Personalized Psychiatry and Neurology

Lecture

Phase I of Antipsychotics Metabolism and its Pharmacogenetic Testing

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Abstract: Antipsychotics (APs) are a class of psychotrophic medication primarily used to manage psychosis (including delusions, hallucinations, paranoia or disordered thought), principally in schizophrenia but also in a range of other psychotic disorders. Biotransformation is a major mechanism for APs elimination. Most APs undergo biotransformation, or metabolism, after they enter the body. There are three phases of APs metabolism. Cytochrome P450 (CYP) monooxygenase (mixed function oxidase) plays a central role in the most APs biotransformation. CYP's functional activity depends on gene-drug and drug-drug interaction and influences on occurrence of adverse drug reactions (ADRs). So, it is extremely important for a practicing psychiatrist to know the oxidation pathway of APs, since most of them are metabolized in the liver and this is important both to prevent ADRs and to avoid unwanted drug-drug interactions, which will undoubtedly increase the effectiveness and safety of AP therapy.

Keywords: *pharmacogenetics, personalized therapy, phase I, antipsychotics.*

Introduction

Antipsychotics (APs), are a class of psychotrophic medication primarily used to manage psychosis (including delusions, hallucinations, paranoia or disordered thought), principally in schizophrenia but also in a range of other psychotic disorders [1][2]. They are also the mainstay together with mood stabilizers in the treatment of bipolar disorder [3]. First-generation APs (FGAs), conventional or typical antipsychotics, have significant potential to cause extrapyramidal syndrome (akathisia, acute distonic reactions, tardive dyskinesia, pseudoparkinsonism and others) [4]. This propensity to cause movement disorders is the primary difference between FGAs and second-generation APs (SGAs) [5]. In other respects, such as other adverse drug reactions (ADRs) and their mechanism of action, the two classes have substantial overlap and comparable efficacy [6].

Most APs pass through a biotransformation process, or metabolism, after they enter the body before being eliminated [7]. The general principle of biotransformation is the metabolic conversion of APs molecules to more water-soluble metabolites that are more readily excreted.

In the process of APs metabolism most initial APs lose their pharmacological action and are removed from the body through excretion. During biotransformation produced metabolites usually are more polar or charged than the parent APs, this increases the rate of clearance; this modification can also decrease reabsorption in the tubules [8].

In many cases, metabolism of APs results in its conversion to compounds that have little or no pharmacologic activity. In other cases, biotransformation of an active compound may lead to the formation of metabolites that also have pharmacologic actions.

As a result of APs biotransformation new metabolites are formed: with changed and new pharmacological actions, these new metabolites may have both lower and higher potencies in comparison with initial APs, new metabolites may also have a toxic effect, or new metabolites may be active, if the parent APs were prodrugs [9].

Many APs undergo several sequential biotransformation reactions. Biotransformation is catalyzed by specific enzyme systems, which may also catalyze the metabolism of endogenous substances such as steroid hormones. The liver is the major site of biotransformation, although specific APs may undergo biotransformation primarily or extensively in other tissues [10].

Biotransformation reactions occur with the participation of specific enzymes or enzyme systems, these enzymes can catalyze both xenobiotics metabolism, in this case APs, and substances with endogenic origin, such as hormones. Most often, APs biotransformation reactions occur in the liver, however, individual APs undergo these reactions to a greater or lesser extent in other organs and tissues of the human body.

The process of APs biotransformation is quite changeable, this variability depends on many factors, for example:

- nutritional status;
- hormonal status;
- genetic factors;
- previous therapy with APs or other class drugs;
- concomitant somatic, neurological or mental status (for example, diseases of the cardiovascular and respiratory systems may decrease biotransformation, etc.);
- the age of the patient (for example, very old patients or children often have a greater sensitivity to APs, due in part to the involutional or immature state of the enzyme systems by which APs are metabolized);
- functional state of the liver [11].

The APs metabolism of is often divided into three phases: modification (phase I) (**Figure 1**), conjugation (phase II), and excretion (phase III). These reactions act in concert to detoxify xenobiotics and remove them from cells. It is noticeable that biotransformation phases I and II can be sequential, can take place in reverse order or simultaneously, as a single reaction [12].

