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## A REVIEW ON ANTIPSYCHOTICS FOR SCHIZOPHRENIA

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### Keywords:

Dopamine,  
Glutamatergic, GABAergic,  
5-hydroxytryptamine(5-HT),  
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**ABSTRACT:** Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves. People with schizophrenia may seem like they have lost touch with reality. Schizophrenia is a split personality disorder which is related to mental illness. Generally, schizophrenia affects approximately 1 percent of all adults' population. Schizophrenia is different types such as paranoid in which auditory hallucinations occur, some time disorganized schizophrenia occurs in which disorganized speech and behavior are shown. The hypothesis of schizophrenia included dopamine hypothesis, glutamatergic hypothesis, GABAergic hypothesis. Pharmacologically, they are characterized as dopamine receptor antagonists, though many of them also act on other targets, particularly 5-hydroxytryptamine (5-HT) receptors. The antipsychotic agents are used for the treatment of schizophrenia. Based on pharmacologic action, the chemical structures of antipsychotic agents contain reserpine- like compounds, phenothiazines derivatives and compounds include various tricyclic derivatives with a central 7-membered ring to which methyl piperazine is linked. The activity of this group is widely scattered, containing among the weakest and more potent of the apomorphine antagonists.

**INTRODUCTION: Antipsychotic Agents:** The term antipsychotic and neuroleptic are used interchangeably to denote a group of drugs that have been used mainly for treating schizophrenia but are also effective in some other psychoses and agitated states <sup>1</sup>. Nature of psychosis & schizophrenia: The term "psychosis" denotes a variety of mental disorders, but the term antipsychotic drugs also known as a neuroleptic drug, antischizophrenic drugs or major tranquilizers conventionally refers to those used to treat schizophrenia, one of the most common and debilitating forms of florid mental illness <sup>2</sup>.

Pharmacologically, they are characterized as dopamine receptor antagonists, though many of them also act on other targets, particularly 5-hydroxytryptamine (5-HT) receptors. Schizophrenia, also sometimes called split personality disorder, is a chronic, severe, debilitating mental illness that affects about 1% of the population, corresponding to more than 2 million people in the United States alone.

Other statistics about schizophrenia include that it affects men about one and a half times more commonly than women. It is one of the psychotic mental disorders and is characterized by symptoms of thought, behavior, and social problems. The thought problems associated with schizophrenia are described as psychosis, in that the person's thinking is completely out of touch with reality at times <sup>3</sup>.

For example, the sufferer may hear voices or see people that are in no way present or feel like bugs are crawling on their skin when there are none.

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The individual with this disorder may also have disorganized speech, disorganized behavior, physically rigid or lax behavior (catatonia), significantly decreased behaviors or feelings, as well as delusions, which are ideas about themselves or others that have no basis in reality (for example, experience the paranoia of thinking others are plotting against them when they are not).

**Different Types of Schizophrenia:** There are five types of schizophrenia, each based on the kind of symptoms the person has at the time of assessment <sup>4</sup>.

**Paranoid Schizophrenia:** The individual is preoccupied with one or more delusions or many auditory hallucinations but does not have symptoms of disorganized schizophrenia.

**Disorganized Schizophrenia:** Prominent symptoms are 1<sup>o</sup>, as well as flat or inappropriate affect. The person does not have enough symptoms to be characterized as catatonic schizophrenic.

**Catatonic Schizophrenia:** The person with this type of schizophrenia primarily has at least two of the following symptoms: difficulty moving, resistance to moving, excessive movement, abnormal movements, and repeating what others say or do.

**Undifferentiated Schizophrenia:** This is characterized by episodes of two or more of the following symptoms: delusions, hallucinations, disorganized speech or behavior, catatonic behavior or negative symptoms, but the individual does not qualify for a diagnosis of the paranoid, disorganized, or catatonic type of schizophrenia <sup>5</sup>.

**Residual Schizophrenia:** While the full-blown characteristic positive symptoms of schizophrenia (those that involve an excess of normal behavior, such as delusions, paranoia, or heightened sensitivity) are absent, the sufferer has less severe forms of the disorder or has only negative symptoms (symptoms characterized by a decrease in function, such as withdrawal, disinterest, and not speaking)

The main clinical features of the disease are:

#### Positive Symptoms:

- Delusion (often paranoid).

- Hallucinations, usually in the form of voices, and often exhortatory in their message.
- Thought disorder, comprising wild trains of thought, garbled sentence, and irrational conclusions, sometimes associated with the feeling that thoughts are inserted or withdrawn by an outside agency.
- Abnormal behaviors, such as stereotyped or occasionally aggressive behaviors <sup>5</sup>.

#### Negative Symptoms:

- Withdrawal from social contacts.
- Flattening of emotional responses.
- Cognitive symptoms (neurocognitive deficits).
- Impaired executive function (poor problem-solving, reduced ability to learn from mistakes or feedback, reduced capacity to form new concepts).
- Attentional deficit (see negative symptoms).
- Impaired memory (problems with encoding, consolidation, retrieval, and recognition).
- Impaired language processing (associational errors).

Also, deficits in cognitive function (*e.g.*, attention, memory) are often present, together with anxiety and depression, leading to suicide in about 10% of cases <sup>5</sup>. The clinical phenotype varies greatly, particularly concerning the balance between negative and positive symptoms, and this may have a bearing on the efficacy of drugs in individual cases <sup>6</sup>.

#### Etiology & Pathogenesis of Schizophrenia: 6

**Genetic and Environmental factors-** The cause of schizophrenia remains unclear, but it involves a combination of genetic and environmental factors. The disease shows a strong, but an incomplete, hereditary tendency. In first-degree relatives, the risk is about 10%; even in monozygotic twins, one of whom has schizophrenia, the probability of the other being affected is only about 50%. Genetic linkage studies aimed at identifying schizophrenia

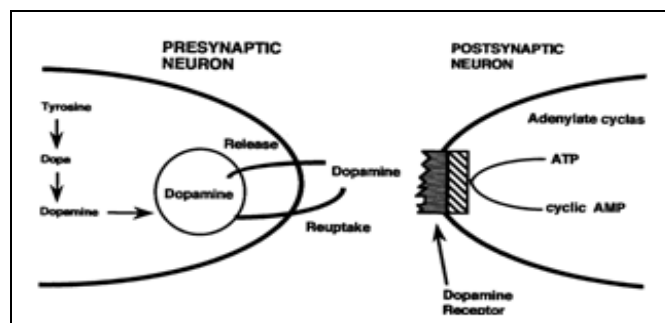
susceptibility genes have identified likely chromosomes, but not yet any specific genes. Some environmental influences early in development have been identified as possible predisposing factors, including maternal virus infections and high blood pressure during pregnancy<sup>7</sup>. This evidence suggests that schizophrenia is associated with a neurodevelopmental disorder, affecting mainly the cerebral cortex, and occurring in the first few months of prenatal development. These structural changes are present in schizophrenic patients presenting for the first and progressive, suggesting that they represent an early irreversible aberration in brain development rather gradual neurodegeneration. Psychological factors, such as stress, may participate in acute episodes but not the underlying cause

The neurodevelopmental hypothesis of schizophrenia: The neurodevelopmental hypothesis of schizophrenia postulates that effects during embryonal and fetal brain development lead to defective neural connectivity and altered biochemical functioning resulting in cognitive, emotional and intentional dysfunction later in life<sup>8,9</sup>. The cerebral alterations observed in schizophrenic post-mortem brain that might be related to neurodevelopmental disturbances have mainly been found for the hippocampal formation and the prefrontal and superior temporal lobe. These regions have also been implicated in imaging studies. Ventricular enlargement, reductions in brain volume and changes of cortical thickness, gyrification, hippocampal shape, and cerebral asymmetry, which are observed in unmedicated first-episode schizophrenic patients suggest a result of an early neurodevelopmental cascade. Signs for disturbed neuronal connectivity and migration deficits are aberrantly located, and neurons cluster in schizophrenic patients in the entorhinal cortex and neocortex. A loss of nonneuronal elements, the so-called neuropil, acts as a correlate of brain atrophy. This reduction in neuropil is mainly caused by synaptic elements.

Indeed, a mother's infection during pregnancy – in particular in the second trimester- or the occurrence of perinatal or postnatal complications has been connected to the development of schizophrenia in the offspring. Also, a fivefold greater risk of developing psychosis has been observed after CNS

infection in early childhood, or hypoxic conditions during birth<sup>10</sup>. Interestingly, more than 50% of genes implicated in schizophrenia are also subject to regulation by hypoxia.

The dopamine hypothesis of schizophrenia: The most widely considered neurochemical hypothesis of schizophrenia is the dopamine hypothesis, which postulates that symptoms of schizophrenia may result from excess dopaminergic neurotransmission particularly in mesolimbic and striatal brain regions, leading to positive symptoms and dopaminergic deficits in prefrontal brain regions, which are responsible for the negative symptoms<sup>10,11</sup>. The caudate dopamine D2 receptor up-regulation has been related to the genetic risk for schizophrenia; *i.e.*, higher dopamine D2 receptor density in caudate was associated with poorer performance on cognitive tasks involving corticostriatal pathways shown in **Fig. 1**.



**FIG. 1: DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA**

Additionally, all common antipsychotic medications are antagonists or partial agonists of the dopamine D2 receptor, which is the main site of action. Besides a central role of dopamine D2 receptors in effective psychopharmacological treatment, these results provide strong evidence that dopamine D2 receptor influences susceptibility to schizophrenia<sup>12</sup>. Neuroimaging evidence also indicates that schizophrenic patients have increased brain dopamine D2 receptor density.

