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REVIEW ARTICLE

A Comprehensive Review on Importance and Quantitation of Atypical Antipsychotic Drugs and their Active Metabolites in Commercial Dosage Forms

Habibur Rahman[1], S.K. Manirul Haque[2,*] and Masoom Raza Siddiqui[3]

[1]*Department of General Studies, Jubail Industrial College, P.O. Box No. 10099, Zip Code–31961, Jubail, Saudi Arabia;* [2]*Department of Chemical & Process Engineering Technology, Jubail Industrial College, P.O. Box No 10099, Zip Code-31961, Jubail, Saudi Arabia;* [3]*Chemistry Department, College of Science, King Saud University, Riyadh 11451, Saudi Arabia.*

Abstract: ***Background*:** Schizophrenia is a severe mental illness that affects more than twenty-one million people throughout the world. Schizophrenia also causes early death. Schizophrenia and other related psychotic ailments are controlled by the prescription of antipsychotic drugs, which act by blocking certain chemical receptors in the brain and thus relieves the symptoms of psychotic disorder. These drugs are present in the different dosage forms in the market and provided in a certain amount as per the need of the patients.

***Objective*:** Since such medications treat mental disorders, it is very important to have a perfect and accurate dose so that the risk factor is not affected by a higher or lower dose, which is not sufficient for the treatment. For accurate assay of these kinds of drugs, different analytical methods were developed ranging from older spectrophotometric techniques to latest hyphenated methods.

***Results*:** The current review highlights the role of different analytical techniques that were employed in the determination and identification of antipsychotic drugs and their metabolites. Techniques such as spectrophotometry, fluorimetry, liquid chromatography, liquid chromatography-mass spectrometry, gas chromatography, and gas chromatography-mass spectrometry employed in the method development of such antipsychotic drugs were reported in the review. Different metabolites, identified using the hyphenated techniques, were also mentioned in the review. The synthesis pathways of few of the metabolites were mentioned.

***Conclusion*:** The review summarizes the analyses of different antipsychotic drugs and their metabolites. A brief introduction of illnesses and their symptoms and possible medications were highlighted. Synthesis pathways of the associated metabolites were also mentioned.

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1. INTRODUCTION

The term "Psychosis" is derived from the Greek word referring to the abnormal ailment of the mind. It is a type of psychiatric disorder that can be characterized by the disturbance of perceptions and reality. More specifically, psychosis can be characterized by several symptoms such as fixed false beliefs, clang associations, disorganized thoughts, hallucinations, word salad, abnormal motor behaviour, and echolalia [1]. It is related to the abnormality of a human brain in which the patient loses contact with the present situation, declining the cognitive function, which manifests especially in their thought, emotion, will, memory, and imagination. There are 12 types of psychosis reported. The details of these types of psychosis and their characteristics are mentioned in Table **1** [2-3].

To overcome these situations, there are several treatment procedures including psychological therapies, antipsychotic medicines along with social support. Antipsychotic medications are believed to be most effective in the treatment of psychosis; the same has been used for the treatment of, ma nia, delirium, depression, and bipolar disorders, both acute and long term [4]. Important antipsychotic drugs like perphenazine, chlorpromazine, haloperidol, etc. have been used for the treatment of psychotic diseases for a long time. The patient's social and occupational desires are challenged and interfere significantly after introducing these drugs into the body [5]. They may also result in adverse effects that may be

*Address correspondence to this author at the Department of Chemical & Process Engineering Technology, Jubail Industrial College, P.O. Box No-10099, Zip Code-31961, Jubail, Saudi Arabia; Tel: +966133425463; Fax: +966133409903; E-mails: Haque_m@jic.edu.sa; manirul1986@gmail.com

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Table 1. Different type of psychosis and their characteristics.

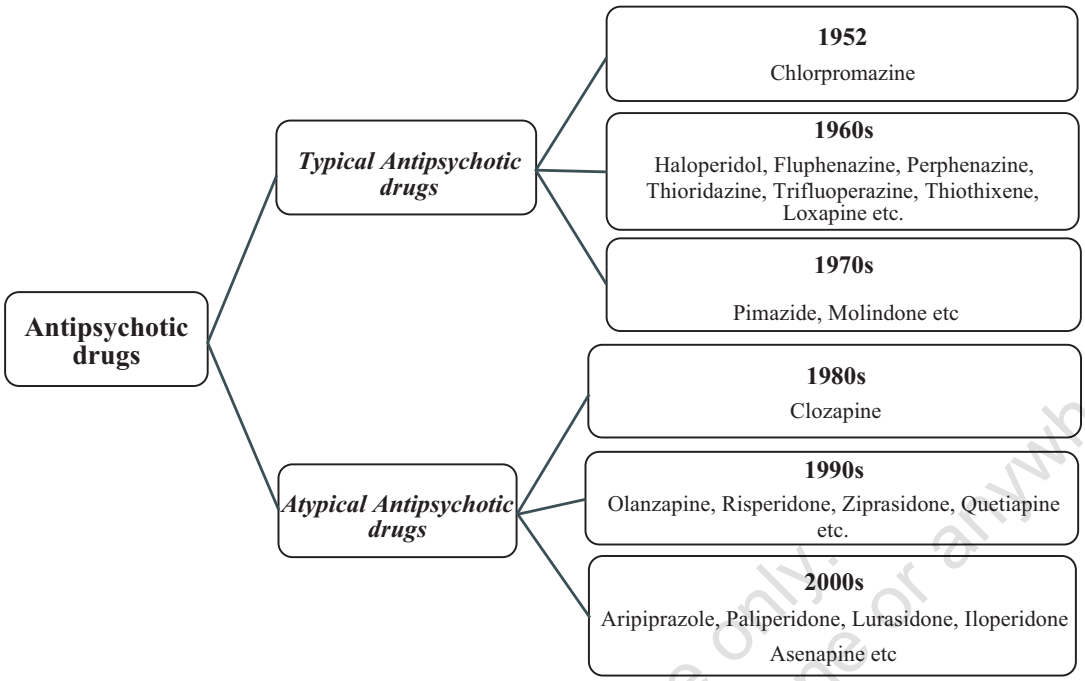
S. No.	Type of Psychosis	Symptoms of the Condition
01	Schizophrenia	Hallucinations, delusion, thought and movement disorder, reduced speaking, feelings of pleasure decreased, difficulty beginning and sustaining activities, problems with "working memory", poor "executive functioning", difficulty in paying attention. Lasts longer than six months.
02	Schizophreniform disorder	Similar to schizophrenia but the condition differs in duration, which is less than that of schizophrenia and is at least 1 month, but less than six months.
03	Schizoaffective disorder	Paranoid thoughts, delusions, hallucinations, confusion, disorganized thoughts or behaviors, catatonia, speaking too quickly, hyperactive, suicidal thought, poor personal hygiene.
04	Delusional disorder	Delusion, other symptoms almost similar to Schizophrenia. Generally, occurs in middle to late life. More common in female than male.
05	Substance-induced psychosis	Use or withdrawal of substances such as drugs or alcohol can lead to psychotic indications. These types of signs vanish as soon as the effects of the substances wear off. However, psychosis related to the stimulant drug may persist.
06	Dementia	Symptoms of psychosis appear with memory disturbance that may result in psychological deterioration of the brain.
07	Bipolar disorder (manic depression)	Also called manic depression, severe mood disturbance, Psychotic.
08	Major depressive disorder	Psychosis can result from major depression.
09	Postpartum psychosis	May develop during the initial six months' period after childbirth. Severe mood disorder may occur.
10	Delirium	Epileptic convulsion, meningitis, septicaemia like medical disorder may result in an acute confusional condition, which may lead to psychosis.
11	Brief psychotic episode	A stressful life event such as violent crime, etc. may lead to the sudden appearance of the psychotic symptoms. These are generally short-lived.
12	Psychosis due to a general medical condition	Medical chronic conditions, epilepsy, and brain tumor can sometimes result in psychotic symptoms.

life threating, disabling, and disfiguring including dyskinesia, neuro malignant syndrome, and parkinsonian symptoms [6-8]. Globally, about forty antipsychotics were introduced between 1954 and 1975. Afterward, there was a break in the development of antipsychotic drugs until the introduction of clozapine, which opened a new era called "atypical" antipsychotic drugs. Clozapine was first introduced in Europe for the treatment of endogenous depression as an atypical antipsychotic drug [9]. Later on, it was shown that it can cause agranulocytosis, leading to the decrease in the number of white blood cells (neutropenia) and causing the death of patients, which forced the manufacturer to withdraw clozapine in 1975. In 1989, the researcher's investigation proved that clozapine is useful for schizophrenia [10]. Finally, the drug was approved for maintaining the white cells and neutrophil in the blood by the United States Food and Drug Administration (USFDA) [11], and it proved that atypical antipsychotics are essential for the treatment of bipolar depression [12-13]. It also worked as an adjunctive and combined therapy in unipolar depression profiles that helped more antipsychotics to get official approval, in terms of efficacy [14-15]. It was reported that extrapyramidal symptoms are the major limitation due to which atypical antipsychotics were preferred over typical antipsychotics [16].

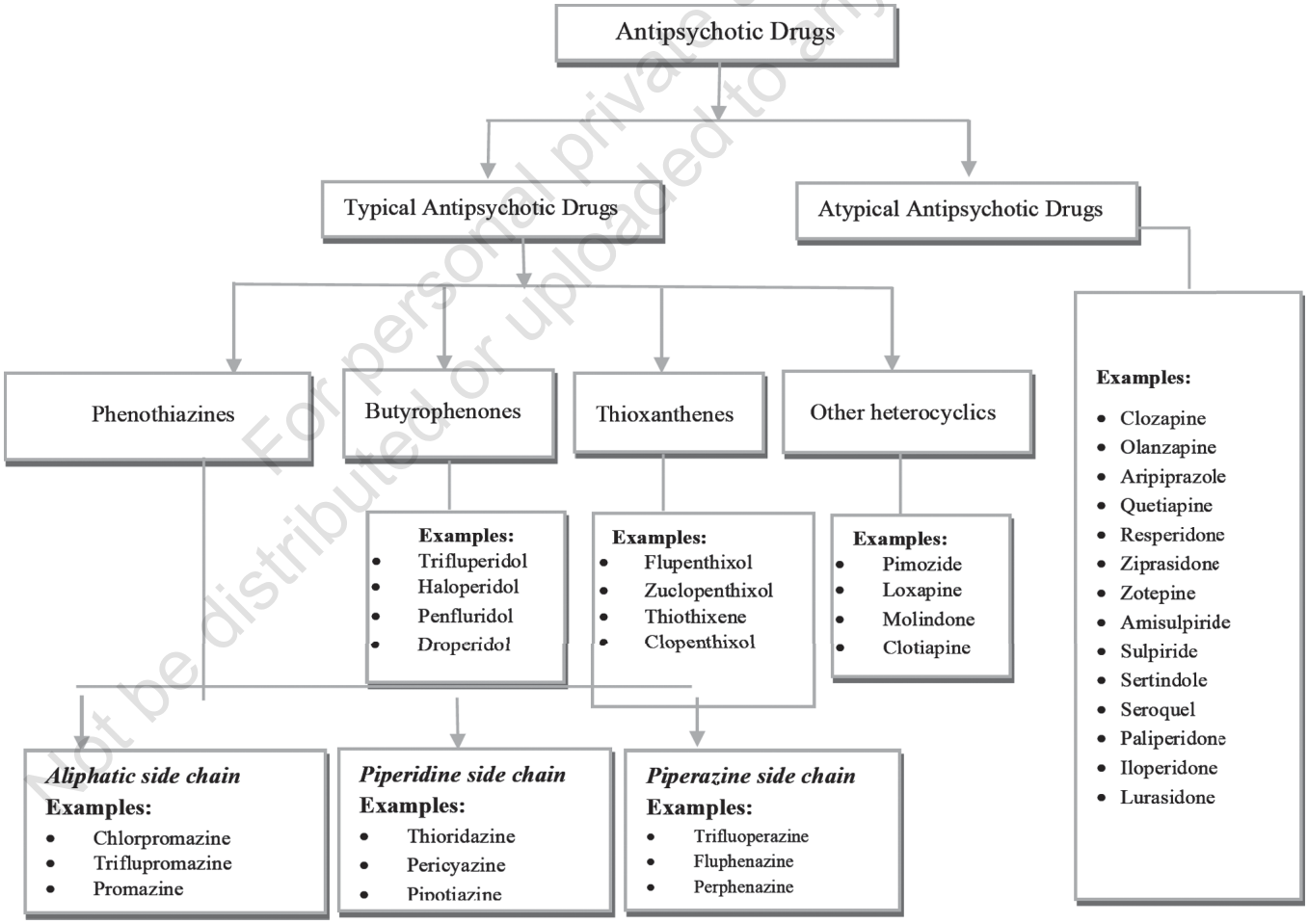
Antipsychotic drugs are classified into two generations, first-Generation Antipsychotics (FGA) being "typical" while second-Generation Antipsychotics (SGA) are referred to as "atypical" antipsychotics [17, 18]. The history of antipsychotics development as typical and atypical drugs is shown in Scheme **1** [19-21] and broader chemical classification of antipsychotics as conventional/typical which include phenothiazines, butyrophenones, and thioxanthenes, and newer/atypical antipsychotics which include dibenzodiazepines, thiobenzodiazepines, dibenzothiazepines, and substituted benzamide schematically is shown in Scheme **2**.

