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Epigenetics in pharmacogenes encoding metabolizing enzymes of second-generation antipsychotics used in schizophrenia and its clinical implications

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Schizophrenia is a neuropsychiatric disorder caused by neurochemical alterations, non-genetic, genetic, epigenetic and environmental factors. Pharmacoepigenetics studies the relationship between epigenetic variability and response to drugs. The objective was to realize a descriptive review of the current state of knowledge on epigenetic molecular mechanisms in pharmacogenes encoding metabolizing enzymes of second-generation antipsychotics drugs used in schizophrenia and their clinical implications. A brief description of the pharmacogenes *CYP2D6, CYP1A2, CYP2C9, CYP2C19* and *CYP3A4*, enzymes and metabolism of second-generation antipsychotic drugs (SGAs) such as clozapine, olanzapine, risperidone, paliperidone and quetiapine was made. The central review was on the epigenetic molecular mechanisms of DNA methylation, histone methylation and acetylation of pharmacogenes, likewise, epigenetic changes due to enzyme-inducing drugs and SGAs, and their clinical implications, were described. Despite the limited scientific literature published on the epigenetics that regulate pharmacogenes, it has been shown that DNA methylation and histone trimethylation and acetylation are the main epigenetic mechanisms in pharmacogenes, alike, some enzyme-inducing drugs would promote epigenetic changes. This review has clinical implications for the medical-clinical care and treatment of schizophrenia.

KEYWORDS

epigenetics, pharmacogenes, schizophrenia, antipsychotic drugs, clinical implications

1 Introduction

Schizophrenia is a neuropsychiatric disease that affects 1% of the general population and is one of the 10 leading causes of disability in developed countries. It has also been published that 5% of patients commit suicide, more than 30% of patients are potentially suicidal, and it is one of the main causes of suicide among young patients (Delphin et al., 2024). Hence, the importance of understanding how epigenetics, pharmacogenetics, and pharmacoepigenetics influence schizophrenia. Epigenetics is the science that studies the molecular mechanisms that modify DNA without altering the sequence of the genetic code, but contribute to hereditary phenotypic variations, and are essential for cells to remember past events, developmental alterations and external stimulation (Ocaña-Paredes et al., 2024; Smith et al., 2023; Fitz-James and Cavalli, 2022; Li, 2021; Srivastava et al., 2021; Zhang et al., 2020). Among the known epigenetic molecular mechanisms are DNA methylation of cytosine residues in CpG dinucleotides (cytosine-phosphate-guanine), histone modifications, processes mediated by non-coding RNAs (ncRNAs), such as small ncRNAs (sncRNAs) and long ncRNAs (lncRNAs) (Smigielski et al., 2020). While pharmacoepigenetics studies the relationship between epigenetic changes and response to drugs, helping to predict adverse drug reactions and their clinical efficacy (Smith et al., 2023; Lisoway et al., 2021).

Studying the pharmacogenetic and pharmacoepigenetic foundations of schizophrenia is crucial to understand how genetics, epigenetics, and environmental factors contribute to the evolution of the disease (Lisoway et al., 2021), also to understand how epigenetic molecular mechanisms influence the pharmacogenes *CYP2D6, CYP1A2, CYP2C9, CYP2C19* and *CYP3A4*, and how their modified allelic variants influence metabolic variability, plasma levels, and adverse drug reactions induced by antipsychotic drugs (Swathy and Banerjee, 2022; Cacabelos, 2020). In this context, pharmacogenetics and pharmacoepigenetics are the basis for the clinical science known as personalized or precision genomic medicine, which seeks to individualize the dose from the beginning of drug therapy, considering the genotype and phenotype profile according to ethnicity, mixed race, origin, sex and lifestyle, the purpose of which is to maintain plasma concentrations within the therapeutic range, minimizing adverse drug reactions, and optimizing the efficacy of the drug (Alvarado et al., 2022; Halbert, 2022; Imani et al., 2022; Hasanzad et al., 2021; Alvarado et al., 2019). To control the symptoms of schizophrenia, "typical" antipsychotic drugs or second-generation antipsychotic drugs (SGAs), also known as "atypical", are used, which include clozapine, amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, and zotepine (Rognoni et al., 2021).

A search was conducted for published evidence in PubMed, MEDLINE, and Scopus databases. Optimizing the search with keywords that included "clozapine," "olanzapine," "risperidone," "pharmacogenes," and combinations with "epigenetic molecular mechanism," "DNA methylation," "histone methylation," and "histone acetylation." The search results were restricted to the last 25 years, so publications from 2000 to 10 April 2025, were retrieved. The descriptive review included articles with a focus on epigenetics in pharmacogenes that encode metabolizing enzymes of second-generation antipsychotics used in schizophrenia. All studies with a theme different from the inclusion criteria were excluded. For these considerations, the objective was to realize a descriptive review of the current state of knowledge on epigenetic molecular mechanisms in pharmacogenes encoding metabolizing enzymes of second-generation antipsychotics drugs used in schizophrenia and their clinical implications. We examined the pharmacogenetics of the *CYP2D6, CYP1A2, CYP2C9, CYP2C19*, and *CYP3A4* genes encoding their respective enzymes that metabolize SGAs such as clozapine, olanzapine, risperidone, paliperidone, and quetiapine. The epigenetic molecular mechanisms in pharmacogenes during the development of the individual, and by enzyme-inducing drugs, are described. In addition, this review analyzes the clinical implications of epigenetic change and its application in the clinical practice of schizophrenia.