D3 receptors are highly localized in limbic brain areas, which are also related to symptoms of the disease, and emotional functions of the brain and the role of D3 receptors in schizophrenia has been implicated in effective treatment but also the pathophysiology of tardive dyskinesia. Meta-analyses indicate that the dopamine D3 receptor gene may have a very small influence on risk for the development of schizophrenia<sup>12</sup>.

Dopamine and adenosine 3',5'-monophosphate (cAMP)-regulated phosphoprotein of 32 kDaltons is phosphorylated at three sites in a pattern predicted to cause a synergistic inhibition of protein phosphatase-1 and concomitant regulation of its downstream effector proteins glycogen-synthase kinase-3 beta cAMP response element-binding protein. Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin growth factor family, promotes the development, regeneration, and survival of neurons and has therefore been linked to the neuropathology of schizophrenia. BDNF plays a critical role in the development of mesolimbic dopaminergic-related systems and regulates the expression of dopamine D3 receptors. Thus, the hypothesis of a link between BDNF neurotrophic properties and the dopamine neurotransmission pathway in schizophrenia has been postulated.

**The Glutamatergic Hypothesis of Schizophrenia:** Several lines of evidence point to the hypothesis that dopaminergic dysfunction in schizophrenia is secondary to an underlying glutamatergic dysfunction. In this concept, a hypofunction of glutamate in cortico-striatal projections leads to an opening effect in the thalamocortical loop resulting in exaggerated sensory flooding and thereby psychotic symptoms and the well-known dopamine concentration changes<sup>13</sup>. The glutamate receptors consist of two groups: ionotropic ligand-gated ion channels and metabotropic G protein-coupled receptors.

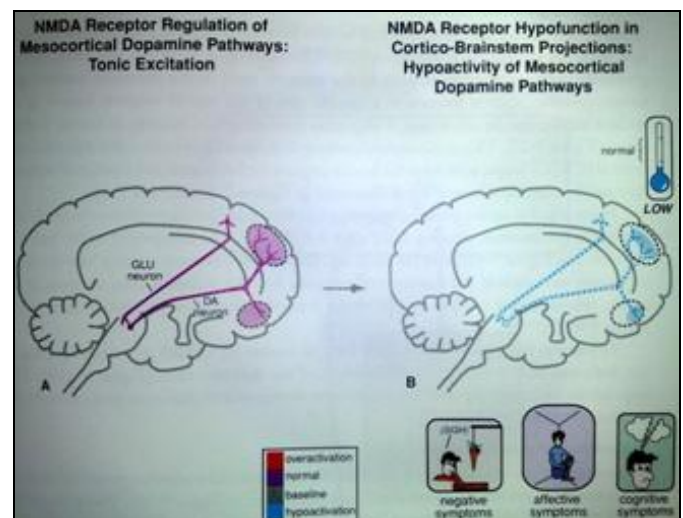
The ionotropic receptors can be subdivided into the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) Kainate and N-methyl d-aspartate (NMDA)-receptors.

These ionotropic glutamate receptors work as ion-channels by opening in response to glutamate binding and creating a depolarising excitatory post-synaptic current. NMDA receptors are tetrameric allosteric and ligand-gated calcium channels, which are modulated by a variety of endogenous ligands and ions that play a pivotal role in memory-related signal transduction due to a voltage-dependent block by magnesium. NMDA receptors are thought to be responsible for excitotoxicity and subsequent downstream events such as neuroinflammation and apoptosis.

In line with the glutamate hypothesis, NMDA receptor antagonists like phencyclidine, ketamine, and MK- 801 are potent activators of dopamine release and thereby can cause marked psychotic symptoms in healthy human volunteers and exacerbation of symptoms in schizophrenic patients. A loss of glutamatergic function in schizophrenia is also supported by decreases in markers for the neuronal glutamate transporter in striatal structures that receive cortical glutamate projections.

Deficits in the vesicular glutamate transporter-1 in both striatal and hippocampal regions support this observation and the association of the density of the transporter with the risk to develop schizophrenia. Beside glycine, D-serine is a potent activator of the NMDA receptors, which has properties of a neurotransmitter. D-serine is synthesized from L-serine depending on several co-factors such as pyridoxal 5-phosphate (vitamin B6), magnesium and adenosine 5'-triphosphate (ATP).

Therefore, the increased availability of glycine or serine may facilitate glutamatergic neurotransmission. In support of this inference, agents that directly or indirectly activate the glycine or serine modulatory site on the NMDA receptor, *i.e.*, D-serine, glycine, D-cycloserine, and N-methyl glycine reduces symptoms in chronic schizophrenia, especially negative symptoms, and cognitive impairments. A reduction of D-serine serum levels of schizophrenic patients was also shown in **Fig. 2**.



**FIG. 2: GLUTAMATERGIC HYPOTHESIS OF SCHIZOPHRENIA**

### The GABAergic Hypothesis of Schizophrenia:

There is an accumulation of evidence for abnormalities in the schizophrenia of both glutamate and gamma-aminobutyric acid (GABA). The 67 and 65 kDa isoforms of glutamic acid decarboxylase (GAD), the key enzymes for GABA biosynthesis, are expressed at altered levels in postmortem brain of subjects diagnosed with schizophrenia. A decrease in GAD67 transcript levels has presumably been found in prefrontal and temporal cortex<sup>13, 14</sup>.

As one of the key susceptibility factors, Disrupted in-schizophrenia (DISC1), has been established as a promising lead in the understanding of the disease. DISC1 is involved in neurite outgrowth and neuronal migration and is expressed in brain regions, which are known to be involved in schizophrenia, including human cerebral cortex and hippocampus. Also, DISC1 plays a role in cell signaling and interacts with phosphodiesterase which degrades cAMP, which may be a regulatory molecule for working memory in the prefrontal cortex. DISC1 interacts with several proteins, including centrosome and cytoskeletal proteins, proteins that localize receptors to membranes and signal transduction proteins. The location of DISC1 at many synapses suggests that it may play a role in synaptic function in the adult brain in Fig. 3.

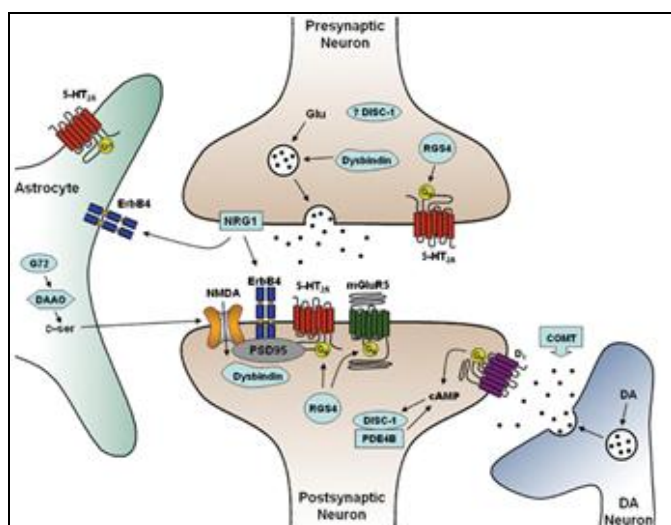


FIG. 3: GABAergic HYPOTHESIS OF SCHIZOPHRENIA

The studies indicate that DISC1 is a general genetic risk factor for psychiatric illness that also influences cognition in healthy subjects. It has been shown that psychiatric diagnosis of schizophrenia, reduced frontal cortical gray matter, and

performance on neurocognitive tests of short and long-term memory are associated with aberrant expression of the DISC1 gene. Further, it has been suggested that the effect of DISC1 genetic variation might be associated with positive symptoms and hippocampal volume in patients with schizophrenia.

Hypothetical roles of schizophrenia genes at a glutamatergic synapse. Pictured is a hypothetical schematic of various putative schizophrenia susceptibility gene products and how they may affect neurotransmitter signaling at a glutamatergic synapse. The schizophrenia genes include: DISC-1 (disrupted in schizophrenia-1), Dysbindin, NRG1 (neuregulin-1), RGS4 (regulator of G protein signaling 4), COMT (catechol-*O*-methyltransferase), PDE4B (phosphodiesterase 4B), G72, and DAAO (D-amino acid oxidase). Other abbreviations are: Glu (glutamate), DA (dopamine), NMDA (*N*-methyl-D-aspartate glutamate receptor), 5-HT<sub>2A</sub> (serotonin receptor 2A), mGluR5 (metabotropic glutamate receptor 5), D<sub>1</sub> (dopamine receptor 1), ErbB4 (ErbB-type tyrosine kinase receptor B4), cAMP (cyclic adenosine monophosphate), G<sub>q</sub>/G<sub>s</sub> (G proteins), PSD95 (postsynaptic density protein 95), D-ser (D-serine).

### Mechanism of Action of Antipsychotic Drugs:

Antipsychotics block postsynaptic dopamine receptors. D1 and D2 receptors are associated with antipsychotic efficacy. Other (D1, D2, D3, D4, D5) dopaminergic receptors have been isolated but not characterized as to their action. D2 receptors are cited as responsible for antipsychotic-induced movement disorders with D1 receptors modulating the intensity of these side effects. 65-70% of patients with schizophrenia respond to traditional (those with primarily D2 blocking action), antipsychotic agents. Newer atypical antipsychotic agents (*i.e.*, Clozapine) have effects on multiple dopaminergic receptors and have been effective in patients whose traditional antipsychotics have been ineffective. Clozapine, olanzapine, and risperidone are effective for negative symptoms as well as<sup>16</sup>.