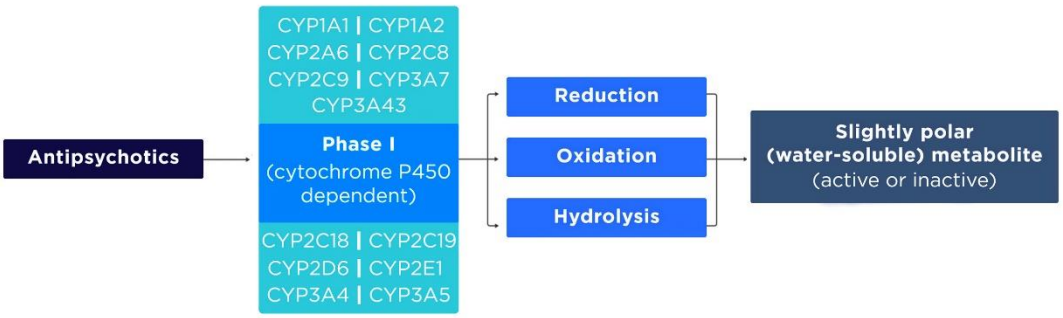

Figure 1. I phase of antipsychotics metabolism.

Phases of Antipsychotics Metabolism

2.1. Phase I of Antipsychotics Metabolism

As a result of phase I reactions, the initial APs usually become less active. These reactions are nonsynthetic or happen in the absence of conjugation processes. Important to note that when the formed metabolites after reaction I become sufficiently polar, they may be immediately excreted from the human body. Otherwise, the following reaction occurs, which combines the formed metabolites with new functional groups to form greatly polar, and therefore more water-soluble active metabolites by unmasking or inserting a polar functional group (-OH, -SH, -NH2) that enable the following stages of biotransformation . APs metabolized via phase I reactions have longer half-lives. Geriatric patients have decreased phase I metabolism, thus geriatric patients metabolism APs by phase II reactions [12, 13].

Reactions of Phase I:

- oxidation;
- hydrolysis;
- reduction.

In these reactions, for subsequent cojugation, functional groups are added to the formed metabolites, which then become the active center in the phase II reaction [14].

Enzymes catalyzing this phase biotransformation are mostly from cytochrome P450 system, flavin-containing monooxygenase system, monoamine oxidase, aldehyde and alcohol dehydrogenase, deaminases, esterases, amidases, and epoxide hydratases [15, 16].

Oxidation reactions, which occur with cytochrome P450 (CYP) enzymes (mixed function oxidases (MFO) or mono-oxygenases) take place in the smooth endoplasmic reticulum (ER) of the cell [28]. These reactions involve cytochrome P450 reductase, Nicotinamide adenine dinucleotide phosphate (NADPH) and oxygen (O2). CYPs enzymes also better metabolize APs with high fat solubility [16].

CYP system is involved in numerous reactions, for example:

- hydroxylation;
- dealkylation;

- deamination;
- sulfoxidation;
- oxidation [17].

NADPH-cytochrome P450 reductase catalyzes reduction reactions mostly in the ER or the cytosol. Which is a membrane-bound enzyme required for electron transfer from NADPH to CYP and other heme proteins including heme oxygenase in the ER of the eukaryotic cell from a flavin adenine dinucleotide (FAD)-and flavin mononucleotide (FMN)-containing enzyme NADPH-cytochrome P450 reductase [18]. The general scheme of electron flow in this system is:

$$NADPH \rightarrow FAD \rightarrow FMN \rightarrow P450 \rightarrow O_2. \quad (1)$$

During reduction reactions, a chemical can enter futile cycling, in which it gains a free-radical electron, then promptly loses it to oxygen (to form a superoxide anion) [19].

Hydrolytic reactions - phase I reaction involving addition of a water molecule with subsequent bond breakage, do not occur in the ER with esterases, amidase and epoxide hydrolase [20].

