs.

For newer medications like cariprazine, CYP3A4 is the primary metabolic pathway, with minor CYP2D6 involvement. Co-administration with erythromycin, a CYP3A4 inhibitor, increased cariprazine plasma levels, indicating that dose adjustments may be needed in patients with impaired metabolism [84]. In contrast, CYP2D6 variants appear to have minimal impact on its pharmacokinetics. While direct PGx data linking CYP polymorphisms to cariprazine ADRs are lacking, awareness of drug–drug interactions remains important, particularly for CYP3A4 substrates.

Guidelines supporting pharmacogenomic implementation

Two key international organizations have developed widely recognized guidelines for integrating pharmacogenomic (PGx) information into clinical practice:

a. Clinical Pharmacogenetics Implementation Consortium (CPIC): CPIC provides peer-reviewed, evidence-based guidance for gene–drug pairs, classifying them by clinical actionability: Level A indicates that genetic results should directly inform therapy; Level B suggests that genetic information may guide treatment; Levels C and D denote gene–drug associations that are not yet clinically actionable [85, 86].
b. Dutch Pharmacogenetics Working Group (DPWG): DPWG offers guidance that is incorporated into European e-prescribing platforms, rating evidence quality from 0 to 4 and clinical relevance from AA to F. This framework informs dosage adjustments, drug selection, and patient monitoring based on genetic profiles [87].

Integration of PGx in the UAE healthcare system

Pharmacogenomics is gradually being adopted in the United Arab Emirates (UAE). The Department of Health–Abu Dhabi has integrated PGx reporting within the Malaffi health information exchange to facilitate personalized medication strategies, prioritizing patients over 40 with prior adverse drug reactions or treatment failure. A pilot UAE study demonstrated the clinical benefits and cost-effectiveness of PGx-guided therapy for cardiovascular medications [88], indicating the potential for broader application across other drug classes. Nevertheless, obstacles remain, including the absence of a national PGx framework, limited clinician training and awareness, and insufficient data on population-specific allele frequencies.

Challenges and limitations

Despite its potential, the clinical integration of pharmacogenomics faces multiple barriers. One major limitation is the inconsistency in availability and interpretation of genetic testing [2]. Access to PGx testing varies widely by healthcare system and region, often restricted to urban or well-resourced centers. Even when available, differences in test platforms, reporting standards, and result interpretation may cause confusion among clinicians, diminishing the reliability and practical utility of PGx information.

Ethical and economic concerns further impede widespread adoption [89, 90]. Sensitive genetic data raises privacy issues and risks of discrimination in insurance or employment. Financially, high upfront costs and limited reimbursement options can discourage institutions from offering testing, despite evidence that PGx-guided therapy may reduce adverse drug reactions and improve long-term outcomes.

Additionally, the lack of standardized implementation protocols restricts routine clinical use [1, 91]. While CPIC and DPWG provide valuable guidance, these frameworks are not consistently applied across countries or healthcare systems. Many clinicians lack clear institutional policies for testing, interpreting results, and integrating PGx information into prescribing decisions, leading to underutilization and uncertainty.

Addressing these challenges requires enhanced infrastructure, regulatory oversight, clinician education, and interdisciplinary collaboration to enable safe, equitable, and effective deployment of pharmacogenomics in clinical settings.

Conclusion

This review explored the mechanisms underlying drug hypersensitivity reactions (DHRs), emphasizing immunological processes, the generation of reactive drug metabolites, and genetic predispositions. Notable contributors include specific HLA alleles and polymorphisms in drug-metabolizing enzymes, particularly within the cytochrome P450 family. We examined pharmacogenomic evidence for major psychiatric drug classes, including anticonvulsants (e.g., carbamazepine, lamotrigine), antidepressants (e.g., SSRIs and novel agents), and antipsychotics (e.g., clozapine and newer-generation compounds), highlighting genetic variants associated with elevated risk for adverse drug reactions. The review underscored the clinical relevance of pharmacogenomic testing, especially for preemptively identifying patients at high risk of DHRs and enabling safer, individualized prescribing strategies. Nevertheless, the field faces ongoing challenges, including inconsistent test availability, variable interpretation standards, ethical concerns around genetic data, and the lack of universally accepted implementation protocols.