### Pharmacologic Effects of Antipsychotic Drugs:

These actions were traced to blocking effects at a remarkable number of receptors. These include dopamine  $\sigma$ -muscarinic, H<sub>1</sub> histaminic, and

serotonin (5-HT<sub>2</sub>) Receptors. Of these, the dopamine receptors effects quickly became the major focus of interest<sup>18, 19</sup>.

**A. Dopaminergic System:** Until 1959, dopamine was not recognized as a neurotransmitter in the central nervous system but was simply regarded as a precursor for norepinephrine. Following the dopaminergic system or pathways is recognized in the brain

**TABLE 1: DOPAMINERGIC PATHWAY FUNCTION**

Dopamine Track	Function	Antipsychotic Drug Effect
Nigrostriatal	Extrapyramidal System	Movement disorder
Mesolimbic	Arousal, memory, stimulus processing, motivation	Relief of Psychosis
Mesocortical	Cognition, social communication function, response to stress	Relief of Psychosis, Akathisia
Tuberoinfundibular	Regulates prolactin release	Increased prolactin Concentrations

**B. Dopamine Receptors and their Effects:** Dopamine receptors consisting of the two families, the D<sub>1</sub>-like and D<sub>2</sub>-like receptor groups. The D<sub>1</sub> receptor is coded by a gene on chromosome 5, increase cAMP by activation of adenylyl cyclase, and is located mainly in the putamen, nucleus accumbens, and olfactory tubercle. The second member of this family, D<sub>5</sub>, is coded by a gene on chromosome 4, also increases cAMP, and is found in the hippocampus and hypothalamus.

The D<sub>2</sub>-receptor is coded on chromosome 11, decrease cAMP (by inhibition of adenylyl cyclase), and block calcium channels but opens potassium channels. The second member of this family, D<sub>3</sub>, is coded by a gene on chromosome 11, also decrease cAMP, and is located in the frontal cortex, medulla, and midbrain. D<sub>4</sub>-receptors, the newest members of the D<sub>2</sub>-like family, also decrease cAMP.

**C. Differences among Antipsychotic Drugs:** Although all effective antipsychotic drugs blocks D<sub>2</sub> receptors, the degree of this blockade about other action on receptors varies considerably between drugs. For example, *in-vitro* binding studies that chlorpromazine and thioridazine block  $\alpha_1$ adrenoreceptors more potently than D<sub>2</sub> receptors. They also block serotonin 5-HT<sub>2</sub> receptors relatively strongly. Drugs such as perphenazine and haloperidol act mainly on D<sub>2</sub> receptors. Pimazole acts almost exclusively on D<sub>2</sub> receptors. Risperidone is equally potent in blocking D<sub>2</sub> and 5-HT<sub>2</sub> receptors. A summary of the relative receptor binding potencies of three key agents in such

**Mesolimbic:** Midbrain to the limbic system.

**Mesocortical:** Midbrain to temporal & frontal lobes of the cerebral cortex.

**Nigrostriatal:** *Substantia nigra* in the midbrain to the caudate nucleus in the basal ganglia.

**Tuberoinfundibular:** Hypothalamus to the median eminence of the anterior pituitary.

comparisons illustrates the difficulty in drawing simple conclusions from such experiments:

Chlorpromazine:  $\alpha_1 = 5\text{-HT}_2 > D_2 > D_1$

Haloperidol:  $D_2 > D_1 = D_4 > \alpha_1 > 5\text{-HT}_2$

Clozapine:  $D_4 = \alpha_1 > 5\text{-HT}_2 > D_2 = D_1$

**D. Psychologic Effects:** Most antipsychotic drugs cause unpleasant subjective effects in the nonpsychotic individual; the combination of sleepiness, restlessness, and autonomic effects creates experiences unlike those associated with more familiar sedatives or hypnotics.

**E. Neurophysiologic Effects:** Antipsychotic drugs shifts in the pattern of electroencephalographic frequencies, usually slowing them and increasing their synchronization.

**F. Endocrine Effects:** Dopamine, released in the median emergence by neuron of the tuberophyseal pathway, acts physiologically *via* D<sub>2</sub> receptors as inhibition of prolactin secretion. The results of blocking D<sub>2</sub> receptors by antipsychotic drugs is thus to increase the plasma prolactin concentration resulting in breast swelling, pain, and lactation, which can occur in men as well as women.

**G. Cardiovascular Effects:** Orthostatic hypotension and resulting pulse rates frequently result from the use of "high-dose" (low potency) phenothiazines. Mean arterial pressure, peripheral resistance, and stroke volume are decreased, and pulse rate is increased. These effects are predictable from the autonomic actions of these agents.

**Chemistry of Antipsychotic Agents:** Based on the structure and pharmacologic activity, these are divided into the following classes.

**Class 1:** Reserpine- like compounds contains all aryl annulated quinolizine derivatives. It includes reserpine, which is not a dopamine antagonist but a mono depleting agent, and butaclamol, which is used mainly as a tool in receptor binding studies.

**Class 2:** The largest group of compounds is phenothiazines, which are subdivided into promazine, perazines, phenazines, and piperidinophenothiazines according to the chemistry of the side-chain. Chlorpromazine, known as a rather sedating antihistamine when its clinical exploration began, is a moderately potent apomorphine antagonist. The potency of the phenothiazines is highly dependent on substitution in carbon 2 of the phenothiazine nucleus:  $-H < -Cl < -CH_3$ .

**Class 3:** Drugs include the thioxanthenes which resemble phenothiazines both chemically and pharmacologically. The introduction of an extra fluoro substitution in pifluthixol results in very high activity as an antagonist of apomorphine.

**Class 4:** Drugs include the butyrophenones, a completely different chemical series of neuroleptics, of which haloperidol is the prototype. Generally, the butyrophenones are potent neuroleptics. An interesting exception is pipam-

perone, which is a weak apomorphine antagonist, but more potent as a serotonin antagonist. Serotonin antagonism is also a component of the action of spiperone, which is widely used to label dopamine  $D_2$ -as well as serotonin  $S_2$ - receptors.

**Class 5:** Compounds include the diphenyl-butylamines with pimozide as the archetype; these drugs are potent apomorphine antagonists. All act longer than the corresponding butyrophenones. The highly lipophilic character of these compounds favors a more gradual occupation of the dopamine receptors.

**Class 6:** Compounds include various tricyclic derivatives with a central 7-membered ring to which methyl piperazine is linked. The activity of this group is widely scattered, containing among the weakest and more potent of the apomorphine antagonists.

**Class 7:** Compounds include the aminoalkyl-benzamides, open-chain alkylamines of the metoclopramide type, pyrrolidines of the sulpride type, and piperidines of the cleboride type.

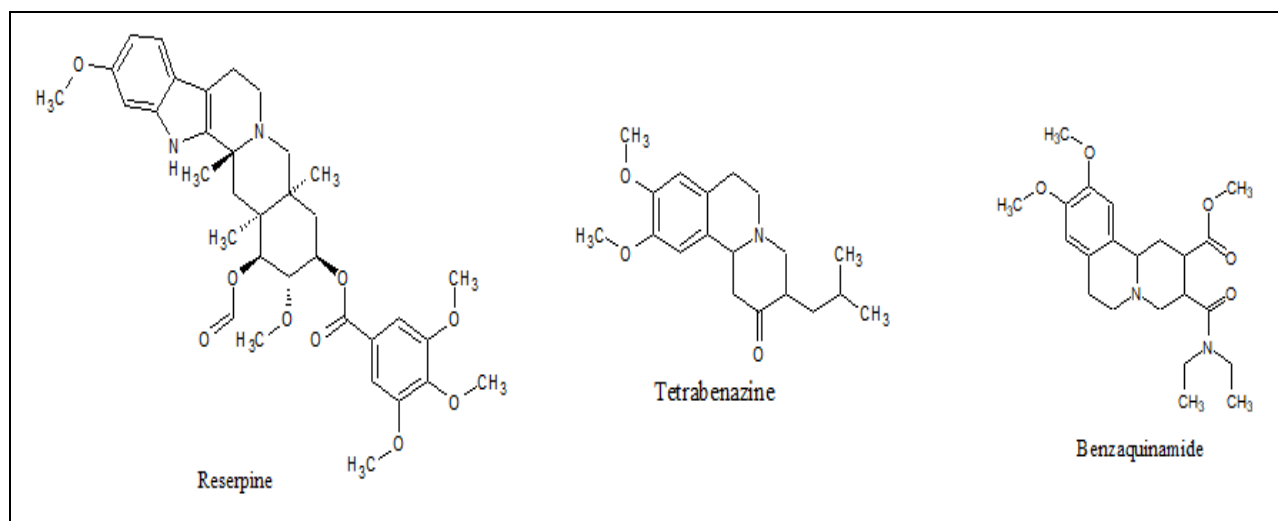
**Class 8:** Compounds include aminoethylindoles.

**Class 9:** Compounds include phenoxyalkylamines, which are more potent than the aminoethylindoles.

**Class 10:** Includes miscellaneous structures, of which risperidone offers the best perspectives for an antipsychotic of a new type.