2 Pharmacogenetics

Pharmacogenetics allows us to know the genotypes that predict metabolic phenotypes that influence plasma levels, therapeutic efficacy and adverse drug reactions (Kappel et al., 2024; Alvarado et al., 2022; Alvarado et al., 2021), hence the importance of analyzing the *CYP2D6, CYP1A2, CYP2C9, CYP2C19* and *CYP3A4* genes that code for their respective enzymes. Likewise, the metabolism of the main SGAs such as clozapine, olanzapine, risperidone, paliperidone and quetiapine are described (Ingelman-Sundberg and Sim, 2010; Ingelman-Sundberg et al., 2007).

2.1 Genes encoding SGA-metabolizing enzymes

The *CYP2D6* gene mapped to the long (q) arm of chromosome 22, region 13.2 (22q13.2) (Wielandt et al., 2022; Dorado et al., 2017; Zanger et al., 2004). The wild-type *CYP2D6*1* allele generates the *CYP2D6*1/*1* genotype that predicts normal metabolizers (NM). The main genotypes predicting intermediate metabolizers (IM) are *CYP2D6*1/*19, CYP2D6*4/*10, CYP2D6*6/*10, CYP2D6*6/*17, CYP2D6*10/*10, CYP2D6*10/*19, CYP2D6*10/*41, CYP2D6*19/*41* and *CYP2D6*49/*49*; while *CYP2D6*3/*3, CYP2D6*4/*4* and *CYP2D6*5/*5* predict poor metabolizers (PM) (Rojas-Macetas et al., 2023; Alvarado et al., 2021). The gene encodes the protein cytochrome P450 2D6 (CYP2D6) that is expressed in the liver (it constitutes 2% of the total content of CYP 450), and in a lower percentage is found in the brain, where it could metabolize antipsychotics (Ur Rasheed et al., 2017; Peñas-Lledó and Llerena, 2014). This enzyme is responsible for metabolizing approximately 25% of the drugs used in clinical practice (Wielandt et al., 2022; Alvarado et al., 2021; Neyshaburinezhad et al., 2021).

The *CYP1A2* gene is located on the long (q) arm of chromosome 15, region 24.1 (15q24.1) (Zhou et al., 2009). The *CYP1A2*1A/*1A* genotype predicts NM and the *CYP1A2*1C/*1C* genotype predicts PM (Forster et al., 2021). This gene encodes the CYP1A2 protein which accounts for 8%–15% of the total CYP 450 content of hepatocytes (Al-Ahmad et al., 2017; Zhou et al., 2009). This enzyme participates in the hydroxylation or dealkylation of various drugs used clinically (Wielandt et al., 2022; Zhou et al., 2009).

The *CYP2C9* gene is mapped to the long (q) arm of chromosome 10, region 24 (10q24) and the wild-type allele *CYP2C9*1* generates the *CYP2C9*1/*1* genotype that predicts NM (Karnes et al., 2021; Céspedes-Garro et al., 2015). *CYP2C9*1/*2, CYP2C9*2/*2* and *CYP2C9*1/*3* genotypes predict IM (Alvarado et al., 2025; de Andrés et al., 2021); *CYP2C9*2/*3, CYP2C9*3/*3, CYP2C9*5/*5* and *CYP2C9*6/*6* predict PM (de Andrés et al., 2021; Karnes et al., 2021). This gene encodes the CYP2C9 enzyme, which is expressed in the liver and represents 18% of CYP 450 proteins and metabolizes approximately 15% of clinically used drugs (Wielandt et al., 2022; Johannessen Landmark et al., 2020; Alvarado et al., 2019).

The *CYP2C19* gene is located on the long arm (q) of chromosome 10, region 24.1 (10q24.1), and the wild allele *CYP2C19*1* generates the *CYP2C19*1/*1* genotype that predicts NM (Maruf et al., 2019; Yin and Miyata, 2011). *CYP2C19*1/*2* predicts MI (de Andrés et al., 2021), *CYP2C19*2/*2, CYP2C19*2/*3, CYP2C9*3/*3, CYP2C19*4/*4, CYP2C19*5/*5, CYP2C19*6/*6* and *CYP2C19*7/*7* predict PM (Alvarado et al., 2023a; de Andrés et al., 2021). This gene encodes the CYP2C19 protein that metabolizes various drugs (Skadrić and Stojković, 2020; Bousman et al., 2019).

The *CYP3A4* gene is mapped to the long (q) arm of chromosome 7, region 22.1 (locus 7q22.1), and the wild-type allele *CYP3A4*1.002* (previously known as *CYP3A4*1A*), generates the *CYP3A4*1/*1* genotype that predicts normal metabolizers (NM) (Musyoka et al., 2024; Wielandt et al., 2022). *CYP3A4*2/*2* is the genotype that predicts MI, while *CYP3A4*3/*3, CYP3A4*20/*20* and *CYP3A4*22/*22* genotypes predict poor metabolizers (Zhou et al., 2019; Apellániz-Ruiz et al., 2015). This gene encodes the CYP3A4 protein that is expressed in the liver (60% of total CYP450) and intestine (70% of total CYP450) (Alvarado et al., 2023b; Zhou et al., 2019). This enzyme is responsible for the oxidative metabolism of 30% of drugs in clinical use, therefore, the allelic variants that encode it can modify the pharmacokinetic parameters, be involved in the toxicity and clinical outcome of pharmacological treatment (Collins and Wang, 2022; Wielandt et al., 2022).