1.1. Atypical Antipsychotic Drugs

Atypical antipsychotic drugs are a class of medicines that are mainly used for the treatment of disorder related to psychosis. The exact mechanism behind the working of atypical antipsychotics is reported to be unknown. However, it is believed that these drugs tend to block certain receptors (chemical) in the brain and relieve the symptoms of the psychotic condition [22]. These atypical antipsychotic drugs are used in animals as well as human beings. It does not affect extrapyramidal symptoms and tardive dyskinesia in humans as well as catalepsy in animals. However, it has a minor or sometimes no effect with prolactin levels in plasma. These drugs are found to be suitable for negative symptoms, non–responders, and classical neuroleptics [23]. Another report by Tony Kendrick summarizes that the new generations of the antipsychotic drugs do not cause extrapyramidal side effects and these drugs are thought to be effective against both positive and negative symptoms, by acting on neurotransmitter pathways in brain [24]. There has been a published report that states that the traditional antipsychotics are poorly effective in case of negative symptoms of schizophrenia and are also associated with several side effects. The article further states that the atypical antipsychotics (such as clozapine, sertindole, olanzapine, and risperidone) and developmental disorder antipsychotics (such as zotepine, quetiapine, and ziprasidone) have better negative symptoms when compared to standard antipsychotics or to placebo [25]. The extrapyramidal symptoms induced by the drug itself as side effects are less or absent for atypical rather than the typical drugs. Although, the clinical efficacy of both types of drugs seem to be similar [26]. Atypical drugs have



Scheme 1. Timeline to Antipsychotic drugs development.



Scheme 2. Classification of Antipsychotic drugs.

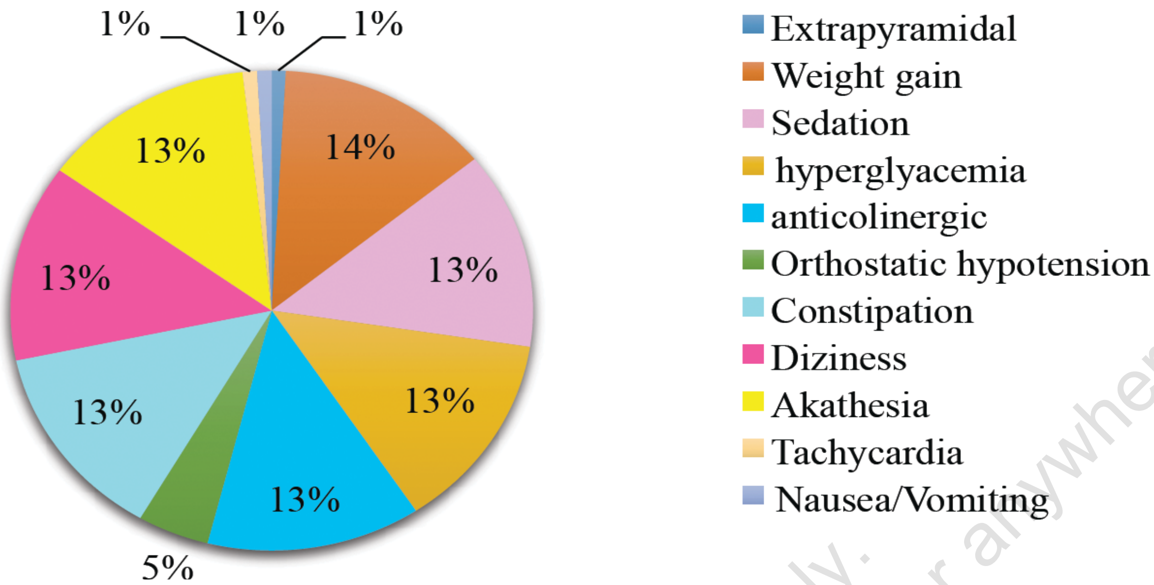


Fig. (1). Adverse effects of clozapine. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

less influence on D2 receptors than the typical drugs because they primarily block the dopamine D2 receptor in mesolimbic pathways.

The most complex psychiatric disorder is schizophrenia. The World Health Organization, in its report, also considered schizophrenia as a severe mental ailment that affects more than 21 million people throughout the world. People with schizophrenia have 2-3 times higher risk of dying than normal people [27]. These drugs are used for schizophrenia symptoms such as hallucination and delusion. They only minimize the intensity and permit the person to attain a supportive environment. But the medication does not have the ability to eliminate and cure the illness. The atypical drug clozapine was approved by the USFDA in 1989 and clinically available for the treatment of schizophrenia in 1990. The main action of clozapine was that it has a low impact to cause extrapyramidal symptoms along with an ability to increase the prolactin levels in serum. After that, many atypical drugs have been brought in the market and these drugs showed capabilities to improve the function of disorder patients. According to the short-term efficacy of schizophrenia and dementia, a few differences were seen between all the atypical drugs. The studies suggested that clozapine is associated with a major adverse effect, which may cause seizures, weight gain, sedation, and agranulocytosis [28, 29]. The other atypical drugs such as olanzapine, quetiapine, ziprasidone, and risperidone are more useful because these drugs did not introduce any major side effect like agranulocytosis [30-31]. The adverse effect can be speculated from the available pharmacological profile of each drug. The most significant side effect from the drug was hyperglycemia and the common effects were weight gain, sedation, constipation, dizziness, akathisia, nausea, or vomiting. The studies suggested that clozapine associated with a major adverse effect is shown in Fig. (**1**) [32-34].

The advantage of clozapine for schizophrenia patients is to reduce suicidal behaviour, but some other drugs were found more favourable than clozapine due to its adverse effects on humans. However, there is no comparative study of atypical drugs used for major depressive disorder and disruptive behaviour in adults and children. It was observed that regular use of olanzapine results in weight gain (6 to 13 pounds or more) and the risk of new-onset diabetes as a side effect. It has been reported and diagnosed that the probability of developing schizophrenia in children and siblings are 13 and 9%, respectively. The possibility of a child to get the disorder from the parent is 6% and the risk is increased up to 48% for identical twins [35, 36]. Lifetime risks of developing schizophrenia for the relatives of schizophrenia sufferers are shown in Fig. (**2**) [37, 38]. Previous studies reported [39-41] that schizophrenia, the most complex mental disorder disease, occurred before the age of 13 years and increased with age as shown in Fig. (**3**). However, severity can be reduced by timely interventions and counseling. In recent years, various pharmaceutical companies developed several atypical drugs such as clozapine, quetiapine, olanzapine, aripiprazole, quetiapine, asenapine, zotepine, risperidone, iloperidone, ziprasidone, sulpiride, paliperidone, lurasidone, and sertindole for the above health conditions.

The present review provides a brief history of atypical antipsychotic drug development, which includes its clinical importance, adverse effects, the lifetime risk, and patient age ratio for schizophrenia. Cytochrome P450 catalyzed metabolic pathways and metabolites formed during biotransformation of twelve important atypical antipsychotic drugs were introduced in the 1980s. Additionally, it provides a comprehensive study of commonly used analytical methods especially spectrophotometric and chromatographic methods for the analysis of selected atypical drugs (clozapine, olanzapine, aripiprazole, and quetiapine) and its metabolites in pure, matrices, blood, tissues, urine, and pharmaceutical formulations.

1.2. Common Atypical Drugs

The atypical drugs are quite popular for the last two decades among patients and clinicians due to their ability to

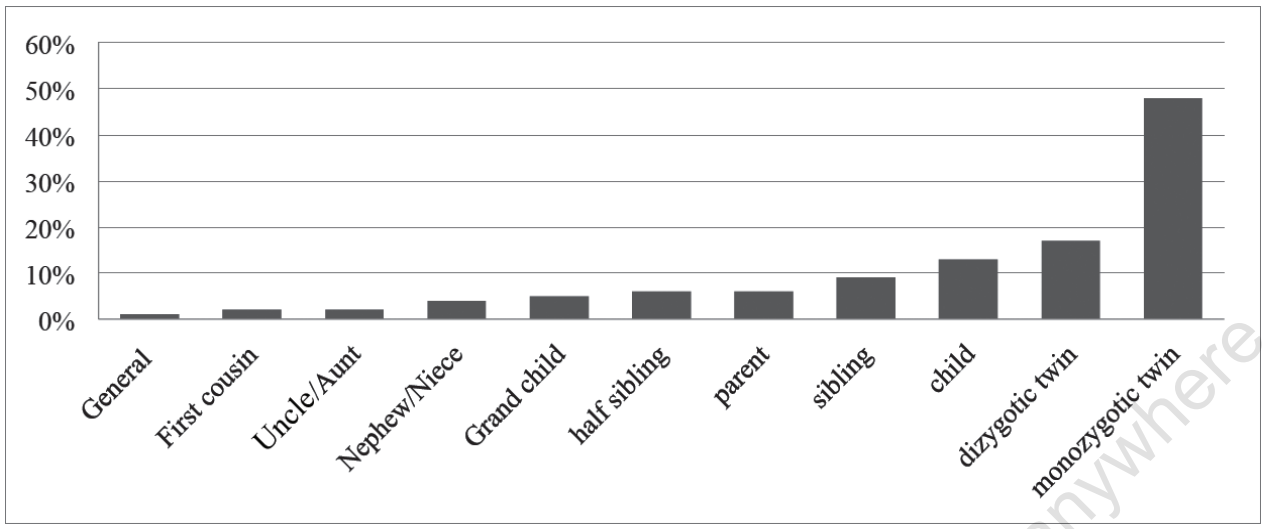


Fig. (2). The lifetime risk of developing schizophrenia.

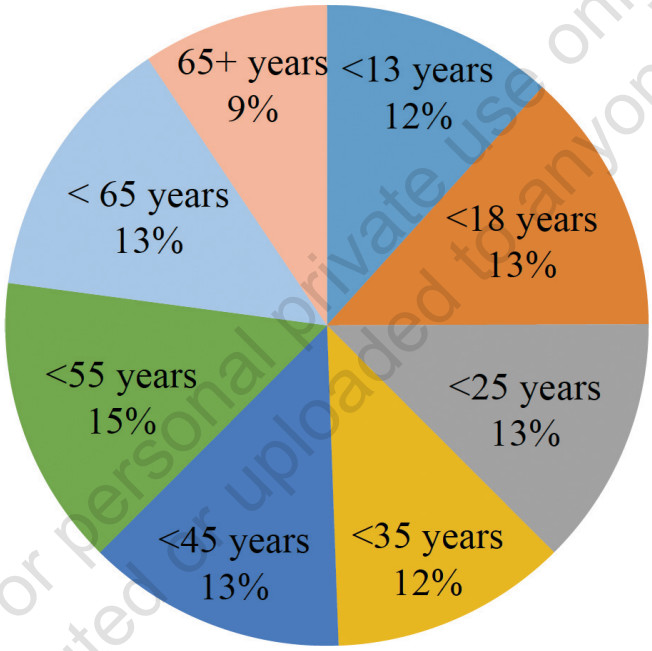


Fig. (3). Schizophrenia with age and % of patients. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

lower the extrapyramidal side effects than the antipsychotics from the first generation. These drugs are extensively used for the treatment of psychotic disorders because they considered higher efficacy and safety than the typical drugs. The structures of common antipsychotic drugs are shown in Fig. (**4**).

1.2.1. Clozapine

Clozapine is an atypical antipsychotic drug of the dibenzodiazepine class and reported to be the last line of atypical antipsychotic drugs. This drug is used to treat the patients where schizophrenia is difficult to treat. It also proves to be more effective in reducing both positive and negative symptoms of schizophrenia and associated with an extremely low level of extrapyramidal side effects. Despite its importance as an atypical antipsychotic agent, several side effects are also associated with clozapine including agranulocytosis and although rare, serious adverse cardiovascular conditions such as myocarditis [42]. It is chemically known as 8-chloro-11-(4-methyl- 1-piperazinyl)-5H-dibenzo [b,e] [1,4] diazepine [43] and has a molar mass of 326.8 $gmol^{-1}$. It is a yellow crystalline powder, highly soluble in chloroform, slightly soluble in water, and soluble in acetone.

1.2.2. Olanzapine

It is an atypical antipsychotic drug approved by the Food and Drug Administration (FDA) that has a stronger serotonin receptor (5HT2) ability as compared to dopamine (D2). Olanzapine is a thienobenzodiazepine derivative, effective in the treatment against the positive and negative symptoms of schizophrenia and has a lower extrapyramidal effect than other antipsychotic drugs. The result of the comparative

study of olanzapine and risperidone in terms of safety and efficacy during the treatment of negative symptoms in schizophrenia revealed that both drugs were efficacious and well tolerant during the treatment of severe illness. Therefore, negative symptoms were greatly reduced with olanzapine continually for 1 year [44]. It was approved by the USFDA in 1996. It can be used in combination with other medicines to treat depression [45-46]. The structure of olanzapine is similar to that of clozapine. It is chemically known as 2-methyl-4-(4-methyl-1-piperazinyl)- 10*H*-thieno[2,3-b][1,5] benzodiazepine, has molecular formula $C_{17}H_{20}N_4S$ and a molar mass of 312.4 $gmol^{-1}$. It is a yellow colored powder, soluble in organic solvents such as ethanol, dimethyl sulphoxide, and dimethyl formamide, and sparingly soluble in aqueous buffers.

1.2.3. Aripiprazole

Aripiprazole is a second-generation atypical antipsychotic drug popular in the market due to its ability to cure the disease with depression and available in tablets, solutions, and injections. It has similar efficacy as olanzapine for long-term treatment of acute psychosis and lower liability for increased lipid levels [47]. It is chemically known as 7-4-[4-(2,3-dichlorophenyl)-1 piprazenyl]butoxy]-3,4-dihydro-(1H)-quinolinone ($C_{23}H_{27}Cl_2N_3O_2$) and has a molar mass 448.38 $gmol^{-1}$.

1.2.4. Quetiapine

This drug has a unique receptor-binding profile, prescribed to cure schizophrenia and manic episodes involved with bipolar disorder. Quetiapine is a dibenzothiazepine derivative, and one of the most recent antipsychotic drug commonly used for the treatment of schizophrenia, major depressive and bipolar disorder. It is chemically known as 2-(2-(4-dibenzo [1,4] thiazepine-11-yl-1-piperazinyl) ethoxy-ethanol (molecular formula; $C_{21}H_{25}N_3O_2S$, molar mass: 383.51 $gmol^{-1}$). It is an antagonist likely selective monoaminergic and has high affinity for the serotonin type 2 (5HT2) and dopamine type 2 (D2) receptors [48].

1.2.5. Zotepine

Zotepine is a substituted dibenzothiepine tricyclic atypical drug developed in 1982. It is chemically similar to clozapine and quetiapine and was found to be active against positive symptoms of schizophrenia. It is a second-generation antipsychotic drug indicated for acute and chronic schizophrenia and chemically known as 2-(3-chloro-benzo[b][1]benzothiepin-5-yl)oxy-N,N-dimethylethanamine (molecular formula; C_{18} $H_{18}ClNOS$, molar mass: 331.8 $gmol^{-1}$) and structurally related to clozapine but with some distinguishing pharmacological and clinical properties [49].