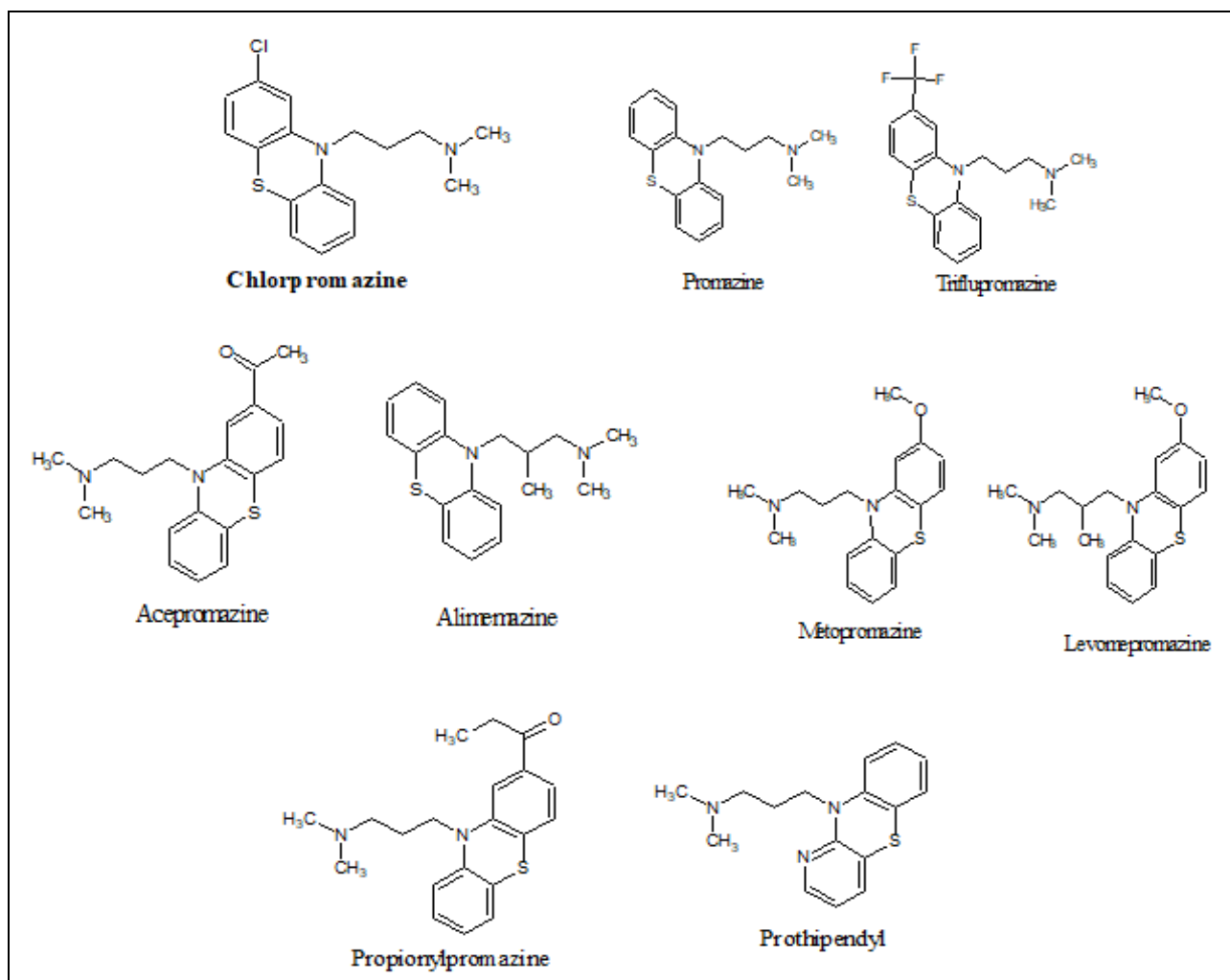
## Chemical Structures of Antipsychotics: <sup>19, 21</sup>

