Introduction

SCHIZOPHRENIA

Schizophrenia is one of the most common, most serious and most mysterious mental illnesses, which affect thinking and judgment. This brain illness also impairs person's ability to organize and communicate thoughts and to function in the society *(Silver, 2001 & Kiefer et al., 2002).*

Prevalence of schizophrenia is one percent of the population with similar prevalence throughout all geographic areas. It usually begins before the age of 25 years and persists throughout life *(Takase et al., 2001 & Wexler et al., 2002).*

It affects all people of all social classes. Both patients and their families suffer from poor care and social burden because of widespread ignorance about schizophrenia *(Bystritsky et al., 2001).*

Each year, only very, few are spent on schizophrenia research in the United States and other countries in comparison with cancer research *(Samele et al., 2001).*

Etiology:

Researches have failed to uncover the definite cause of schizophrenia. Therefore, we have only a number of unproved theories to go on *(Potkin et al., 2002).*

Genetic factors:

Convenient evidences are indicating that a predisposition for schizophrenia is transmitted genetically. Family studies have revealed that there is an increased risk for schizophrenia in the first-degree relatives of schizophrenics ***(Egan et al., 2001 & Malaspina et al., 2001)***.

"Schizophrenogenic mother" is also a term that describes a cold dominant conflict-inducing parent who was said to produce schizophrenia in their off springs ***(Malaspina et al., 2001).***

Recent studies showed that the concordance rates of schizophrenia are approximately 50% in monozygotic twins and 14% in dizygotic twins while the rates not reaching 100% indicating that non-genetic factors do play a role in the pathogenesis of schizophrenia ***(Kumra et al.,2001).***

Adoption studies have also demonstrated a high rate of schizophrenia among the biological children of schizophrenics, even when they are reared by healthy adoptive parents ***(Miller et al., 2002).***

Schizophrenia is assumed to have a complex inheritance pattern because of its high prevalence and sporadic familial transmission ***(Freedman et al., 2001).***

Early studies concentrated on the idea of monozygotic inheritance of schizophrenia, where both recessive and more or less irregular dominant models were suggested, however typical Mendelian inheritance patterns are generally not observed in schizophrenia ***(Marsha et al., 2002).***

The genetic complexity of schizophrenia may be explained by the effects of the combination of multiple genes and by non-genetic components, or by the few genes acting together causing the illness ***(Marsha et al., 2002).***

Recent development of technologies permits the systematic screening of the entire human genome as a strategy for identification of susceptibility genes that influence the risk of schizophrenia. Several studies provide evidence that both genes and environment play a role in the etiology of schizophrenia ***(Vaswani and Kapur, 2001).***

Previous studies of the genetic linkage analysis of schizophrenic families have reported a genetic linkage evidence for schizophrenia on chromosome 15q.Other genes have showed also a suggestive linkage to the pathogenesis of schizophrenia, such as chromosome 10q13, 6q21 and 9q32 ***(Freedman et al., 2001 & Tsuang et al., 2001).***

Dynamic mutations in the DNA explain a number of cases of schizophrenia. Several investigators have reported an association of the trinucleotide repeat length with adult- and child-onset schizophrenia, which have been found at the CTG18.1 locus on the 18th chromosome, SEF2-1 gene, and hKCa3 gene, which codes for a Ca-activated potassium channel ***(Vaswani and Kapur, 2001).***

Moreover, new mutations occur in schizophrenia vulnerability genes, in those with older parents, because advanced paternal age is the major source of new mutations in humans ***(Malaspina, 2001).***

Overall, it is clear that the genetic factors do play a role in the etiology of schizophrenia without explaining the whole picture.

Non-genetic factors:

Many theories consider non-genetic factors as the probable causes of schizophrenia.

(A) Social and environmental factors:

Social class can be specified in various ways using combinations of income, occupation, education, and place of residence. The prevalence and number of newly identified cases of schizophrenia are reported to be higher among those of low socioeconomic status (SES). This high risk for low social classes is due to more life event stressors, increased exposure to environmental and occupational hazards, and infectious agents, poorer prenatal care, and fewer support resources if stress does occur ***(Samele et al.,2001).***

Social-stress theory hypothized that the stressful social conditions like harmful family influences or faulty child rearing may contribute to the pathogenesis of schizophrenia ***(Kumra et al., 2001).***

Reports based on first hospital admissions have shown higher rates of schizophrenia for single than married patients have, and some have inferred that single status contributes to the development of schizophrenia ***(Miller et al., 2002).***

A higher risk for schizophrenia among recent immigrants than native populations has been reported but no study to date to confirm that immigration stress leads to schizophrenia ***(Eklund and Hansson, 2001).***

The prevalence of schizophrenia has been reported to be higher in urban environments than in rural areas. This higher prevalence incites because of rapid change and social disorganization, while rural areas are more socially stable and inhabitants are more integrated ***(Eklund and Hansson, 2001).***

Differences in ethnicity and racial factors are also included as risk factors for development of schizophrenia. These differences may be due to environmental characteristics (***Miller et al., 2002).***

(B) Viral hypothesis of schizophrenia:

This hypothesis supposed that the children born to mothers exposed to viral infection (like, influenza virus, retrovirus, and tick-born flaviviruses) during the second trimester of pregnancy, but not the first or third trimesters, have an increased risk for the development of schizophrenia. This theory can be supported by the observation of prevalence of winter births among schizophrenics ***(Borrell et al., 2002 & Fritzsche and Schmidli, 2002).***

Some viruses such as the influenza virus may mimic certain naturally occurring substances in evoking some symptoms that look like schizophrenia ***(Horing and Lipkin, 2001).***

Different brain studies have identified retroviral RNA in the cerebrospinal fluid and brains of schizophrenics ***(Karlsson et al., 2001).***

It was also observed that the geographical distribution of schizophrenia correlated with the global distribution of the tick-born flaviviruses ***(Brown, 2001).***

(C) Brain pathology in schizophrenia:

A good percentage of schizophrenics, especially those with chronic and negative symptoms have observable brain pathology as proved by autopsy studies, which demonstrated structural problems in the limbic areas, diencephalon and the prefrontal cortex, like atrophy of the prefrontal cortex and enlarged ventricles *(Jones, 2001& Miller et al., 2002).*

The neurodevelopmental hypothesis of schizophrenia have gained increasing acceptance. This hypothesis assumed a disruption in the normal development of the brain, which is secondary to genetic factors, environmental factors, or most likely a combination of both *(Mjellem and Kringlen, 2001).*

(D) Brain chemistry and schizophrenia:

The biological events that lead to schizophrenia are still largely unknown. Several mechanisms involving many neurotransmitters and their receptors are linked to explain the biochemical phenomena that are standing behind the illness *(Mukaetova-Ladinska et al., 2002).*

Dopamine:

Dopamine is the molecular structural backbone of catecholamines. It is converted from tyrosine to L-dopa by tyrosine hydroxylase enzyme. L-Dopa is subsequently decarboxylated to dopamine by an L-aromatic amino acid decarboxylase. In noradrenergic neurons, dopamine is converted to norepinephrine by dopamine β-hydroxylase enzyme (DBH). Dopamine and norepinephrine are metabolized to inactive products that can be removed from CNS. These include 3-methoxytyramine, dihydroxyphenylacetic acid (DOPAC),

homovanillic acid (HVA), and 3-methoxy -4- hydroxy phenylglycal (MHPG) ***(Schwartz et al., 1998).***

Dopaminergic neurons from the substantia nigra ascend to the striatum via the nigrostriatal pathways and modulate motor function. Neurons from the ventral tegmental area connect via the mesolimbic projections to the limbic region and via the mesocortical projections to the prefrontal cortex. The limbic region and prefrontal cortex are involved in cognition, emotional memory and the initiation of behavior ***(Lewis, 1997).***

Initial pharmacological studies discriminated between two subtypes of dopamine receptors, D_1 (by which dopamine activates adenyl cyclase) and D_2 (by which dopamine inhibits adenylcyclase), but subsequent cloning studies identified at least 5 subtypes for dopamine receptors ***(Civelli, 1995).***

The dopamine receptors are now classified into D_1-like receptors which include D_1 and D_5 receptors, whereas the D_2-lik receptors include the two isoforms of the D_2 receptors, D_2 short(D_{2S}) and D_2 long (D_{2L}) according to the length of their third cytoplasmic loop, and the D_3 and the D_4 receptors ***(Schwartz et al., 1998).***

The positive symptoms (hallucinations, delusions, bizarre behavior, and disorganized speech) of schizophrenia are believed to result from dopaminergic overactivity in the mesolimbic system of the dominant hemisphere, although direct evidence for this hypothesis is still patchy ***(Emsley and Oosthuizen, 2003).***

Amphetamines can release dopamine and result in shizophrenia-like symptoms. There is a positive correlation between the potency of antipsychotic drugs and their ability to bind and inhibit dopamine D_2 receptors ***(Friedman, 2003).***

Although D_1 receptor has a low affinity for neuroleptics and has not gained much attention as a target for schizophrenia researches, yet recent experiments demonstrated that the selective D_1 receptor antagonist, SCH23390, could inhibit the ketamine-induced behavioral changes in wild-type mice ***(Neumeyer and Booth, 2001).***

Norepinephrine:

Norepinephrine is the neurotransmitter for neurons in the peripheral autonomic nervous system, like dopamine, norepinephrine widely distributed in the brain. It is most highly concentrated in the hypothalamus, thalamus, limbic system, and cerebellum. Cell bodies of noradrenergic neurons are prominent in locus ceruleus, located beneath the floor of the fourth ventricle ***(Foote, 1997).***

Hypotheses concerning the normal functioning of CNS norepinephnine neurons include a role in learning and memory, reinforcement, sleep-wake cycle regulation, anxiety and nociception, as well as a more general role in the regulation of CNS blood flow and metabolism ***(Elman et al., 2002).***