Looking forward, advances in genomic technologies, particularly next-generation sequencing (NGS), are transforming the landscape by enabling rapid, cost-effective evaluation of genetic variation across populations [92]. Beyond single-gene analyses, NGS facilitates multiomic approaches that integrate genomic, epigenomic, transcriptomic, proteomic, and metabolomic information, providing a more comprehensive understanding of drug response and disease biology [93]. Multi-layered datasets offer superior predictive capacity compared to single-layer genomics, particularly in psychiatric disorders where treatment response is influenced by complex biological networks. For example, a recent study in schizophrenia combined DNA methylation profiles with polygenic risk scores from six cortical genes to predict antipsychotic drug response in over 3,600 patients, demonstrating high predictive accuracy and translational potential for clinical decision-making [94].

Regionally, initiatives such as the Emirati Genome Program are establishing population-specific genetic references through large-scale NGS efforts [95]. These datasets are critical for applying pharmacogenomics in a contextually relevant manner and may support future multiomic analyses to further refine individualized therapeutic strategies.

Globally, equitable access to pharmacogenomic knowledge and data sharing remain crucial. Incorporating diverse populations into research ensures that precision medicine is broadly applicable and avoids perpetuating health disparities [96]. Open-access platforms such as PharmGKB, alongside guidance from CPIC and DPWG, are instrumental in translating genomic discoveries into clinical practice. However, adoption of these frameworks is uneven worldwide. Expanding international collaboration, fostering participation from underrepresented populations, and developing shared global pharmacogenomic databases will be essential for converting localized findings into practical, scalable tools for personalized psychiatric care.

In summary, pharmacogenomics offers substantial promise for enhancing psychiatric therapy, minimizing adverse reactions, and improving patient outcomes. Realizing this potential will require continued investment in research, infrastructure, education, and cross-border collaboration to integrate genomic insights effectively into routine clinical practice.