1.2.6. Iloperidone

It is a second-generation antipsychotic agent and mood stabilizer, recently approved for the acute treatment of schizophrenia in adults especially for patients who cannot tolerate antipsychotics. It is well absorbed orally, with a bioavailability of 96% [50–51]. It is benzisoxazole phenylethanone and chemically named as1-[4-[3-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]propoxy]-3-methoxyphenyl]ethanone having the molecular formula $C_{24}H_{27}FN_2O_4$ with a molar mass of 426.48 $gmol^{-1}$.

1.2.7. Asenapine

Asenapine is a dibenzoxepinopyrolidine derivative antipsychotic drug used for the manic or mixed feature of bipolar I disorder and acute treatment of schizophrenia. It primarily works by controlling the psychotic symptoms with or without psychotic features in adults. Asenapine belongs to the class dibenzo-oxepino pyrroles used for the treatment of bipolar mania/mixed episodes and schizophrenia. It is chemically known as (3aRS, 12bRS)-5-chloro-2-methyl2, 3, 3a, 12b-tetrahydro-1H dibenzo [2, 3:6, 7] oxepino [4, 5c] pyrrole (2Z)-2-butenedioate. It is an approved drug for schizophrenia in the United States of America, Japan, and other countries, but not in the EU. It has molecular formula $C_{17}H_{16}ClNO{\cdot}C_4H_4O_4$ and a molar mass of 401.84 $gmol^{-1}$. The exact function of asenapine is unknown but it is believed that the combined antagonistic action involves D2 and 5-HT2A receptors. Somnolence, dizziness, extrapyramidal symptoms, weight gain, and oral hypoesthesia are the most common adverse effects associated with asenapine. However, studies show the occurrence of these conditions, particularly weight gain, is generally lower than with olanzapine and to improve health-related quality of life [52].

1.2.8. Risperidone

It is a selective blocker of serotonin 5-HT2 and dopamine D2 receptors and effective drug for the treatment for positive and negative symptoms of schizophrenia and manic symptoms of bipolar disorder in children and adolescents. It binds 10-20 times greater to 5-HT2A receptors as compared to D2 receptors. Effectiveness of risperidone on negative symptoms was studied through clinical trial and compared to haloperidol. The clinical trial's results revealed that the drugs haloperidol and risperidone were found to be effective in the treatment of negative symptoms of schizophrenia. The second week of the treatment showed the initiation of improvement in the condition, however, the most noticeable response rate for treated risperidone group was observed in the eighth week [53]. Paliperidone, the main metabolite of risperidone, is also used as an antipsychotic but quantitatively different from risperidone with respect to pharmacodynamics and pharmacokinetics [54]. It is chemically known as 3-{2-[4[(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl}-2-methyl-6,7,8-tetrahydro-4H-pyrido[1,2 a]pyrimidin-4-one (molecular formula: $C_{23}H_{27}FN_4O_2$, molar mass of 410.5 $gmol^{-1}$). It is a white to off-white powder, freely soluble in methylene chloride, practically insoluble in water and sparingly soluble in alcohol. However, it is soluble with dilute acid solutions.

1.2.9. Lurasidone

Lurasidone is a recently FDA approved benzisothiazolone derivative and antipsychotic medication used for the treatment of schizophrenia and depression associated with bipolar disorder. It is chemically known as (3aR,4S,7R,7aS)-2-[((1R,2R)-2-{[4-(1,2-benzisothiazol-Michele3-yl)-piperazin-1–yl]methyl}cyclohexyl} hexahydro-1H-4,7 methanisoindol-1,3-dione and has a molecular formula $C_{28}H_{36}N_4O_2S$ and a molar mass of 492.68 $gmol^{-1}$ [55].

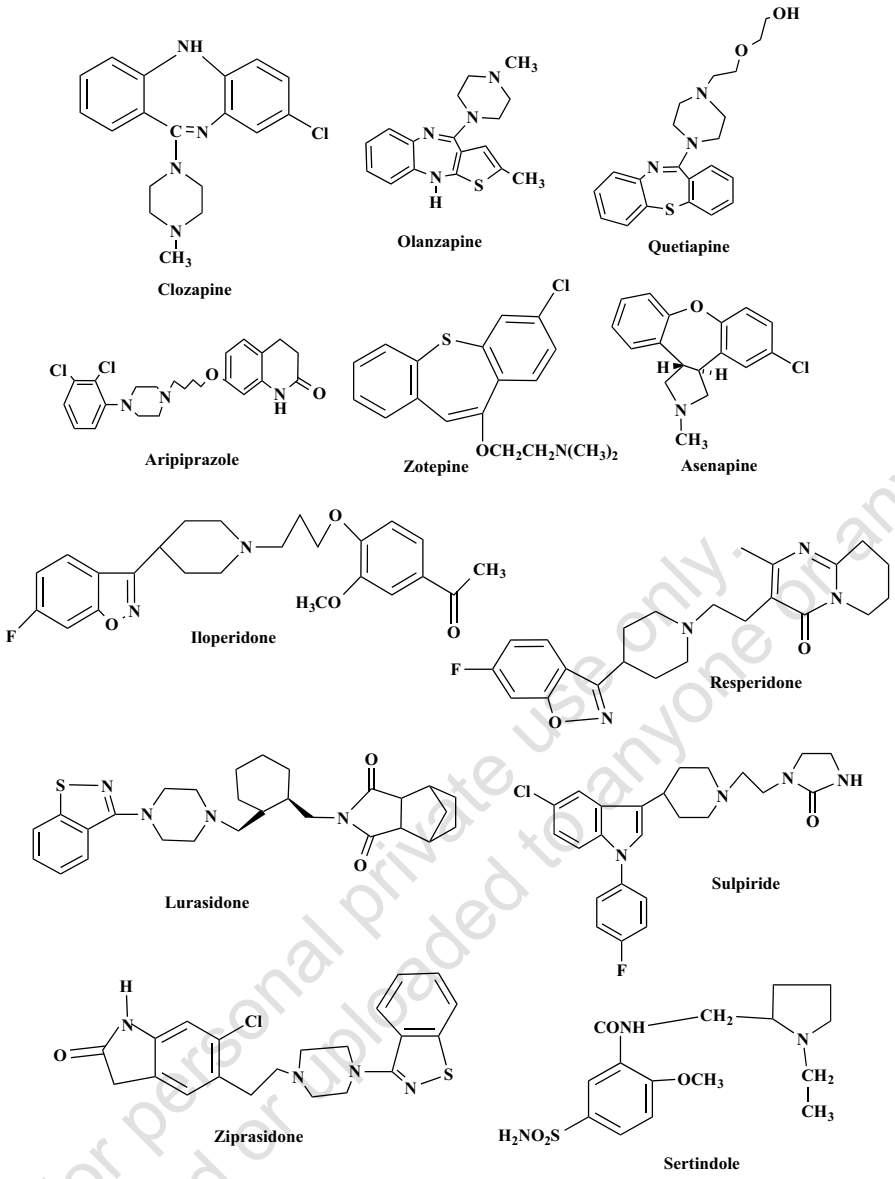


Fig. (4). Chemical structures of atypical antipsychotic drugs.

1.2.10. Ziprasidone

Ziprasidone is a recently approved benzylisothiazolylpiprazine antipsychotic drug for the treatment of schizophrenia, acute, mixed mania, adjunctive for the treatment of the bipolar disorder. Ziprasidone is a novel benzyl isothiazolyl piperazine antipsychotic and has highly selective antagonistic activity on the D2 and 5HT2A receptors. It is a novel benzylisothiazolylpiperazine antipsychotic drug, which effectively stabilizes mood in schizophrenia and bipolar disorder [56]. It is chemically known as 5-[2-[4- (1,2-benzisothiazol-3- yl)-1-piperazin-1yl] ethyl]-6-chloro-1, 3-dihydroindol-2-one hydrochloride ($C_{21}H_{21}ClN_4OS$). It is a white to slightly pink powder, freely soluble in organic solvents such as primary alcohols and chloroform and sparingly soluble in acetonitrile and octanol.

1.2.11. Sulpiride

Sulpiride is an atypical drug widely prescribed as a neuroleptic agent or behaviour regulator in the psychopathology of senescence for the treatment of depression and schizophrenia. It is a substituted benzamide derivative class and a selective dopamine D2 receptor used in the treatment of psychosis associated with schizophrenia and major depressive disorder. It may be used in low dosage to treat anxiety and mild depression and marked as a low incidence of adverse effects [57]. It is chemically and clinically similar to amisulpride and is chemically known as 5-(aminosulfonyl)-N-((1-ethyl-2-pyrrolidinyl) methyl)-2-methoxybenzamide (molecular formula: $C_{15}H_{23}N_3O_4S$ and molar mass 341.43 $gmol^{-1}$).

1.2.12. Sertindole

Sertindole is an *important* arylpiperidylindole antipsychotic medication used for the treatment of neuroleptic-resistant schizophrenia and is effective in improving negative symptoms. Phase III trials revealed that a dose range of 12-24 mg sertindole per day was found to be effective against both the positive and the negative symptoms of schizophre-

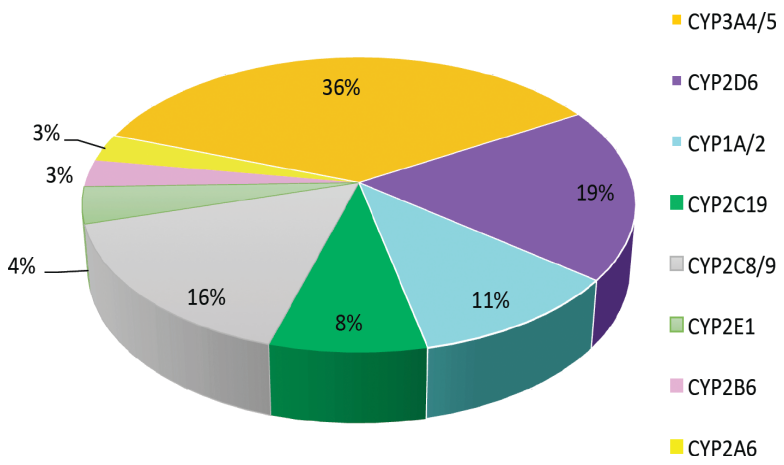


Fig. (5). Contribution of cytochrome P450 (CYPs) enzymes in drug metabolism. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

nia. Starting dose of 16 mg daily was reported to be optimal [58]. It has an affinity for 5-HT2c, 5-HT2a, D2, α1, and α2 receptors [59]. Its International Union of Pure and Applied Chemistry (IUPAC) name is 1-(2-{4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl}ethyl)-imidazolidinone **(**molecular formula:$C_{24}H_{26}ClFN_4O$ and molar mass 440.94 $gmol^{-1}$).

2. BIOTRANSFORMATION

To cure diseases in living organisms, medicines (drugs) are required, but at the same time, drugs are considered as foreign objects in the body, which are excreted and eliminated after showing their action. The human body can naturally eliminate these drugs with the biologically known process as drug metabolism. Metabolism can be defined as a biochemical modification of one chemical form to another, which occurs usually through specialized enzymatic systems. It often involves the conversion of lipophilic chemical compounds (drugs) into highly polar derivatives that can be easily excreted from the body [60]. However, in some cases, the same metabolic process can also lead to the generation of reactive metabolites, which are toxic to the human body [61]. This bioactivation process fully depends on the structural features involved with drug molecules [62]. The *metabolism* of a drug in a body is an example of *biotransformation and* metabolites can be defined as the products of biotransformation. Biotransformation produces metabolites that are chemically stable but pharmacologically and toxicologically inactive [63-64]. The metabolites that are chemically stable and pharmacologically active are known as active metabolites. Thermodynamic and pharmacokinetic properties of active metabolites may be similar or different from the original drug compound. Active metabolites may completely or partially involve in drug's therapeutic effect. A number of metabolites are formed through major biotransformation pathways such as hydroxylation, N-dealkylation, deamination, desulfuration, dehydrogenation, oxidation, reduction, and conjugation [65]. In general, most metabolic interactions take place with atypical antipsychotic drugs, which changes the activity of major drug-metabolizing enzymes such as cytochrome P450 (CYP450) monooxygenases and/or uridine diphosphate-glucuronosyl transferases (UGT) involved in their biotransformation. The most important isoenzyme system cytochrome P-450 (CYP450) catalyzes the drugs through oxidation [66]. The enzymes involved in metabolism are present in many tissues but in general, the liver is the principal site of drug metabolism. Cytochromes P-450 family of enzymes are capable of catalyzing the oxidative biotransformation of most drugs and lipophilic xenobiotics and are particularly relevant for clinical pharmacology [67-68]. The highest expressed intrahepatic forms are CYPs 3A4/A5, 2C9, 2C8, 2E1, and 1A2 while 2A6, 2B6, 2C19, 2D6, and 3A5 are less abundant whereas CYPs 1A1, 1B1 and 2J2 are expressed outside the liver. Fig. (**5**) shows the involvement and contribution of CYPs in major metabolism of drugs. UGT enzymes catalyze not only the glucuronidation of several drugs located in the endoplasmic reticulum, especially in the liver, but also in the skin, lungs, kidney, intestine, prostate, and brain. Drugs that induce or inhibit the CYP or UGT isoenzymes and are involved in metabolic activity of the various atypical antipsychotic drugs may change their plasma concentrations with subsequent risk of adverse effects. A list of atypical drugs with their active as well as inactive metabolites is given in Table **2** and major biotransformations are shown in Figs. (**6a-l**) [69-80].