The role of noradrenergic neurotransmission in normal cognitive functions has been extensively investigated, however, the involvement of noradrenergic function in cognitive impairments associated with schizophrenia has not been intensively considered. The limited ability of

the typical antipsychotic drugs to treat the cognitive deficits of schizophrenia may be related to the influence of multiplicity of neurotransmitter abnormalities including noradrenergic dysfunction ***(Friedman et al., 1999).***

Previous brain studies showed that the binding of the radiolabelled clonidine to beta-1 adrenoceptors, but not beta-2 adrenoceptors, was significantly lower in the most hippocampal fields of schizophrenic subjects when compared to controls, which provides a further evidence of a role of the central noradrenergic neurons in the neurochemical pathology of schizophrenia ***(Klimek et al.,1999).***

Other brain studies also have observed that the addition of α-2 adrenoceptor antagonist to a selective dopamine D_2 receptor antagonist enhances the antipsychotic-like effect of the D_2 blocker and selectively increases the dopamine output in the medial prefrontal cortex in rats ***(Linner et al., 2002).***

Moreover, the norepinephrine transporter (NET) gene may be a candidate gene for the study of the genetics of schizophrenia ***(Leszczynska-Rodziewicz et al., 2002).***

Serotonin:

Serotonin (5-hydroxytryptamine [5-HT]), a derivative of the amino acid tryptophan, is thought to have an inhibitory function in the CNS. The cell bodies of serotonergic neurons are located in the midline raphe nuclei in the lower midbrain and upper pons, although their axons are widely distributed throughout the brain. In general, activation of serotonergic receptors have been demonstrated to inhibit animal behavior, whereas,

the activation of serotonergic mechanisms appear to enhance some behaviors *(Hoyer and Martin, 1996)*.

Molecular biological approaches have led to identification of 14 **distinct mammalian serotonin (5-HT) receptor subtypes** *(Murphy et al., 1999)*.

These subtypes exhibit characteristic ligand-binding profiles, couple to different intracellular signaling systems, exhibit subtype-specific distributions within the CNS, and mediate distinct behavioral effects of serotonin *(Murphy et al., 1999)*.

The known 5-HT receptor subtypes are grouped into multiple classes, the 5-HT1 and the 5-HT2 classes of receptors are both G-protein coupled receptors and include multiple isoforms within each class, while the 5-HT3 receptor is a ligand-gated ion channel, moreover, the 5-HT4, 5-HT5, 5-HT6, and 5-HT7 classes of receptors are all apparent G-protein-coupled receptors but have not yet been well studied *(Hoyer and Martin, 1996)*.

The 5-HT1 receptor subset is composed of at least five receptor subtypes (5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, and 5-HT1F) that are linked to inhibition of adenylcyclase activity or to regulation of potassium or calcium channels and are abundantly expressed on the 5-HT neurons of the dorsal raphe nucleus, where they are involved in temperature regulation and they are also found in the regions of the CNS associated with mood and anxiety as the hippocampus and amygdala *(Pike et al., 2001)*.

Three receptor subtypes constitute the 5-HT2 receptor class, 5-HT2A, 5-HT2B, and 5-HT2C receptors, which are linked to activation of phospholipase C and are enriched in forebrain regions such as neocortex and olfactory tubercle and in several nuclei arising from the brain stem ***(de-Paulis, 2001).***

Receptors of the 5-HT3 class firstly were recognized in the peripheral autonomic nervous system, they also are expressed in the brain areas such as posterma and nucleus tractus solitarius ***(Aghajanian and Marek, 1999).***

There is growing evidence from experimental investigations that neurotransmitters can facilitate the working memory in humans and that acute modulation of dopamine in particular and serotonin may influence the working memory-performance in humans ***(Ellis and Nathan, 2001).***

Low serotonin activity in man has been also related to the impulsive and self-destructive violence as supported by a study in violent offenders which has demonstrated a significant low cerebrospinal fluid concentrations of 5-hydroxindoleacetic acid, a 5-HT metabolite (5-HIAA) 5 which seems to link the outward-directed aggression of psychosis to serotonergic hypofunction ***(Soderstrom et al., 2001).***

Sleep studies have also reported various polysomnographic findings including increased rapid eye movement (REM) time and REM activity in suicidal patients with schizophrenia. One mechanism, which may be responsible for this association between suicide and sleep, could be the role of serotonin, as serotonergic function has been found to be low in patients who attempted and/or complete suicide; particularly those who

used violent methods, additionally, agents that enhance serotonergic transmission have been found to decrease suicidal behavior ***(Singareddy and Balon, 2001).***

Disturbances of the serotonergic pathway have been implicated in many psychiatric disorders including schizophrenia ***(Parsian and Cloninger, 2001).***

Serotonin has also documented to play an important role in the onset and maintenance of the slow wave sleep and in the REM sleep, also, cerebrospinal fluid concentrations of 5-HIAA have been correlated with the slow wave sleep in schizophrenics ***(Singareddy and Balon, 2001).***

In situ radioligand binding and autoradiography studies of the brain demonstrated that there are changes in the cortical serotonergic system in schizophrenia ***(Dean et al., 2001).***

The occurrence of human cerebellar serotonin 5-HT2A receptors (which are important for modulation of mood and perception) is equivocal and their status in schizophrenia is undergoing many investigations ***(Eastwood et al., 2001).***

The 5-HT2A receptor imaging studies have investigated the cerebellar 5-HT2A receptor expression in healthy and schizophrenic subjects and found that the 5-HT2A receptor expression is altered in schizophrenia ***(Eastwood et al., 2001).***

In vivo studies have also demonstrated a paradoxical phenomenon of the 5-HT2A receptor down-regulation by chronic treatment with antipsychotics, which could be explained by antagonist-induced internalization of the 5-HT2A receptors ***(Gray and Roth, 2001).***

Now, the evidence from different receptor studies shows that there is a change in the density of the cortical 5-HT2A receptors in the post-mortem brains of schizophrenics and that also some antipsychotic drugs have been shown to cause a decrease of the density of the 5-HT2A receptors in brains of schizophrenic patients which emphasizes on a role of serotonin in the CNS and provides a further support to the hypothesis that 5-HT receptors could be involved in the pathogenesis of schizophrenia ***(Dean, 2003).***

The 5-HT2C receptor has a high affinity for clozapine, atypical neuroleptic, and has therefore been postulated to play a role in mediating the negative symptoms and neuroleptic response in schizophrenia (***Murad et al., 2001).***

It is also hypothized that the ability of the atypical antipsychotics to improve negative symptoms of schizophrenia is due to 5-HT receptor antagonism and enhanced frontal lobe function, it was also demonstrated that 5-HT2C receptors selectively modulate speed and motor control mechanisms related to the frontal lobe functions ***(Chaudhry et al., 2002).***

The 5-HT1A receptor is also of interest in the pathophysiology of schizophrenia and the mechanism of action of antipsychotic drugs. A neuroendocrine study using a 5-HT1A receptor agonist (ipsapirone) was performed to test the hypothesis that the 5-HT1A receptor responsivity is

significantly different in schizophrenia and the mentioned study suggested that postsynaptic 5-HT1A-mediated endocrine response is diminished in female schizophrenics compared to female control subjects *(Lee and Meltzer, 2001).*

The 5-HT6 receptor displays a high affinity for antipsychotic drugs, particularly, clozapine which displays competitive antagonistic activity at the 5-HT6 receptor which indicate a possible role for this receptor in the pathogenesis of schizophrenia *(Purohit et al., 2003).*

Genetic polymorphism of the serotonin receptor gene has been also reported to be associated with the expression of the clinical signs characteristic of the major psychoses, including schizophrenia *(Parsian and Cloninger, 2001).*

Amino acids and other biogenic amines:

γ-Aminobutyric acid "GABA":

The GABA receptor system provides the major inhibitory control in the CNS, and it is widely distributed within the brain, the highest concentrations are in the substantia nigra, globus pallidus, caudate, medial thalamus, hippocampus, hypothalmus and occipital, frontal and cerebellar cortices. The brain contains large amounts of glutamic acid, the main precursor of GABA (metabolized by pyridoxal-dependent enzyme, glutamic acid decaroxylase (GAD) and itself a possible neurotransmitter) *(Macdonald and Olsen, 1994).*

The observation of behavioral abnormalities in animals following mesolimbic injections of GABA antagonists led to the hypothesis that

there are changes in the cortical GABAergic system in schizophrenia ***(Dean et al., 2001).***

Neurochemical and structural prefrontal cortex abnormalities, including decreased reelin and glutamic acid decarboxylase (GAD) expression are characteristics of schizophrenia neuropathology ***(Costa et al., 2002).***

Reelin is an extracellular matrix protein secreted by GABAergic interneurons that acting through pyramidal neuron integrin receptors, providing a signal for dendritic spine plasticity, the studies revealed that the GABAergic and integrin receptor signal transduction mechanisms are likely to be downregulated by reelin deficiency in the brains of schizophrenic patients ***(Costa et al., 2002).***

Histamine:

Histamine is normally present and partially metabolized in the brain. It is of interest that schizophrenic patients have a relatively low incidence of allergies and a decreased wheal response to histamine injected intradermally. The onset of schizophrenia has been noted in other cases to coincide with a remission of asthmatic symptoms. Many earlier investigators reported abnormalities in histamine metabolism in schizophrenic patients ***(Schwarts et al., 1995).***

Recent studies have suggested a link between the histamine H_1 receptor and H_2 receptor polymorphism and the etiology of schizophrenia, there is also a relationship between the clinical response to some antipsychotic drugs such as clozapine and the antagonism at histamine receptors in the brain ***(Miller, 2003).***