2.2. Phase II of Antipsychotics Metabolism

Phase II (synthetic) reactions include conjugation reactions, adding highly polar groups (such as glutathione (GSH), sulfate, glycine, acetyl, or glucuronic acid, amino acids, methyl) to the APs to increase renal elimination, which involve the enzyme catalyzed combination of APs (or APs metabolite) with an endogenous substance, though these reactions the activity of drugs is decreased, polarity is increased . Phase II reactions require a functional group—an active center—as the site of conjugation with the endogenous substance [21]. Carboxyl (-COOH), hydroxyl (-OH), amino (NH2) and thiol (-SH) groups that were attached in the previous reactions are now the sites on the APS for conjugation [22]. In this phase less active products are formed that have higher molecular weight than previous substrates in comparison. Also through the attachment of large anionic groups like GSH, more polar metabolites are produced and reactive electrophiles are detoxified. Now these metabolites cannot actively move and diffuse through cell membranes [22]. Phase II reactions can take place on their own or after phase I. The synthesis of endogenous substances, the so-called "activated carriers" that are needed in the conjugation reaction (e.g., uridine diphos-phate-glucuronate) requires energy [23].

Phase II reactions, in particular glucuronidation, take place in the ER. For this uridine diphosphate glucuronic acid (UDPGA) is formed with the help of glucose, the forned acid with the participation of glucuronyl transferase attaches the glucuronide to APs. Also, APs can be conjugated with other substances through transferases, these reactions often occur in the cytosol of the cell.

Numerous transferases in various combinations can metabolize most hydrophobic substances that have nucleophilic or electrophilic groups in phase II reactions [22, 24].

Below are some conjugation enzymes of phase II biotransformation:

- acetylases;
- glucuronyl transferase;
- transacylases;
- sulfotransferase;
- ethylase;
- glutathione transferase;
- methylases [22, 25].

Biotransformation enzymes are present in various organs and tissues in the human organism, also in plasma. In the cell, phase I and II enzymes are found in the mitochondria, ER, and cytosol [12, 22, 25].

2.3. Phase III of Antipsychotics Metabolism

Phase III is the final point of APs transformation and its excretion. Often, phase II products are transported out of the cell via transport proteins of the ATP-binding cassette transporter family, where they undergo further metabolism or excretion. These proteins provide ATP-dependent transport of a wide range of hydrophobic anions. Anionic groups from previous reactions are now affinity tags for these membrane carrier proteins [26].

Oxidation of Antipsychotics in the Liver

The most important role in the metabolism of most APs is played by CYP monooxygenase (mixed function oxidase) [27]. In mammals at least 18 families of enzymes of the CYP system have been discovered so far. Individual enzymes of this system are involved in the biotransformation of certain APs, having a unique substrate specificity, this specificity may partially coincide in different enzymes of the CYP system (Table 1) [28]. Currently at least 50 different P450 enzymes are known, but approximately 12 of them provide biotransformation of the most APs. As mentioned above, the CYP family catalyzes Phase I reactions. Nomenclature: the family number is indicated immediately after the word "CYP" with an Arabic numeral, the subfamily is named by capital letter of the Latin alphabet, the second Arabic numeral after the letter indicates a particular enzyme in a subfamily, as a result, the enzyme designation has next form: CYP2D6, CYP3A4, CYP3A5, etc. [29].

CYP2D6, CYP3A4, CYP3A5, CYP2C9 and CYP2C19 provide most of the activity (more than 50%) of P450, these enzymes prevail among liver enzymes and are involved in the metabolism of most APs [30].

CYP catalyzes numerous reactions, including aromatic and aliphatic hydroxylations; dealkylation at nitrogen, sulfur, and oxygen atoms; heteroatom oxidations at nitrogen and sulfur atoms; reductions at nitrogen atoms; and ester and amide hydrolysis.

Most often, CYP enzymes are located in the liver, but they are also found in other organs and tissues of the human body, for example, in the small and large intestines, testicles or ovaries, duodenum, pancreas, kidneys, spleen, lymph node and others [31,32]. In cells, the enzymes of the CYP system are located in the ER [16].

Phase I involving CYP has an oxidative and a reduction reactions. Synthesis of NADPH is dependent on cytochrome P450 reductase. The cofactor NADPH is involved in the reduction of oxygen to water in the general reaction where AP is oxidized.

The overall reaction for aromatic hydroxylation can be described as:

$$\text{Drug} + O_2 + \text{NADPH} + H^+ \rightarrow \text{Drug} + OH + \text{NADP}^+ + H_2O \text{ [33].} \quad (2)$$

CYP activity is variable and depends, among other things, on drug-drug interaction, APs and other drugs may modulate the work of particular CYP enzymatic pathways. Thus, the metabolism of concomitantly administered drugs may be changed. All drugs, including APs, can be divided into 3 groups related to the CYP system: substrates, inducers and inhibitors of this system. Substrates are drugs metabolized under the CYP enzymes catalytic activity [34].