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References

1. Alchakee A, Ahmed M, Eldohaji L, Alhaj H, Saber-Ayad M. Pharmacogenomics in psychiatry practice: the value and the challenges. Int J Mol Sci. 2022;23(21):13485. doi:10.3390/ijms232113485
2. Bousman CA, Bengesser SA, Aitchison KJ, Amare AT, Aschauer H, Baune BT, et al. Review and consensus on pharmacogenomic testing in psychiatry. Pharmacopsychiatry. 2021;54(1):5-17. doi:10.1055/a-1288-1061
3. Wei BM, Fox LP, Kaffenberger BH, Korman AM, Micheletti RG, Mostaghimi A, et al. Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms. Part I. Epidemiology, pathogenesis, clinicopathological features, and prognosis. J Am Acad Dermatol. 2024;90(5):885-908. doi:10.1016/j.jaad.2023.02.072
4. Böhm R, Cascorbi I. Pharmacogenetics and predictive testing of drug hypersensitivity reactions. Front Pharmacol. 2016;7:396. doi:10.3389/fphar.2016.00396
5. Elzagallaai AA, Rieder MJ. Genetic markers of drug hypersensitivity in pediatrics: current state and promise. Expert Rev Clin Pharmacol. 2022;15(6):715-28. doi:10.1080/17512433.2022.2100345
6. Kaniwa N, Saito Y. The risk of cutaneous adverse reactions among patients with the HLA-A* 31:01 allele who are given carbamazepine, oxcarbazepine or eslicarbazepine: a perspective review. Ther Adv Drug Saf. 2013;4(6):246-53. doi:10.1177/2042098613499791
7. Szegedi A, Remenyik É, Gellén E. Drug hypersensitivity reactions. In: European handbook of dermatological treatments. Springer International Publishing; 2023. p. 229-245. doi:10.1007/978-3-031-15130-9_22
8. Kalesnikoff J, Galli SJ. New developments in mast cell biology. Nat Immunol. 2008;9(11):1215-23. doi:10.1038/ni.f.216
9. Bajwa SF, Mohammed RH. Type II hypersensitivity reaction. 2025.
10. Uzzaman A, Cho SH. Chapter 28: classification of hypersensitivity reactions. Allergy Asthma Proc. 2012;33(3):96-9. doi:10.2500/aap.2012.33.3561
11. Posadas SJ, Pichler WJ. Delayed drug hypersensitivity reactions – new concepts. Clin Exp Allergy. 2007;37(7):989-99. doi:10.1111/j.1365-2222.2007.02742.x
12. Hung SI, Mockenhaupt M, Blumenthal KG, Abe R, Ueta M, Ingen-Housz-Oro S, et al. Severe cutaneous adverse reactions. Nat Rev Dis Prim. 2024;10(1):30. doi:10.1038/s41572-024-00514-0
13. Roujeau JC. Clinical heterogeneity of drug hypersensitivity. Toxicology. 2005;209(2):123-9. doi:10.1016/j.tox.2004.12.022
14. Del Pozzo-Magaña BR, Liy-Wong C. A concise review of cutaneous adverse drug reactions. Br J Clin Pharmacol. 2024;90(8):1838-55. doi:10.1111/bcp.15490
15. Graudins LV, Trubiano JA, Zubrinich CM, Elliott AS, Aung AK. Medication-related anaphylaxis treated in hospital: agents implicated, patient outcomes, and management lessons. Pharmacoepidemiol Drug Saf. 2018;27(9):1029-33. doi:10.1002/pds.4587
16. Mockenhaupt M. Epidemiology of cutaneous adverse drug reactions. Allergol Sel. 2017;1(1):96-108. doi:10.5414/ALX01508E
17. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Orphanet J Rare Dis. 2010;5(1):39. doi:10.1186/1750-1172-5-39
18. Chowdhury D, Chin L, Odabashian R, Fawaz A, Canil C, Ong M, et al. Diagnosis and management of skin toxicities in systemic treatment of genitourinary cancers. Cancers. 2025;17(2):251. doi:10.3390/cancers17020251
19. Moore MJ, Sathe NC, Ganipisetti VM. Acute generalized exanthematous pustulosis. Acute generalized exanthematous pustulosis. Treasure Island, FL: StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK592407/?utm_source (Accessed September 9, 2025).
20. Muzumdar S, Rothe MJ, Grant-Kels JM. The rash with maculopapules and fever in children. Clin Dermatol. 2019;37(2):119-28. doi:10.1016/j.clindermatol.2018.12.005
21. Verheyden M, Murrell D, Bilgic A. A systematic review of drug-induced pemphigoid. J Am Acad Dermatol. 2020;83(6):AB113. doi:10.1016/j.jaad.2020.06.539