Endogenous opoid peptides: EOP

Opoids are present throughout the CNS. Those that occur naturally are called endogenous opoid peptides, at least nine substances isolated from brain or pituitary has opoid properties. These include, dynorphin A, dynorphin B, Met-enkaphalen, Leu-enkaphalen, α-neoendorphin, and the recently discovered class of novel endogenous opoids, endomorphines ***(Zadina et al., 1997).***

β-endorphin, the most potent of the endogenous opoid agonists, is found in highest concentrations in the hypothalamus, pituitary, mid brain, pons and medulla. It can directly increase the formation of dopamine and serotonin precursors when injected intraventricularly ***(Zadina et al., 1997).***

Three classical opoid receptor types, mu μ, sigma δ, and κ kappa have been studied extensively. The more recently discovered N/OFQ receptor, initially called opoid-receptor-like 1 (ORL-1) receptor or "orphan" opoid receptor has added a new dimension to the study of opoids, and each major opoid receptor has a unique anatomical distribution in the brain, spinal cord, and the periphery ***(Neal et al., 1999b).***

The observation that opoids may play a role in psychiatric disorders dates back to early reports of the use of morphine for the treatment of schizophrenia, and also the observation that schizophrenic patients appear to have reduced sensitivity to pain, studies also proposed that an excess in central opoids, which induce catalepsy in rats, might have a role in the pathology of schizophrenia ***(Peckys and Hurd, 2001).***

Brain studies also demonstrated a relationship between the polymorphism of mu and delta opoid receptor genes and tardive dyskinesia in patients with schizophrenia ***(Ohmori et al., 2001).***

Recent brain studies demonstrated an up-regulation of sigma-1 receptors in the prefrontal cortex and in response to atypical antipsychotic treatment ***(Ovalle et al., 2001).***

Abnormal nicotinic receptor expression

Biological and genetic evidence suggests a role for the neuronal nicotinic receptors in the neuropathophysiology of schizophrenia ***(Leonard et al., 2000).***

Nicotine normalizes an auditory-evoked potential deficit seen in subjects who suffer from the disease. Nicotinic receptors with both high and low affinity for nicotine are decreased in postmortem brains of schizophrenics compared to control subjects which suggests a relation between smoking and development of schizophrenia ***(Leonard et al.,2000).***

Recent studies also have demonstrated an enhancement of the working spatial memory by nicotine, so cigarette smoking is highly prevalent between schizophrenics (three times that of the general population), who may smoke to remediate cognitive deficits and working memory impairment ***(George et al., 2002).***

Cannabinoid / anandamide system and schizophrenia:

The recently discovered cannabinoid receptor system with its endogenous ligand anandamide can be regarded as an extremely relevant

regulation system, a dysfunction of which may explain at least one sub-type of endogenous psychosis including schizophrenia ***(Schneider et al., 1998).***

Studies showed that cerebrospinal concentrations of two endogenous cannabinoids (anandamide and palmitylethanolamide) were significantly higher in schizophrenic patients than non-schizophrenic controls and these findings did not seem to be attributed to gender, age or medication ***(Leweke et al., 1999).***

Elevated anandamide and palmitylethanolamide levels in cerebrospinal fluid of schizophrenic patients may reflect an imbalance in endogenous cannabinoid signaling, which may contribute to the pathogenesis of schizophrenia ***(Leweke et al., 1999).***

A number of studies suggested that cannabinoids can cause or exacerbate psychoses and may increase the risk of developing of schizophrenia. These findings suggest that changes in the cannabinoid system of the brain may be involved in the pathology of schizophrenia ***(Dean et al., 2001).***

Non-competitive N-methyl D-aspartate (NMDA) receptor antagonists:

Schizophrenia is characterized by alterations in the glutametergic system as indicated by studies with phencyclidine and ketamine, which are non-competitive N-methyl D-aspartate receptor antagonists (NMDA) ***(Adam and Moghaddam, 2001).***

Studies showed that NMDA receptor antagonists have psychotomimetic effects and in healthy humans, a single phencyclidine injection produces clinical symptoms similar to schizophrenia ***(Morris, 2003).***

Repeated administration of phencyclidine can evoke long-lasting symptoms such as neuropsychological deficits, social withdrawal, hallucinations, paranoia, and delusions in humans ***(Morris, 2003).***

Most chronic phencyclidine-abusers develop reduced and disturbed cognitive functions and it has been proposed that cognitive deficits result from frontal lobe dysfunction because frontal lobe lesions in humans are associated with comparable cognitive dysfunctions i.e. working memory deficits ***(Farber et al., 2002).***

Furthermore, phencyclidine induces neuronal degeneration and alters glucose utilization in limbic structures including hippocampus and various cortical regions. There is morphological and functional evidence that alterations in the limbic regions are present in schizophrenia ***(Morris, 2003).***

In addition, postmortem analysis of schizophrenics revealed a hypofunction of GABAergic interneurons in the brain as revealed by loss of GABAergic neurons, decreased GAD_{67} activity (the enzyme responsible for GABA synthesis) and mRNA, and upregulation of $GABA_A$ receptors. It is thought that phencyclidine can alter the activity of GABAergic neurons through NMDA receptors on GABAergic interneurons in cortical and limbic structures ***(Akbarian et al., 1995).***

Furthermore, it was shown in human postmortem and rodent studies that NMDA receptor hypofunction as well as NMDA antagonism could result in a dopaminergic hyperactivity, showing that glutamatergic neurons may act on dopaminergic neurons and GABAergic interneurons and thus be involved in the pathogenesis of psychosis ***(Farber et al., 2002).***

Therefore, phencyclidine and ketamine have been used to induce schizophrenia-like symptoms similar to those induced by dopamine-related drugs. Phencyclidine evokes a complex syndrome of behaviors with both positive and negative symptoms. The administration of phencyclidine to rats disturbs learning performance in various hippocampus-dependent tasks ***(Ballmaier et al., 2001).***

Phencyclidine became a popular drug of abuse, which can generate a wide range of subjective effects. These subjective effects have been generally characterized as perceptual disorders, thinking disorders and intellectual impairment, hallucinatory experiences, flattened or blunt affect, and heightened evocation of affectively charged personal experiences ***(Jaffe, 1990).***

Chronic phencyclidine users reported persistent problems with memory and speech; laboratory tests also validated persisting impairments of recent memory, especially for verbal material ***(Adams and Moghaddm, 2001).***

Ketamine is a dissociative anesthetic with pharmacological effects similar to phencyclidine, including induction of a blockade of the NMDA

ion channel. ***Jansen (1990)*** reported that chronic use of ketamine also leads to persistent memory disturbances.

Molecular mechanisms underlying phencyclidine and ketamine effects have been now identified. These agents interfere with the action of the excitatory amino acid (EAA) neurotransmitters, including glutamate and aspartate. The EAAs are the most prevalent excitatory neurotransmitters in the brain and are particularly important in cortico-cortical and cortical-subcortical interactions ***(Farber et al., 2002).***

The EAAs act via four main types of receptors; three of these receptors contain ion channels, the N-methyl D-aspartate (NMDA), kainate, and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. The fourth principal EAA subtype is a metabotropic glutamate receptor coupled by G proteins to the inositol signal trasduction pathway ***(Scott et al., 2002).***

In human brain, the NMDA receptor is most densely localized in the cerebral and hippocamal cortices, where EAA binding activates neurons by opening a voltage-dependent cation channel that is permeable to calcium ***(Javitt and Zukin, 1991).***

Phencyclidine and ketamine, which are non-competitive NMDA antagonists, bind to a site that is distinct from NMDA within the ion channel and block calcium influx (***Javitt and Zukin, 1991).***

Diagnosis of schizophrenia

The diagnostic criteria for schizophrenia according to the DSM-IV (fourth edition of the Diagnostic and Statistical Manual of Mental Disorders) are:

1. Characteristic symptoms: two or more and each present during a period of one month:

- Delusions: false beliefs held with absolute certainty and unexplained by the patient's socioeconomic background.
- Hallucinations: sensory experiences in the absence of any stimulation from the environment, the most characteristic of schizophrenia is the auditory hallucinations, which are threatening or commenting about the patient's behavior.
- Disorganized speech: problem in organization of ideas and in speaking so that a listener can understand.
- Grossly disorganized behavior.

2. Social and occupational dysfunction.

3. Presence of disturbed behavior for at least six months including at least one month of active symptoms.

4. Exclusion of other conditions:

- Schizoaffective and mood disorders.
- Drug abuse or addiction.
- Developmental disorders.

(Taiminen et al., 2001).

It is also important to point to the concept of positive and negative symptoms of schizophrenia, where, negative symptoms refer to behavioral deficits including, avolition (apathy), alogia (poverty of speech), anhedonia (inability to experience pleasure), and flat affect

(absence of emotional expression), on the other hand, positive symptoms consist of excesses in the form of, hallucinations, delusions, bizarre behavior, and disorganized speech ***(Sharma and Antonova, 2003).***

ANTIPSYCHOTIC DRUGS

Chemotherapy of psychoses (schizophrenia, manic-depressive illness, and other acute idiopathic psychotic illnesses) was virtually nonexistent before the discovery of chloropromazine. Chemically, chloropromazine was developed from antihistamines of the promethazine type, and it was first tested clinically in anaesthia to potentiate the narcotic activity of meperidine. Chloropromazine produced a state of quietness and indifference, which suggested further studies of possible uses in psychiatry. The specific antipsychotic activity of chloropromazine in acute psychosis was first described in 1952 ***(Laborit et al., 1952).***

In the ensuming years, this activity was confirmed, and therapy was extended to chronic schizophrenia. These clinical observations led to the introduction of the term "ataractic" or "neuroleptic" activity, which in its original definition indicates the improvement of psychotic symptoms in association with some neurologic and neurovegetative effects ***(Swazy,1974).***

For several years, neuroleptic activity was considered to be an exclusive property of a few phenothiazine derivatives closely related to chloropromazine and of rauwolfia alkaloid, reserpine. A further experimental development followed in 1958 with the synthesis of Haloperidol, the archetype of the butyrophenone series of neuroleptics, which eliminated certain actions of chloropromazine chemically, this butyrophenone resulted from progressive modifications of meperidine-like analgesics, unrelated to phenothiazine ***(Baldessarini, 1985).***

Pharmacologically, the new compounds showed gradually more neuroleptic and less analgesic activity untill full specificity was reached with haloperidol.