### 1. Reserpine Related Structures:

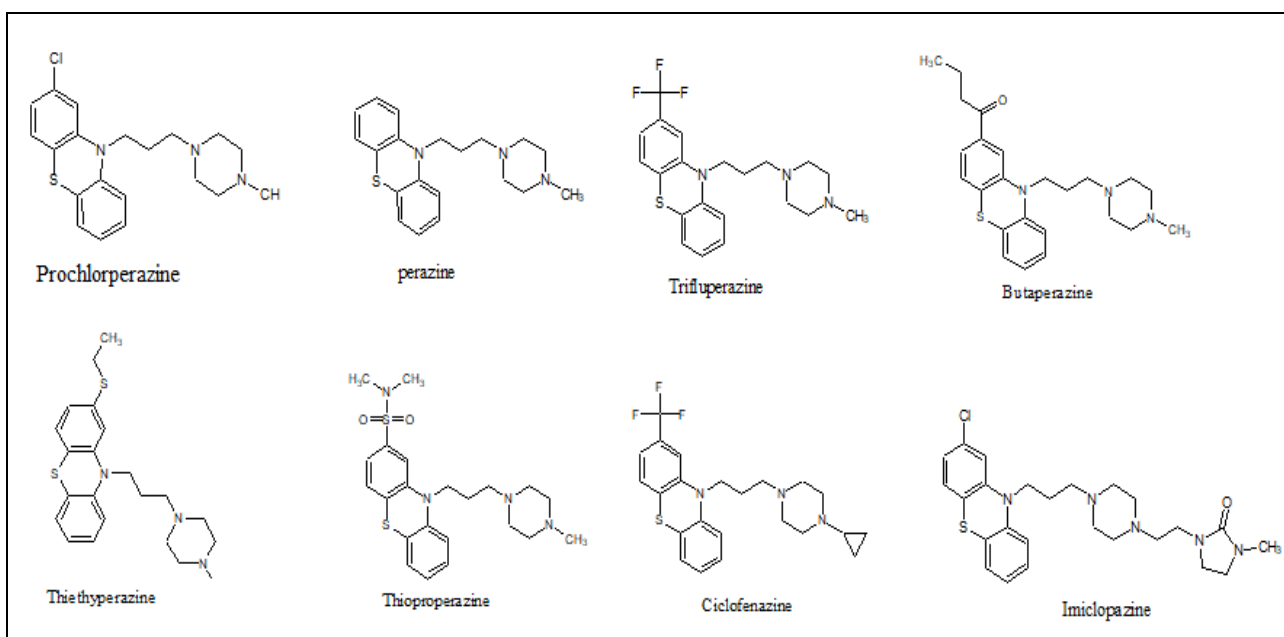


## 2. Phenothiazine Derivatives:

### A. Promazines:

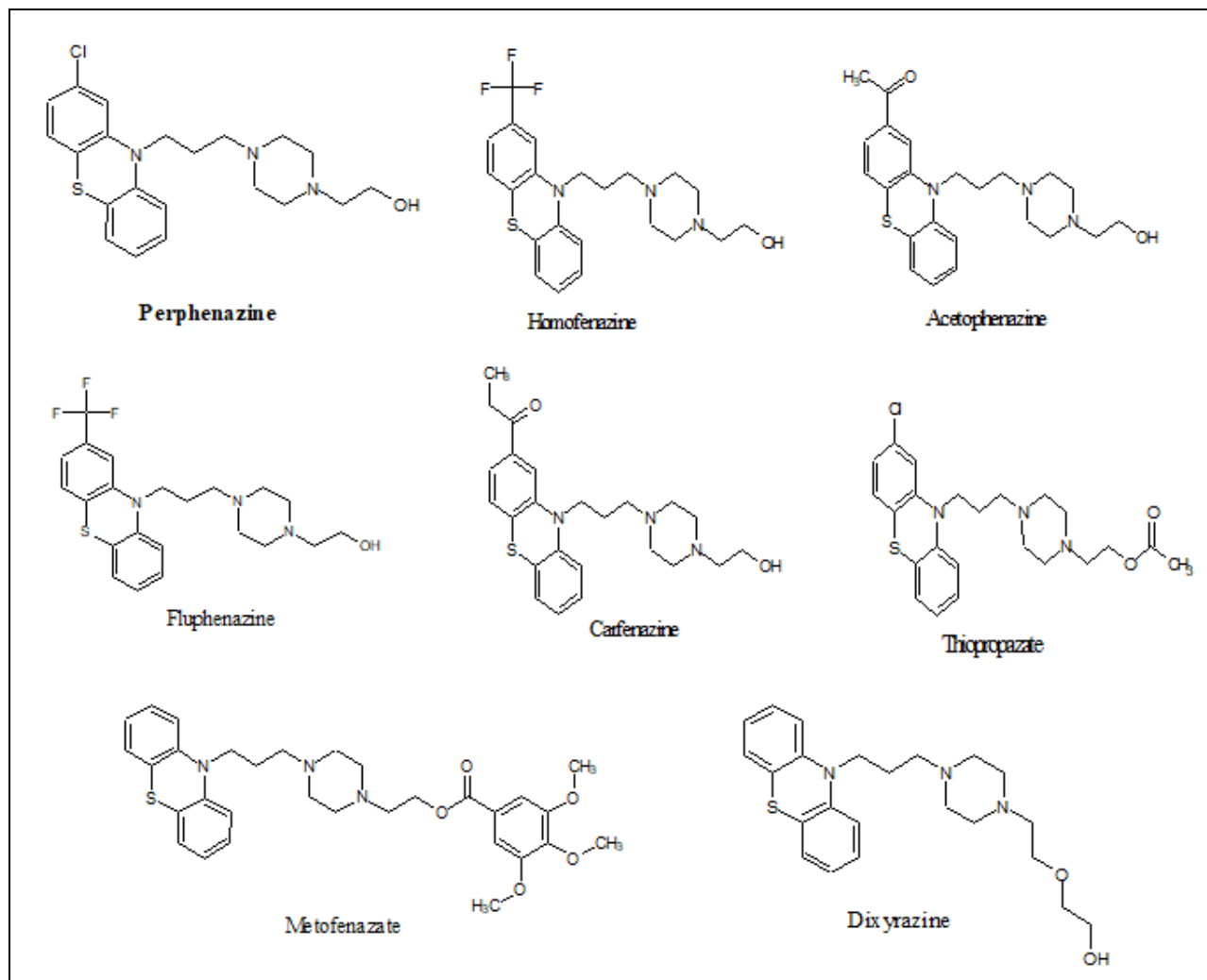


### B. Perazines:

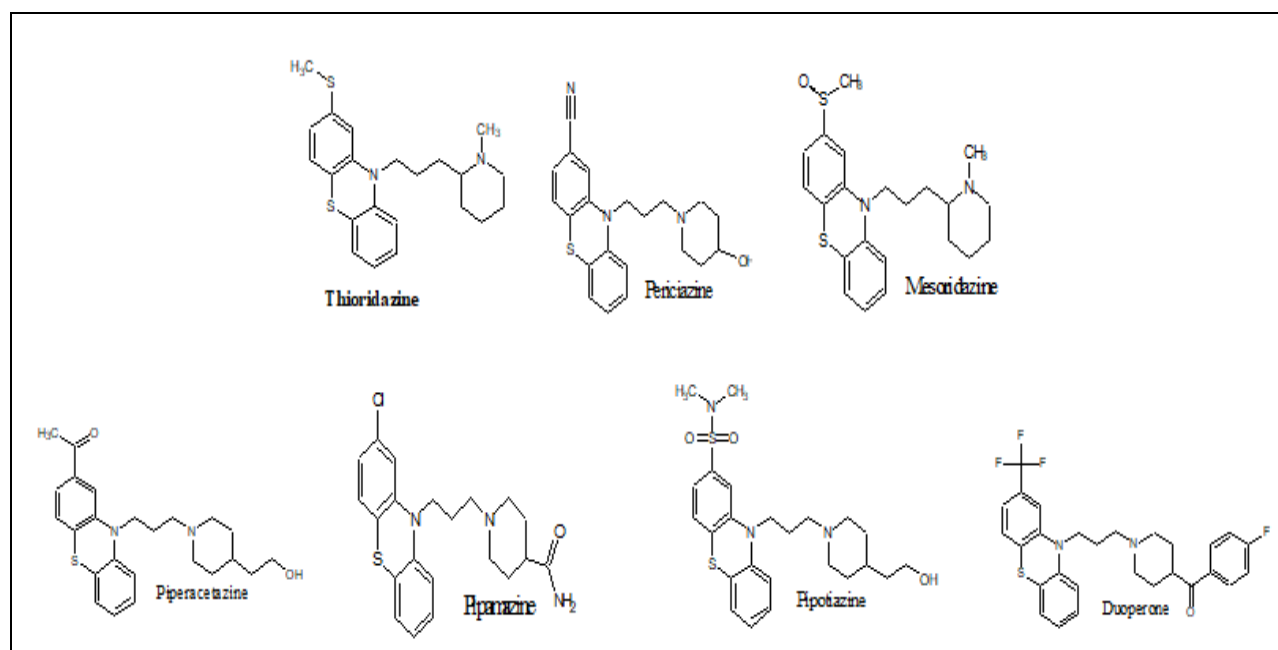




**C. Phenazines:**

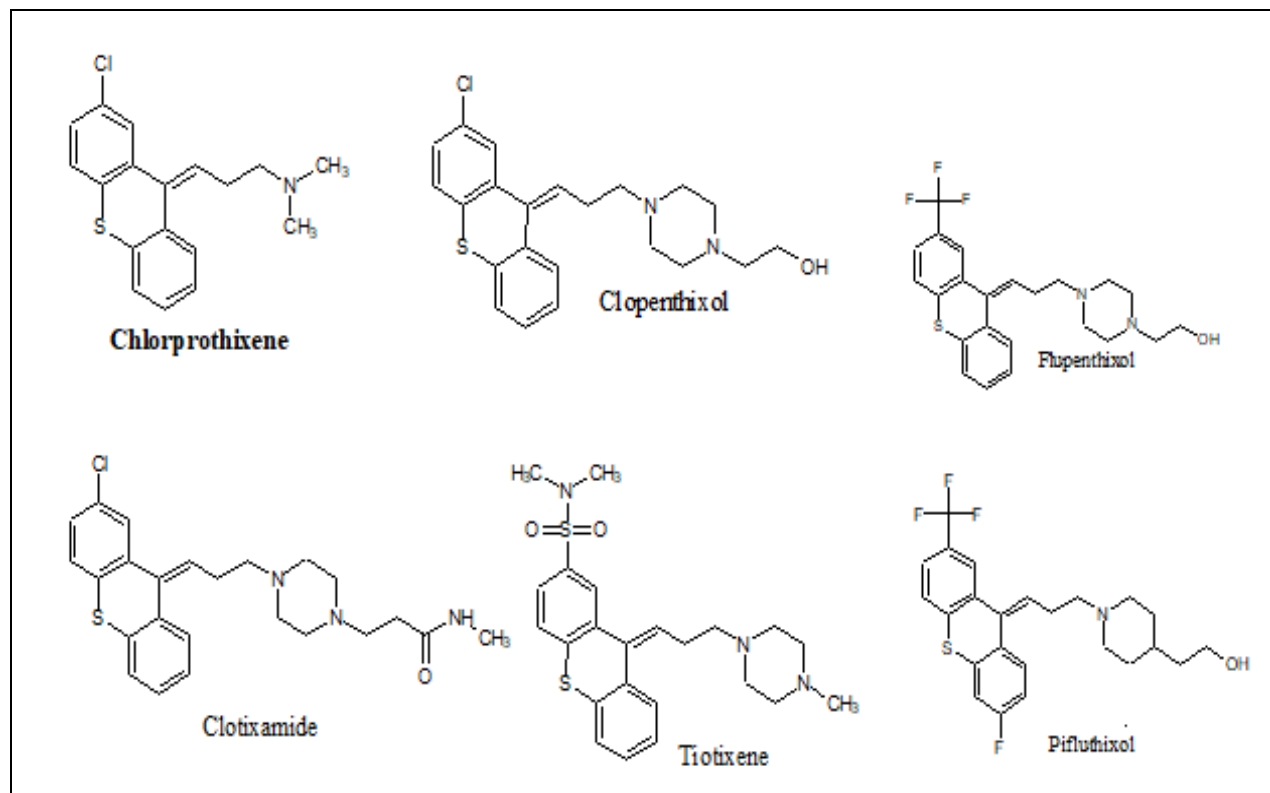


**D. Piperidino Phenthiazine**



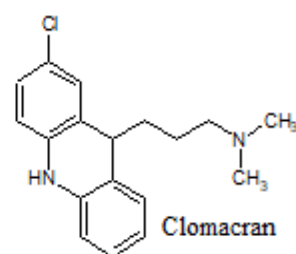
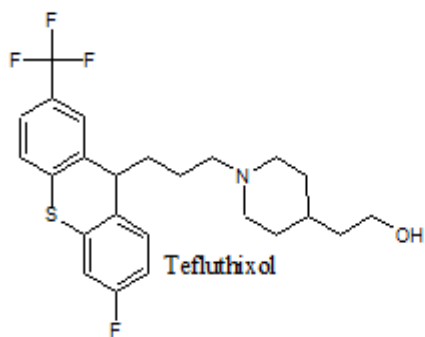
## 2. Thioxanthenes (Xanthene/ Acridine):

### A. Unsaturated Thioxanthenes Derivatives:



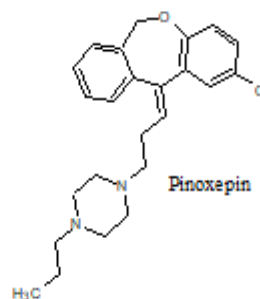
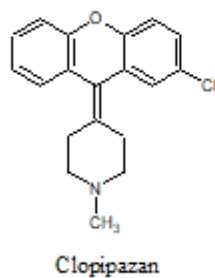
### B. Saturated Xanthene derivatives