P450 inhibitors are drugs that inhibit the biotransformation of drugs metabolized by the certain CYP enzyme, inhibiting drug if metabolized by the same CYP enzyme is also suppressed. There is competitive inhibition, if drugs compete for the CYP enzyme, and non-competitive, if a certain drug tightly binds to the CYP. Inhibition raises therapeutic drug level (danger of toxicity) [34]. The are a lot of inhibitors among different drug groups, for example: APs (haloperidol, olanzapine, clozapine and others), ADs (fluvoxamine, clomipramine, duloxetine and others), antiepileptic drugs (valproic acid, phenytoin, topiramate and others), somatic drugs (isoniazid, cimetidine, ketoconazole, fluconazole and others) [35], acute alcohol abuse, grapefruit juice [36].

P450 inducers increase the amount of P450 enzymes *in vivo*. This process is associated with the activation of enzyme synthesis, lowers therapeutic drug level. A decrease in the therapeutic level of the drug, in particular APs, may occur due to the induction of the CYP enzymes, since the metabolism of drugs catalyzed by a certain enzyme is accelerated, as well as the metabolism of the inducer itself is accelerated too if it is metabolized by the same CYPs [37]. Induction can be caused by a wide variety of clinically useful drugs (drug–drug interactions), such as APs (clozapine, chlorpromazine and others), antiepileptic drugs (phenytoin, carbamazepine, topiramate and others), somatic drugs (griseofulvin, troglitazone, omeprazole [35], St. John's wort [36] and others), chronic alcohol abuse [36] and by environmental agents such as tobacco smoke [38].

Inducing drugs as well as inhibiting drugs induces or inhibits a certain CYP enzyme or a certain group of CYP enzymes. [35, 36, 38].

Considering APs metabolism in the liver we should also concern the extraction ratio and first-pass effect definitions.

Liver has a large size (1,500 g) and high blood flow (1 mL/g/min), which provides massive excretion of drugs, in particular APs, by the liver. The amount of drug remoted by liver divided by the amount of drug entering the organ is the extraction ratio; extraction ratio is 1, when a drug removed totaly by the liver [39]. Hepatic clearance may be close to 1,500 mL/min if APs is highly extracted by the liver [40]. The bioavailability of some orally administered drugs is reduced because its fraction was removed during the first pass through the liver. This effect is called the first pass effect. APs taken orally pass across

membranes of the gastrointestinal tract into the portal vein and through the liver before entering the general circulation have first-pass effect. For example, a drug with a hepatic extraction ratio of 1 would have 0% bioavailability; a drug such as aripiprazole, with an extraction ratio of 0.13, would have 87% bioavailability. In the presence of hepatic disease, APs with a high first-pass extraction may reach the systemic circulation in higher than normal amounts, and dose adjustment may be required. The rate of metabolism is first order for most APs. First-order metabolism is proportional to the concentration of free drug. A constant fraction of drug is metabolized per unit of time (i.e., the metabolism of the drug has a half-life) [39].

Some clinically relevant CYPs, such as CYP2C and CYP2D, have genetic polymorphisms, which influences on metabolic variability in individuals. For example, different races and ethnic groups have different variability of certain enzymes. Since a genetically determined difference in the properties of CYP enzymes, such as Vmax or Km, affects the rate of APs metabolism, this should be taken into account when selecting therapy [41]. For example: the CYP3A subfamily is responsible for up to half of the total cytochrome P-450 in the liver. CYP3A4 is the most abundant hepatic enzyme and is involved in the metabolism of over 50% of clinically important APs. APs or other agents that are inhibitors or inducers of the CYP system can cause adverse drug reactions (ADRs) due to altered metabolism of these enzymes, which affects the concentration of metabolized drugs by influencing Phase I reactions [42].

Enzymes of Cytochrome P450 Function and Antipsychotics Metabolism

The FGAs can interact with drugs that have potent effects on CYP metabolism, including the antidepressants (fluoxetine, paroxetine, and bupropion), which inhibit CYP2D6, and the mood stabilizer (carbamazepine), which induces CYP1A2 and CYP3A4 (Table 1) [43, 44]. The impact of CYP induction or inhibition on serum levels of most FGAs is moderated somewhat in the drugs that have multiple pathways for clearance, including chlorpromazine, haloperidol, loxapine, perphenazine, and thioridazine [35].