The predicted antipsychotic activity of haloperidol was soon confirmed in the clinic. The introduction of haloperidol greatly stimulated the exploration of newly synthesized molecules for neuroleptic activity, resulting in the availability of more than 100 compounds that have received detailed study. Such availability of drugs has facilitated the discussion of similarities and differences between neuroleptics ***(Neumeyer and Booth, 2001).***

Mechanism of action of Antipsychotic drugs

The antipsychotic effects of neuroleptic agents might be mediated by the antagonism of dopaminergic neurotransmission in the limbic, mesocortical, and the hypothalamic systems, where blockade of the D2 family of receptors is common to all effective neuroleptics, the extrapyramidal side effects of antipsychotic drugs arise from D2-receptor blockade in the negrostriatal pathways ***(Moller, 2000).***

Drugs with antipsychotic actions increase the rate of production of dopamine metabolites, the rate of conversion of the precursor amino acid tyrosine to dopamine and its metabolites, and the rate of firing of putative dopamine containing cells in the midbrain, Neuroleptic drugs also block the effects of agonists on a dopamine – sensitive adenyl cyclase system in caudate and limbic tissue ***(Duggan and Brylewski, 2001).***

Almost all of the clinically effective antipsychatic agents have characteristically high affinity for D_2 sites (efficacy is directly related to their ability to bind to the D2 receptors), but some neuroleptics especially thioxanthenes and some phenothiazines bind avidly to D_1 sites, those with relatively high affinity for D_1 receptors also bind and block D_2 receptors ***(Neve and Neve, 1997)***.

The butyrophenones (e.g., haloperidol) have a relatively high selectivity for the D_2 and D_3 receptors with variable D_4 affinity, on the other hand, atypical antipsychotic agents such as clozapine and risperidone have weak antidopaminergic activity at the D_2 receptors and show more selective affinity for the D_4 receptors which could explain their propensity to produce extrapyramidal side effects and their effectiveness with some patients who are not responding to the classical antipsychotics ***(Friedman, 2003)***.

Many antipsychotic drugs, particularly atypical agents such as clozapine and risperidone also affect the function of the serotonin system, where they block the 5-HT_{2A} receptors which may explain their greater efficacy in controlling the negative symptoms of schizophrenia,so new antipsychotics like risperidone, have been selected as clinically effective drugs on the basis of a very potent serotonin antagonism ***(Chaudhry et al.,2002)***.

The lack of brain region selectivity of most antipsychotics means that they act on many different dopamine receptors including those in the hypothalamus, basal ganglia, and the CTZ (chemoreceptor trigger zone) in the brain stem, where these actions are responsible for many of the

unwanted effects of these drugs and the effects at the CTZ give their antiemetic activity *(Moller, 2000).*

Many antipsychotic drugs are also antagonists at α-adrenoceptors and histamine H1 receptors and these actions do not influence their efficacy in the treatment of the psychotic illness but can produce unwanted effects, the sevirity of which varies considerably among the individual drugs *(Kroeze et al.,2003).*

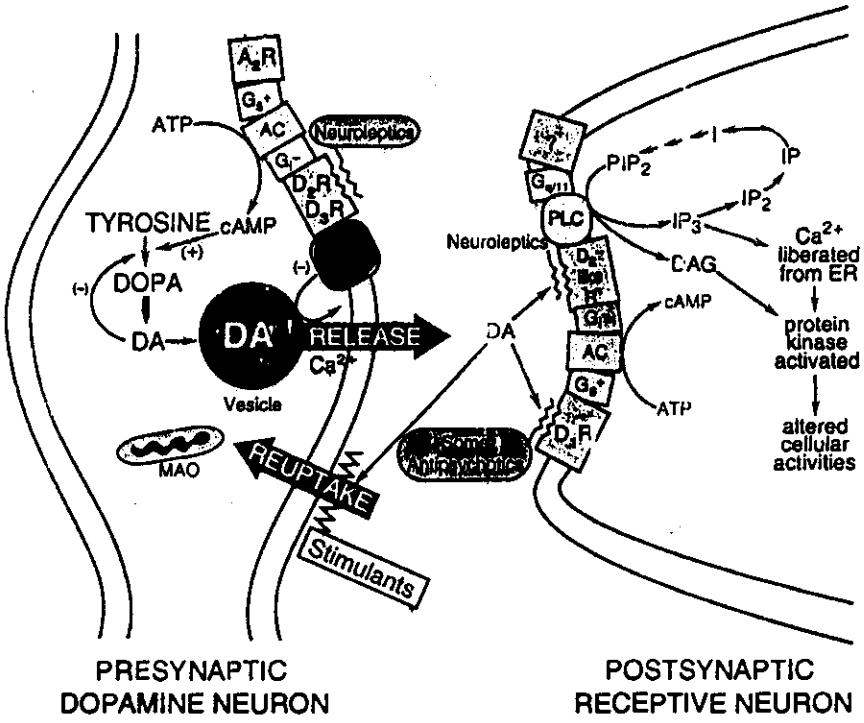

Fig. (1): Site of action of antipsychotic drugs ***(Quoted from Richelson, 1999).***

Chemistry of Antipsychotic drugs

Antipsychotic drugs belong to many different chemical classes and are discussed here on the basis of structure and pharmacologic activity concerning central dopaminergic antagonism *(Neumeyer and Booth, 2001).*

(1) : The reserpine-like compounds :

Contains all aryl-annulated quinolizine derivatives. It includes reserpine, which is in fact not a dopamine antagonist but a monoamine depleting agent, and the butaclamol, which is used mainly as a tool in receptor binding studies *(Baldessarini, 1985).*

(2) : Phenothiazines :

The largest group of compounds which are subdivided into promazines, perazines, phenazines and piperidinophenothiazines according to the chemistry of the side chain.Substitution of an electron-withdrawing group at position 2 increases the efficacy of phenothiazines, the nature of the substituent at position 10 also infleunces the pharmacological activity.Compounds with aliphatic side chain as chloropromazine, are relatively low in potency, those with piperidine ring inside chain as thioridazine are with lower incidence of extrapyramidal symptoms (EPS) due to increased central anticholinergic activity *(Neumeyer and Booth, 2001).*

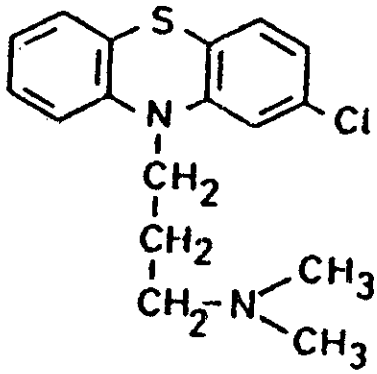

Fig.(2): Chlorpromazine

(3) : Thioxanthene compounds:

Drugs include the thioxanthenes, which resemble phenothiazines both chemically and pharmacologically (chlorprothixene vs. chlorpromazine, flupenthixol vs. fluphenazine) ***(Neumeyer and Booth, 2001).***

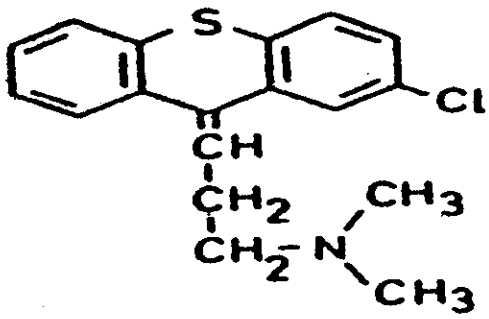

Fig.(3): Chlorprothixene

(4) : Butyrophenones :

A completely different chemical series of neuroleptics, of which haloperidol (with a molecular weight of 375.9) is the protype. Generally, the butyrophenones are potent neuroleptics with prolonged action ***(Neumeyer and Booth, 2001).***

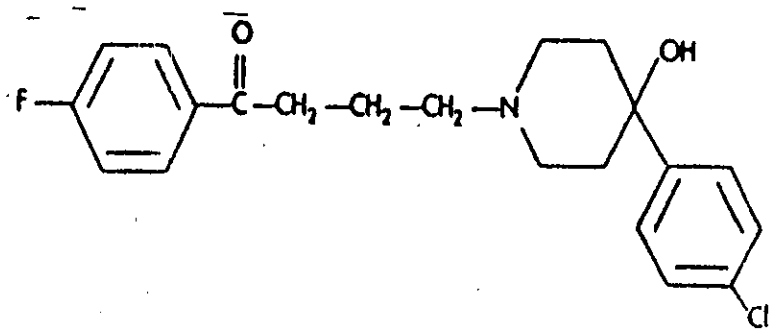

Fig.(4): Haloperidol

(5) : Diphenylbutylpiperidine:

Diphenylbutylpiperidine, with pimozide as the archetype, these drugs are potent dopamine antagonists. All act longer than the corresponding butyrophenones. The highly lipophilic character of these compounds favours a more gradual occupation of the dopamine receptors ***(Neumeyer and Booth, 2001).***

(6): Tricyclic antipsychotic compounds :

