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# An Overview of Schizophrenia

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**Schizophrenia is a major psychiatric disorder, characterized by disturbances in thought, mood and behaviour. It affects about 1% of the world's population. The clinical features of schizophrenia overlap with other psychiatric disorders and their diagnosis remains difficult. Although its etiology remains unclear, a good deal of risk factors which develop schizophrenia is known. The typical and atypical antipsychotics used in the management of schizophrenia produce various adverse effects which affect almost all the systems of the body and produce extra pyramidal symptoms such as dystonia, akathisia, pseudoparkinsonism, tardive dyskinesia and neuroleptic malignant syndrome causing misery to the patients throughout life time. Research is being carried to study the effectiveness of herbal antipsychotic drugs in schizophrenia, which are expected to be devoid of side effects. Developing a potent neuroleptic with minimum or no side effects will be a major breakthrough in the treatment of schizophrenia. This article attempts to touch on some of the important recent developments in the understanding of schizophrenia.**

Schizophrenia is one of the most complex and challenging of psychiatric disorders. It is the paradigmatic illness of psychiatry. It represents a heterogeneous syndrome of disorganized and bizarre thoughts, delusions, hallucinations, inappropriate affect and impaired psychosocial functioning[1]. The expression of these symptoms varies across patients and overtime, but the cumulative effect of the illness is always severe and usually long lasting. It is one of the two major mental illnesses affecting the young and middle-aged adult today[2]. A measure of the severity[3] of the illness is the cost in treating schizophrenia[4]. Schizophrenia is appropriately and accurately conceptualized as a disease process. It seems to be more likely that more than one disease entity exists within the clinical syndrome of schizophrenia, with each having a distinguishable etiology and pathophysiology. However, schizophrenia remains for many patients a chronic and debilitating disorder[5].

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## HISTORICAL BACKGROUND

Written descriptions of symptoms commonly observed today in patients with schizophrenia are found throughout recorded history[6]. Early Greek physicians[7] described delusions of grandeur, paranoia and deterioration in cognitive functions and personality. Although earlier descriptions of schizophrenia like illness are recorded in literature[8], the study of the disorder began in 1896, with the description by Emil Kraepelin, a German psychiatrist, who coined the term dementia praecox[9], in which he recognized the characteristic features of illness, e.g., delusions, hallucinations, disturbances of affect and motor disturbances[10].

In 1911, Eugene Bleuler, a Swiss physician recognized that this disorder was due to a splitting of mind and renamed dementia praecox as schizophrenia (splitting of mind). He introduced the concepts of 1st degree and 2nd degree schizophrenic symptoms. He identified association loosening (thought disorder), affective incongruity (blunting of emotion), autism (withdrawal from reality), ambivalence (marked inability to decide) as specific fundamental symptoms of

schizophrenia[11,12]. In 1959, Kurt Schneider defined a number of symptoms called first rank symptoms (FRS or SFRS) to be of first rank importance in making the diagnosis of schizophrenia. They are categorized into delusional perception, hallucination, thought alienation phenomena and passivity phenomena[13].

## EPIDEMIOLOGY

Schizophrenia is a leading public health problem that leads to enormous personal and economic costs world wide. It affects just under 1% of the world's population (approximately 0.85%, WHO report)[14]. The onset of schizophrenia occurs before adolescence or after the age of forty. The onset of illness tends to be earlier in males (15-24 y) than females (25-34 y)[15]. Reports by Jablenski[16,17] indicated that the prevalence rate of the disorder is between a low of about 1 per 1000 and a high of 10 per 1000. The morbidity risk of schizophrenia in the general population is estimated to be 1%.

## ETIOLOGY

The etiological process or processes by which a causal agent creates the pathophysiology of schizophrenia is not yet known. However, a good deal is known about the risk factors for developing schizophrenia which leads to direct inferences regarding possible etiopathophysiologies[18]. The principal hypotheses regarding causation include genetic factors[19], environmental[20] neuroimmunovirological factors[21,22] and birth and pregnancy[23] complications such as hypoxic and neurotoxic damage[24,25]. The genetic influence in the development of schizophrenia is supported by the findings of family, twin and adoption studies[26]. The lifetime incidence of schizophrenia in the general population is about 1.5% but is 13.5% in the first degree relatives of schizophrenic patients indicating the risk to biological relatives[27]. In a US study, the incidence of schizophrenia was compared in children born to 47 schizophrenic mothers with that of children born to psychiatrically well mothers. Five of the children born to schizophrenic mothers developed schizophrenia, but none of the children of non-schizophrenic mothers did so[28]. In a Danish study, the research workers started with individuals who had been adopted and develcped schizophrenia. They found that 20% of 118 biological parents also had schizophrenia, compared with only 6% of 224 adoptive parents of schizophrenic patients which was the same rate as in parents of control adoptees[29].