Fluphenazine: This AP has a single primary pathway via CYP2D6 and is more susceptible to interactions with inhibitors of this enzyme than are other FGAs. Fluphenazine is not recommended for concurrent use with strong CYP2D6 inhibitors [45].

Pimozide levels are moderately sensitive to inhibition of CYP2D6, but due to the risk for QTc interval prolongation, the use of pimozide with strong CYP2D6 inhibitors is contraindicated [46].

Chlorpromazine: It is also sensitive to induction of CYP1A2, such as occurs with heavy smoking, a quality it shares with thiothixene. A patient who is stabilized on one of these drugs in a nonsmoking environment, such as a hospital, may experience a drop in serum levels upon returning home and resuming smoking. In each of these cases, a moderate dose increase may be required [47-49].

Most SGAs depend on cytochrome P450 enzymes for metabolism, and some have significant increases or decreases in serum levels when used with inducers or inhibitors of these enzymes. As a general rule, however, these interactions are mild and readily

manageable with dose adjustments as noted below. A list of common medications that are significant inhibitors or inducers of CYP3A4 is provided in the table (Table 1) [43, 44]. In a few cases, specific medications with overlapping side effects should be avoided, most notably those with cardiac, sedative, anticholinergic, or metabolic risk. Even in these cases, however, the risk is relative and can usually be managed without a radical change in treatment. The most noteworthy interactions are described below:

Aripiprazole: Dopamine D2 receptor blockade may be unpredictable when the partial agonist aripiprazole is given simultaneously with other APs (all of which are dopamine antagonists), as might occur during a transition between drugs. This can lead in some cases to a paradoxical reduction in dopamine blockade and reduced antipsychotic effect as the dose of aripiprazole is increased. Aripiprazole is metabolized via CYP2D6 and CYP3A4 [50]. The manufacturer recommends a twofold dose increase when administered with inducers such as carbamazepine, twofold dose reduction in dose with inhibitors such as fluoxetine, quinidine, or ketoconazole [35].

Asenapine: This AP with substantial metabolism occurring through both CYP1A2 and glucuronidation, in cases of drug-drug interactions involving asenapine generally dose change is not necessary. Mild drug-drug interactions are possible with medications having similar ADRs, such as sedation, weight gain, or parkinsonism [51] .

Brexpiprazole: The drug is metabolized by CYP2D6 and CYP3A4; inhibitors of either enzyme cause a twofold increase in serum levels, and the CYP3A4 inducer rifampin caused a 75% reduction in serum level [52]. The manufacturer recommends dose adjustments accordingly. As with aripiprazole, the combination of this dopamine partial agonist with a dopamine antagonist can lead to unpredictable levels of dopamine D2 receptor blockade and a paradoxical reduction in efficacy when the drug is combined with a dopamine antagonist. However, when compared with aripiprazole, brexpiprazole has lower intrinsic activity at the dopamine D2 receptor [53].

Cariprazine: Both the parent drug and its active metabolites are primarily eliminated via CYP3A4, and are susceptible to changes in the activity of that enzyme. A dose reduction of 50% is recommended in the presence of CYP3A4 inhibitors [54]. The effect of CYP3A4 inducers has not been evaluated.

Clozapine: Drug-drug interactions are significant with clozapine and can arise through several possible mechanisms [55]. Metabolism occurs primarily via CYP1A2 and CYP3A4, with a smaller contribution from CYP2D6; strong CYP1A2 inhibitors, such as fluvoxamine or ciprofloxacin, may require a reduction to one-third of the original dose. Because of clozapine's risk of agranulocytosis and its strong anticholinergic, sedative, cardiac, and hypotensive properties, other agents with these characteristics should be avoided or used with care. Smokers may require a twofold increase in dose compared with nonsmokers, and a reduction of 30 to 40% may be required when a smoker is admitted to a hospital or other nonsmoking environment [56].

Iloperidone: Serum levels of iloperidone increase with CYP2D6 and CYP3A4 inhibitors, and the manufacturer recommends dosage reduction by half for simultaneous use of inhibitors: fluoxetine, paroxetine [57].