3. METABOLITES

Clozapine forms polar metabolites during the metabolism in the liver by cytochrome P450 and is eliminated through urine and feces [81]. Two major metabolites (clozapine N-oxide and norclozapine are formed by hepatic cytochrome P450s through N-oxidation and demethylation. Norclozapine (N-desmethylclozapine) was reported as the most pharmacologically active metabolite. The cytochrome P450 (CYP1A2) enzyme was catalyzed in the liver, intestine, kidney, lung, and brain through oxidation. The CYP1A2 pathway is mainly responsible for the metabolism and other pathways like CYPs (2C, 2D6, 2E1, 3A and 3A4) are also helpful [82–83]. Cytochrome P450s were also able to bioactivate clozapine to a glutathione-reactive nitrenium ion. Studies reported that dose optimization, prevention to toxicity, metabolism, and compliance with efficacy are the main parameters to use

clozapine and norclozapine, proved by monitoring plasma levels in humans [84]. Aripiprazole is mainly metabolized via CYP3A4 and 2D6 through dehydrogenation and forms dehydroaripiprazole as an active metabolite. Other metabolites of a*ripiprazole* were also formed through hydroxylation and N-dealkylation catalyzed by CYP3A4 [85]. Olanzapine undergoes hepatic metabolism by direct glucuronidation and CYP1A2 mediated oxidation forming 10-,4'-N-glucuronides and 4'-N-desmethylolanzapine, respectively. Minor metabolic pathways catalyzed by flavin-containing monooxygenase produce olanzapine N-oxide and 2-hydroxymethylolanzapine via CYP2D6 [86] and mainly excreted in urine and feces. Quetiapine is extensively metabolized by the liver following oral administration *via* CYP3A4 with a minor influence of CYP3A5. The quetiapine metabolism involves sulfoxidation, N and O-dealkylation and to some extent, hydroxylation of the dibenzothiazepine ring. *N*-desalkylquetiapine (norquetiapine) is the most important active metabolite while quetiapine sulfoxide is considered as the most important pharmacological inactive metabolite. In addition, CYP3A metabolizes norquetiapine into 7-hydroxyquetiapine, which is pharmacologically active. The elimination of quetiapine and its metabolites are mainly by urine (73%) and feces (21%) [72]. Zotepine blocks 5HT receptors more potently than DA receptors. N-demethylation is the major metabolic pathway by cytochrome P450 (CYP) to form norzotepine. N-demethylation and S-oxidation mediated mainly by CYP3A4 produce norzotepine and zotepine S-oxide, whereas 2 and 3-hydroxylation mediated by CYP1A2/2D6 produce 3-hydroxyzotepine and 2-hydroxyzotepine [87]. Iloperidone undergoes hepatic metabolism involving CYP540 isozymes (CYP 3A4 and CYP2D6) mediated through O-dealkylation (CYP3A4), hydroxylation (CYP2D6), and decarboxylation/reduction processes and excreted in bile and feces. It was observed that iloperidone has a high binding affinity for D2, D3, and 5-HT_{2A} receptors, which results in improving negative symptoms, anxiety, and substance abuse and has less extrapyramidal side effect as compared to risperidone [50, 51, 88]. Asenapine undergoes hepatic metabolism via direct glucuronidation by UGT1A4 and oxidative metabolism via CYP1A2. In general, glucuronidation is considered as the detoxification pathway which transforms the lipophilic drug molecules to hydrophilic metabolite. Asenapine-N^{+}- glucuronide is the principal metabolite formed by this pathway [75, 89]. Risperidone is primarily metabolized by CYP2D6 to produce an active metabolite called 9-hydroxy risperidone (paliperidone) through hydroxylation. Many articles demonstrated that risperidone and its active metabolite have neither the same pharmacological nor the same toxicological activity. Therefore, most patients who have taken this drug orally would exhibit 5-10 times higher plasma levels than risperidone, hence the active metabolite paliperidone plays an effective role in antipsychotic's antidepressant effect [90, 91]. Lurasidone is eliminated by hepatic metabolism primarily by CYP3A4. Oxidative N-dealkylation, hydroxylation of cyclohexane ring or norbornane ring, and S-oxidation are the major biotransformation pathways. They show better results than the quetiapine and have almost no effect on weight, prolactin, glucose, lipids, and QT. The excretion of lurasidone was recovered in urine (9%) and feces (80%) [92]. Ziprasidone undergoes extensive metabolism after oral administration in humans

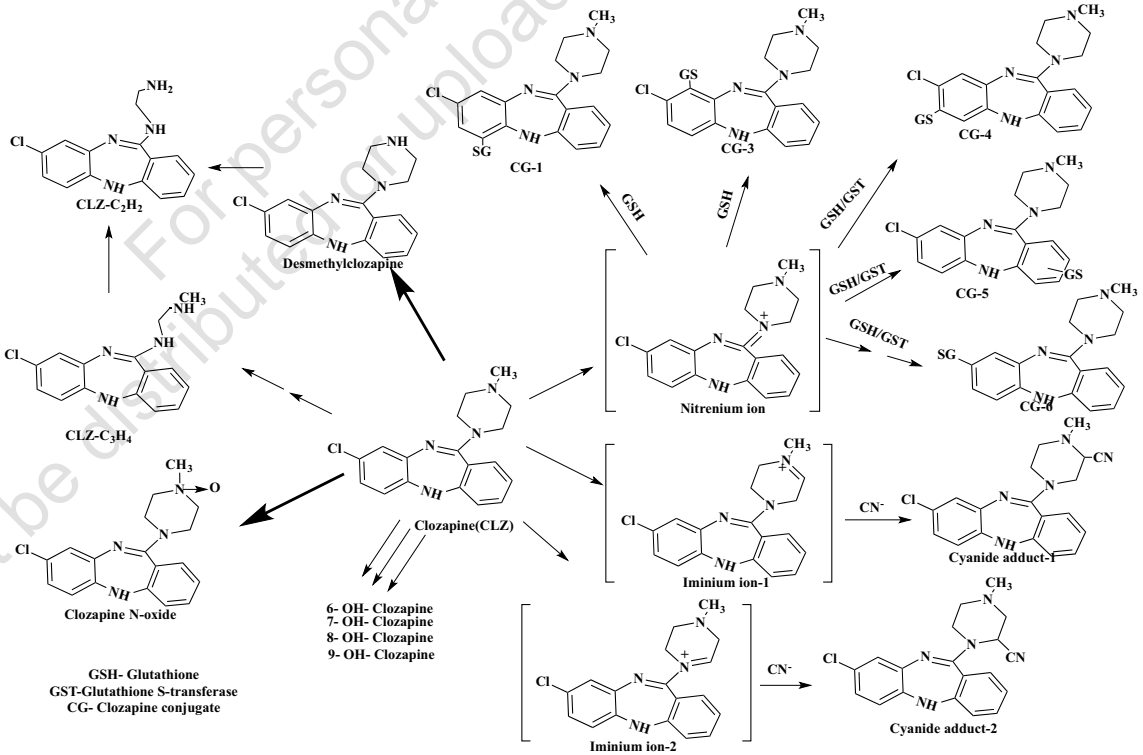


Fig. (6a). Metabolic pathway of Clozapine by cytrochrome P450s.

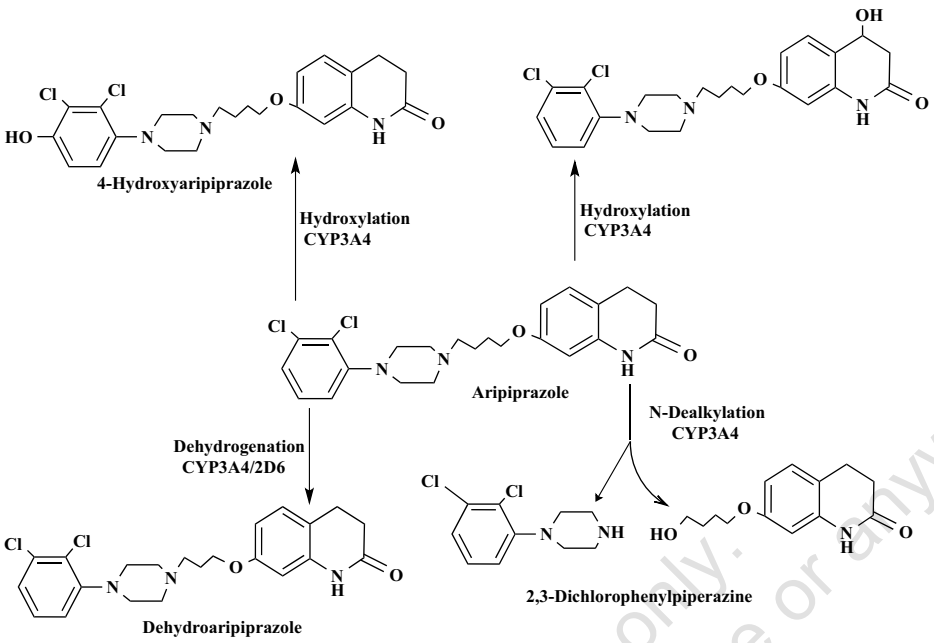


Fig. (6b). Metabolic scheme and metabolites of Aripiprazole.

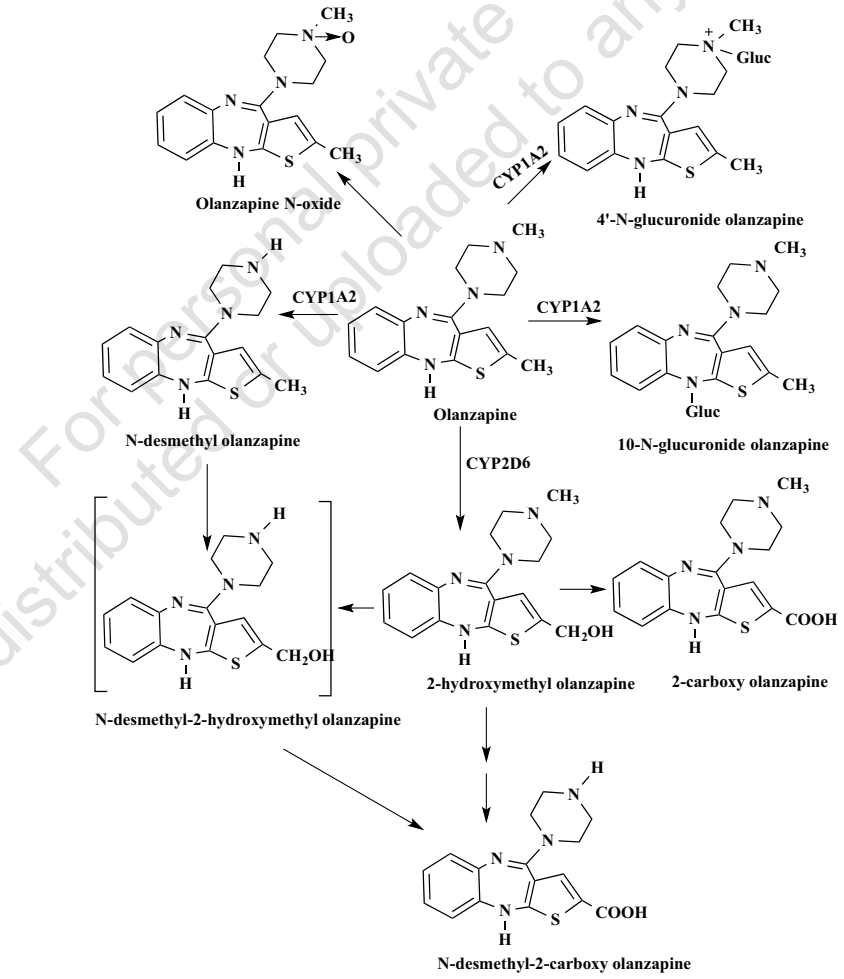


Fig. (6c). Active and inactive metabolites of Olanzapine.

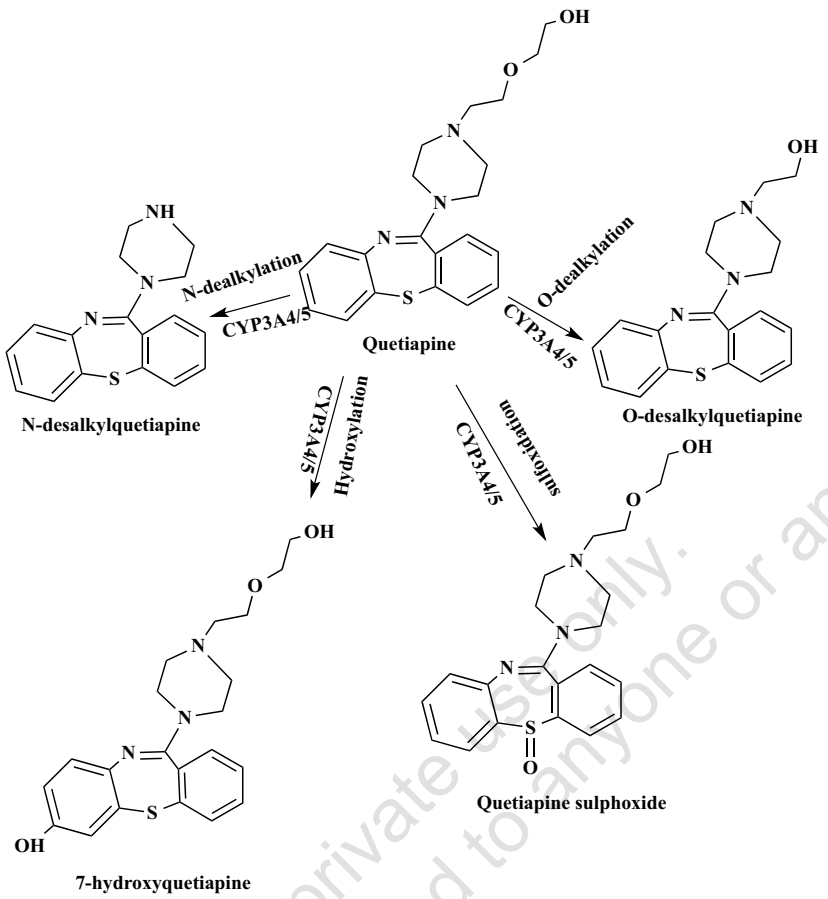


Fig. (6d). *In vitro* metabolite of Quetiapine.