Include various tricyclic derivatives with a central seven-membered ring to which methyl piperazine is linked, which include loxapine, clozapine, and clozapine-like drugs which lack a ring substituent as quetiapine, or have analogous methyl substituents as olanzapine, and can interact at several receptor types, alpha 1 & alpha 2 adrenoceptors, 5-HT2A, 5-HT2C, muscarinic, and H_1 receptors ***(Worrell et al., 2000).***

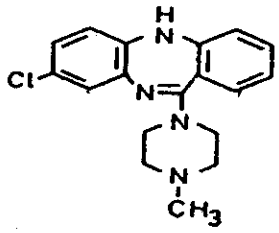

Fig.(5): Clozapine

(7): Other classes of heterocyclic compounds :

Which have antipsychotic effects, but too few are available or sufficiently well characterized to permit conclusions regarding structure-activity relationships. These include indole compounds like molindone and oxypertine *(Neumeyer and Booth, 2001).*

(8) : Gastroenterologic agents:

like metoclopramide and cisapride which have antiserotonergic and antidopaminergic actions *(Neumeyer and Booth, 2001).*

(9): Miscellaneous compounds :

Risperidone is a member of this group and it offers the best perspectives for an antipsychotic of a new type *(Waddington and Casey, 2000).*

Pharmacological properties of antipsychotic drugs

The antipsychotic drugs share many pharmacological effects and therapeutic applications. Chloropromzine and haloperidol are commonly taken as protypes for the older, standard neuroleptic-type agents, and new agents can be compared and contrasted to them *(Jibson and Tandon, 1998).*

Many antipsychotic drugs, and especially chlorpromazine and other agents of low potency, have sedative effect. This is particularly apparent early in treatment, although tolerance to this effect is typical, sedation may not be noticeable when very agitated psychotic patients are treated. Despite their sedative effects, they generally are not used to treat anxiety disorders, largely because of their autonomic and neurological side effects, which paradoxically include sever anxiety and restlessness ***(Moller, 2000).***

In human beings, the neuroleptic drugs reduce initiation and interest in the environment, and they reduce displays of emotion or affect. Initially, there may be some slowness in response to external stimuli and drowsiness. However, subjects are easily aroused, capable of giving appropriate answers to direct questions, and seem to have intact intellectual functions, ataxia, incoordination, or dysarthria do not occur at ordinary doses ***(Keck and Licht, 2000).***

Typically, psychotic patients soon become less agitated and restless, and withdrawn patients sometimes become more responsive and communicative. Aggressive and inpulsive behaviour diminishes. Gradually usually over a peroid of days", psychotic symptoms of hallucinations, delusions, and disorganised or incoherent thinking tend to disappear ***(Keck and Licht, 2000).***

The pharmacological actions of antipsychotic drugs include their effects on many body systems:

The motor activity

Nearly all of the neuroleptic agents used in psychiatry can diminish spontaneous motor activity in every species of laboratory animal, including man. However, one of the most disturbing side effects of these agents in man, akathesia which is manifested by an increase in restless activity, parkinsonism, and other extrapyramidal side effects ***(Blanchet, 2003).***

These effects are mainly due to the ability of neuroleptic agents to antagonize the actions of dopamine as a neurotransmitter in the basal ganglia ***(Richelson, 1999).***

Limbic system

Because of dopamine hypothesis of schizophrenia, much attention has also been giving to the mesolimbic and the mesocortical systems as possible sites of mediation of some of the antipsychotic effects of neuroleptic agents through dopamine antagonism ***(Lahti et al., 1998).***

The finding that D_3 and D_4 receptors are expressed in limbic areas of the CNS has led to increased efforts to identify agents that are selective for these receptors and that might have antipsychotic efficacy with a reduced tendency to cause extrapyramidal symptoms (EPS) ***(Tarazi and Baldessarini, 1999).***

Hypothalamus.

Endocrine changes occur due to effects of neuroleptics on the hypothalamus or pituitary. Prominent among these effects is the ability of most neuroleptics to increase the secretion of prolactin in man ***(Dickson and Glazer, 1999).***

The effect of neuroleptics on prolactin secretion is probably due to a blockade of the tuberoinflundibular dopaminergic system that projects from the arcuate nucleus of the hypothalamus to the median eminence by a direct antagonistic action at dopaminergic receptors localised on cells of the anterior pituitary. **D2-dopaminergic receptors on mammotrophic cells** in the anterior pituitary mediate the prolactin-inhibiting action of dopamine secreted at the median eminence into the hypophyseal portal system ***(Dickson and Glazer, 1999).***

The correlation between the potencies of the antipsychotics in stimulating prolactin secretion causing behavioural effects are excellent for many types of agents, for example, risperidone has an unusual potent prolactin-elevating effect ***(Kinon et al., 2003).***

The effects of neuroleptics on other hypothalamic neuroendocrine functions are much less well characterized, although it is known that they inhibit the release of growth hormone and chloropromazine may reduce the secretion of corticotropin-regulatory hormone in response to stress ***(Daniel, 2003).***

In addition to neuroendocrine effects, it is likely that other autonomic effects of some antipsychatic drugs may be mediated by hypothalamus. An important example is piokilothermic effect of chlorpromazine and other neuroleptic agents, which impairs the ability to regulate body temprature such that hypo-or hyperthermia ***(Brevik and Farver, 2003).***

Chemorecptor trigger zone CTZ

Most neuroleptic agents have a marked protective action against the nausea-and emesis-inducing effects of apomorphine and certain ergot alkaloids, all of which can interact with central dopaminergic receptors in the CTZ of the medulla. The potent antipsychotic drugs like, piperazines and butyrophenones (like haloperidol) are sometimes effective against nausea caused by vestibular stimulation.This antiemetic effect of neuroleptics occures at low doses ***(Bharti and Shende, 2003).***

Autonomic nervous system

The effects of neuroleptics on autonomic nervous system are complex and unpredictable, since they have peripheral cholinergic blocking activity, α-adrenergic blocking actions, Antihistaminic H_1 and antiserotonergic 5-HT_{2A} effects ***(Findling et al., 1998).***

Chlorpromazine has a significant α- adrenergic antagonistic activity and can block the pressor effects of norepinephrine.Haloperidol and risperidone have antipsychotic effects even when used in low doses and show little antiadrenergic activity in patients.The phenothiazines inhibit ejaculation without interfering with erection which limits their acceptance by male patients and this effect may be due to antiadrenergic action ***(Bizouard et al., 2001).***

The anticholinergic effects of antipsychotic drugs are relatively weak, but the blurring of vision commonly experienced with chloropromazine may be due to anticholinergic action on ciliary muscle. Chloropromazine regularly produces miosis in man, which can be due to α-adrenergic blockade. Other phenothiazines can cause mydriasis, this is

especially is likely to occur with thioridazine which is the most potent antimuscarinic of the group *(Rabinowitz et al., 1996).*

Chlorpromazine has an intermediate antimuscarinic potency and **can cause constipation and decreased gastric secretion and motility.** Decreased sweating and salivation also occur. Urinary retention is rare, but can occur in males with prostatism and benign prostatic hypertrophy *(Rabinowitz et al., 1996).*

Anticholinergic effects are least frequently caused by piperazines and other potent neuroleptics, including haloperidol and risperidone *(Waddington and Casey, 2000).*

Kidney

Chlorpromazine may have weak diuretic effects in animals and man, due to either a depressant action on the secretion of antidiuretic hormone (ADH), or inhibition of reabsorption of water and electrolytes by a direct action on the renal tubule, or both.The syndrome of idiopathic polydepsia with potential hyponatremia has been improved with clozapine, may be through CNS mechanisms *(Siegel et al., 1998).*

Cardiovascular system

The actions of chlorpromazine on cardiovascular system are complex because the drug produces direct effects on the heart and blood vessels, and indirect ones through the actions on CNS and autonomic reflexes *(Van den Buuse, 2003).*

Chlorpromazine and other low-potency or atypical antipsychotics can cause orthostatic hypotension (which is due to combination of central

action and periphral alpha-adrenergic blockade), systolic blood pressure being affected more than diastolic, tolerance develops to the hypotensive effect, so that after several weaks of administration the pressure return towards normal. However, some degree of orthostatic hypotension may persist indefinitely, especially in elderly patients ***(Van den Buuse, 2003).***

Because of its vasodilating effect due to both its actions on the autonomic nervous system and to a direct action on blood vessels, chlorpromazine may increase coronary blood flow ***(Findling et al., 1998).***

Chlorpromazine has a direct negative inotropic action and a quinidine-like antiarrhythmic effect on the heart. ECG changes include prolongation of Q-T and P-R intervals, blunting of T-waves and depression of S-T segment ***(Carroll et al., 2002).***

Thioridazine, in particular, causes a high incidence of Q-T and T-wave changes and can produce ventricular arrhythmias and sudden death. These effects are uncommon when potent antipsychotic agents are given ***(Bums, 2001).***

Other pharmacological effects

Many neuroleptics enhance the turnover of acetylcholine, especially in the basal ganglia, perhaps secondary to blockade of the inhibitory dopamine heteroceptors on cholinergic neurons. In addition, there is an inverse relationship between antimuscarinic potency of antipsychotic drugs in the brain and the possibility of occurrence of extrapyramidal side effects ***(Meltzer, 1999).***

Chlorpromazine and low-potency antipsychotic agents have mild antagonistic action at histaminic receptors that probably contribute to their sedative effects ***(Findling et al., 1998).***

Antagonistic interactions are also known to occur at 5-hydroxytryptamine (5-HT2A) receptors in the forebrain. The significance of this effect is not certain, but several antipsychotic agents, notably risperidone, have been developed to mimic the relatively potent and selective $5HT_{2A}$ antagonstic activity of clozapine at 5-HT2A receptors ***(Ichikawa and Meltzer, 1999).***