Lumateperone: This drug is metabolized by CYP3A4, 2C8, and 1A2 enzymes. Medications that are moderate or strong inhibitors or inducers of CYP3A4 should be avoided. Concomitant use with uridine diphosphoglucuronate glucuronosyltransferase inhibitors, such as valproic acid, may increase levels of lumateperone and should be avoided [58].

Lurasidone: The major route of metabolism of lurasidone is via CYP3A4. The co-administration of strong inhibitors or inducers of CYP3A4 such as rifampin or ketoconazole with lurasidone is contraindicated [59].

Olanzapine: the medication is dependent on CYP1A2 metabolism [60]. Co-administration with strong inhibitor or inducers CYP1A2 drugs can affect olanzapine serum level, for example cigarette smoking decreases its serum concentration.

Paliperidone: This drug is not dependent on liver metabolism and therefore has no significant drug-drug interactions based on enzyme induction or inhibition. However, it may be necessary to increase the dose of paliperidone when a strong inducer of both CYP3A4 and P-glycoprotein 1 (eg, carbamazepine, rifampin, St. John's wort) is co-administered. Conversely, on discontinuation of the strong inducer, it may be necessary to decrease the dose of paliperidone. Mild interactions are possible with medications having similar ADRs, such as sedation, weight gain, or parkinsonism [61].

Pimavanserin: The major route of metabolism of this drug is via CYP3A4 and to a lesser extent CYP3A5, both of which convert it to an active metabolite. Dose adjustment is recommended when the drug is used simultaneously with strong CYP3A4 inhibitors. Additionally, the drug is not recommended for use with other agents that may prolong QT interval [62].

Quetiapine: Metabolism depends on CYP3A4 functioning, and the manufacturer recommends up to a fivefold increase in dose with inducers such as carbamazepine and a reduction to one-sixth the dose with strong CYP3A4 inhibitors such as voriconazole or ritonavir [63, 64]. A list of strong inhibitors and inducers of CYP3A4 is provided in the Table 1 [35, 36, 38, 43, 44]. ADRs may worsen when the drug is combined with other agents that cause sedation, anticholinergic effects, arterial hypotension, or weight gain.

Risperidone: Drug-drug interactions involving risperidone are infrequent, but it is metabolized primarily through CYP2D6, and its serum levels are increased by strong CYP2D6 inhibitors such as fluoxetine and paroxetine, and to a lesser degree by bupropion [65].

Ziprasidone: Metabolic clearance of ziprasidone occurs mostly via glutathione and aldehyde oxidase, with a minor contribution from CYP3A4, so inhibitors and inducers of the cytochrome P450 system show only modest effects [66].

The most drugs, including APs, which are substrates, inducers and inhibitors related to the CYP system, are shown in Table 1 [35, 36, 38, 43, 44].

Table 1. Antipsychotics substrates, inducers and inhibitors of cytochrome P450.

Antipsychotics		
Substrates	**Inhibitors**	**Inducers**
	CYP1A1	
Partly: Haloperidol Olanzapine Perospirone		Clozapine
	CYP1A2	
Primary: Asenapine Clozapine Loxapine Olanzapine Pimozide Thiothixene Trifluoperazine Partly: Chlorpromazine Haloperidol Lumateperone Perphenazine Promazine Quetiapine Thioridazine Zotepine	Promazine Remoxipride	
	CYP2A6	
Partly: Clozapine Promazine		
	CYP2C8	
Partly: Clozapine Lumateperone Perospirone Perphenazine		
	CYP2C9	
Partly: Clozapine Haloperidol Olanzapine Perphenazine Promazine		
	CYP2C18	
Partly: Perphenazine		
	CYP2C19	
Partly: Clozapine	Clozapine Olanzapine	

Haloperidol	
Perphenazine	
Promazine	
Pipotiazine	
Quetiapine	
Risperidone	
Thioridazine	
	CYP2D6
Primary:	Amoxapine
Aripiprazole	Chlorpromazine
Brexpiprazole	Clozapine
Chlorpromazine	Fluphenazine
Fluphenazine	Haloperidol
Haloperidol	Melperone
Iloperidone	Methotrimeprazine
Loxapine	Olanzapine
Perphenazine	Perphenazine
Pimozide	Pimozide
Risperidone	Pipotiazine
Thioridazine	Risperidone
	Thioridazine
Partly:	Thiothixene
Alimemazine	
Amoxapine	
Aripiprazole lauroxil	
Azenapine	
Cariprazine	
Clozapine	
Clozapine	
Flupentixol	
Levomepromazine	
Mesoridazine	
Methotrimeprazin	
Olanzapine	
Paliperidone	
Perospirone	
Pipotiazine	
Prochlorperazine	
Promazine	
Quetiapine	
Remoxipride	
Sertindol	
Trifluperazine	
Zuclopenthixol	
	CYP2E1
Partly:	Fluphenazine
Clozapine	Methotrimeprazine
Iloperidone	Thioridazine