2.2 Metabolism of the principal SGAs

Regarding the metabolism of the six SGAs, it has been described that aripiprazole is metabolized by phase I of hydroxylation and dehydrogenation. Aripiprazole is converted to 4-hydroxy-aripiprazole by CYP3A4/CYP2D6 and subsequently metabolized by glucuronidation; dehydrogenation produces the active metabolite dehydroaripiprazole (Caccia, 2007). The metabolite dehydroaripiprazole undergoes two reactions, the first reaction is hydroxylation to generate 4-hydroxy-dehydroaripiprazole, this process occurs through the action of CYP3A4/CYP2D6, subsequently 4-hydroxy-dehydroaripiprazole is metabolized by glucuronidation; The second reaction is by N-dealkylation at the piperazinyl nitrogen, originating dehydroaripiprazole acid and 1-(2,3-dichlorophenyl)-piperazine, this process is generated with the participation of the CYP3A4 isoenzyme (Caccia, 2007). The CYP3A4 isoenzyme participates in a third metabolic pathway of N-dealkylation of aripiprazole at the piperazinyl nitrogen level, producing butoxy-3,4-dihydro-1H-quinolin-2-one acid and 1-(2,3-dichlorophenyl)-piperazine. The metabolite 1-(2,3-dichlorophenyl)-piperazine is converted into p-hydroxy-(2,3-dichlorophenyl)-piperazine with the participation of CYP2D6, and subsequently this last metabolite undergoes phase II of glucuronidation, for this, UDP-glucuronosyl transferase (UGT) transfers the glucuronic group from UDP-α-D-glucuronic acid (UDPGA) to generate the metabolite O-β-glucuronide of (2,3-dichlorophenyl)-piperazine (Caccia, 2007).

Clozapine is a tricyclic dibenzodiazepine derivative that is metabolized by phase I N-demethylation by CYP1A2 and CYP3A4 to generate the active metabolite norclozapine or N-desmethylclozapine (Kappel et al., 2024; Albitar et al., 2020), by hydroxylation with the participation of CYP2D6, CYP2C19 and CYP3A4, hydroxy-clozapine is formed. Clozapine N-oxidation generates the clozapine N-oxide metabolite, and the isoenzymes CYP3A4, CYP3A5, CYP1A2, CYP2C8 and CYP2C19 participate in this metabolic reaction. In phase II of N-glucuronidation, UDP-glucuronosyl transferase 1A3 (UGT1A3) transfers the glucuronic acid group from UDP-α-D-glucuronic acid (UDPGA) to generate the clozapine N-glucuronide metabolite (Hiemke et al., 2018; Mauri et al., 2018).

Olanzapine is a thienobenzodiazepine derivative that is metabolized by phase I into 4′-N-desmethylolanzapine and 7-hydroxyolanzapine by CYP1A2. CYP2D6, CYP3A4, and CYP2C9 convert olanzapine to 2-hydroxymethylolanzapine; CYP2D6 and flavin-containing monooxygenase 3 (FMO3) produce olanzapine N-oxide, all of which have low pharmacological activity (Kolli et al., 2023; Soria-Chacartegui et al., 2021). By the phase II reaction, olanzapine is directly conjugated (N-glucuronidation) with the participation of UDP-glucuronosyl transferase 1A4 (UGT1A4) and UGT2B10, which catalyzes the transfer of the glucuronic acid group from UDP-α-D-glucuronic acid (UDPGA), forming the metabolite 10-N-glucuronide of olanzapine (Kolli et al., 2023; Rojas-Macetas et al., 2023; Soria-Chacartegui et al., 2021).

Risperidone is a benzisoxazole derivative metabolized by phase I into (+)-9-hydroxyrisperidone (paliperidone) catalyzed by CYP2D6, and to a lesser extent it is metabolized by CYP3A4 forming (−)-9-hydroxyrisperidone (Soria-Chacartegui et al., 2021; Spina et al., 2020). A fraction of the drug is metabolized by N-dealkylation with the participation of CYP3A4 and CYP3A5, originating inactive metabolites (Soria-Chacartegui et al., 2021), the hydroxylated metabolites are then metabolized by phase II conjugation with UDP-glucuronosyl transferase (UGT) which transfers the glucuronic acid group from UDP-α-D-glucuronic acid (UDPGA) to the drug to form the O-β-glucuronide metabolite of risperidone which is eliminated in the urine (Rojas-Macetas et al., 2023). The half-life ($t_{1/2}$) of risperidone is 3 h, and the active metabolite is between 20 and 24 h (Soria-Chacartegui et al., 2021). Conjugated and inactive metabolites are eliminated 70% in the urine and 14% in the bile; in cases of liver and kidney dysfunction, dose adjustment is required (Schoretsanitis et al., 2017).

Paliperidone is a metabolite of risperidone and chemically is a benzoisoxazole derivative (Vermeir et al., 2008) which is metabolized by phase I oxidation by CYP3A4 and minimally by CYP2D6 (Kanu et al., 2024). In normal metabolizers (NM), inducers (carbamazepine and others) of CYP3A4 and ABCB1 increase metabolism and decrease the plasma level of the drug (de Leon,

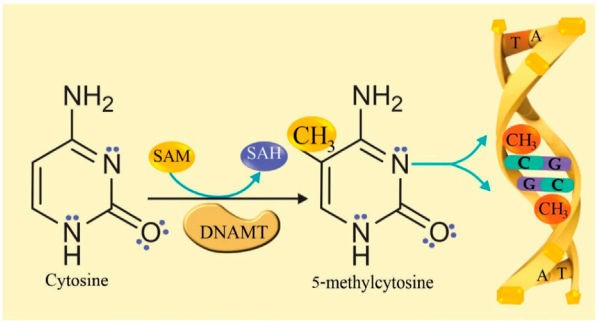

FIGURE 1
DNA methylation reaction mechanism. The enzyme DNA methyltransferase (DNMT) transfers a methyl group from S-adenosylmethionine (SAM) to C-5 of cytosine, forming 5-methylcytosine (5 mC). SAM is converted to S-adenosylhomocysteine (SAH).