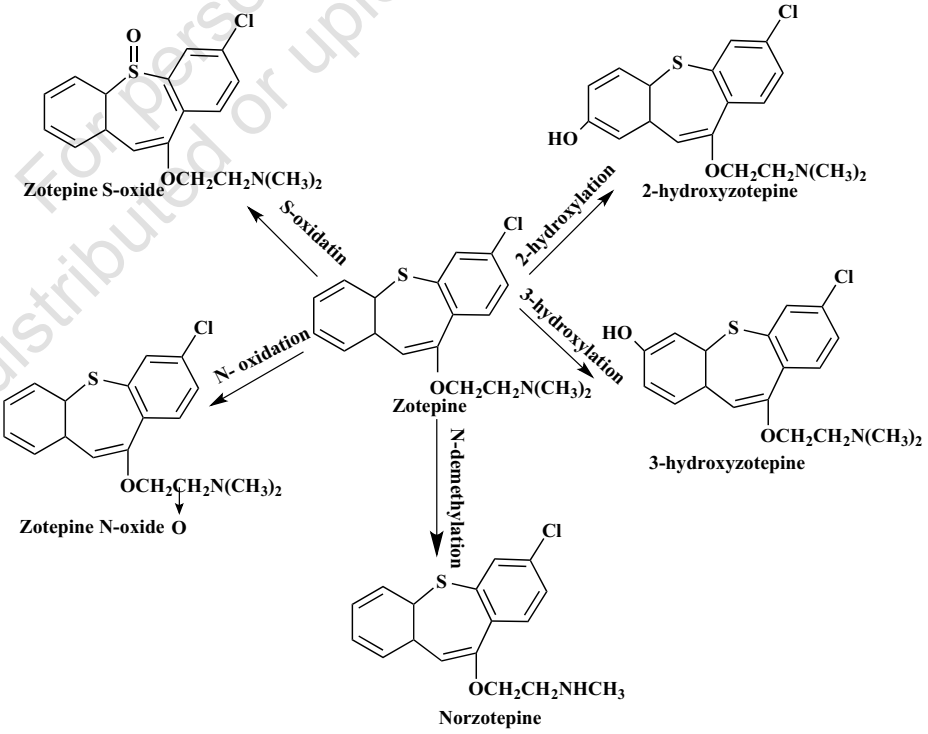


Fig. (6e). Metabolic study route for Zotepaine in human.

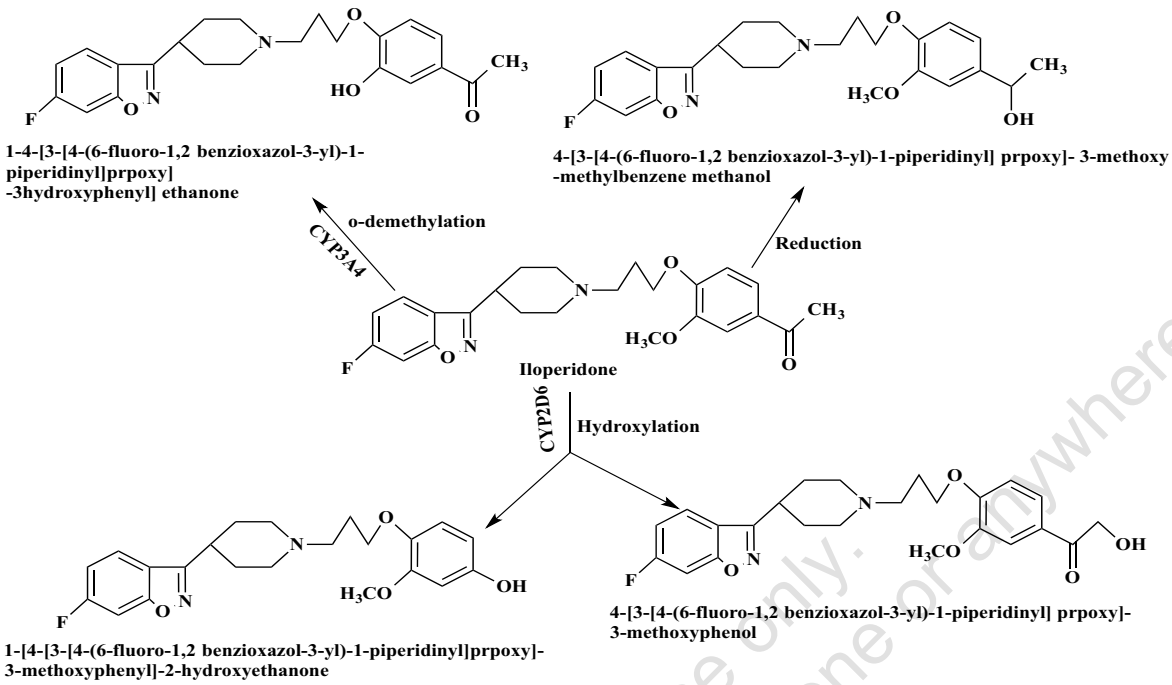


Fig. (6f). Metabolic pathway of Iloperidone to form active metabolites.

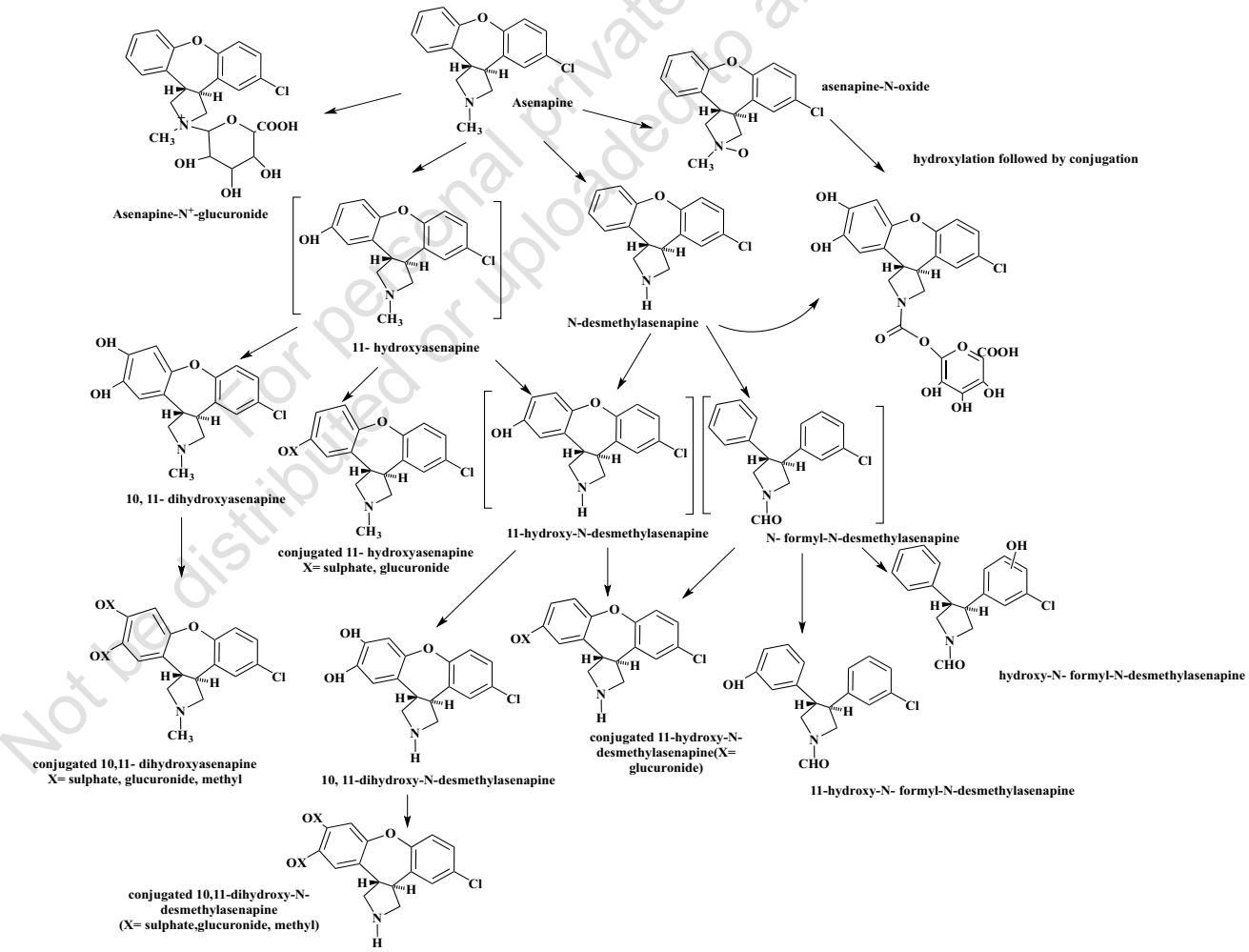
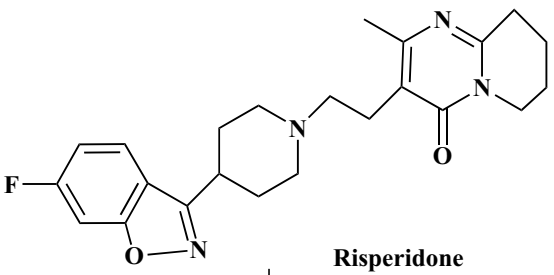
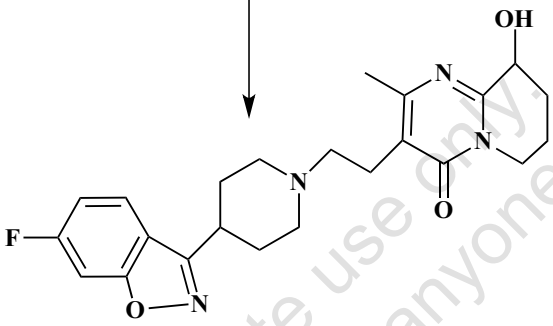


Fig. (6g). Proposed biotransformation pathways for Asenapine based on LC-MS data of human plasma.



Risperidone

9-hydroxylation
CYP3A4
CYP2D6



9-OH risperidone (Paliperidone)

Fig. (6h). Proposed metabolic route of Risperidone.

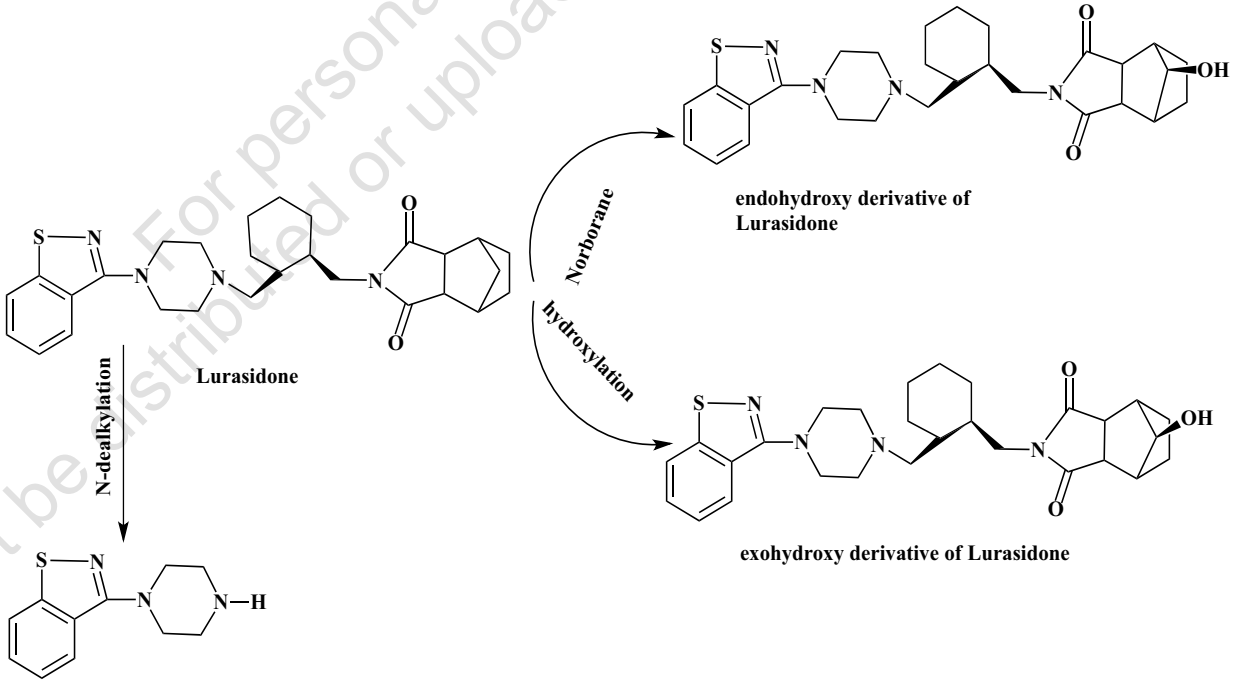


Fig. (6i). Metabolism pathway of Lurasidone to form active metabolite.