22. Adair K, Meng X, Naisbitt DJ. Drug hapten-specific t-cell activation: current status and unanswered questions. PROTEOMICS. 2021;21(17-18):e2000267. doi:10.1002/pmic.202000267
23. Pichler WJ. Immune pathomechanism and classification of drug hypersensitivity. Allergy. 2019;74(8):1457-71. doi:10.1111/all.13765
24. Hammond S, Thomson P, Meng X, Naisbitt D. In-Vitro approaches to predict and study T-Cell mediated hypersensitivity to drugs. Front Immunol. 2021;12:630530. doi:10.3389/fimmu.2021.630530
25. Ostrov DA, Grant BJ, Pompeu YA, Sidney J, Harndahl M, Southwood S, et al. Drug hypersensitivity caused by alteration of the MHC-Presented self-peptide repertoire. Proc Natl Acad Sci. 2012;109(25):9959-64. doi:10.1073/pnas.1207934109
26. Almeida CA, van Miert P, O'Driscoll K, Zoet YM, Chopra A, Witt C, et al. Virus-specific T-cell clonotypes might contribute to drug hypersensitivity reactions through heterologous immunity. J Allergy Clin Immunol. 2019;144(2):608-11.e4. doi:10.1016/j.jaci.2019.05.009
27. White KD, Chung WH, Hung SI, Mallal S, Phillips EJ. Evolving models of the immunopathogenesis of T cell–mediated drug allergy: the role of host, pathogens, and drug response. J Allergy Clin Immunol. 2015;136(2):219-35. doi:10.1016/j.jaci.2015.05.050
28. Land WG. Perspectives of the danger/injury model of immunology as applied to antigen-related human disorders. In: damage-associated molecular patterns in human diseases. Springer international publishing; 2023. p. 3-44. doi:10.1007/978-3-031-21776-0_1
29. Pirmohamed M, Naisbitt DJ, Gordon F, Park BK. The danger Hypothesis—potential role in idiosyncratic drug reactions. Toxicology. 2002;181(182):55-63. doi:10.1016/S0300-483X(02)00255-X
30. Azoury ME, Filì L, Bechara R, Scornet N, de Chaisemartin L, Weaver RJ, et al. Identification of T-cell epitopes from benzylpenicillin conjugated to human serum albumin and implication in penicillin allergy. Allergy. 2018;73(8):1662-72. doi:10.1111/all.13418
31. Crux NB, Elahi S. Human leukocyte antigen (HLA) and immune regulation: how do classical and non-classical HLA Alleles Modulate Immune Response to Human Immunodeficiency Virus and Hepatitis C Virus Infections?. Front Immunol. 2017;8:832. doi:10.3389/fimmu.2017.00832
32. Anaya JM, Shoenfeld Y, Rojas-Villarraga A, Levy RA, Cervera R. Autoimmunity: from bench to bedside. 2013.
33. Meng X, Yerly D, Naisbitt DJ. Mechanisms leading to T-cell activation in drug hypersensitivity. Curr Opin Allergy Clin Immunol. 2018;18(4):317-24. doi:10.1097/ACI.0000000000000458
34. Masmoudi HC, Afify N, Alnaqbi H, Alhalwachi Z, Tay GK, Alsafar H. HLA pharmacogenetic markers of drug hypersensitivity from the perspective of the populations of the greater Middle East. Pharmacogenomics. 2022;23(12):695-708. doi:10.2217/pgs-2022-0078
35. Locharernkul C, Loplumlert J, Limotai C, Korkij W, Desudchit T, Tongkobpetch S, et al. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. Epilepsia. 2008;49(12):2087-91. doi:10.1111/j.1528-1167.2008.01719.x
36. Pavlos R, Mallal S, Phillips E. HLA and pharmacogenetics of drug hypersensitivity. Pharmacogenomics. 2012;13(11):1285-306. doi:10.2217/pgs.12.108
37. González-Galarza FF, Takeshita LY, Santos EJM, Kempson F, Maia MHT, Silva ALS da, et al. Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations. Nucleic Acids Res. 2015;43(D1):D784–D8. doi:10.1093/nar/gku1166
38. Wang Q, Zhou J, Zhou L, Chen Z, Fang Z, Chen S, et al. Association between HLA-B*1502 allele and carbamazepine-induced severe cutaneous adverse reactions in Han people of southern China mainland. Seizure. 2011;20(6):446-8. doi:10.1016/j.seizure.2011.02.003
39. Koomdee N, Pratoomwun J, Jantararoungtong T, Theeramoke V, Tassaneeyakul W, Klaewsongkram J, et al. Association of HLA-A and HLA-B alleles with Lamotrigine-Induced cutaneous adverse drug reactions in the Thai population. Front Pharmacol. 2017;8:879. doi:10.3389/fphar.2017.00879
40. McCormack M, Alfirevic A, Bourgeois S, Farrell JJ, Kasperavičiūtė D, Carrington M, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med. 2011;364(12):1134-43. doi:10.1056/NEJMoa1013297
41. Kim SH, Lee KW, Song WJ, Kim SH, Jee YK, Lee SM, et al. Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. Epilepsy Res. 2011;97(1-2):190-7. doi:10.1016/j.eplepsyres.2011.08.010