2020). The elimination half-life ($t_{1/2}$) is 23–30 h, allowing a daily dose to be administered to maintain therapeutic plasma levels (Mauri et al., 2018; Vermeir et al., 2008). 60% is excreted unchanged in the urine and 10% in the bile (Mauri et al., 2018).

Quetiapine is a dibenzothiazepine that undergoes three phase I metabolic reactions: CYP3A4 metabolizes 89% of the quetiapine dose forming norquetiapine or N-desalkyl quetiapine, which is further metabolized by CYP2D6 to form 7-hydroxy N-alkyl quetiapine, this metabolite is converted into an inactive molecule by the action of the enzyme catechol O-methyltransferase (COMT). The second reaction is generated by the action of CYP2D6, converting quetiapine into 7-hydroxyquetiapine, which is biotransformed by COMT into an inactive metabolite. A third metabolic pathway activated by CYP2C9, CYP2C19, CYP1A2 and CYP3A5 biotransforms quetiapine into an inactive metabolite (Zubiaur et al., 2021; Kim et al., 2016).

3 General epigenetic molecular mechanisms

3.1 DNA methylation

DNA methylation is a normal mechanism that is generated in cytosine and in specific loci, and regulates gene transcription by direct or indirect process, directly prevents the binding of transcription factors in short DNA sequences in gene promoters, and indirectly interferes with the recruitment of corepressors by the action of methyl-CpG binding proteins (MBP) (Fitz-James and Cavalli, 2022; Li and Tollefsbol, 2021). DNA methylation occurs when DNA methyltransferase (DNMT) transfers a methyl group from S-adenosylmethionine (SAM) to C-5 of the cytosine ring that is linked to guanine (CpG) forming 5-methylcytosine (5 mC), and SAM is converted to S-adenosylhomocysteine (SAH), which loses adenosine to form homocysteine. Ten-eleven translocation (TET) enzymes subsequently convert 5mC to 5-hydroxymethylcytosine (5hmC), this occurs in the sequence of the dinucleotide CpG (Cytosine-Guanine) or CpHpG (where H can be A, T, C). The conversion occurs in the 5′to 3′direction of DNA during replication where a cytosine and a guanine are adjacent (Li and Tollefsbol, 2021; Richa and Sinha, 2014). The reaction mechanism of DNA methylation is proposed in Figure 1.

3.2 Histone methylation

Histones (H) are proteins that package DNA into nucleosomes, are found in chromosomes (Strahl and Allis, 2000; Liu et al., 2023) and regulate gene expression (Strahl and Allis, 2000). This molecule experiment methylation and acetylation reactions at specific amino acid residues, generating suppression or activation of transcription (Strahl and Allis, 2000). Methylation, dimethylation or trimethylation of lysine 9 (K9) of histone 3 (H3K9, H3K9me2 or H3K9me3), di- or tri-methylation of K27 of H3 (H3K27me2 or H3K27me3) in the promoter regions of genes and transcription start sites, they are epigenetic marks that produce suppression of gene transcription and, therefore, the genes that code for their respective proteins or enzymes are not expressed (Wang et al., 2008; Strahl and Allis, 2000; Abu-Hanna et al., 2022; Duan et al., 2022). Dimethylation of K4 (H3K4me2) (Wang and Helin, 2025), tri-methylation of K4 on H3 (H3K4me3) (Park et al., 2015), di- or tri-methylation at K36 of H3 (H3K36me2 or H3K36me3) (Wang et al., 2008; Duan et al., 2022) activate gene transcription and, therefore, the gene is more likely to be expressed and encode enzymes or proteins with greater activity, but it is not a unique and absolute signal of activation since there are other activating factors (Strahl and Allis, 2000; Park et al., 2015; Zhang et al., 2019; Liu et al., 2023; Wang and Helin, 2025). Histone methylation is a molecular mechanism that can alter the structure of chromosomes. This mechanism is catalyzed mainly by histone methyltransferase (HMT). These are two enzymes, the first is histone lysine methyltransferase (KMT) and depending on the sequence of the catalytic domain they can be SET and non-SET type, the SET domain includes SUV39H1/2, G9a, GLP, SMYD, SETDB1, EZH2 and others. The second HMT is the protein arginine methyltransferase (PRMT) which are of two classes, the first class consists of PRMT1, PRMT3, PRMT4, PRMT6 and PRMT8, responsible for the monomethyl arginine reaction (Guccione et al., 2021; Saha and Muntean, 2021; Torcal Garcia and Graf, 2021; Barghout et al., 2022). The amino acid sequence of the N-terminus of histone 3 is schematically represented in Figure 2 for illustrative purposes (not an accurate representation of the sequence): alanine (A), arginine (R), threonine (T), lysine (K4), glutamine (Q), threonine (T), alanine (A), arginine (R), lysine (K9), serine (S), threonine (T), glycine (G), glycine (G), lysine (K), alanine (A), proline (P), arginine (R), lysine (K), glutamine (Q), leucine (L), alanine (A), threonine (T), lysine (K), alanine (A), alanine (A), arginine (R), lysine (K27), serine (S), alanine (A), and proline (P). K4 and K27 are susceptible to methylation and K9 is susceptible to acetylation (Strahl and Allis, 2000). The reaction mechanism of histone methylation is proposed in Figure 2.