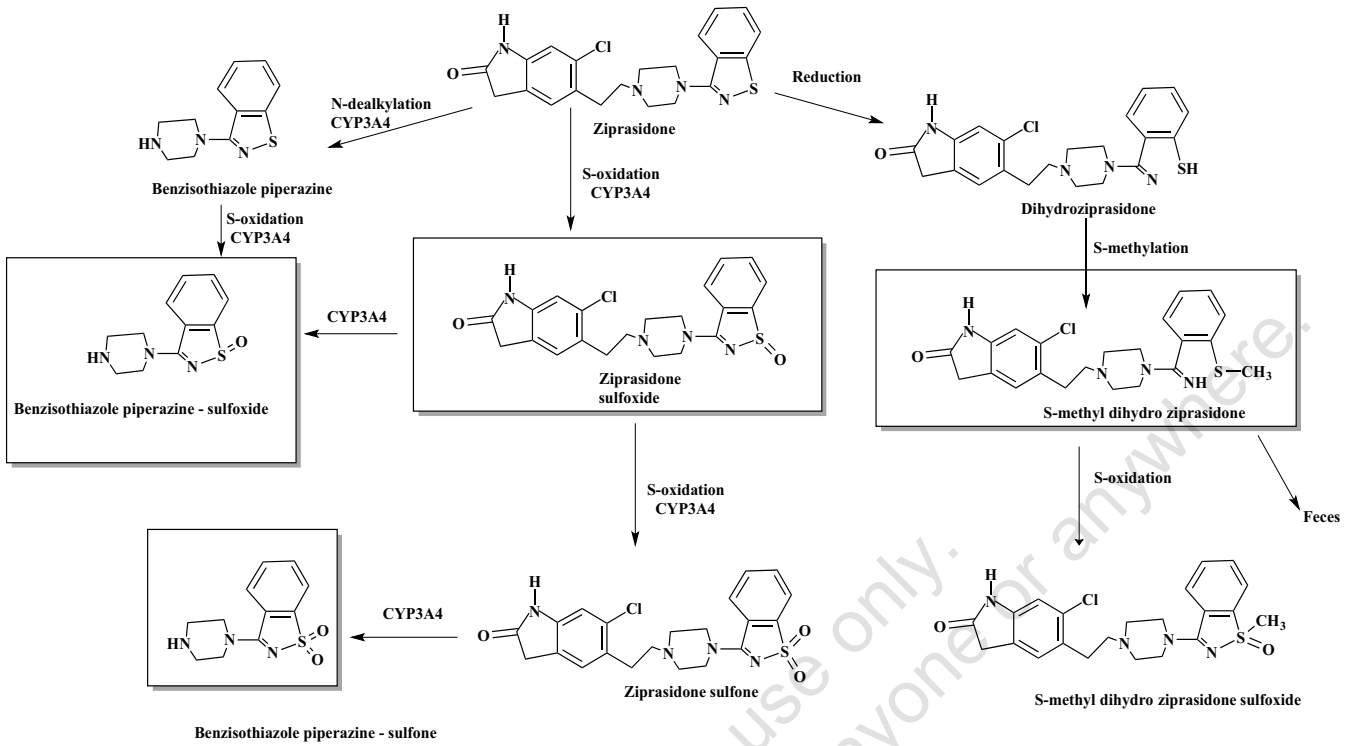


Fig. (6j). Proposed metabolic route of Ziprasidone in human.

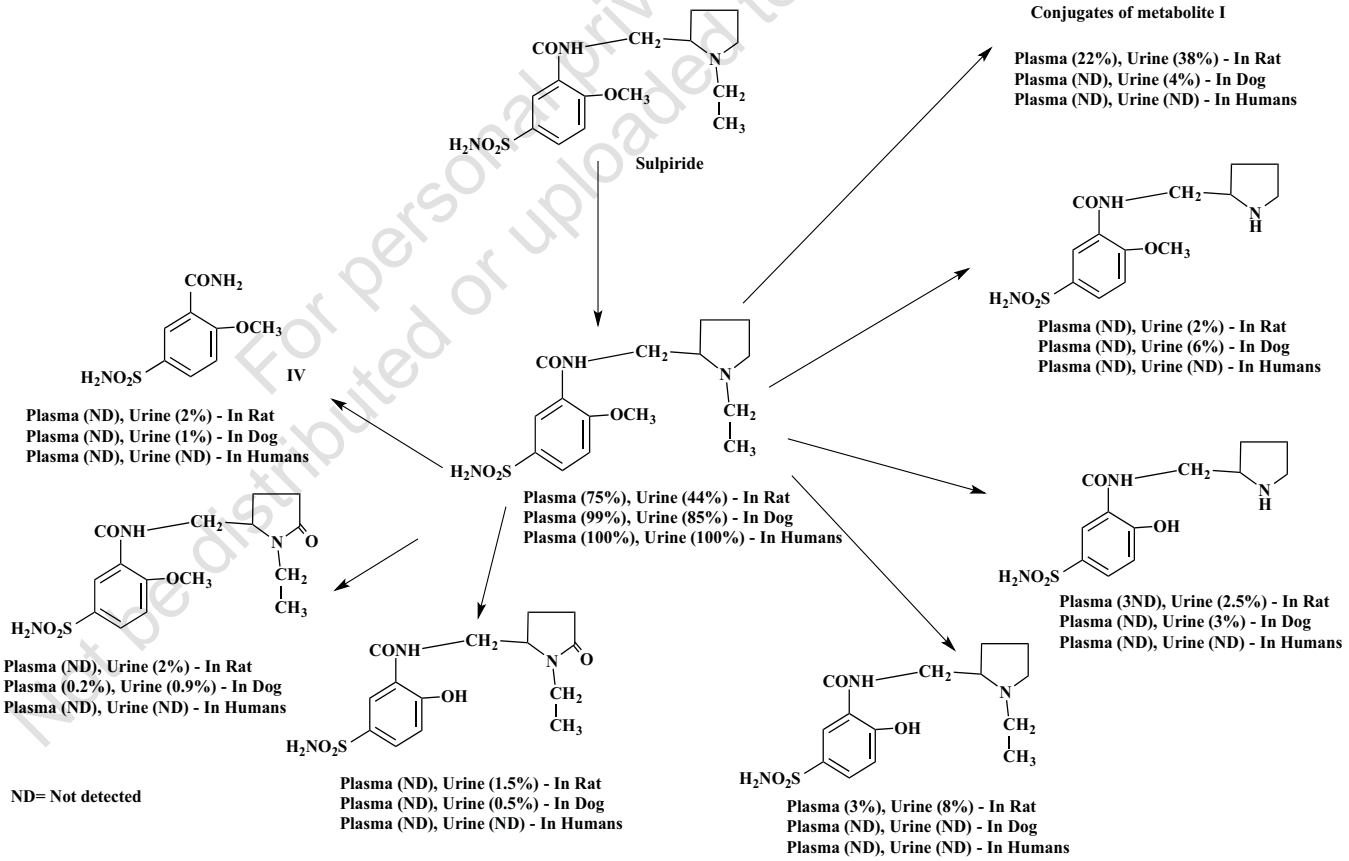


Fig. (6k). Proposed biotransformation route of Sulpiride.

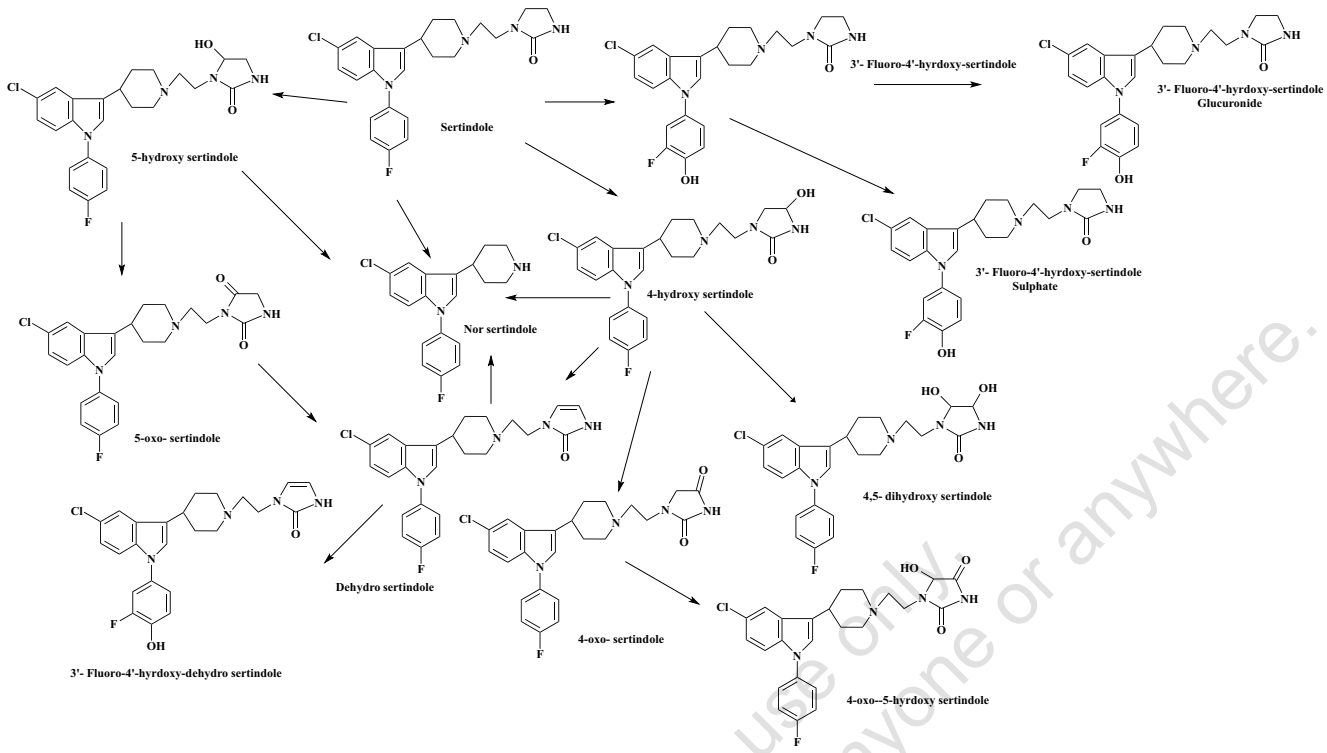


Fig. (6l). Metabolism and metabolic route of Sertindole.

Table 2. List of atypical antipsychotic drugs and their metabolites.

Atypical Antipsychotic Drug	Active Metabolites	Other Metabolites	References
Clozapine	N-desmethylclozapine (norclozapine); Clozapine N-oxide	-	[94, 95]
Olanzapine	*N*-desmethylolanzapine	10-*N*-glucuronide; 4-N-oxide-olanzapine; 2 hydroxymethylolanzapine; 4-*N*-glucuronide	[71, 96, 97]
Aripiprazole	Dehydroaripiprazole	*2-3* dichlorophenylpiperazine; *m*- Chlorophenylpiperazine	[98, 99]
Risperidone	9-OH-risperidone (Paliperidone)	-	[100, 101]
Quetiapine	N–desalkylquetiapine (norquetiapine); 7–Hydroxyquetiapine	O-desalkylquetiapine; Quetiapine sulfoxide	[72, 102, 103]
Asenapine	N-Desmethylasenapine; Asenapine 11 –O–sulfate Asenapine N^+-Glucuronide; N–desmethylasenapine N– carbamoylglucuronide	Asenapine N–oxide; N–Formylasenapine; 11–Hydroxyasenapine; 11–Hydroxy–N–desmethylasenapine; 7–Hydroxyasenapine; 11–Hydroxy–N–formylasenapine; 11–Methoxyasenapine; 11–Hydroxyasenapine N–oxide	[75, 104]

(Table 2) contd…

Atypical Antipsychotic Drug	Active Metabolites	Other Metabolites	References
Zotepine	Norzotepine; Zotepine S-oxide; 2-Hydroxyzotepine; 3-Hydroxyzotepine	Zotepine N-oxide	[73, 105, 106]
Iloperidone	1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-hydroxyphenyl]ethanone; 4-[3-[4-(6-fluoro-1,2-benzisoxazol- 3-yl)-1-piperidinyl]propoxy]-3-methoxy-a-methylbenzene methanol; 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]-2-hydroxyethanone; 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy-3-ethoxyphenyl]ethanone	-	[67, 74, 107-117]
Lurasidone	Endohydroxy derivative of Lurasidone (ID-14326); Endohydroxy derivative of Lurasidone (ID-14283)	1-(1,2-benzisothiazol-3-yl)-piperazine (ID – 11614)	[77,118]
Ziprasidone	S-methyldihydroziprasidone sulfoxide S-methyldihydroziprasidone	Ziprasidone sulfone Ziprasidne sulfoxide	[78]
Sulpiride	Not detected in humans	-	[79]
Sertindole	5-hydroxy-serindole; 4-hydroxy-serindole;	Nor-sertindole; dehydro-sertindole	[80]

with a very small amount excreted in the urine (<1%) or feces (<4%) as unchanged drug. It was observed that CYP3A4 contributes as a major isozyme in the oxidative metabolism of ziprasidone and S-methyl-dihydroziprasidone. There are four major circulating metabolites of sulpiride namely benzisothiazole (BITP) sulphoxide, ziprasidone sulphoxide, BITP-sulphone, and S-methyldihydroziprasidone. Ziprasidone was primarily removed through three main metabolic routes [78, 93], which were determined in humans, dogs, rat's plasma, and urine. Six isolated metabolites along with unchanged product obtained by biological pathways established through chemical structures that none of these metabolites were found in human urine. Thus, the pharmacological properties of sulpiride could be attributed to the unchanged product [79]. Sertindole, an oral arylpiperidylindole antipsychotic, improves negative symptoms and is effective in the treatment of neuroleptic-responsive schizophrenia. It was metabolized through hydroxylation at the 4- and 5-positions of the imidazolidinone ring, *N*-dealkylation, and 1, 2-hydride shift at the fluorophenyl group via CYP2D6 and CYP3A4. Dehydration, oxidation, hydroxylation, glucuronidation, and sulphation were also observed in metabolism. 5-hydroxy-sertindole and 4-hydroxy-sertindole were reported as major metabolites whereas nor-sertindole and dehydro-sertindole were minor ones in liver microsomal metabolic patterns in rat, monkey, and man. It was reported that the metabolism of sertindole in man, rat and, monkey resembles each other but is different in the dog. Oxidation at the imidazolidinone ring and *N*-dealkylation are the main metabolic reactions in the rat [80].

4. DETERMINATION OF IMPORTANT ATYPICAL ANTIPSYCHOTIC DRUGS

Several analytical techniques, traditional to sophisticated, were used for the quantification of drugs in pure and pharmaceutical formulations, urine, tissues, and plasma. Impurities were also determined to evaluate the toxicity profiles and distinguish them from active pharmaceutical ingredients (API). This review presents the analytical methods used in the qualitative and quantitative analysis of atypical drugs, their metabolites in biological samples and in pharmaceuticals such as chromatographic and spectroscopic and other methods including voltammetry, electrophoresis, flow injection and sequential injection analysis, and hyphenated techniques.