42. Ahmed AF, Sukasem C, Sabbah MA, Musa NF, Mohamed Noor DA, Daud NAA. Genetic determinants in HLA and cytochrome P450 genes in the risk of aromatic antiepileptic-induced severe cutaneous adverse reactions. J Personalized Med. 2021;11(5):383. doi:10.3390/jpm11050383
43. Islam F, Hain D, Lewis D, Law R, Brown LC, Tanner JA, et al. Pharmacogenomics of clozapine-induced agranulocytosis: a systematic review and meta-analysis. Pharmacogenomics J. 2022;22(4):230-40. doi:10.1038/s41397-022-00281-9
44. Athanasiu L, Smorr LLH, Tesli M, Røssberg JI, Sønderby IE, Spigset O, et al. Genome-wide association study identifies common variants associated with pharmacokinetics of psychotropic drugs. J Psychopharmacol. 2015;29(8):884-91. doi:10.1177/0269881115584469
45. Cacabelos R, Cacabelos P, Aliev G. Genomics of schizophrenia and pharmacogenomics of antipsychotic drugs. Open J Psychiatry. 2013;3(1):46-139. doi:10.4236/ojpsych.2013.31008
46. Li Y, Deshpande P, Hertzman RJ, Palubinsky AM, Gibson A, Phillips EJ. Genomic risk factors driving immune-mediated delayed drug hypersensitivity reactions. Front Genet. 2021;12:641905. doi:10.3389/fgene.2021.641905
47. Clayden RC, Zaruk A, Meyre D, Thabane L, Samaan Z. The association of attempted suicide with genetic variants in the SLC6A4 and TPH genes depends on the definition of suicidal behavior: a systematic review and meta-analysis. Transl Psychiatry. 2012;2(10):e166. doi:10.1038/tp.2012.96
48. Alhaj HA, Massey AE, McAllister-Williams RH. Effects of cortisol on the laterality of the neural correlates of episodic memory. J Psychiatric Res. 2008;42(12):971-81. doi:10.1016/j.jpsychires.2007.11.008
49. Alhaj HA, McAllister-Williams RH. Chapter 5.7 adrenal steroids and episodic memory: relevance to mood disorders. In: chapter 5.7 adrenal steroids and episodic memory: relevance to mood disorders. 18:585-95. doi:10.1016/S1569-7339(08)00232-4
50. Andrews MH, Matthews SG. Programming of the hypothalamo–pituitary–adrenal axis: serotonergic involvement. Stress. 2004;7(1):15-27. doi:10.1080/10253890310001650277
51. McAllister-Williams RH, Alhaj HA, Massey A, Pankiv J, Reckermann U. Somatodendritic 5-hydroxytryptamine1A (5-HT1A) autoreceptor function in major depression as assessed using the shift in electroencephalographic frequency spectrum with buspirone. Psychol Med. 2014;44(4):767-77. doi:10.1017/S0033291713001475
52. Calabrese F, Molteni R, Racagni G, Riva MA. Neuronal plasticity: a link between stress and mood disorders. Psychoneuroendocrinology. 2009;34:S208–S16. doi:10.1016/j.psyneuen.2009.05.014
53. Alhaj HA, Selman M, Jervis V, Rodgers J, Barton S, McAllister-Williams RH. Effect of low-dose acute tryptophan depletion on the specificity of autobiographical memory in healthy subjects with a family history of depression. Psychopharmacology. 2012;222(2):285-92. doi:10.1007/s00213-012-2644-x
54. De la Cruz-Cano E. Association between FKBP5 and CRHR1 genes with suicidal behavior: a systematic review. Behav Brain Res. 2017;317:46-61. doi:10.1016/j.bbr.2016.09.032
55. Malekpour M, Shekouh D, Safavinia ME, Shiralipour S, Jalouli M, Mortezanejad S, et al. Role of FKBP5 and its genetic mutations in stress-induced psychiatric disorders: an opportunity for drug discovery. Front Psychiatry. 2023;14:1182345. doi:10.3389/fpsyt.2023.1182345
56. Langmia IM, Just KS, Yamoune S, Müller JP, Stingl JC. Pharmacogenetic and drug interaction aspects on ketamine safety in its use as antidepressant - implications for precision dosing in a global perspective. Br J Clin Pharmacol. 2022;88(12):5149-65. doi:10.1111/bcp.15467
57. Willemin M-E, Zannikos P, Mannens G, de Zwart L, Snoeys J. Prediction of drug-drug interactions after esketamine intranasal administration using a physiologically based pharmacokinetic model. Clin Pharmacokinet. 2022;61(8):1115-28. doi:10.1007/s40262-022-01123-4
58. Goldstein JI, Jarskog LF, Hilliard C, Alfirevic A, Duncan L, Fourches D, et al. Clozapine-induced agranulocytosis is associated with rare HLA-DQB1 and HLA-B alleles. Nat Commun. 2014;5:4757. doi:10.1038/ncomms5757
59. Pattanaik S, Jain A, Ahluwalia J. Evolving role of pharmacogenetic biomarkers to predict drug-induced hematological disorders. Ther Drug Monit. 2021;43(2):201-20. doi:10.1097/FTD.0000000000000842
60. Zhang X, Xiang Q, Zhao X, Ma L, Cui Y. Association between aripiprazole pharmacokinetics and CYP2D6 phenotypes: a systematic review and meta-analysis. J Clin Pharm Ther. 2019;44(2):163-73. doi:10.1111/jcpt.12780