3.3 Histone acetylation

Acetylation of the lysine residue of histones is the main mechanism (Li and Tollefsbol, 2021; Duan et al., 2022). Histone

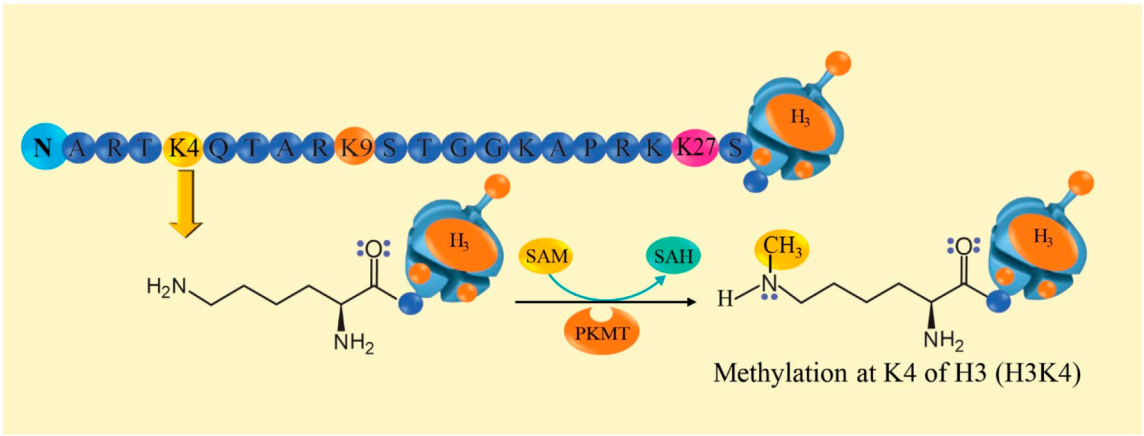

FIGURE 2
Histone methylation reaction mechanism. At the top, an amino acid sequence of the long tail of histone 3 (H3) is observed, with lysine 4 (K4) being susceptible to methylation. The mechanism of methylation is proposed: the histone lysine methyltransferase (PKMT) transfers a methyl group from S-adenosylmethionine (SAM) to the amino terminal group of histones 3 K4 (H3K4), this alters the binding of the histone to DNA. SAM is converted to S−adenosylhomocysteine (SAH).

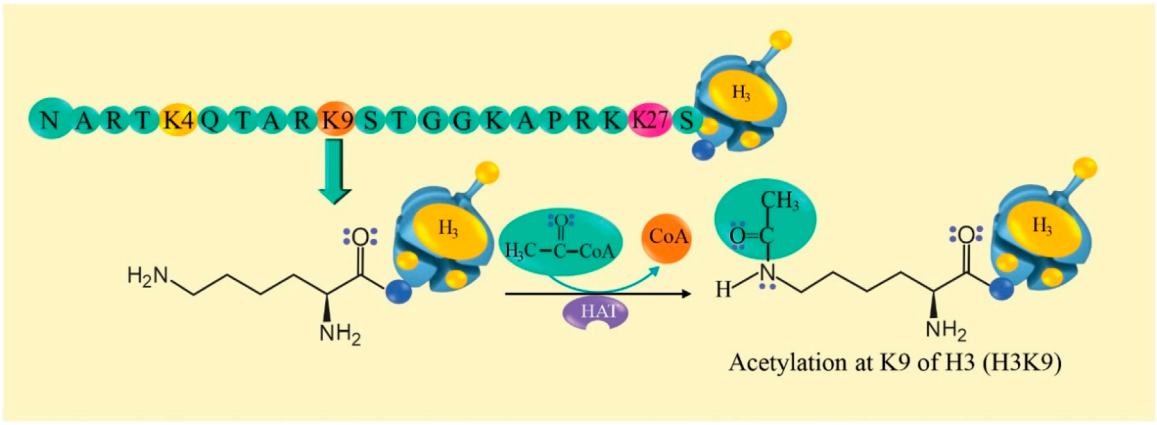

FIGURE 3
Histone acetylation reaction mechanism. At the top, an amino acid sequence of the long tail of histone 3 (H3) is observed. Lysine 9 (K9) of H3 is susceptible to the acetylation reaction. In the reaction, it is observed that histone acetyl transferase (HAT) transfers an acetyl group from "acetyl-CoA" to K9 of H3 (H3K9ac) and this could activate gene transcription.

TABLE 1 Epigenetic molecular mechanism in pharmacogenes DNA.

Author	Pharmacogenes	Epigenetic molecular mechanism	Conclusions and their importance
Helsby and Burns. (2012)	*CYP2C19*	Methylation in the promoter region of DNA.	It causes silencing in one of the *CYP2C19* alleles, affecting the hepatic expression of the CYP2C19 enzyme
Habano et al. (2015)	*CYP2D6* *CYP1A2* *CYP2C19*	Methylation of the exons and the 5′regulatory region (5′UTR) of the *CYP2D6, CYP1A2* and *CYP2C19* genes	The DNA methylation mechanism silences one of the alleles of the genes studied, decreasing the expression of the enzymes, and this contributes to inducing adverse drug reactions
Vyhlidal et al. (2016)	*CYP3A4*	Methylation occurs in the promoter region of DNA.	Changes occur in the expression of mRNA for its enzyme
Shi et al. (2017)	*CYP2D6* *CYP3A4*	DNA methylation in the body of the *CYP2D6* gene CpG dinucleotide methylation in the promoter region of the *CYP3A4* gene	The CYP2D6 enzyme could decrease its functional activity and induce risperidone-induced adverse reactions

TABLE 2 Epigenetic molecular mechanism in pharmacogene histones and its clinical importance.