4.1. Spectrophotometry

In recent years, this technique has witnessed a rapid increase in its application for the analysis of pharmaceutical dosage forms due to low time and labor consumption with excellent precision. It provides quantitative measurement based on natural UV absorption and chemical reactions known as spectrophotometry. The technique has several advantages including quick analysis, easy to use, cost-effectiveness; another important feature is that it can be applied with a higher dynamic range of samples. However, stray light from the instruments could influence and interfere with the spectral measurement accuracy, may result in a decrease in linear range and get decreased absorbances. Selectivity might be a disadvantage for spectrophotometer as it

does not differentiate between the target analyte and the contaminants that absorb exactly at the same wavelength [119].

4.1.1. Clozapine

UV-Visible technique is well known for the quantification of clozapine in its pure form as well with degradation product [120]. The technique can be applied based on a colored complex with potassium salt of boric acid and eriochrome black T in pharmaceutical formulations and biofluids [121, 122]. For further determination, the traditional extractive method was proposed in tablets and biological samples. It has the ability to make ion-pair complexes with acid-base indicators that can be quantified in the visible region [123, 124].

4.1.2. Olanzapine

An ion pair complex formed after reaction with olanzapine and methyl orange measured at 428 nm [124]. Redox reactions between olanzapine with strong oxidizing agents Ce (IV), iodate, chloramine–T, and *p*- dimethylaminobenzaldehyde [125-128] were studied. In the 1950s, derivatization between drug and reagent idea was established to improve the analytical technique, presently a key parameter for drug analysis. Derivative products of olanzapine with 1,2- naphthoquinone-4-sulphonate [129], iodate [130-132], potassium permanganate [133], and sulphonphthalein acid dyes [134] were investigated. Diazepine ring in olanzapine is mainly secondary amine as it involves condensation with p-dimethylaminobenzaldehyde. As a result, stable enamine with carbon-carbon double bond forms with the help of carbinolamine. However, primary amine is unable to produce a stable product as it undergoes condensation. It is not necessary to separate excipients with main ingredients for developing analytical method applying ICH guidelines proposed by vierordt's method. It also confirmed no effect from excipients to quantify the target analyte. Olanzapine and available dosage forms were kinetically studied by utilizing the increase in absorbance with potassium iodate [135], N- bromosuccinimide [136], and N-bromosuccinimide with two dyes [137]. Accurate and reproduced result can be generated with first and second order help of UV derivative technique [138]. Methanol, used as a solvent in pharmaceutical formulations [139] absorbs maximally at 226 nm. The results remain unaffected in the presence of excipients. The combined form of olanzapine and fluoxetine was simultaneously determined by UV spectrophotometry at 258 nm [140]. The complex product was developed in the visible region for olanzapine based on the color of the complex with potassium hexacyanoferrate (III), potassium cerium (IV) sulphate, or potassium hexacyanoferrate (III) at 425 and 540 nm using batch and flow injection spectrophotometric approach successfully applied for the quantification of olanzapine in pharmaceutical formulations [142]. In recent years, charge transfer complexes and coupling products were produced with olanzapine and successfully applied in the analysis of pharmaceutical formulations [143, 144].

4.1.3. Aripiprazole

A simple and low-cost ultraviolet technique is involved in the pharmaceutical formulation for aripiprazole. Methyl and ethyl alcohol are used as a solvent and simultaneously detected at 256 and 219 nm, respectively. The result shows excellent accuracy and precision of the proposed method with widely quantified range 5-30 and 2-10 mgl^{-1}, respectively [144, 145]. Analysis of aripiprazole tablets was performed with a mixture of acetonitrile and phosphoric acid (0.05 M) with ratio (60:40, v/v). Absorbance measured at 218 nm and the solution was thermally stable. Finally, the method was validated according to guidelines and assay percentage of aripiprazole was evaluated in tablets, which shows excellent recovery and no effect noted from bulking agent exist in formulations [146]. Multivariate calibration technique was also utilized to study and determine the aripiprazole in dosage forms [147]. An economical method was proposed for the analysis of aripiprazole in pharmaceutical formulations, prepared in acidic medium, which was mixed with buffer, and bromocresol green to form a yellowish orange ionic complex, which absorbs maximally at 414 nm [148]. Another spectrophotometric analysis of aripiprazole was performed by taking the bulk powder, dissolved with sodium hydroxide and refluxed in methanolic hydrochloric acid for one hour. After refluxing, the remaining part was diluted to prepare standard solution followed by addition of 3-methyl-2-benzothiazolinone-hydrazone and Fe (III) [149], which formed a coloured complex after 5 minutes and quantified at 480 nm. Other coloured products of aripiprazole were also formed by charge transfer complexation reaction with iodine, chloranilic acid and 2, 3-dichloro-5, 6-dicyano-p-benzoquinone. A few more articles reported on ion-pair complexes formed by reaction with acidic dyes and successfully developed a visible spectrophotometric method for pharmaceutical formulations [150, 151].

4.1.4. Quetiapine

Spectrophotometry has been utilized quantitatively by measuring the 2D-values at 254.76 nm where 0.1N HCl was used as a background solvent [152]. Methanol: water (50:50) was used for simple UV determination of quetiapine [153]. In another attempt to quantify quetiapine, ion-pair complexation reaction was used where the target drug was analyzed using dye tropaeolin OOO [154]. Details of all drugs are mentioned in Table **3**.

4.2. Fluorimetry

Fluorimetry is the luminescent phenomenon that involves electromagnetic radiation and measures the enhanced fluorescent signal. Sensitivity is a major advantage of fluorimetry and fluorimetric methods are many folds more sensitive than spectrophotometric ones. This technique can detect the sample even at lower concentration and requires potentially less sample for analysis. Since it detects fluorescence material, it has greater specificity as compared to the traditional spectrophotometric methods. On the other hand, it can not be applied to a wide range of samples as it detects only fluorescent materials or those which are made fluorescent. In addition, the results could be hampered by the pH. Bubbles too can create fluctuated reading [155].

The clozapine was oxidized by a strong oxidant such as Ce (IV) in acidic medium and determined fluorometrically [156]. 4-chloro-7-nitrobenzofurazan (NBD-Cl) was used for fluorimetric determination of quetiapine in McIlvaine buffer. The authors reported that nuclear substitution reaction resulted in the formation of the fluorescent product [157].

Table 3. Use of spectrophotometric methods in the analysis of clozapine, olanzapine, aripiprazole, and quetiapine.

Name of Drug	Method/ Reagents Used	λ_{max} (nm)	Linear Range (μgml^{-1})	LOD (μgml^{-1})	Applications	References
Clozapine	UV	315 305 295 325	3-10 3-10 4-10 10-25	1.21 1.35 1.59 3.85	Bulk powder and pharmaceutical formulations	[120]
	Eriochrome black T	514	2–18	0.530	Tablets and biological fluids	[121]
	$KBrO_3$	308	0-12	0.1	Dosage forms	[122]
	Bromophenol blue Bromothymol blue	408 406	1–11 1–7	0.123 0.081	Tablets and biological fluids	[123]
	Methyl Orange	428	2-14	0.0734	Dosage forms and biological fluids	[124]
Olanzapine	Methyl Orange	428	2-14	0.0765	Dosage forms and biological fluids	[124]
	Ce (IV) + N-phenyl-anthranilic acid or sulphanilic acid	440 545	0.3-1.8 5.0-75.0	0.03 0.61	Tablets	[125]
	Bromocresol purple Bromothymol blue	405 410	1-10 1-8	0.15 0.32	Pharmaceutical formulations	[126]
	KIO_3 + leuco crystal violet	598	0.05-2	0.038	Pharmaceuticals	[127]
	chloramine-T + rhodamine B	550	0.1-1.6	0.064	Pharmaceuticals	[127]
	p-dimethylaminobenzaldehyde	410	5-160	6	Pharmaceuticals	[128]
	1,2-naphthoquinone-4-sulphonate	454	0.4-4	0.09	Dosage forms	[129]
	Iodine + Nile blue	400	15-120	3.93	bulk drug and tablet	[130]
	ICl and thymol blue Ce (IV) + leuco crystal violet	536 580	0.2-1.6 0.1-1.4	0.0218 0.0149	Pure and dosage forms.	[131]
	Ce (IV)+ iron (II)+ thiocyanate, tiron or ferrocyanide	480 640 or 700	0.2-2.0 1.0-9.0 0.3-3.0	0.02, 0.11 0.03	Bulk drug and in tablets	[132]
	$KMnO_4$ in either acid or alkaline medium	550 610	2.0- 20 1.0- 10	0.37 0.16	Tablets	[133]
	N-bromosuccinimide (NBS) with quinoline yellow and metanil yellow	410 530	0.1-1.2 0.1-1.5	0.07 0.05	Tablets	[134]
	KIO_3	537	4-7	0.1 and 0.15	Dosage forms and spiked serum	[135]
	N-Bromosuccinimide Cerium (IV) sulfate Clestine Blue	532 538 538	10 – 120 0.5 – 6.0 0.6 – 3.0	6.99 0.3 0.37	Pure and pharmaceutical formulations	[136]
	N-bromosuccinimide with amaranth and janus green B	520 620	0.1-0.9 0.1-1.2	0.05 0.09	Dosage forms	[137]

(Table 3) contd…

Name of Drug	Method/ Reagents Used	λ_{max} (nm)	Linear Range (μgml^{-1})	LOD (μgml^{-1})	Applications	References
Olanzapine	UV	222 230	2–12 2–12	0.5 0.499	Bulk and dosage form	[138]
	UV	226	0.1-50	0.1	Pure and dosage forms	[139]
	UV	258	1-100	1-10	Bulk Drug and formulations	[140]
	Potassium hexacyanoferrate (III)	425	2.5-40	2.17	Pharmaceutical formulations	[141]
	Diazotized p-Nitroaniline	405	0.5-45	0.3148	Tablets	[142]
	p-chloranilic acid	520	2–40	1.57	Tablets	[143]
Aripiprazole	UV	256	5-30	-----	Soild dosage forms	[144]
	UV	219	2-10	-----	Pharmaceutical preparations	[145]
	UV	218	2.5-20	0.01	Pure form and Tablets	[146]
	UV	255	5-30	0.3	pharmaceutical formulations	[147]
	Bromocresol green	414	10-60	-----	Tablets	[148]
	3-methyl-2-benzothiazolinone-hydrazone (MBTH) + Fe (III)	480	2-12	0.5835	Pharmaceutical formulations	[149]
	2,3-dichloro-5,6-dicyano-p-benzoquinone Iodine (I_2) Bromocresol green Bromocresol purple	457 364 413 400	10-120 2-28 2-24 2-20	2.44 0.39 0.50 0.30	Tablets	[150]
	p–chloranillic acid	543	80-400	5.17	Bulk and pharmaceutical formulations	[151]
	Methyl Orange	428	2-14	0.0716	Dosage forms and biological fluids.	[124]
Quetiapne	Derivative UV	254.76	10-30	------	Tablet	[152]
	UV	290	15.99-24.09	------	Bulk and tablets	[153]
	Tropaeolin OOO	480	2-20	0.43	Bulk drug, tablets, and human urine	[154]

Oxidation reaction using Cerium (IV) was exploited for quantitative analysis of quetiapine along with flupentixol dihydrochloride spectrofluorimetrically [158].

4.3. Chromatographic Methods

Chromatography and their related techniques stimulate the development of new methods in pharmaceutical laboratories and provide a more accurate procedure for the analysis of various drugs in bulk and tablets. These chromatographic techniques also enable to assess the stability of corresponding drugs, test for impurities and degradation products as well as in pharmacokinetic studies. Atypical drugs and their metabolites were determined using HPLC/HPTLC/ UPLC/TLC in bulk, pharmaceutical dosage forms.

4.3.1. High Performance Liquid Chromatography (HPLC)

HPLC provides information about the main ingredient and its metabolites in biological fluids during metabolism and clinical studies. The technique can be applied to raw

materials, finished products, dosage forms, and quality control samples. During organic synthesis and degradation monitoring, impurities and degradants obtained can also be analyzed by HPLC. HPLC is both a preparative and analytical tool. It is so versatile that it can separate compounds with a molecular weight ranging from 54 Dalton to 450,000 Dalton, simultaneously. It has a long range of detection limit ranging from picogram going through nanogram to milligrams. Compounds with a wide range of polarity can be separated using HPLC. Despite the several advantages, this technique is too expensive to be afforded by various laboratories in developing and poor countries. Expensive column combined with short operating life makes it rather tough for the researcher and disposal of expensive solvents is becoming a problem [159].

Clozapine was extracted (liquid–liquid extraction) from a biological matrix using methyl terbutyl ether and determined by HPLC [160]. Two major metabolites norclozapine and clozapine N-oxides were identified and quantified by HPLC in humans and dog plasma [161, 162]. Clozapine was quantified in the presence of degraded product and pharmaceutical preparation. Clozapine and degraded peak were eluted isocratically at 30.9 and 14.4 min [163]. HPLC with UV detector was used to quantify clozapine and its metabolites in tablets and human plasma [164-171]. Olanzapine and its major metabolites were quantified using HPLC with ultraviolet and diode array detector in bulk, tablets, rat brain, human breast milk, and plasma [172-181]. Aripiprazole was estimated using RP-HPLC in bulk and pharmaceutical dosage forms [182-200].

HPLC has always been a good choice for the pharmaceutical scientists; the majority of the literature dealing in the quetiapine determination involves chromatographic analysis. Quetiapine was analyzed in human plasma, where phosphate buffer (pH 1.9) was used as a mobile phase along with methanol and acetonitrile as organic modifiers and solid phase extraction process used for the sample preparation. The detection limit was found to be 4 $ngml^{-1}$ [201]. It can be quantified in the presence of its degradation products, namely quetiapine N-oxide, quetiapine lactam with acetonitrile, and phosphate buffer as mobile phase [202]. Quetiapine along with other psychotropic drugs was determined using DAD and MS detector [203]. These drugs were analyzed on XSELECT CSH phenyl-hexyl column with methanol acetate buffer and diethylamine. Magnetic ODS-PAN thin film was prepared by Li and his co-worker for the microextraction of quetiapine and clozapine, which were further detected in plasma and urine samples [204]. The linear range of 0.070–9.000 $\mu g\ ml^{-1}$ was reported for both the drugs in plasma and 0.012–9.000 $\mu g\ ml^{-1}$ for urine. The results further show that LOD for quetiapine using the method was found to be 0.013 $\mu g\ ml^{-1}$ in plasma and 0.003 μgml^{-1} in the urine.