CYP3A4		
Primary:	Clozapine	Chlorpromazine
Aripiprazole	Haloperidol	Clozapine
Brexpiprazole	Olanzapine	
Cariprazine	Remoxipride	
Haloperidol		
Loxapine		
Lumateperone		
Lurasidone		
Perphenazine		
Pimavanserin		
Pimozide		
Quetiapine		
Ziprasidone		
Partly:		
Alimemazine		
Asenapine		
Clozapine		
Fluspirilene		
Iloperidone		
Paliperidone		
Penfluridol		
Perospirone		
Pipotiazine		
Promazine		
Risperidone		
Sertindol		
Zotepine		
Zuclopenthixol		
CYP3A5		
Primary:	Remoxipride	
Aripiprazole	Reserpine	
Aripiprazole lauroxil		
Clozapine		
Haloperidol		
Iloperidone		
Olanzapine		
Paliperidone		
Partly:		
Pimavanserin		
Pimozide		
Quetiapine		
Risperidone		
CYP3A7		
Partly:	Remoxipride	
Aripiprazole		
Aripiprazole lauroxil		
Haloperidol		

Iloperidone Pimozide Quetiapine	
CYP3A43	
Olanzapine Remoxipride	

Use of Pharmacogenetic Testing for Oxidation of Antipsychotics

As mentioned above, it is extremely important for a practicing psychiatrist to know the oxidation pathway of APs, since most of them are metabolized in the liver and this is important both to prevent ADRs and to avoid unwanted drug-drug interactions, which will undoubtedly increase the effectiveness and safety of AP therapy [67]. At the same time, it is possible to study the activity of one or another cytochrome and changes in the oxidation of the enzyme due to changes in its activity only experimentally. In the organism of a patient suffering from mental disorders, we can only indirectly judge the change, taking into account modifiable and non-modifiable factors, including genetically determined changes.

Currently, the rapid development of molecular genetics and fundamental and clinical pharmacogenetics indicate that the study of non-functional and low-functional single nucleotide variants (SNVs)/polimorphism of the genes encoding CYP enzymes can help in translating fundamental knowledge about the oxidation of APs into real clinical practice. Currently depending on the genetically determined change in the degree of enzymes activity, four phenotypes are distinguished (Figure 2) [68].

In connection with this, it is very promising to introduce various pharmacogenetic panels, for example, the AmpliChip CYP450 pharmacogenetic test, which allows obtaining information about the pharmacogenetic profile of a patients with mental disorders, depending on the carriage of allelic genotypes of two non-functional SNVs/polymorphisms of cytochrome P450 genes (CYP2D6 and CYP2C19). According to the test results, patients are divided into 2 phenotypes for the CYP2C19 gene: an extensive metabolizer and a poor metabolizer, by testing for 3 SNVs and into 4 phenotypes for the CYP2D6 gene by testing for 27 SNVs/polymorphisms, including 7 duplications [69].

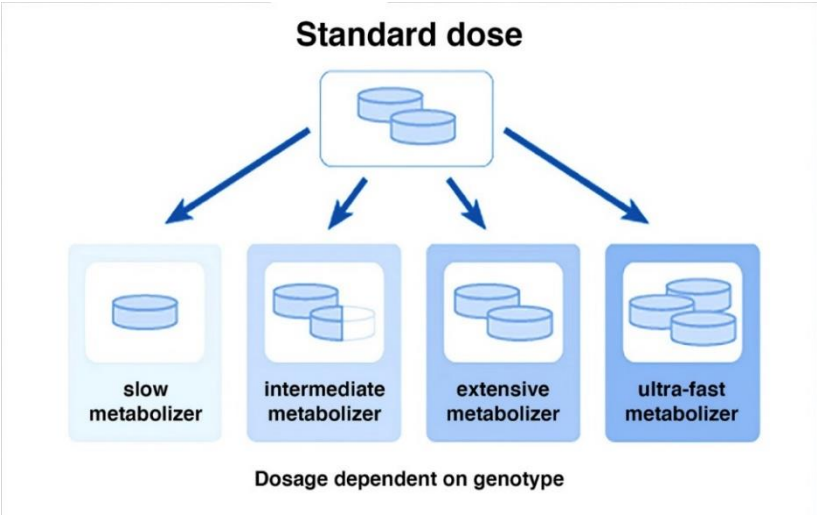

Figure 2. Pharmacogenetic phenotypes [86, modificated by authors]