Author	Pharmacogenes	Epigenetic molecular mechanism	Conclusions and their importance
Kacevska et al. (2012)	*CYP3A4*	CpG hypermethylation of the *CYP3A4* regulatory region	Hypermethylation of the *CYP3A4* gene results in repression of gene transcription and therefore the CYP3A4 enzyme is not expressed. This allows us to understand interindividual differences in drug response
He et al. (2016)	*CYP3A4*	Di-methylation at K4 of H3 (H3K4me2) activates gene transcription Tri-methylation at K27 of H3 (H3K27me3) suppresses gene transcription	Methylation may affect *CYP3A4* mRNA expression in adult liver Epigenetic changes in H3K27me3 and H3K4me2 are associated with development from conception to adulthood
Park et al. (2015)	*CYP2D6* *CYP1A2*	Tri-methylation at K4 of H3 (H3K4me3) of the *CYP2D6* promoter region in hPH. Tri-methylation at K27 of histone-3 (H3K27me3) in hESC-Hep suppresses *CYP1A2* transcription Tri-methylation of K4 on H3 (H3K4me3) in the *CYP1A2* body region activates transcription in hPH.	The limited expression of *CYP2D6* and *CYP1A2* genes in hESC-Hep is modulated by epigenetic regulatory factors such as DNA methyltransferases (DNMTs)

H3K27me3: tri-methylation at lysine 27 (K27) of histone-3 (H3); H3K4me2: di-methylation at lysine 4 (K4) of histone-3 (H3); hESC-Hep: human embryonic stem cells; hPH: human primary hepatocytes; CpG: dinucleotides.

acetyl transferase (HAT) transfers an acetyl group from "acetyl-CoA" to histone lysine, which causes structural changes in the nucleosome and activation of transcription, while histone lysine deacetylase inhibitors deacetylate histones (HDAC) and repress gene transcription, this establishes a balance (Sun et al., 2015; Narita et al., 2019; Liu et al., 2023). Histones H3 and H4 are characterized by a long tail that protrudes from a specific position in the nucleosome core (Liu et al., 2023). Lysine (K9) acetylation of histone 3 (H3K9ac) has an activating effect (Strahl and Allis, 2000). The reaction mechanism of histone acetylation is proposed in Figure 3.

4 Pharmacoepigenetics

Pharmacoepigenetics studies the relationship between epigenetic variability and drug response, which could help with personalized drug treatment (Smith et al., 2023).

4.1 Epigenetic molecular mechanisms in pharmacogenes

Pharmacoepigenetic mechanisms such as DNA methylation, post-translational modifications of histones and regulation of microRNAs do not alter the nuclear DNA sequence but affect gene transcription that is expressed in hereditary phenotypic changes that alter the pharmacological response (Li, 2021; Recillas-Targa, 2022). Epigenetic changes in CYP genes are generated during the human growth process (from neonate to adulthood) (Thakur et al., 2021). In each human being and individually, epigenetic changes are generated by two factors, the first by liver dysfunction, which leads to a decrease in the metabolic activity of enzymes (Diep et al., 2017; Bao et al., 2020; Thakur et al., 2021), and the second individual factor is due to pharmacological treatment with enzyme-inducing drugs, which increase the expression of the enzymes and decrease the plasma levels of the drugs, resulting in therapeutic failure (Hakkola et al., 2020; Jin and Zhong, 2023).

4.1.1 DNA methylation in pharmacogenes

Helsby and Burns (2012) observed that the 3′-untranslated region (3′UTR) of the *CYP2C19* gene contains two recognition sites (MRE) for the non-coding RNA microRNA and is susceptible to methylation generating suppression of gene translation. The tissue used was Human Hepatoma HepG2 Cells. In another study, DNA methylation of the *CYP2C19* gene was confirmed after using 5-aza-2′-deoxycytidine (5azaDC) as a methyltransferase inhibitor, but the existence of other, yet unidentified, epigenetic regulators of *CYP2C19* transcription was also suggested (Burns et al., 2018). Habano et al. (2015) described epigenetic methylation changes in DNA of *CYP2D6, CYP1A2* and *CYP2C19* genes, additionally methylation was evidenced in CpG sites in *CYP2C19* genes. These epigenetic changes were observed in fetal liver tissue (NLF), adult small intestine (NSI) tissue, and three hepatoma cell lines (HepG2, HuH7, and JHH1).

In *CYP3A4* genes, methylation occurs in the DNA promoter region, affecting the binding of RNA polymerase and transcription factors that initiate gene transcription. This study was performed in pediatric and prenatal human liver tissue (Vyhlidal et al., 2016). In another study, methylation was observed in CpG dinucleotides in the promoter region of the *CYP3A4* gene and in the body of the *CYP2D6* gene (Shi et al., 2017). By induced epimutation on the *CYP2D6* gene, cytosine (C) is lost from position 188 and is replaced by thymine (T) in exon 1 (C>T), giving rise to the *CYP2D6*10* allele that expresses low-activity enzymes, which could explain the individual differences in pharmacokinetic parameters and provide new knowledge for the personalized treatment (Yingyuan et al., 2023). Table 1 describes the epigenetic molecular mechanism in pharmacogenes DNA and its clinical implications.