61. Elmokadem A, Bruno CD, Housand C, Jordie EB, Chow CR, Lesko LJ, et al. Brexpiprazole pharmacokinetics in CYP2D6 poor metabolizers: using physiologically based pharmacokinetic modeling to optimize time to effective concentrations. J Clin Pharmacol. 2022;62(1):66-75. doi:10.1002/jcph.1946
62. Frederiksen T, Areberg J, Raoufinia A, Schmidt E, Stage TB, Brøsen K. Estimating the in vivo function of CYP2D6 alleles through population pharmacokinetic modeling of brexpiprazole. Clin Pharmacol Ther. 2023;113(2):360-9. doi:10.1002/cpt.2791
63. Periclou A, Phillips L, Ghahramani P, Kapás M, Carrothers T, Khariton T. Population pharmacokinetics of cariprazine and its major metabolites. Eur J Drug Metab Pharmacokinet. 2021;46(1):53-69. doi:10.1007/s13318-020-00650-4
64. Szabó M, Hujber Z, Harsányi J, Szatmári B, Dombi ZB, Magyar G, et al. Coadministration of cariprazine with a moderate CYP3A4 inhibitor in patients with schizophrenia: implications for dose adjustment and safety monitoring. Clin Pharmacokinet. 2024;63(10):1501-10. doi:10.1007/s40262-024-01431-x
65. Šimić I, Potočnjak I, Kraljičković I, Stanić Benić M, Čegec I, Juričić Nahal D, et al. CYP2D6 *6/*6 genotype and drug interactions as cause of haloperidol-induced extrapyramidal symptoms. Pharmacogenomics. 2016;17(13):1385-9. doi:10.2217/pgs-2016-0069
66. Naisbitt DJ, Gordon S, Pirmohamed M, Park B. Immunological principles of adverse drug reactions: the initiation and propagation of immune responses elicited by drug treatment. Drug Saf. 2000;23(6):483-507. doi:10.2165/00002018-200023060-00002
67. Tailor A, Waddington JC, Meng X, Park BK. Mass spectrometric and functional aspects of drug–protein conjugation. Chem Res Toxicol. 2016;29(12):1912-35. doi:10.1021/acs.chemrestox.6b00147
68. Fujita H, Matsukura S, Watanabe T, Komitsu N, Watanabe Y, Takahashi Y, et al. The serum level of HMGB1 (high mobility group box 1 protein) is preferentially high in drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms. Br J Dermatol. 2014;171(6):1585-8. doi:10.1111/bjd.13162
69. Nakajima S, Watanabe H, Tohyama M, Sugita K, Iijima M, Hashimoto K, et al. High-mobility group box 1 protein (HMGB1) as a novel diagnostic tool for toxic epidermal necrolysis and Stevens-Johnson syndrome. Arch Dermatol. 2011;147(9):1110-2. doi:10.1001/archdermatol.2011.239