Family based epidemiological studies clearly demonstrate that environmental factors such as stressful life events, emotional aspects play a role in the pathophysiology of schizophrenia[30]. In a matched case control study of 100 schizophrenics between age of 18 and 64 in London, it was evidenced that socio-environmental factors such as unemployment and stress account for the pathogenesis[31]. It is widely accepted that there is an association between obstetric complications and the later development of schizophrenia[23]. Infants born with a history of foetal dysfunction and hypoxic damage in the brain are at increased risk for developing schizophrenia[32]. Zornberg *et al.*[33] studied 693 adults born between 1959 and 1966 and followed up for an average of 19 years. Their experience of fetal and neonatal complications had been recorded at the time of their birth. Hypoxic ischemia related complications predicted a doubling of the risk of psychosis, especially schizophrenia.

McNeil *et al.*[34] found that pregnancy and delivery complications among monozygotic twin pairs were more common among those discordant for schizophrenia than among those concordant for schizophrenia. Further, among monozygotic twins discordant for schizophrenia, pregnancy and delivery complications were more likely to involve the twin with schizophrenia than the co-twin without schizophrenia[35]. In a pair of monozygotic twins discordant for schizophrenia, magnetic resonance imaging (MRI) revealed high intensity signals in the white matter and enlarged ventricles in the affected twin, while no such abnormality was detected in the normal twin. Marked differences in sociability and intelligence were observed between the twins from childhood. This twin pair suggests a possibility that hypoxic brain damage associated with prenatal development may be a causal factor for abnormalities in psychosocial development and subsequent schizophrenia[36].

The idea that schizophrenia is caused by a virus is consistent with epidemiologic and clinical observations[37]. Several indices of heightened immune system responsiveness are apparent in schizophrenia patients, including elevations in herpes antibody titre, immumoglobulins, cytomegalovirus antibody titre, interleukin-2 receptors, alpha interferon and auto antibodies have been reported[38-40]. Mednick *et al.*[41] reported those exposed to the influenza epidemic of 1957 during their second trimester of development were at risk for subsequent schizophrenia[37]. Takei *et al.*[42] found that female subjects exposed to influenza epidemics, five months prior to birth had an increased rate of schizophrenia in adulthood. Sham *et al.*[43] found a link between schizophrenia and maternal influenza but suggested that it would account for less than

2% of schizophrenia cases.

## CLINICAL TYPES AND DIAGNOSTIC CRITERIA FOR SCHIZOPHRENIA

According to International Statistical Classification of Diseases and Related Health Problems, tenth division, (ICD-10), WHO, Geneva, 1992[44], schizophrenia can be classified into paranoid, hebephrenic, catatonic, undifferentiated, residual, post schizophrenic depression, simple schizophrenia and other schizophrenia, schizophrenia unspecified. The history of the diagnosis of schizophrenia is often misunderstood, which has lead to erroneous conclusions about the validity of the diagnostic process[45]. Throughout most of the twentieth century, there have been international differences among the diagnosticians throughout the world, in the recognition of the typical cases of schizophrenia[46].

The diagnosis of schizophrenia is more difficult because symptoms of schizophrenia can be similar at times to other major brain disorders such as bipolar disorder or even depression[47]. Like many mental illness, the diagnosis of schizophrenia is based upon the behaviour of the person, who is being assessed[48]. There are lists of diagnostic criteria which must be met for a person to be diagnosed as having the condition[49]. This depend both on the presence of certain signs and symptoms as well as their duration. The diagnostic instruments of schizophrenia include standardized diagnostic criteria, structured interviews and psychiatric rating scales[50]. The ICD-10 diagnostic criteria published by WHO and diagnostic and statistical manual of mental disorders (DSM-IV), fourth edition, American Psychiatric Association are the two main types of diagnostic criteria which provide characteristic signs and symptoms of schizophrenia and its subtypes[51]. The structured interview such as present state examination (PSE)[52], composite international diagnostic interview (CIDI)[53] schedule for affective disorders and schizophrenia (SADS)[54], diagnostic interview schedule (DIS)[55] and comprehensive assessment of symptoms and history (CASH)[56] are designed to provide comprehensive information base concerning past psychopathology and functioning relevant to evaluation of diagnosis, prognosis, overall severity of illness, current episode, level of severity for the symptomatological assessment of the psychiatric illness[57,58].