4.1.2 Histone methylation of pharmacogenes

In experimental studies carried out with tissues, methylation has been observed in pharmacogene histones. The study reported by He et al. (2016) has described methylation in the long tail of histone H3 of the *CYP3A4* gene. In another investigation carried out by Park et al. (2015) it has been described that the promoter region of the *CYP2D6* gene contains 12 CpG dinucleotides (cytosine-phosphate-guanine)

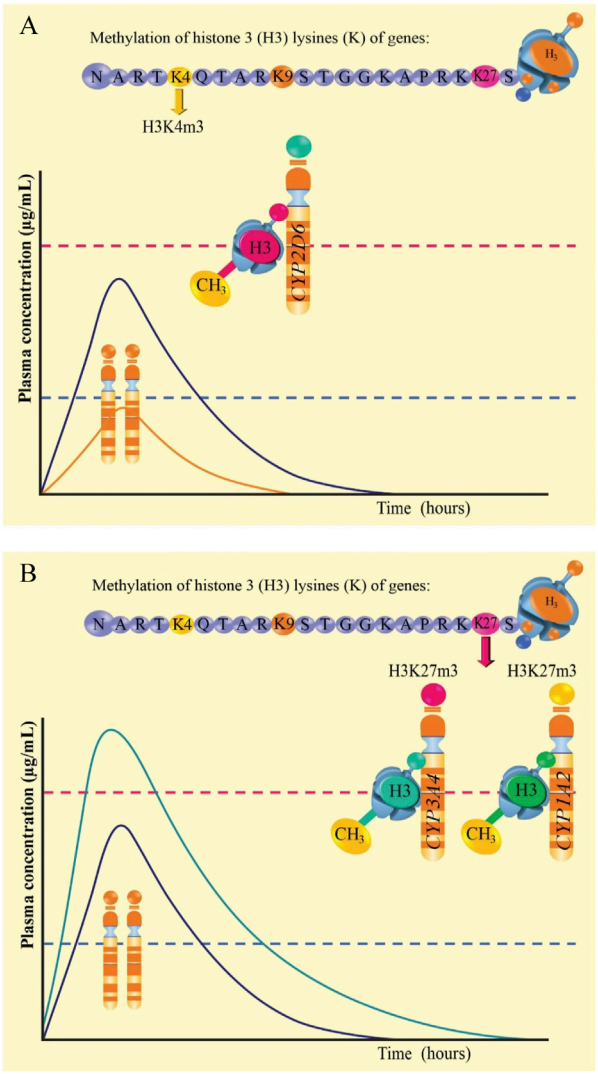

FIGURE 4
Graphic representation of methylation of histone 3 lysine 4 of the *CYP2D6* gene **(A)** and methylation of histone 3 lysine 27 of the *CYP3A4* and *CYP1A2* genes **(B)**.

that are methylated, this has been observed in hepatocytes derived from human embryonic stem cells (hESC-Hep) with a frequency of 96.3%, the body region contains 32 CpG dinucleotides and the methylation frequency was 45.5% in human primary hepatocytes (hPH) and 90.3% in hESC-Hep. The *CYP1A2* gene contains 10 CpG dinucleotides in the promoter region and is fully methylated in hPH and hESC-Hep; the body region of the gene contains 20 CpG dinucleotides, and they are methylated 40.0% and 76.7% in hPH and hESC-Hep, respectively. Table 2 summarizes the epigenetic molecular mechanism in pharmacogenomic histones, the conclusions and their importance.

In Figures 4A,B it is observed the amino acid sequence of the long tail of histone 3 of the *CYP2D6*, *CYP3A4,* and *CYP1A2* genes. In 4A, trimethylation is proposed in lysine 4 (K4) of histone 3 of the *CYP2D6* gene (H3K4m3), generating major genetic transcription and, therefore, active CYP2D6 enzymes would be expressed. This would generate major metabolism and decrease in the plasma level of the drug, even below the minimum effective concentration (below the dashed blue line and orange curve), at the same time, a curve (purple) is indicated within the therapeutic range in patients with normal genotype and phenotype. Figure 4B shows trimethylation at K27 of histone 3 of the *CYP3A4* (H3K27m3) and *CYP1A2* (H3K27m3) genes. This would generate scares or null metabolism, increasing the plasma level of the drug beyond the minimum toxic concentration (above the dashed red line and green curve green), compared to the curve (purple) which is within the therapeutic range.

4.2 Epigenetic molecular mechanisms by enzyme-inducing drugs

Carbamazepine, phenytoin, rifampicin, and others induce *CYP3A4* transcription resulting in increased enzymes (Hakkola et al., 2020), which leads to increased metabolism and decreased plasma levels of aripiprazole, so it may be necessary to double the dose of aripiprazole (DeLeon et al., 2004).

Rifampicin has been reported to activate histone H3 acetylation, activate histone 3-lysine-4 tri-methylation (H3K4me3), and decrease histone-3-lysine-27 tri-methylation (H3K27me3) at promoter regions, which contributes to the induction of *CYP3A4* mRNA expression (Yan et al., 2017). Long non-coding RNAs (lncRNAs) are involved in the induced expression of CYP450 enzymes during treatment with inducing drugs such as rifampicin and phenobarbital (Chen et al., 2018), in another study, hepatocyte nuclear factor 4 alpha antisense RNA 1 (HNF4A-AS1) was reported to induce histone 3 tri-methylation generating H3K4me3 and H3K27me3 (Wang et al., 2021).