4.3.2. High Performance thin Layer Chromatography (HPTLC)/UPLC

It offers a wide range of separation and short analysis time with outstanding clarity of visual evaluation of the sample and its components. The sample preparation is simple because it consists of a single stationary phase and multiple evaluations are possible by a storing fraction of all samples in the plate. The technique is very fast and reproducible. Identification of compounds by HPTLC is highly demanding because of the independent sample application, chromatogram development, easy detection, and identification as compared to Thin Layer Chromatography (TLC). It can be used for the qualitative and quantitative analysis for a broad range of matrix. It is the only chromatographic technique that has the ability to present the obtained result as an image. One of the advantages of HPTLC is that many analysts can work together on the system, having low analysis time and low maintenance cost and larger range of the stationary phases. The solvents to be used do not require to be degassed and filtered. However, it is not suitable for lipid sample analyses [205].

HPTLC was used previously to study the stability of clozapine in pharmaceutical formulations in the presence of acids, bases, and hydrogen peroxide under the influence of heat and light. The degraded products were well separated and validated according to the guidelines [206]. Olanzapine, aripiprazole, and quetiapine were also studied in bulk, tablets, human plasma, rat brain, plasma, and raw materials using TLC, HPTLC [207-209], and UPLC [210-212] in pharmaceutical formulations. The complete details of the phases and the detectors for the analysis of four selected atypical antipsychotic drugs are summarized in Table **3**.

4.3.3. Hyphenated Techniques

Hyphenated techniques refer to the online combination/coupling of different analytical techniques that mainly consist of chromatographic with spectroscopic detection techniques. The hyphenation provides a remarkable improvement that significantly broadened their applications in the analysis of various types of drugs in bulk and dosage forms. With the advancement of the instrumentation, the hyphenated technique finds a great application in the analysis of pharmaceuticals. Various hyphenated techniques such as HPLC-MS, UPLC-MS-MS, and GC-MS were used to determine many important atypical antipsychotic drugs and their active metabolites in the pharmaceutical dosage forms, urine, serum, and plasma. Easy and faster analysis can be performed using LC-MS where many analytes in a single sample can easily be analyzed using the technique. Analyte specific reagent is not required and the technique is highly specific and sensitive. Two analytes at the same retention time could be analyzed using LC-MS as the determination process is based on the molecular mass. LC-MS/MS does not require derivatization of the sample. However, the instruments are very expensive, and the data interpretation required trained analysts. Moreover, working with biological samples at trace level, extra pre-treatment procedure in term of sample preparation is required to avoid interferences [213].

4.3.3.1. HPLC- Electrospray Ionization Mass Spectrometry (HPLC- ESI/MS)

Electrospray ionization mass spectrometry (ESI/MS) is an accurate and reliable tool for studying nonvolatile and thermally liable analytes. HPLC coupled with ESI/MS is a dynamic technique for the quantification of small and large molecules with different polarities. Plasma sample of schizophrenia patient was collected and investigated by HPLC-ESI/MS [214]. The compounds were extracted from plasma and eluted isocratically with electrospray mass spectrometer.

The results of ion transitions confirmed the presence of clozapine and its metabolites [215].

Clozapine along with five other antipsychotics was quantified by employing liquid chromatography combined with tandem mass spectrometry and electrospray ionization in rat plasma [216]. The method required liquid-liquid extraction and midazolam as an internal standard. The extraction was followed by separation on Waters Atlantis column with gradient elution and detected on multiple reactions monitor.

Olanzapine and its active metabolite were also determined using LC-MS in human urine, serum, and cerebrospinal fluids [217–218]. Aripiprazole was determined in the presence of other forty-seven antidepressants in human serum using methanol and 5 mM acetate buffer of pH 3.9 as a mobile phase with monolithic column C_{18} (50×4.6 mm) combined with multiple reactions monitoring detector ESI-MS/MS [219]. The investigation was continued for aripiprazole in serum and plasma because the technique needs a small volume of sample for the determination [220–222].

4.3.3.2. Liquid chromatography-mass spectrometry (LC-MS/MS)

LC-MS/MS was developed for plasma sample based on solid phase extraction with electrospray ionization detector in which quetiapine was used as an internal standard [223]. The triple quadrupole tandem mass spectrometer combined with electrospray ionization detector worked as an ionization source and a mobile phase (methanol, ammonium acetate buffer) was found to be suitable for the separation of olanzapine in plasma [224]. The method used olanzapine-d3 as an internal standard and pharmacokinetic studies were discussed for healthy patients.

Dehydroaripiprazole can be determined in basic medium with gradient mode in human plasma applying solid phase extraction continued with LCMS [225]. Papaverine was the internal standard used for quantification of metabolite in human plasma [226]. Sodium hydrogen carbonate was added in the plasma sample to make it slightly basic and extract the metabolite in the presence of internal standard OPC-14714. The reverse phase C_{18} column with a flow rate of 0.2 ml/min and less than 7.5 minutes were needed for the analysis [227]. Barette *et al.* used the HPLC-MS/MS technique for quetiapine determination in human plasma. Solid phase extraction process was used for sample extraction while the extracted sample was found to be linear over the concentration range of 1.0–382.2 $ngml^{-1}$ subjected to analyses by HPLC-MS/MS [228]. In another attempt, LC-MS/MS was used for the photodegradation study of quetiapine. The study observed five degradation products whose formulae and masses were established [229].

4.3.3.3. Ultra-pressure Liquid Chromatography-tandem Mass Spectrometry (UPLC-MS-MS)

Presently, the ultra-pressure liquid chromatography–tandem mass spectrometry technique has high demand in pharmaceutical and food industries. The polar contaminants from biological, environmental samples can be investigated and quantified. The technique needs efficient extraction and cleanup procedure of the sample before analysis of the sample. It has a shorter run time compared to the other techniques.

Clozapine and its major metabolites were identified in human serum using UPLC-MS-MS with triple quadrupole detection system [230]. The metabolites determined by SPE-LC-MS in serum [231] were more favourable because of its concern about sample handling and throughput in therapeutic drug monitoring. Sensitive liquid chromatography–tandem mass spectrophotometry was used to quantify clozapine and norclozapine in serum, plasma, and brain tissues of rat and human, and to discuss their pharmacokinetic studies [232–235]. All metabolites of clozapine can be determined in serum and urine by extraction with ethyl acetate in alkaline medium followed by LC-MS/MS [236].

It was reported that the main drug transporter *p-glycoprotein* controls the drugs to the central nervous system. However, there is no clear justification that aripiprazole penetrates through the blood-brain barrier or it interacts with its metabolites on drug transporters. Fast and high-speed UPLC-MS/MS technique was developed to give answers to the questions. The analysis was carried out with acquity UPLC BEH C_{18} (100×2.1mm, 1.7µm). 30 mM ammonium acetate and acetonitrile with ratio 38:62 (v/v) used as mobile phase and required 3 minutes for the separation [237]. The ESI mode was helpful for the determination of aripiprazole and its metabolites in biofluids. The sensitive and validated method was applied in human plasma to determine aripiprazole. The main advantages of the technique involved are solid phase extraction, aripiprazole d_8 as internal standard, multiple reactions monitoring in the positive ionization mode, and isocratic elution [238].

4.3.3.4. Gas Chromatography (GC) and Gas Chromatography-Mass Spectrometry (GC-MS)

Gas chromatography is a powerful technique for the separation and identification of volatile compounds. High molecular and thermally unstable samples can be determined. The gas chromatographic techniques are characterized by good resolution along with sharp and symmetric peaks, high repeatability and reproducibility, and least thermal decomposition of crucial samples. However, the main drawback of the GC methods is that only those samples that are volatile or are made volatile can be analyzed. The samples must be thermally stable so that they do not degrade when heated [239]. Clozapine was determined by using capillary GC [240]. Gas chromatography coupled with mass spectrophotometry combined with microextraction is a well known advanced technique to determine the concentration of clozapine and metabolites in human plasma [241–242]. GC-MS method was studied with plasma samples collected from seven schizoaffective disorder patients receiving 10-20 mg aripiprazole per day. This technique introduced solid phase extraction with N-methyl-N-trimethylsilylfluoro acetamide for aripiprazole and dehydroaripiprazole in blood samples [243].Other techniques involved in atypical drug analysis

4.3.4. Capillary Zone Electrophoresis

Capillary Zone Electrophoresis (CZE) is a powerful separation technique for small and large molecules. However, the disadvantage of this method is that it requires an extraction step for the analysis. It was used for the determination of clozapine utilizing end column amperometric detection involving carbon fiber array microdisk electrode [244]. The

characteristics of the CZE separation is higher separation efficiency, low cost, faster separation, and low sample volume requirement. However, this technique is not so useful when there is insufficient mass sensitivity and sometimes poor reproducibility can be evident with CE methods when the qualitative and quantitative data are collected [245]. The CZE method combined with factorial design can be helpful for the separation of atypical antipsychotics. It was useful to determine the effect of concentration and pH during the separation of four atypical drugs [246]. Studies revealed that pH 3.5 (80 mM sodium phosphate buffer) is the best for separation. This method is well established and employed to quantify clozapine in serum and plasma [247]. This technique was applied for the determination of clozapine in human plasma using fused silica capillary combined with background electrolyte at low pH and separate analyte as well as metabolite within three minutes [248].

The CZE analysis of olanzapine was carried out using phosphate buffer and uncoated fused silica capillary in pharmaceutical tablets. Studies revealed a high pH of background electrolyte would cause the loss of analyte as well as distortion in the peak shape. Hence, the analysis was performed at pH 3 to reduce the electroosmotic flow and to increase the separation efficiency in pharmaceutical formulations [249]. CZE is performed to separate and quantify olanzapine simultaneously with other antipsychotic drugs, chlorpromazine hydrochloride, fluphenazine hydrochloride, perphenazine, and pipotiazine [250]. The separation was accomplished with a fused silica capillary column and measured at 254 nm with an applied voltage of 18 kV. The reproducibility of the method was efficient for the determination of olanzapine. The analysis of aripiprazole was also carried out in human plasma using a fused silica tube and capillary. It was able to detect aripiprazole in human plasma. 50 mM phosphate buffer of pH 2.5 worked as a background electrolyte with +20 kV and loxapine used as an internal standard. The analyte was initially pretreated on cyano cartridge for solid phase extraction [251].

4.3.5. Voltammetry

Clozapine was determined by utilizing glassy carbon electrode and thin film carbon nanotubes by doping with polypyrrole and sodium dodecyl sulphate (SDS) [252–253]. The investigation was continued with TiO_2 nanoparticles modified carbon paste electrode [254]. The adsorption and electrochemical properties of clozapine were studied in pharmaceutical preparations [255]. This method can be applied for quantification of the drug in spiked urine samples. The carbon ionic electrode with SDS was used for blood serum and plasma samples [256]. The adsorptive cyclic voltammetry with mercury electrode combined with supportive electrolyte is helpful to determine clozapine in pharmaceutical products [257]. The drug is reducing in the mercury electrode followed by reduction of azomethine group in the heterocyclic ring. This method can be utilized to determine clozapine in human serum. The main advantages of this technique are that it does not require any pretreatment process and short analysis time.

The voltammetric technique has been successfully used for the determination of two antipsychotics quetiapine and olanzapine. The behavior of these drugs was monitored on a glassy carbon electrode, where the oxidation peak was obtained with Britton-Robinson (BR) pH 2.0 buffers. This voltammetric procedure was reported to be fast and the analyses time was less than 5 minutes [258]. Lawrywianiec and coworker voltammetrically quantified quetiapine on a carbon black nanoparticle modified glassy carbon electrode. This method was able to detect quetiapine in a concentration as low as 7×10^{-9} $moll^{-1}$ with a recovery of 99%-107% [259].

CONCLUSION

Antipsychotic medications are one of the fastest growing pharmaceutical products in the industry and have great importance in our daily life as well. Currently, these kinds of medication are frequently prescribed all over the world for a psychotic disorder. Over the past several decades, the number of psychiatric patients has gradually declined.

Three structurally related atypical antipsychotics, clozapine, olanzapine, and aripiprazole are used for a psychotic disorder or treatment of schizophrenia. Studies reported that all are effective for both positive and negative symptoms. They have less pyramidal side effects than classical antipsychotics. The investigation of the three drugs with respect to the therapeutic profile shows many advantages and enhances their application for the treatment of schizophrenia.

However, a high dose of these atypical antipsychotics is suspected to pose an increased risk factor. From the above studies, we could know their metabolic pathways and products during metabolism. Various analytical techniques developed for atypical drugs are commonly used in long-term treatment for all stages of schizophrenia. Antipsychotic drug analysis is important in psychiatry similar to sports. According to predictions, the consumption of atypical drugs will be increasing, especially in high-income countries. Moreover, treatment of mental diseases usually demands chronic, often combined therapy. High consumption of psychiatric pharmaceuticals also leads to their accumulation in the environment. Many analytical methods were used for the determination of atypical drugs, however, chromatographic, spectroscopic, and spectrometric methods were the most often applied. This review summarizes analytical applications of potentiometry, high performance liquid chromatography, liquid chromatography, gas chromatography, ultra performance liquid chromatography, mass spectrometry, capillary electrophoresis, voltammetry, spectrophotometry, and hyphenated techniques such as LC-MS, LC-MS/MS, and GC/MS for selected antipsychotics such as clozapine, olanzapine, aripiprazole, and quetiapine, and their metabolites. Applications of all analytical methods are discussed for quantification of antipsychotic drugs with environmental, biological, and pharmaceutical samples.

AUTHOR'S CONTRIBUTIONS

Habibur Rahman: Formulated the study, helped in literature searches, wrote the first draft, contributed to reviewer's comments, and approved the final version to be submitted.

SK Manirul Haque: Managed literature survey, contributed in the first draft, answered the reviewer's comments, communicated with the journal, and approved the final version to be submitted.

Masoom Raza Siddiqui: Helped in the literature survey, extensively reviewed the first draft and provided information for improvement, contributed to the reviewer's comments, and approved the final version to be submitted.

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