### C. Acridine derivatives

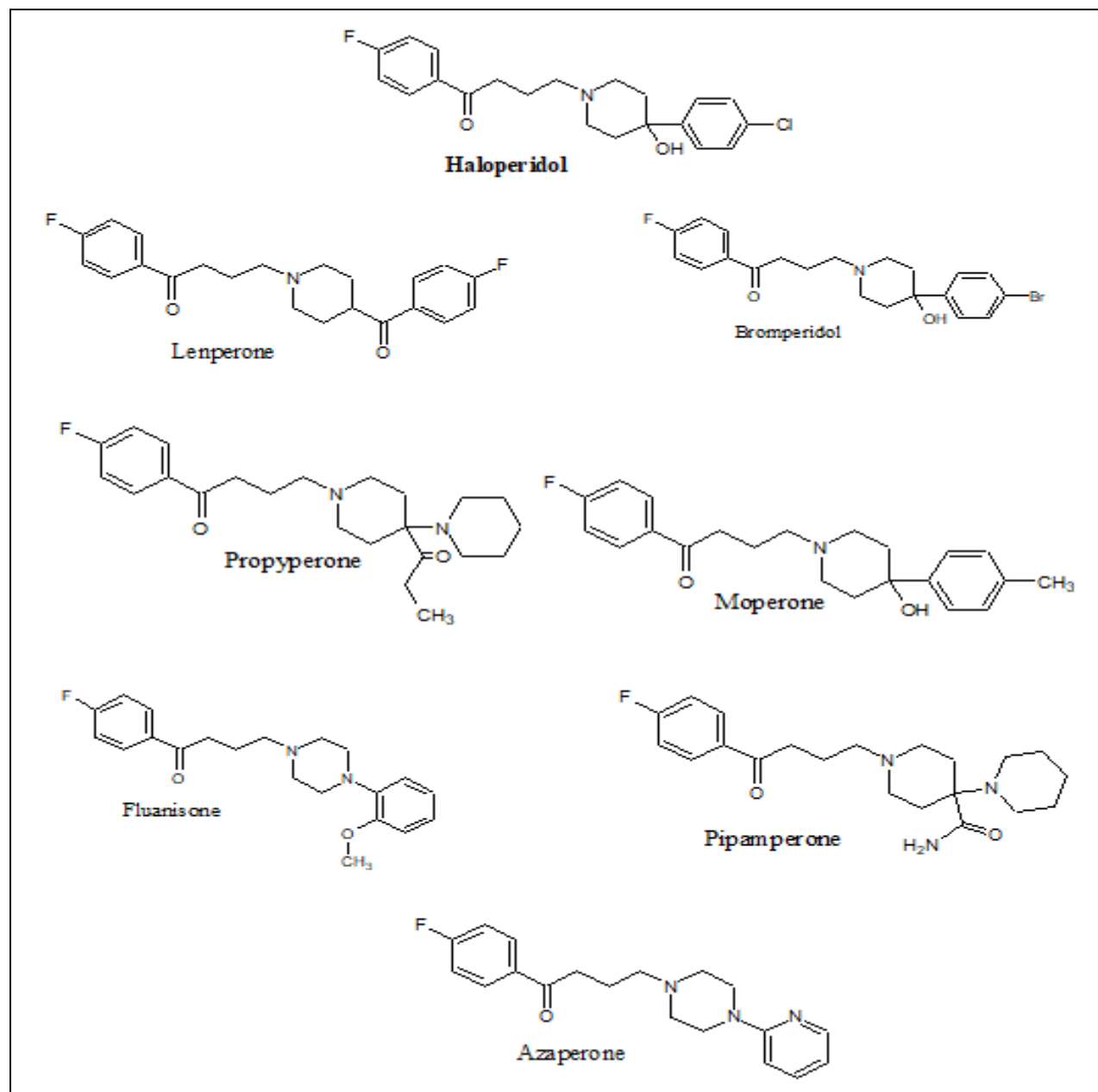


### D. Xanthene derivatives

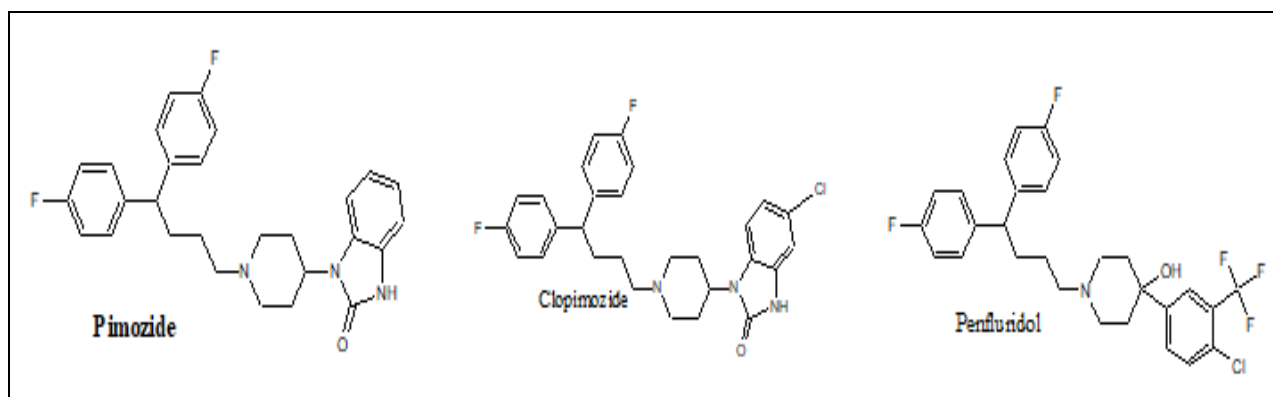
### E. Pinoxepin



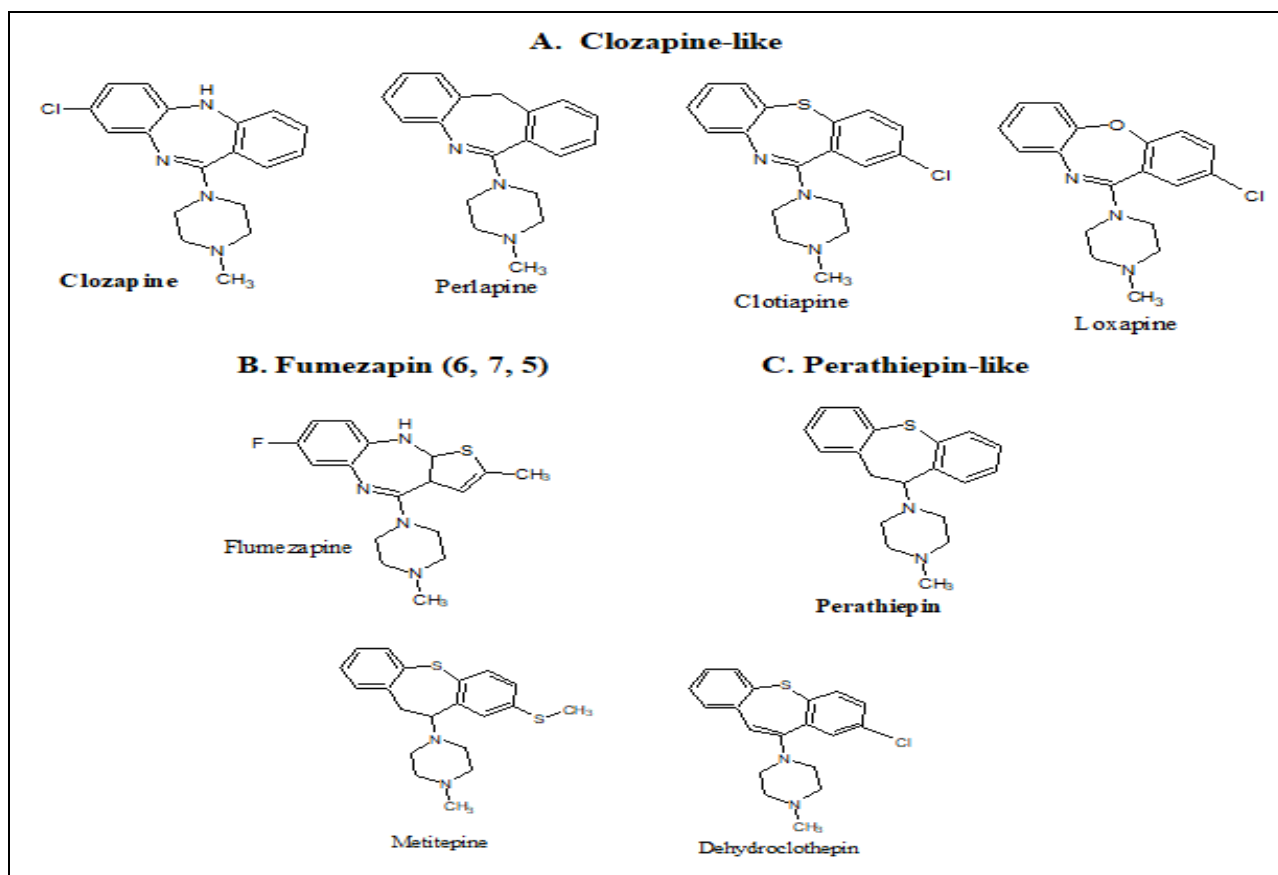
### 3. Butyrophenones:



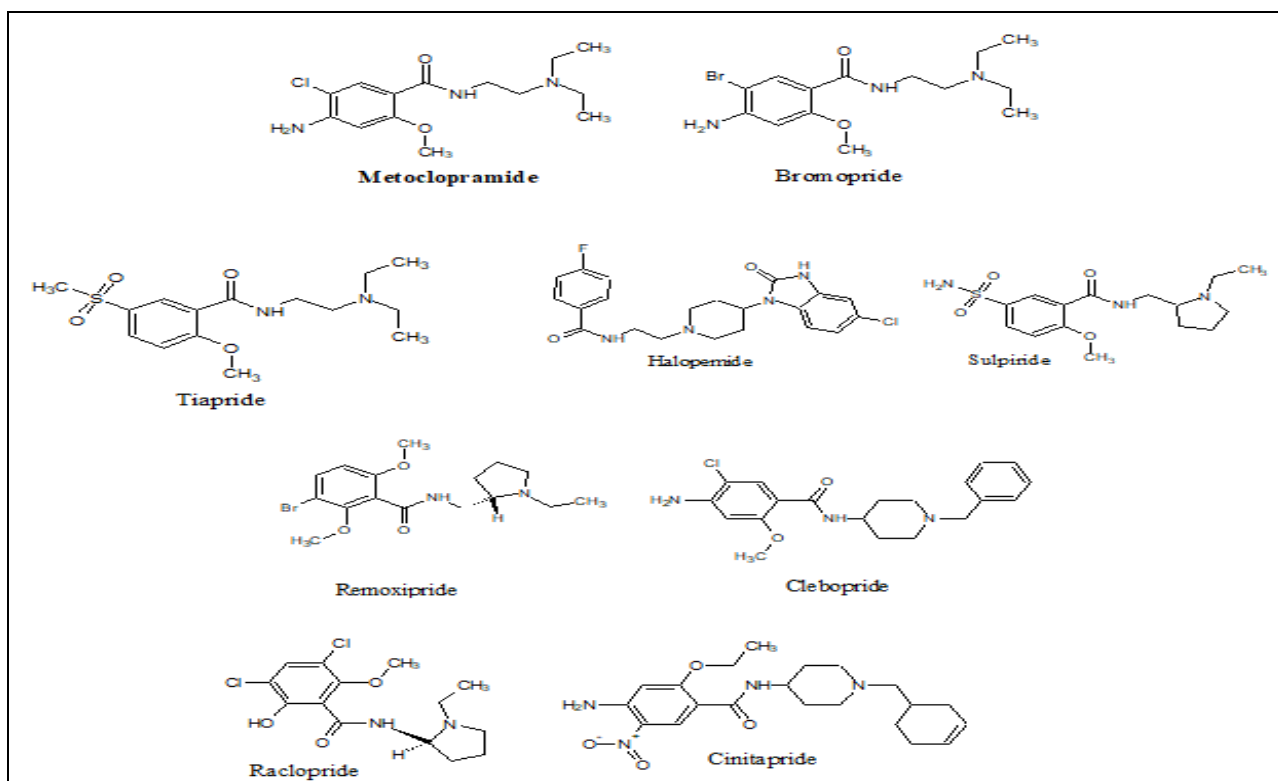
### 4. Diphenylbutylamines:



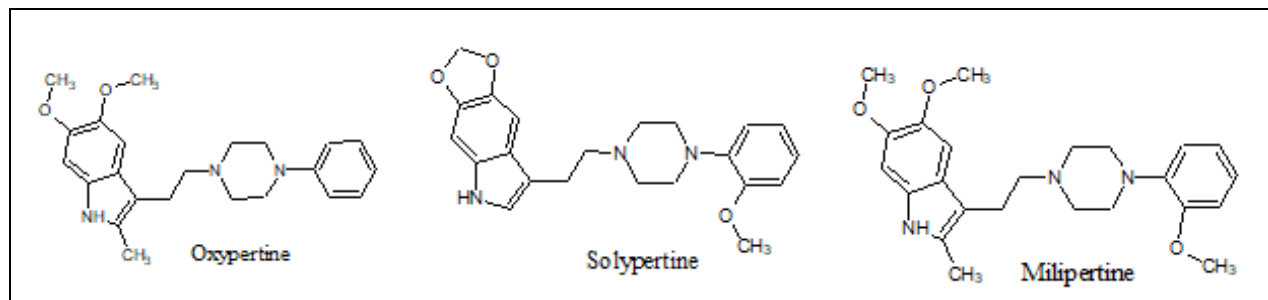
## 5. Tricyclic (6,7,6)-derivatives:



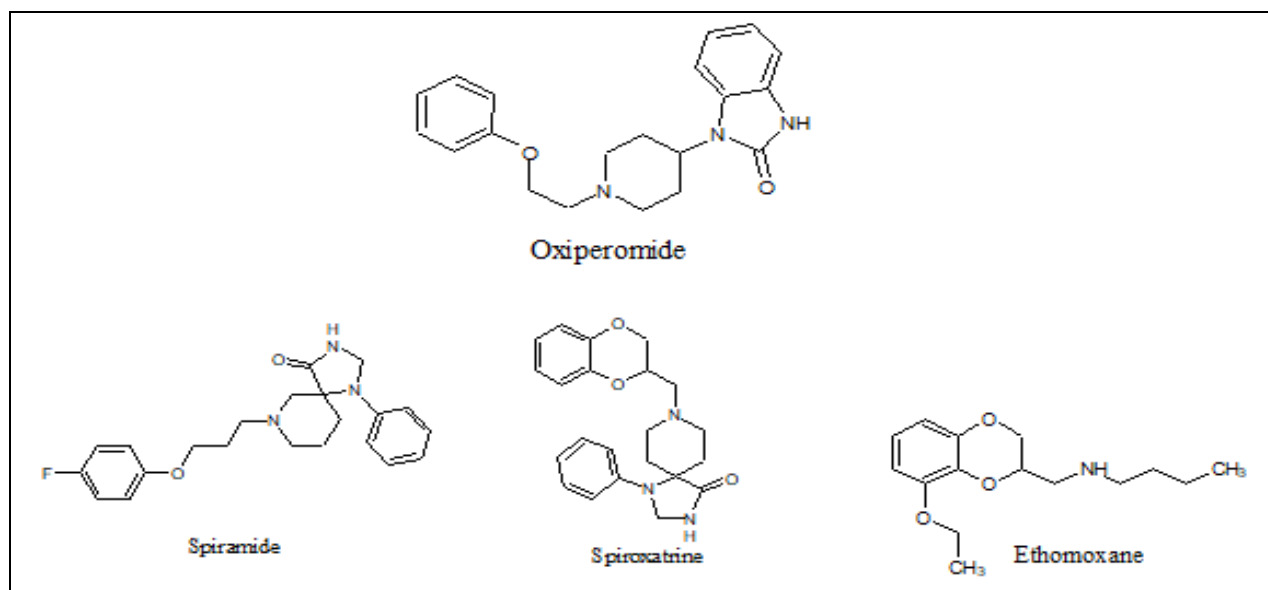
## 6. Aminoalkylbenzamides:



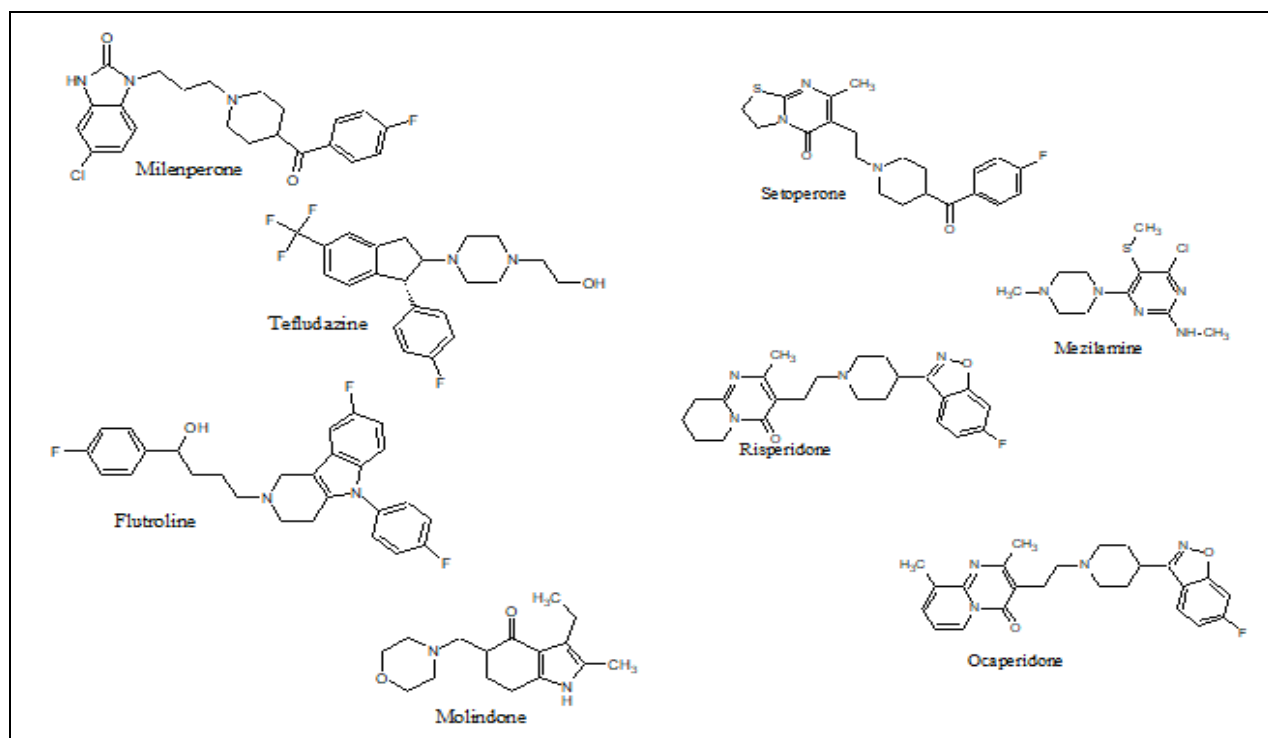
### 7. Aminoethylindoles:



### 8. Phenoxyalkylamines:



### 9. Miscellaneous:



**Adverse Effects of Antipsychotic:**<sup>21, 24</sup> The use of antipsychotic medications entails a difficult trade-off between the benefit of alleviating psychotic symptoms and the risk of troubling, sometimes life-shortening adverse effects. There is more variability among specific antipsychotic medications than there is between the first- and second-generation antipsychotic classes. The newer second-generation antipsychotics, especially clozapine and olanzapine, generally tend to cause more problems relating to metabolic syndromes, such as obesity and type 2 diabetes mellitus. Also, as a class, the older first-generation antipsychotics are more likely to be associated with movement disorders, but this is primarily true of medications that bind tightly to dopaminergic neuroreceptors, such as haloperidol, and less true of medications that bind weakly, such as chlorpromazine. Anticholinergic effects are especially prominent with weaker-binding first-generation antipsychotics, as well as with the second-generation antipsychotic clozapine. They should be vigilant for the occurrence of adverse effects, be willing to adjust or change medications as needed, and be prepared to treat any resulting medical sequelae.

**Sedation:** Sedation is common with antipsychotic medications and is dose-related. It can be a cause of poor compliance and, if persistent, can interfere with social and vocational functioning. Many patients become tolerant to the sedative effect over time. Low-potency FGAs and clozapine are the most sedating, with some effect from olanzapine (Zyprexa) and quetiapine (Seroquel). Somnolence can be alleviated by lowering the dosage, changing to a single bedtime dose, or switching to a less sedating medication.