70. Adachi A, Komine M, Tsuda H, Nakajima S, Kabashima K, Ohtsuki M. Differential expression of alarmins: IL-33 as a candidate marker for early diagnosis of toxic epidermal necrolysis. J Allergy Clin Immunol Pract. 2019;7(1):325-7. doi:10.1016/j.jaip.2018.05.037
71. Kim SH, Naisbitt DJ. Update on advances in research on idiosyncratic drug-induced liver injury. Allergy Asthma Immunol Res. 2016;8(1):3-11. doi:10.4168/aair.2016.8.1.3
72. Pallardy M, Bechara R. Chemical or drug hypersensitivity: is the immune system clearing the danger? Toxicol Sci. 2017;158(1):14-22. doi:10.1093/toxsci/kfx084
73. Naisbitt DJ, Nattrass RG, Ogese MO. In vitro diagnosis of delayed-type drug hypersensitivity: mechanistic aspects and unmet needs. Immunol Allergy Clin North Am. 2014;34(3):691-705. doi:10.1016/j.iac.2014.04.009
74. Cardona V, Guilarte M, Luengo O, Labrador-Horrillo M, Sala-Cunill A, Garriga T. Allergic diseases in the elderly. Clin Transl Allergy. 2011;1(1):11. doi:10.1186/2045-7022-1-11
75. Castrejon JL, Berry N, El-Ghaiesh S, Gerber B, Pichler WJ, Park BK, et al. Stimulation of human T cells with sulfonamides and sulfonamide metabolites. J Allergy Clin Immunol. 2010;125(2):411-8. doi:10.1016/j.jaci.2009.10.031
76. Hammond S, Olsson-Brown A, Grice S, Gibson A, Gardner J, Castrejón-Flores JL, et al. Checkpoint inhibition reduces the threshold for drug-specific T-cell priming and increases the incidence of sulfasalazine hypersensitivity. Toxicol Sci. 2022;186(1):58-69. doi:10.1093/toxsci/kfab144
77. Line J, Thomson P, Naisbitt DJ. Pathology of T-cell-mediated drug hypersensitivity reactions and impact of tolerance mechanisms on patient susceptibility. Curr Opin Allergy Clin Immunol. 2022;22(4):226-33. doi:10.1097/ACI.0000000000000834
78. Skokou M, Karamperis K, Koufaki MI, Tsermpini EE, Pandi MT, Siamoglou S, et al. Clinical implementation of preemptive pharmacogenomics in psychiatry. EBioMedicine. 2024;101:105009. doi:10.1016/j.ebiom.2024.105009
79. Roberts B, Cooper Z, Lu S, Stanley S, Majda BT, Collins KR, et al. Utility of pharmacogenetic testing to optimise antidepressant pharmacotherapy in youth: a narrative literature review. Front Pharmacol. 2023;14:1267294. doi:10.3389/fphar.2023.1267294