A good example of a system for evaluating the genetic contribution to APs metabolism in foreign practice is the GeneSight Psychotropic algorithm developed by a group of scientists based at the Mason Clinic (USA). The test is non-invasive and easy to use. GeneSight is based on a multi-gene multivariate genetic test that takes into account the characteristics of the genotype, phenotype, as well as information about the metabolism of the drug. The analysis is performed on allelic variants of 14 genes *(CYP1A2, CYP2C9, CYP2C19, CYP3A4, CES1A1, CYP2B6, UGT1A4, UGT2B15, CYP2D6, HTR2A, HLA-A*3101, ADRA2A, HLA-B*1502, SLC6A4).* The psychiatrist is provided with information already analyzed by the program based on the results of pharmacogenetic test (PGx). Conclusion GeneSight contains a list of APs and Ads divided into 3 categories: "use as directed"; "use with caution"; "Use with increased caution and with more frequent monitoring." It also provides additional information that helps the psychiatrist decide whether to prescribe or cancel the drug in a particular patient. [70].

Another PGx test, Genecept Assay, developed in the USA, makes it easier for the clinical pharmacologist to make decisions about prescribing APs and ADs. The Genecept Assay makes it possible to predict the efficacy and safety of pharmacotherapy with these drugs in a wide range of mental disorders, including depression, obsessive-compulsive disorder, schizophrenia, attention-deficit/hyperactivity disorder, bipolar disorder, and others. SNVs are being studied in 20 genes encoding targets of APs and ADs action, including *5HT2C 5HT2C, MC4R, DRD2, COMT*, and genes encoding isoenzymes of the cytochrome P450 system [71].

However, the data obtained for a cumulative assessment of the safety and efficacy of APs are not enough, since it should be noted that 13 cytochrome P450 enzymes are involved in the oxidation of APs, and only a few of them are used in most real-life pharmacogenetic testing tools.

Limitation

The limitation of this entry paper is that it only took into account the oxidation pathway, although, undoubtedly, in order to predict and manage ADRs, it is necessary to take into account the role of other pathways, including oxidation not only in the liver, but also in brain neurons, in particular CYP1A1, CYP1B1 are expressed in the ER not only in the liver, but also in the brain [32].

In addition, the studies of the P450 enzymes expression have shown that some of them are expressed not only in the liver, but also in other organs and systems. For example, CYP1A1 is expressed in the cerebellum, cerebral cortex , hippocampus, thyroid gland, parathyroid glands, adrenal glands, bronchi, lungs, tissues of the nasopharynx, oral mucosa, stomach, duodenum, rectum, liver, gallbladder, pancreas, kidneys, bladder, ovaries, testicles, epididymis , endometrium, placenta, tonsils, salivary glands, esophagus, prostate, fallopian tubes, cervix, heart muscle, skin, spleen, lymph nodes [72]. This fact can probably cause the development of specific ADRs from certain organs and systems, and the translation of these pathways can help a practicing psychiatrist to suggest which organs and systems, when prescribing APs, need to pay special attention when managing

psychiatric patients. However, this approach has only just begun to be studied, and we have not found large studies [73].

Conclusion

Knowledge of the pathways of liver APs oxidation is very important from theoretical and practical points of view, since it can help to achieve an optimal balance between the efficacy and safety of APs in the practice of a psychiatrists and other specialists.

In addition, it is important to remember that in order to translate fundamental knowledge about oxidation into real practice is possible by expanding knowledge in the field of psychopharmacogenetics and developing, and introducing into clinical practice pharmacogenetic panels that would be useful to prescribe not at the stage of development of ADRs, but before the start of APs prescription.

However, it should be recognized that the solution of the tasks set is far from being solved.

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