4.3 Epigenetic molecular mechanisms induced by drugs used in schizophrenia

It has been studied that some second-generation antipsychotic drugs such as clozapine, risperidone, olanzapine and quetiapine can induce epigenetic demethylation changes (Swathy and Banerjee, 2017). Table 3 summarizes the various studies that describe drug-induced epigenetic molecular mechanisms in schizophrenia.

5 Clinical implications of epigenetic mechanisms

The epigenetic mechanisms of histone trimethylation and DNA methylation in *CYP3A4, CYP2D6, CYP1A2* and *CYP2C9* genes cause silencing in one of the alleles, which would explain the presence of genotypes that predict metabolic phenotypes associated with a higher risk of adverse drug reactions and therapeutic failure in patients receiving second-generation antipsychotic drugs. Therefore, a strategy to demethylate the DNA of GABAergic promoters and dopaminergic receptor type 2 (DR2) would be to use clozapine, olanzapine and risperidone associated with valproic acid (histone deacetylase inhibitor) to ensure the efficacy of the drug in patients with schizophrenia and bipolar disorder. These findings have clinical implications for

TABLE 3 Epigenetic molecular mechanism induced by second-generation antipsychotic drugs and its importance.

Author	Study type	Drug	Epigenetic molecular mechanism	Conclusions and their importance
Dong et al. (2008)	Experimental study in mice	Clozapine	Clozapine increases promoter-associated H3K9 and H3K14 acetylation and causes demethylation of RELN and GAD67 gene promoters (hypermethylated) in striatal GABAergic neurons	DNA demethylation could mediate hypomethylation of the promoter of GABAergic genes (inhibited in psychosis), increasing their expression, alleviating GABA deficiency pathology in schizophrenia and bipolar disorder
Guidotti et al. (2011)	Experimental study in mice	Clozapine and olanzapine	Activates demethylation of the GAD67 promoter in GABAergic neurons	Activating DNA demethylation with clozapine and olanzapine with VPA (histone deacetylase inhibitor, HDAC) may be considered a promising therapeutic strategy to normalize GABAergic promoter hypermethylation and decreased GABAergic gene expression detected in postmortem brains of patients with schizophrenia and bipolar disorder
Melka et al. (2014)	Experimental study in rats	Olanzapine	Olanzapine induces DNA methylation of genes in the dopaminergic pathway that encodes transporter proteins, receptors, nervous system development, and hippocampal functions	Epigenetic changes could be the cause of the improvement in symptoms and could also explain certain adverse effects
Li et al. (2004)	Experimental study in mice	Risperidone	Risperidone blocks DR2 to induce histone 3 phosphoacetylation (H3pS10-acK14) through cAMP-dependent PKA and postsynaptic NMDA receptor signaling H3pS10-acK14 is overexpressed in the striatum	Histone modifications and chromatin structure in striatal neurons are dynamically regulated by dopaminergic and glutamatergic stimuli
Rami et al. (2022)	Experimental study in mice	Risperidone	Methylation at the cytosine-phosphate-guanine 2 (CpG2) site of DRD2 in risperidone-treated mice	Risperidone generates low methylation in DRD2 of PFC and AMY, which improves their expression levels

AMY, amygdala; PFC, prefrontal cortex; DRD2, dopaminergic receptor type 2; H3K9, histone 3 lysine 9; H3K14, histone 3 lysine 14; RELN, RELN, gene encoding the reelin protein; GAD67, glutamate decarboxylase 67; PKA, protein kinase A; cAMP, adenosine 3′,5′-cyclic monophosphate; NMDA, N-methyl-D-aspartate.

schizophrenia, given that specialist physicians have scientific evidence for medical care, their daily clinical practice, and consider it before initiating pharmacological treatment.

The results of this descriptive review have limitations, which may lead to bias. The main one is the limited or scarce scientific literature published on pharmacoepigenetics in schizophrenia, the limited specific literature on epigenetic changes in genes encoding second-generation antipsychotic drug-metabolizing enzymes, and articles with limited methodology (small sample size, *in vitro* study of different tissue types, and experimental animal models). However, this research contributes to updating and synthesizing the pharmacoepigenetic knowledge published to date, while also generating scientific evidence for conducting prospective longitudinal cohort studies, observational studies in humans, standardized epigenetic clinical trials, and integrated pharmacoepigenetic-pharmacokinetic study.

6 Conclusion and future perspectives

Based on the review of published scientific evidence, it is concluded that DNA methylation, histone methylation and acetylation are the most frequent epigenetic mechanisms in the *CYP3A4, CYP2D6*, *CYP1A2* and *CYP2C19* pharmacogenes. At the same time, the use of enzyme-inducing drugs can also generate epigenetic changes.

These epigenetic changes could explain the expression of intra- and interindividual allelic variants and, therefore, influence the efficacy and safety of second-generation antipsychotic drugs used in schizophrenia. On the other hand, further epigenetic studies are required on pharmacogenes and on a greater number of biological samples from patients with schizophrenia, to corroborate the published research that has been summarized in this descriptive review.

These studies are also relevant for medical specialists, who will have an additional tool to consider epigenetic mechanisms as a possible factor influencing drug treatment. At the same time, this study will contribute to the scientific evidence base for promoting the inclusion of epigenetic data in a Pharmacogenomic Guide and implementing personalized or precision genomic medicine in healthcare systems, with the goal of improving the quality of life of patients with schizophrenia.

Author contributions

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