80. Scherf-Clavel M, Frantz A, Eckert A, Weber H, Unterecker S, Deckert J, et al. Effect of CYP2D6 pharmacogenetic phenotype and phenoconversion on serum concentrations of antidepressants and antipsychotics: a retrospective cohort study. Int J Clin Pharm. 2023;45(5):1107-17. doi:10.1007/s11096-023-01588-8
81. Westergaard N, Søgaard Nielsen R, Jørgensen S, Vermehren C. Drug use in Denmark for drugs having Pharmacogenomics (PGx) based Dosing Guidelines from CPIC or DPWG for CYP2D6 and CYP2C19 drug–gene pairs: perspectives for introducing PGx test to polypharmacy patients. J Pers Med. 2020;10(1):3. doi:10.3390/jpm10010003
82. Wang S, Xu Q, Qu K, Wang J, Zhou Z. CYP1A2 polymorphism may contribute to agomelatine-induced acute liver injury: case report and review of the literature. Medicine. 2021;100(45):e27736. doi:10.1097/MD.0000000000027736
83. Song L, Du Q, Jiang X, Wang L. Effect of CYP1A2 polymorphism on the pharmacokinetics of agomelatine in Chinese healthy male volunteers. J Clin Pharm Ther. 2014;39(2):204–9. doi:10.1111/jcpt.12118
84. Tsermpini EE, Terzi T, Kores Plesničar B, Dolžan V. Pharmacogenomics and antipsychotics: efficacy and adverse drug reactions. In: Psychiatric Genomics. Elsevier; 2022. p. 161–88. doi:10.1016/B978-0-12-819602-1.00010-3
85. Caudle KE, Dunnenberger HM, Freimuth RR, Peterson JF, Burlison JD, Whirl-Carrillo M, et al. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the clinical pharmacogenetics implementation consortium (CPIC). Genet Med. 2017;19(2):215–23. doi:10.1038/gim.2016.87
86. Morris SA, Alsaidi AT, Verbyla A, Cruz A, Macfarlane C, Bauer J, et al. Cost effectiveness of pharmacogenetic testing for drugs with clinical pharmacogenetics implementation consortium (CPIC) guidelines: a systematic review. Clin Pharmacol Ther. 2022;112(6):1318–28. doi:10.1002/cpt.2754
87. Swen JJ, Nijenhuis M, De Boer A, Grandia L, Maitland-Van Der Zee AH, Mulder H, et al. Pharmacogenetics: From bench to byte an update of guidelines. Clin Pharmacol Ther. 2011;89(5):662–73. doi:10.1038/clpt.2011.34
88. Al-Mahayri ZN, Khasawneh LQ, Alqasrawi MN, Altoum SM, Jamil G, Badawi S, et al. Pharmacogenomics implementation in cardiovascular disease in a highly diverse population: initial findings and lessons learned from a pilot study in United Arab Emirates. Hum Genomics. 2022;16(1):42. doi:10.1186/s40246-022-00417-9
89. Karamperis K, Koromina M, Papantoniou P, Skokou M, Kanellakis F, Mitropoulos K, et al. Economic evaluation in psychiatric pharmacogenomics: a systematic review. Pharmacogenomics J. 2021;21(4):533–41. doi:10.1038/s41397-021-00249-1
90. Pardiñas AF, Owen MJ, Walters JTR. Pharmacogenomics: a road ahead for precision medicine in psychiatry. Neuron. 2021;109(24):3914–29. doi:10.1016/j.neuron.2021.09.011
91. Kabbani D, Akika R, Wahid A, Daly AK, Cascorbi I, Zgheib NK. Pharmacogenomics in practice: a review and implementation guide. Front Pharmacol. 2023;14:1189976. doi:10.3389/fphar.2023.1189976
92. Behjati S, Tarpey PS. What is next generation sequencing? Arch Dis Child Educ Pract Ed. 2013;98(6):236–8. doi:10.1136/archdischild-2013-304340
93. Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. Genome Biol. 2017;18(1):83. doi:10.1186/s13059-017-1215-1
94. Guo LK, Su Y, Zhang YYN, Yu H, Lu Z, Li WQ, et al. Prediction of treatment response to antipsychotic drugs for precision medicine approach to schizophrenia: randomized trials and multiomics analysis. Mil Med Res. 2023;10(1):24. doi:10.1186/s40779-023-00459-7
95. Ateia H, Ogrodzki P, Wilson HV, Ganesan S, Halwani R, Koshy A, et al. Population genome programs across the Middle East and North Africa: successes, challenges, and future directions. Biomed Hub. 2023;8(1):60–71. doi:10.1159/000530619
96. Relling MV, Klein TE. CPIC: clinical pharmacogenetics implementation consortium of the pharmacogenomics research network. Clin Pharmacol Ther. 2011;89(3):464–7. doi:10.1038/clpt.2010.279