**Hypotension:** Orthostatic hypotension can occur with all antipsychotic medications, depending on the degree of  $\alpha_1$ -adrenoreceptor antagonism, particularly with low-potency FGAs and clozapine. It can also occur with risperidone (Risperdal) and quetiapine, especially with rapid titration. This effect is more common in older adults (with the risk of falls), those on blood pressure medications, and those who have other cardiovascular diseases. With careful dose titration, patients may become tolerant to this effect. Treatment options include decreasing or dividing doses or switching to a medication with a lesser antiadrenergic effect<sup>24, 25</sup>.

**Anticholinergic Effects:** Anticholinergic effects include constipation, urinary retention, dry mouth, blurred vision, and, at times, cognitive impairment. These symptoms can lead to other problems such as tooth decay, falls, or gastrointestinal obstruction. Low-potency FGAs and clozapine are highly likely to cause anticholinergic effects, olanzapine and quetiapine have been shown to do so at high dosages. When needed, doses can be lowered or divided to help alleviate this problem.

**Extrapyramidal Symptoms:** Antipsychotic medications cause four main extrapyramidal symptoms: pseudoparkinsonism, akathisia, acute dystonia, and tardive dyskinesia. The first three usually begin within a few weeks of starting a new medication (or increasing the dosage). These symptoms may cause discomfort, social stigma, and poor compliance. They are more likely to occur with higher dosages of high-potency FGAs, such as haloperidol (formerly Haldol), and are less likely with FGAs that have weaker dopamine blockade. Several meta-analyses, most comparing SGAs with haloperidol, have shown that SGAs are less likely to cause extrapyramidal symptoms. However, recent studies comparing SGAs with lower potency FGAs have not shown this difference.

**Pseudoparkinsonism:** Pseudoparkinsonism is a reversible syndrome that includes tremulousness in the hands and arms, rigidity in the arms and shoulders, bradykinesia, akinesia, hypersalivation, masked facies, and shuffling gait. The presence of bradykinesia or akinesia can create a diagnostic dilemma, with symptoms resembling depression or even the negative symptoms of schizophrenia (*i.e.*, an inability to pay attention, the loss of a sense of pleasure, the loss of will or drive, disorganization or impoverishment of thoughts and speech, flattening of affect, and social withdrawal). Treatment options include dosage reduction or the addition of oral anticholinergic agents (*e.g.*, benztropine, diphenhydramine [Benadryl]); physicians should keep in mind that these medications can cause their adverse effects.

**Akathisia:** Akathisia is described subjectively as a feeling of inner restlessness that can be manifested as excessive pacing or inability to remain still for any length of time. It can be difficult to differentiate akathisia from psychiatric anxiety and

agitation. Treatment of akathisia can include a dosage reduction when possible or the addition of a low-dose beta-blocker.

**Dystonic Reactions:** Dystonic reactions are spastic contractions of the muscles, including oculogyric crisis, retrocollis, torticollis, trismus, opisthotonos, or laryngospasm. These reactions are uncomfortable and can be life-threatening if left untreated. Intervention often requires the administration of intravenous or intramuscular anticholinergic agents.

**Tardive Dyskinesia:** Tardive dyskinesia is an involuntary movement disorder that can occur with long-term antipsychotic treatment, and may not be reversible even if the medication is discontinued. Tardive dyskinesia usually involves the orofacial region, but all parts of the body can be involved. Abnormal movements can include myoclonic jerks, tics, chorea, and dystonia. They become most evident when patients are aroused, but ease during relaxation and disappear during sleep. Risk factors for developing tardive dyskinesia include long-term therapy with FGAs at higher dosages, older age, female sex, and concurrent affective disorders. Attempts to treat tardive dyskinesia usually begin by discontinuing the offending agent or switching to one with a lower risk, but the evidence is insufficient to show that this or any other treatment markedly reduces symptoms after onset.

**Hyperprolactinemia:** Antipsychotics cause high prolactin levels by blocking the normal tonic inhibition on pituitary mammotrophic cells of dopamine produced in the hypothalamus. Hyperprolactinemia is common with the use of any FGAs, as well as with the SGAs, risperidone (up to 60 percent of women and 40 percent of men), and is dose-dependent. It appears to be much less common with other SGAs but has been reported with the use of olanzapine and ziprasidone (Geodon) at high dosages. Hyperprolactinemia can be asymptomatic but may cause gynecomastia, galactorrhea, oligo- or amenorrhea, sexual dysfunction, acne, hirsutism, infertility, and loss of bone mineral density. Symptoms often appear within a few weeks of beginning the antipsychotic or increasing the dosage, but can also arise after long-term stable use. There is growing evidence that chronic hyperprolactinemia from anti-

psychotics can cause osteoporosis and an increased risk of hip fracture. Physicians should routinely inquire about symptoms that might reflect hyperprolactinemia in patients taking prolactin-raising antipsychotics and, if present, measure the serum prolactin level. Presence of osteoporosis, sexual side effects, or prolactin-dependent breast cancer may necessitate switching to an antipsychotic that does not raise prolactin levels, such as aripiprazole or quetiapine<sup>26</sup>.

**Sexual Dysfunction:** Up to 43 percent of patients taking antipsychotic medications report problems with sexual dysfunction, a distressing adverse effect that can lead to poor medication adherence. Use of antipsychotics can affect all phases of sexual function, including libido, arousal, and orgasm. Both FGAs and SGAs can impair arousal and orgasm in men and women. FGAs especially have been found to cause erectile and ejaculatory dysfunction in men, including spontaneous, painful, or retrograde ejaculation, as well as priapism.

**Agranulocytosis:** In rare cases, clozapine may cause neutropenia (absolute neutrophil count [ANC] of less than 1,500 cells per mm<sup>3</sup> [ $1.50 \times 10^9$  per L]) and agranulocytosis (ANC of less than 500 cells per mm<sup>3</sup> [ $0.50 \times 10^9$  per L]) that can lead to potentially fatal infections. Agranulocytosis occurs in slightly less than 1 percent of patients, almost always within three months of starting treatment (84 percent). Risk increases with older age, female sex, and Asian race. The U.S. Food and Drug Administration (FDA) requires that clozapine be available only through programs that monitor white blood cell counts weekly for the first six months, every two weeks for the next six months and months after that. According to FDA guidelines, the medication should be stopped if the white blood cell count drops below 3,000 cells per mm<sup>3</sup> ( $3.00 \times 10^9$  per L) or the ANC level below 1,500 cells per mm<sup>3</sup><sup>26, 27</sup>.

**Cardiac Arrhythmias:** All antipsychotics can contribute to the prolongation of ventricular repolarization (prolonged QT interval), which can, in turn, lead to torsades de pointes and sudden cardiac death. This effect is most marked with the low-potency FGAs, thioridazine and the SGAs, ziprasidone, and is dose-dependent. The incidence of sudden cardiac death among patients taking

antipsychotics is about twice that of the general population. Physicians should avoid combining antipsychotic medications with other medications that prolong the corrected QT interval (e.g., classes I and III antiarrhythmic drugs, tricyclic antidepressants, some antibiotics). Before initiating an antipsychotic medication, the risks and benefits should be carefully weighed and reviewed with patients. Physicians should be especially vigilant in assessing potential cardiac symptoms in this population. Although, it may be prudent to check baseline or post-treatment electrocardiography, especially with higher-risk patients, the effectiveness of doing so has not been proven.

**Seizures:** All antipsychotics can lower the seizure threshold. They should be used with caution in patients who have a history of seizures and in those with organic brain disorders. Generally, the more sedating the antipsychotic, the more it lowers the seizure threshold. Seizures are most common with low-potency FGAs and clozapine, especially at higher dosages. Depot antipsychotics should not be used in patients with epilepsy because they cannot be quickly withdrawn.

**Metabolic Syndrome Issues:** Weight gain is a common adverse effect of using antipsychotic medications, and can be rapid and difficult to control. Weight gain does not seem to be dose-dependent within the normal therapeutic range. The effect is worse with clozapine and olanzapine, minimal with aripiprazole and ziprasidone, and intermediate with other antipsychotics, including low-potency FGAs<sup>29, 32</sup>.

Antipsychotic medications can contribute to a wide range of glycemic abnormalities, from mild insulin resistance to diabetic ketoacidosis, as well as worsening of glycemic control in patients with preexisting diabetes. Although FGAs and SGAs can cause these problems, the risk is variable - the greatest risk is with clozapine and olanzapine. The magnitude of risk is difficult to quantify because so many other diabetes risk factors are present in this population. Although the weight gain associated with antipsychotics clearly contributes, there appear to be other independent effects as well<sup>33</sup>.

Dyslipidemia is also associated with several antipsychotic medications, with increases noted

primarily in triglyceride levels. Low-potency FGAs and the SGAs clozapine, olanzapine, and quetiapine are associated with a higher risk of hyperlipidemia. Overall, metabolic disturbances appear to be greatest with clozapine and olanzapine, intermediate with quetiapine and low-potency FGAs, and lowest with aripiprazole, risperidone, ziprasidone, and high-potency FGAs.

**CONCLUSION:** Different types of schizophrenia are present according to their nature of symptoms which are treated by antipsychotic drugs containing many types of chemical moieties. Antipsychotics block post synaptic dopamine receptors. D1 and D2 receptors are associated with antipsychotic efficacy. Other (D1, D2, D3, D4, D5) dopaminergic receptors have been isolated but not characterized as to their action. D2 receptors are cited as responsible for antipsychotic-induced movement disorders with D1 receptors modulating the intensity of these side effects. 65-70% of patients with schizophrenia respond to traditional (those with primarily D2 blocking action), antipsychotic agents. Chemically aryl piperazine derivatives are most effective due to apomorphine antagonists actions.

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