Pharmacokinetics of antipsychotic drugs

Some antipsychotic drugs tend to have unpredictable patterns of absorption, particularly after oral administration and even when liquid preparations are used ***(Ereshefsky, 1996).***

Intramuscular administration of antipsychotic drugs can increase the bioavailability of the active drug by four to ten times. The drugs are highly lipophilic, high – membrane – or protien – bound, and accumulate in the brain, lung, and other tissues with a high blood supply, they also enter the fetal circulation quite easily and breast milk. It is vitrually impossible (and usually not necessary) to remove these agents by dialysis ***(Marder, 1998).***

The usually stated elimination half-lives with respect to total concentrations in plasma are typically 20 to 40 hours, but complex patterns of delayed elimination may occur with some agents particularly butyrophenones. The biological effects of single doses of most neuroleptics usually persist for at least 24 hours. Elimination from the

plasma may be more rapid than from sites of high lipid content and binding, notably in the CNS ***(Caccia, 2002).***

Metabolites of some agents have been detected in urine for as long as several months after the drug has been stopped, this slow removal of the drug may contribute to the typically slow rate of exacerbation of psychosis after stopping drug treatment (***Kratzsch et al., 2003).***

The main routes of metabolism of the antipsychotic drugs are by oxidative processes mediated largely by genetically controlled hepatic cytochrome P450 (CYP) microsomal oxidases and by conjugation processes to glucouronic acid ***(Prior and Baker, 2003).***

Hydrophilic metabolites of the drugs are excreted in urine, and to some extent, in the bile. Most oxidized metabolites of antipsychotic drugs are biologically inactive, but a few are not (notably, 9-hydroxy-risperidone) and may contribute to the biological activity of the parent substance, as well as complicate the problem of correlating assays of drug in blood with clinical effects ***(Caccia, 2002).***

The less potent antipsychotic drugs may induce their own hepatic metabolism, since concentration of chlorpromazine and other phenothiazines are lower after several weaks of treatment with the same dose, it is possible that alterations of gastrointestinal motility are partially responisble ***(Kutcher, 1997).***

The fetus, the infant, and the elderly have diminished capacity to metabolize and eliminate antipsychotic agents; children tend to metabolize these drugs more rapidly than do adults ***(Caccia, 2002).***

Haloperidol, as a protype for antipsychotic agents, it is metabolized mainly by N-dealkylation reaction, the resultant inactive metabolites can be conjugated with glucuronic acid, the hydroxylated product of haloperidol which produced by the reduction of the keto moity is exceptionally active and may be reoxidized to haloperidol *(Castagnoli et al., 1999).*

A potentially neurotoxic derivative of haloperidol, a substituted phenylpiperidine, analogous to the parkinsonism-inducing agent methylphenyltetrahydropyridine (MPTP), has been described and found in nanomolar quantities in postmortem brain tissue of persons who had been treated with haloperidol *(Galetin et al.,2002).*

Typical plasma concentrations of haloperidol encountered clinically are about 5-10 ng/mL, and those correspond to 80 to 90 % occupancy of D_2 receptors in human basal ganglia as demonstrated by positron emission tomography (PET) brain scanning *(Castagnoli et al., 1999).*

Dosage of antipsychotic drugs

Optimal dosage of antipsychotic drugs requires individualization to determine doses that are effective, well tolerated, and accepted by the patient. Dose-response relationships for antipsychotic action and side effects overlap, and an end point of a desired therapeutic response can be difficult to determine *(DeBattista and Schatzberg, 1999).*

Typical effective doses are approximately 300 to 500 mg of chlorpromazine, 5 to 15 mg of haloperidol, or their equivalent, daily. Dose of as little as 50 mg to 200 mg of chlorpromazine per day (or 2 to 6

mg of haloperidol per day) may be effective and better tolerated by many patients, especially after the initial improvement of acute symptoms *(Liu et al., 2003).*

Adverse effects of antipsychotic drugs

The antipsychotic drugs have a high theraputic index and are remarkadly safe agents. Furthermore, most phenothiazines and haloperidol have a relatively flat dose-response curve and can be used over a wide range of dose *(Wirshing et al., 2003).*

Although occasional deaths from over dosage have been reported, it is rare if the patient is given medical care and if an overdosage is not complicated by concurrent ingestion of, alchol or other drugs *(Bums, 2001).*

Adult patients have survived doses of chloropromazine up to ten grams, and deaths from an overdose of haloperidol alone appear to be unknown *(Trenton et al, 2003).*

The most important side effects of antipsychotic drugs are those on the CNS, cardiovascular system, autonomic nervous system, and endocrine functions and the extrapyramidal side effects. Other dangerous effects are agranulocytosis and pigmentary degeneration of retina, both of which are rare *(Alao et al., 2002).*

Neurological side effects

A variety of neurological syndromes, involving particularly the extrapyramidal system, (EPS) extrapyramidal side effects, which include, akathesia, acute dystonia, and parkinsonism, occur following the use of

almost all antipsychatic drugs due to D2 receptor blockade in the nigrostriatal pathways. These reactions are particualrly prominent during treatment with the high – potency neuroleptic agents (tricyclic piperazines and butyrophenones). There is less liklihood of acute extrapyramidal side effects with clozapine, quetiapine, olanzapine, thioridazine or low doses of risperidone ***(Tarsy et al., 2001).***

Six varieties of neurological syndromes are characteristic of antipsychotic drugs. Four of them (acute dystonia, akathisia, parkinsonism, and the rare neuroleptic malignent syndrome) usually appear concomitantly with administration of the drug, and two (the rare perioral tremor and tardive dyskinesia) are late- appearing syndormes that occur following prolonged treatment for many months or years ***(Tarsy et al., 2001).***

Acute dystonic reactions

Irrigular spasms of facial, neck, and trunk muscle and sustained abnormal postures. They can appear early in the treatment and respond dramatically to parentral therapy of anticholinergic antiparkinsonian drugs. Oral administration of anticholinergic agents can also prevent dystonia ***(Blanchet, 2003).***

Akathesia

Refers to strong subjective feelings of distress or discomfort, and is experienced by the patient as an irresistible urge to move within minutes from any sitting, lying, or standing position. Because the response of akasithia to antiparkinsonian drugs is frequently unsatisfactory, treatment typically requires reduction of antipsychotic drug dosage. Antianxiety

agents may help partially, and moderate doses of propranolol have been reported to be beneficial in many cases ***(Leong and Silva, 2003).***

Parkinsonism

Parkinson–like symptoms may develop during administration of antipsychotic drugs. These symptoms may be indistinguishable from idiopathic parkinsonism. The intensity and time of occurance (days to several weeks) are dose – related and in some patients, the parkinsonian syndrome may not be seen at all. Clinically, there is generalised slowing of movement (akinesia) with mask facies and a reduction in arm movements. The most noticeable signs are rigidity and tremor at rest, especially involving the upper extermities ***(Tarsy et al., 2001).***

This reaction is usually managed by the use of either antiparkinsonian agents with anticholinergic properities ***(Tarsy et al., 2001).***

Neuroleptic malignant syndrome

Rare unpredictable disorder, which may be contributed to dopamine antagonism, which resembles a very sever from of parkinsonism with catatonia, flactuation in the intensity of tremor, signs of autonomic instability (tachycardia, hypertension, hyperthermia), stupor, elevation of creatine kinase in plasma, and sometimes myoglobinaemia. It develops within weeks after starting antipsychotic therapy. In its most sever form; this syndrome may persist for more than a week after stopping the offending agent ***(Beauchemin et al., 2002).***

This reaction has been associated with various types of neuroleptics, but its prevelance may be greater with relatively high doses

of the more potent agents especially when used parentrally *(Viejo et al., 2003).*

Since the mortality is high (over ten percent), immediate medical attention is required with immediate cessation of neuroleptic treatment, administration of dantorlene or dopaminergic agonist bromocriptine may be helpful. Antiparkinsonian agents are not effective in the mangement of this syndorme *(Beauchmin et al., 2002).*

Rabbit syndrome: (Perioral tremor)

A rare movement disorder that can appear late in the treatment of chronically ill patients with antipsychotic agents (after months or years of the treatment). In the form of perioral tremor which may be a late varient of parkinsonism (*Dethi and Bhargava, 2003*).

The tremor have a favorable response to anticholinergic agents and to the removal of the offending agent *(Dethi and Bhargava, 2003).*

Tardive dyskinesia

It is a late – appearing neurological syndrome (after months or years of treatment and worse on withdrawal) associated with antipsychotic drug use. It occurs more frequently in older patients. It has been associated with every class of neuroleptic agents. The incidence appears to be very low with the atypical antipsychotic agent clozapine *(Miller, 2003).*

Tardive dyskinesia is characterized by stereotypical, repetitive, involuntay movements consisting of sucking of lips, lateral jaw movements, and pushing or twisting of the tounge. There may be

chorioform or purposeless, quick movements of the extremities. Slower, more dystonic movements and postures of the extremities, trunk, and neck may be also seen, especially in younger males. All of these movements disappear during sleep, as in parkinsonism *(Soares and McGrath, 1999).*

There is no established neuropathology in tardive dyskinesia, but recent studies have been demonstrated a genetic variant of the 5-HT2A receptor, which may be implicated in the pathophysiology of tardive dyskinesia, which may involve dopamine-serotonin interaction *(Tan et al., 2001).*

Antiparkinsonian drugs typically exacerbate tardive dyskinesias, and no adequate therapy has been yet advised the best approach is preventive *(Soares and McGarth, 1999).*

Autonomic side effects

Antipsychotic drugs, particularly those with higher levels of antimuscarinic activity, are capable of producing a variety of autonomic effects, including dizziness, faintness, weakness, dry mouth, nasal congestion, nausea, vomiting, constipation, urinary disturbances, blurred vision, orthostatic hypotension *(Rabinowitz et al.,1996).*

Orthostatic hypotension is particularly likely to develop with the aliphatic phenothiazines. It most frequently appears during the first several days of treatment and is most apparent when the patient arises from bed. Tolerance to this affect usually develops rapidly; however, occasionally it can be a significant problem. Explaining this effect and reassuring the patient can also be helpful *(Van den Buuse, 2003).*

Blood dyscriasis

Mild leukocytosis, leukopenia, and esinophilia occasionally occur with clozapine and less often with low-potency phenothiazine medication. It is difficult to determine whether a leukopenia occuring during the administration of a phenothiazine is a forewarning of impending agranulocytosis. This serious but rare complication occurs in not more than 1 in 10,000 patients receiving chloropromazine or other low-potency agents other than clozapine particularly in high doses, it usually appears within the first 8 to 12 weeks of treatment ***(Abdullah et al.,2003).***

suppression of the bone marrow or, less commonly, agranulocytosis has particularly been associated with use of clozapine, the incidence approaches 1%, independent of the dose, and close monitoring of the patient is recommended. The appearance of an apparent upper respiratory infection in a patient being treated with an antipsychotic drug should be followed immediately by complete blood count ***(Worrel et al., 2000).***

Ocular and skin reactions

Dermatological reactions to the phenothiazines are common. Several types of skin disorders may occur including, hypersensitivity reaction in the form of urticaria, maculopapules, petechieae or edema which occurs between the first and eight week of treatment, the skin clears after discontinuation of the drug and may remain so even if the drug therapy is reinstituted. Photosensitivity occurs, which resembles lesion seen with sever sunburn ***(Warnock and Morris, 2002).***

Gray-blue pigmentation induced by long-term administration of low potency phenothiazines in high doses is rare ***(Koo and Ng, 2002).***

Epithelial keratopathy is often observed in patients on long-term therapy with chlorpromazine and opacities in the cornea and in the lens of the eye have been noted, which disappear after discontinuation of the drug. Pigmentary retinopathy has been reported, particularly following doses of thioridazine in excess of 1000 mg per day, a maximal daily dose of 800 mg is currently recommended ***(Blaho, 2000).***

Recently, it was suggested that thioridazines and other phenothiazines can cause degenerative retinopathies with histological, electrophysiological and symptomatological features similar to those of primary retinitis pigmentosa and this may be due to dopamine antagonism as dopamine and its receptors especially D4 subtype is involved in the control and synthesis of melatonin which regulate retinal physiology ***(Fornaro et al., 2002).***

Endocrine and metabolic effects

Disturbances of sexual functioning may occur because of the sympathetic and parasympathetic effects of these drugs, and may be related to effects on peripheral 5-HT3 receptors in blood vessels. There is difficulty in achieving and maintaining erection, and inability of ejaculation. Thioridazine appears more likely than other phenothiazines to cause such sexual dysfunctions ***(Bizouard et al., 2001).***

Antipsychotic agents may also cause amenorrhea, and gynecomastia and weight gain which is prominent with clozapine and olanzapine and less with risperidone and quetiapine ***(Allison et al., 1999).***

Associated adverse responses include new-onset diabetes mellitus or worsening of type II DM (diabetes mellitus), hypertension, and hyperlipidaemia *(Wirshing et al., 2003).*

Teratogenicity

There is no substantial evidence of teratogenicity from human surveys, but cautious use (such as avoiding prescription for antiemetic effects) during pregnancy is recommended because very high doses in animals induce malformations, but decisions as to how to manage pregnant women who require antipsychotic drugs should be discussed thoroughly with expert consultants, the patient, and the family *(Patton et al.,2002).*

Electrocardiograph changes

Many phenothiazines, but most frequently thioridazine, are associated with electrocardiographic (ECG) abnormalities consisting of increast Q.T. interval and flattened T-wave *(Bums, 2001).*

Interactions with other drugs

The phenothiazines and thioxanthenes, especially those of low potency, affect the actions of a number of other drugs, sometimes with important clinical consequences *(De Vane and Nemeroff, 2000).*

A well-known valuable interaction is potentiation of analgesia in anaesthesia generally without increasing recovry time. Such drugs can strongly potentiate sedatives and analgesics, as well as alcohol, hypnotics and antihistaminics. Chlorpromazine increases the miotic and sedative effects of morphine and may increase its analgesic actions, furthermore, the drug markedly increases the respiratory depression produced by

meperidine obviously, and neuroleptics will inhibit the actions of direct dopaminergic agonists and of levodopa ***(De Vane and Nemeroff, 2000).***

Chlorpromazine and some other antipsychotic drugs, as well as their N. demethylated metabolites, may block the antihypertensive effects of guanithidine, probably by blocking its uptake into sympathetic nerves. low potency phenothiazines can pormote postural hypotension, possibly due to their α- adrenergic blocking properties ***(Daniel, 2003).***

Thioridazine may partially nullify the inotropic effect of digitalis by its quinidine-like action, which can cause myocardial depression, decreased efficiency of repolarization, and increase the risk of tachyarrhythmias ***(Daniel, 2003).***

The antimuscarinic action of thioridazine can cause tachycardia and enhance the periphral and central effects of other anticholinergic agents, such as tricyclic antidepressants and antiparkinsonian agents ***(Ereshefsky, 1996).***

Sedatives or anticonvulsants (e.g., phenobarbital, carbamazepine) that induce microsomal drug-metabolizing enzymes can enhance the metabolism of antipsychotic agents, sometimes with significant clinical consequences ***(Mula and Monaco, 2002).***

Conversely, serotonin-reuptake inhibitors including fluoxetine compete for hepatic oxidases and elevate the circulating levels of neuroleptics ***(Spina et al., 2002).***

Uses of antipsychotic drugs

The antipsychotic drugs are clearly effective in acute psychosis of unknown etiology, including mania, acute idiopathic psychoses, and acute exacerbation of schizophrenia, the greatest amount of controlled clinical data exists for the acute and chronic phases of schizophrenia. In addition, antipsychotic drugs are used empirically in many other disorders, whether idiopathic or organic, in which psychotic symptoms and sever agitation are prominent *(Emsley and Oosthuizen, 2003).*

The "target" symptoms for which the neuroleptic agents seem to be especially effective include tension, hyperactivity, hostility, hallucinations, insomnia, anorexia, poor-self care, negativism, and sometimes withdrawal, less likely is improvement in insight, judgment, memory, and orientation *(Moller, 2000).*

Emesis is one of the indications of antipsychotic agents, as dopamine mediated stimulation of chemoreceptor trigger zone (CTZ) and gastric motor reflexes is inhibited by neuroleptics. Several phenothiazines, the butyrophenones droperidol and haloperidol, and the benzamide metoclopramide are widely used as antiemetics. All can be used in the management of nausea and vomiting in cancer chemotherapy *(Bharti and Shende, 2003).*

A combination of fentanyl-droperidol, either in a fixed proportion or administered separately at a selected time and dose, is a well-known preparation for neuroleptanalgesia "poteniators of analgesia" *(Lavenstein, 2003).*

Antipsychotic drugs are useful in the management of several neurological conditions with psychiateric features that are characterized by movement disorders. These include, in particular, Gilles de la Tourette's syndorme (marked by tics, other involuntary movements and vocalization) ***(Lavenstein, 2003).***

Huntington's disease (marked by sever and progressive choreoathetosis, psychiatric symptoms and dementia with a clear genetic basis). Haloperidol is currently regarded as the drug of choice for these conditions ***(Sadock and Sadock, 2000).***

Antipsychotic drugs can be used safely and effectively in certain psychoses associated with chronic alcoholism, especially the syndrome known as alcoholic hallucinosis, but they are not useful in the management of withdrawal from opoids, and their use in the management of withdrawal from barbiturates and other sedatives is contraindicated, owing to the high risk of seizures. This risk also precludes the use of neuroleptics during withdrawal from alchol ***(Sadock and Sadock, 2000).***

Clozapine and quetiapine are relatively well tolerated in psychosis arising with dopamine-receptor agonist treatment in Parkinson's disease ***(Tarsy and et al., 2001).***

RISPERIDONE

Risperidone belongs to a new group of substances called **benzisoxsole derivatives. The chemical structure of Risperidone is, 3-[2-**[4- (6-fluoro-1, 2-benzisoxazol-3-yl) -1-piperidinyl] - 6, 7, 8, 9-tetrahydro-2-methyl-4H-pyr-ido [2-a] pyrimidin-4-one C23 H_{27} F-N_4 O_2 ***(Neumeyer and Booth, 2001).***

The molecular weight of the drug is 410 ***(Janssen, 1997).***

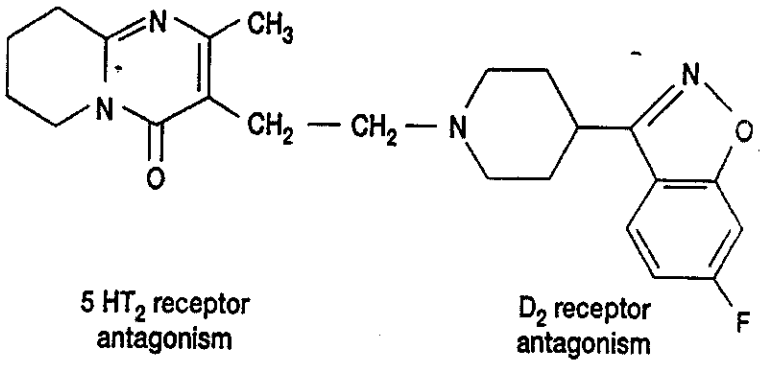

Fig.(6): Chemical structure of risperidone.

Pharmacokinetics of risperidone

Risperidone is well absorbed and the peak plasma concentration is reached after one to two hours. The rate of absorption is not influenced by concomitant intake of food and thus risperidone may be taken with or without meals ***(Zhao et al., 2003).***

The absolute bioavailability of risperidone a "parent compound" is about 66%, and that of the whole antipsychotic fraction is approximately 100% in rapid metabolizes. This suggests that risperidone is metabolized

to 9-OH-risperidone during first passage through the liver. In slow metabolizers, absolute bioavailability of risperidone is higher than for rapid metabolizers. This suggests that the degree of metabolism during the first passage through the liver is lower in slow metabolizers ***(Zhao et al., 2003).***

The volume of distribution is 1-2 L/Kg. In plasma, risperidone "parent compound" is mainly bound to albumin and α_1-glycoprotein. The degree of protein binding in plasma is about 88% for risperidone and 77% for 9-OH – risperidone ***(Caccia, 2002).***

Hydroxylation and N.dealkylation are the main pathways of risperidone metabolism, mainly by the isoenzyme CYP2D6 "cytochrome P450" and to a lesser extent by CYP3A4, to a major active circulating metabolite, 9-OH-risperidone ***(Prior and Baker, 2003).***

In a rapid metabolizer, risperidone "parent compound, represents 10% and 9-OH-risperidone 70% of the plasma radioactivity after a single oral dose of ^{14}C-labelled risperidone. In a slow metabolizer, risperidone "parent compound" represents 71% of the plasma radioactivity and the levels of 9-OH-risperidone are hardly measurable. This suggests that the sum of the concentrations of risperidone "parent compound" and 9-OH-risperidone, i.e. the active antipsychotic fraction, is equal for slow and rapid metabolizers ***(Berecz et al., 2002).***

Since 9-hydroxy-risperidone and the parent compound, risperidone are nearly equipotent, the clinical efficacy of the drug reflects both compounds ***(Berecz et al., 2002).***

The half-life in rapid metabolizers is approximately 3 hours for risperidone "parent compound" and approximately 20 hours for 9-OH-risperidone. In slow metabolizers the half-life is approximately 16 hours for risperidone. The half-life for the antipsychotic fraction is 20-24 hours in both slow and rapid metabolizers *(Caccia, 2002).*

When risperidone is administered twice daily, the steady state concentration in plasma is reached within 24 hours for risperidone "parent compound" and after about 5 days for 9-oH-risperidone active metabolite". Within the therapeutic dose range, the plasma concentration of risperidone is linearly correlated to the dose *(Yasui-Furukori et al., 2002).*

One week after intake of a single dose of 1 mg of ^{14}C-labelled risperidone, 70% of the radioactivity was excreted in the urine and 14% in the faeces. In total, 84% of the administered radioactivity has been excreted after one week *(Bums, 2001).*

Mechanism of action of risperidone

Risperidone has a strong binding affinity for the central 5-HT_{2A} receptor, a receptor to which the neurotransmitter serotonin binds. Besides, its high affinity for 5-HT_{2A} receptors, risperidone also has substantial affinity for central dopamine D_2, α_1 adrenergic and histamine H_1 receptors *(Love and Nelson, 2000).*

In vivo studies of receptor binding in laboratory animals, showed that a low dose of risperidone is sufficient to block 50% of the 5-HT_2 receptors in frontal cortex, a higher dose is required to block 50% of dopamine D_2 receptors in the dopaminergic pathways. Therefore,

risperidone displays a fine balance between 5-HT_2 and D_2-receptor blockade and like conventional neuroleptics, it also binds to D_2 receptors but, unlike conventional neuroleptics, risperidone has a high binding affinity for serotonin $5HT_2$ receptors *(Tarazi et al., 2002 & Tauscher et al., 2002).*

Based on these properties, many hypotheses have been formulated for the mechanisms of clinical action of risperidone. One of these hypotheses is the hypothesis of blockade of dopamine D_2 receptors which explains the reduction of positive symptoms of schizophrenia. Another hypothesis of blockade of serotonin 5-HT_2 receptors that increases the dopamine concentration in the nigrostriatal system, thereby reducing the risk of extrapyramidal symptoms (EPS) *(Yamada et al., 2002).*

Pharmacological actions of risperidone

Risperidone was consistently effective in the treatment of patients with schizophrenia and ameliorated both positive (by blocking the postsynaptic dopaminergic receptors and blockade of mesolimbic and mesocortical pathways) and negative symptoms (due to 5-HT receptor antagonism and enhanced frontal lobe function). The beneficial effects of risperidone were apparent during the first few weeks of treatment and were maintained throughout the short-term and long-term trials *(Aloa et al., 2002 & Chaudhry et al., 2002).*

Recent brain studies demonstrated that risperidone therapy is associated with a greater decrease in the regional cerebral blood flow (rCBF) in cerebellum bilaterally compared to haloperidol *(Miller et al., 2001).*

Dose of risperidone

Risperidone in a dose of 4, 6 and 8 mg per day provide the optimal antipsychotic efficacy and have a low risk of extrapyramidal side effects *(Liu et al., 2003)*.

In order to avoid the risk of hypotension, the dose should be increased gradually. Treatment should start with 1 mg bid, increasing the dose to 2 mg bid per day, and 3 mg bid is the third step per day. Thereafter, the dose may be optimized individually if required. The maximum dose is 16 mg per day *(Liu et al., 2003)*.

Indications

Risperidone is indicated for treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and / or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperidone also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia *(Love and Nelson, 2000)*.

Adverse effects

Risperidone is generally well tolerated and in many instances, it has been difficult to differentiate adverse from symptoms of the underlying disease *(Yamada et al., 2002)*.

The common side effects of risperidone include insomnia, agitation, anxiety and headache. Less common side effects are fatigue,

dizziness, impaired concentration, constipation, dyspepsia, nausea/ vomiting, abdominal pain, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, urinary incontinence, rhinitis, rash and other allergic reactions (***Conlon et al., 2002).***

Risperidone has a lower propensity to induce extrapyramidal side effects than classical neuroleptics. However, in some cases some extrapyramidal symptoms may occur which include tremor, rigidity, hypersalivation, bradykinesia, akathesia, and acute dystonia ***(Tauscher et al., 2002).***

These symptoms are usually mild and reversible upon dose reduction and/ or administration of Antiparkinsonian drugs, if necessary ***(Tauscher et al., 2002).***

Occasionally, orthostatic dizziness, orthostatic hypotension and reflex tachycardia have been observed following administration of risperidone, particularly with higher initial doses. Orthostatic hypotension can occur due to α-blocking activity of risperidone especially during initial period of treatment. So, risperidone should be used with caution in patients with known cardiovascular disease as heart failure, myocardial infarction, dehydration, hypovolemaemia or cerebrovascular disease. The dose should be gradually increased. A dose reduction should be considered if hypotension occurred (***Himstreet and Daya, 1998).***

Risperidone can increase plasma prolactin concentration. Possible associated manifestations are galactorrhoea, gynaecomastia, disturbances of the menstrual-cycle and amenorrhea ***(Kinon et al., 2003).***

Weight gain, edema and increased hepatic enzyme levels have been observed during treatment with risperidone *(Ravasia, 2001 & Bobes et al., 2003).*

some side effects have occasionally been reported in psychotic patients in the form of water intoxication due to either polydipsia or the syndrome of inappropriate secretion of antidiuretic hormone ADH, tardive dyskinesia, neuroleptic malignant syndrome, body temperature dysregulation and seizures *(Kruse et al., 2001;Yamada et al., 2002 & Brevik and Farver, 2003).*

Overdosage and toxicity:

The symptoms of risperidone overdose are drowsiness, sedation, tachycardia, hypotension and extrapyramidal side effects. Overdosages up to 360 mg have been reported. The available evidence suggests a wide safety margin *(Acri and Henreting, 1998).*

In a patient with concomitant hypokalaemia who had ingested 360 mg, a prolonged QT interval was reported *(Acri and Henreting, 1998).*

Drug interactions:

Drugs that inhibit cytochrome P4502D enzyme (CYP4502D6) or stimulate or inhibit CYP3A4 enzyme may alter risperidone plasma concentration *(Prior and Baker, 2003).*

Given the primary CNS effects of risperidone, it should be used with caution in combination with other centrally acting drugs. Risperidone may antagonize the effect of levodopa and other dopamine agonists. Carbamazepine has been shown to decrease the plasma levels of

the active antipsychotic fraction of risperidone ***(DeVane and Nemeroff, 2000).***

Similar effects may be observed with other hepatic enzyme inducers. On discontinuation of carbamazepine or other enzyme inducers, the dose of risperidone should be re-evaluated and if necessary decreased ***(DeVane and Nemeroff, 2000).***

Phenothiazines, tricyclic antidepressants and some B-blockers may increase the plasma concentrations of risperidone but not those of the antipsychotic fraction. When risperidone is taken together with other highly protein-bound drugs, there is no clinically relevant displacement of either drugs from the plasma proteins ***(Mula and Monaco, 2002).***

Teratogenicity :

The safety of risperidone for use during human pregnancy has not been established. Although, in experimental animals, risperidone did not show direct reproductive toxicity, some indirect prolactin and CNS-mediated effects were observed ***(Rosengarten and Quartermain, 2002).***

No teratogenic effect of risperidone was noted in any study. Therefore, risperidone should only be used during pregnancy if the benefits outweigh the risks ***(Ratnayake and Libretto, 2002).***

It is not known whether risperidone is excreted in human milk. In animal studies, risperidone and 9-hydroxy-risperidone are excreted in milk. Therefore, women receiving risperidone should not breast-feed ***(Hill et al, 2000).***

Effects on driving ability and use of machinery:

Risperidone may interfere with activities requiring mental alertness therefore, patients should be advised not to drive or operate machines until their individual susceptibility is known ***(Peuskens, 1995).***