Although the structured interviews and diagnostic criteria are used to make diagnosis to identify broad range of symptoms in patients, rating scales are usually be used in order to measure changes in clinical status overtime[59]. The brief psychiatric rating scale (BPRS), which is the prototype of rating scale, contains scales for rating different symptoms such as conceptual disorganization, blunted affect, emotional withdrawal, distorted thinking, depressed mood and psychic anxiety[60]. The scale for assessment of thought, language and communication, (TLC) was developed to evaluate formal thought disorder in schizophrenia[61]. The scale for assessment of negative symptoms (SANS) was developed in order to provide a comprehensive method for evaluating negative symptoms and the scale for assessment of positive symptoms (PANS) for assessing the positive symptoms for schizophrenia[62]. The scale for emotional blunting (SEB) is another scale developed to rate abnormality in affect[63].

## CLINICAL FEATURES

Schizophrenia is characterized by disturbances in thought and verbal behaviour, perception, affect, motor behaviour and relationship to the external world. The diagnosis is entirely clinical and is based on the following clinical features, none of which are pathognomonic alone[64,65]. The clinical features are thought and speech disorders (autistic thinking, loosening of associations, thought blocking, neologisms, mutism, poverty of speech, echolalia, perseveration, verbigeration, delusions and ambivalence), disorders of perception (auditory and visual hallucinations), disorders of affect (apathy, emotional blunting and anhedonia), disorders of motor behaviour (either decrease or increase in psychomotor activity) and negative symptoms which include alogia, affective flattening, inattentiveness, anhedonia and avolition-apathy[10]. Delusions, hallucinations and thought disorder are called positive symptoms because these phenomenas are not present in normal individuals[66].

## NEUROCHEMICAL BASIS FOR SCHIZOPHRENIA

The major investigations of neurochemical basis for schizophrenia have focused on the deficiency in monoamine oxidase (MAO) activity, impairment of noradrenergic function (NA), impairment of neuroactive peptide systems, impairment of gamma-amino butyric acid (GABA) system function, impairment of serotonergic function, excessive dopaminergic function and impairment of excitatory amino acid systems[67-69]. The most widely replicated biochemical finding in schizophrenia has been the low peripheral MAO activity in chronic schizophrenics[70]. A low MAO activity has been found in the examination of platelet MAO activity and amine metabolites in cerebrospinal fluid (CSF) of 22 schizophrenia patiets[71]. Owen *et al.*[72] reported decrease in MAO activities in seven regions of post

mortem brains from 39 patients with schizophrenia and 44 control subjects. Stein *et al.*[73] postulated that a degeneration of the cortical noradrenergic system could account for the lack of goal directed behaviour observed in schizophrenics. They strengthened this hypothesis by reporting a significant reduction in the activity of dopamine beta hydroxylase (DBH) activity in post mortem brain samples from schizophrenics. Hartmann *et al.*[74] elaborated on the hypothesis of Stein and Wise by suggesting that a deficit in cortical DBH activity could lead to an increased concentration of dopamine and a decreased concentration of NA in cortical region and that this imbalance in dopamine and NA may be involved in the pathogenesis of schizophrenia.

However, the evidence for a central noradrenergic deficit in schizophrenics is not strong. Cross *et al.*[75] assessed DBH activity in 6 brain regions from 12 control and 12 schizophrenics and reported no significant difference in DBH activity between controls and schizophrenics in any brain region. There have been several attempts to assess central noradrenergic function in schizophrenia using peripheral body fluids and tissues such as plasma serum and lymphocytes. The results, in general have been equivocal and often of dubious relevance to control noradrenergic function[76].

The role of neuropeptides in schizophrenia, abnormal metabolism of brain opioids, and possibility of altered levels has been extensively studied. Terenius *et al.*[77] from Sweden reported an increase in endogenous opioid peptide concentration in CSF of schizophrenia patients. Lindstorm *et al.*[78] investigated schizophrenics and reported two of nine chronic schizophrenia patients, four of six acute schizophrenia patients had elevated CSF fraction of the neuro peptide. However, Naber *et al.*[79] reported significant reduction in CSF opioid activity using a radioreceptor assay in male schizophrenics. This proposal of schizophrenia may be associated with an activity of opioid system has also proved difficult to substantiate clinically. The administration of beta endorphins to schizophrenics has proved inconclusive results[80]. Roberts[81] postulated the reduction of GABA in schizophrenics and suggested that it could be readily verified by measuring the activity of glutamate decarboxylase (GAD), the enzyme that catalases the decarboxylation of glutamate to form GABA and is marker for GABA-ergic neurons.

Subsequently, Bird *et al.*[82] reported significant reduction in GAD activity in postmortem brain samples from schizophrenics. The CSF level of 87 subjects, 29 normal control subjects, 11 patients with schizophrenia, 26 with depression, 6 with mania and 15 with anorexia nervosa was examined and findings suggested lower GABA level[83]. However, Cross *et al.*[84] found the concentrations of GABA in the brain regions to be similar in control and schizophrenics. Pharmacological evidence does not support a significant reduction in GABA-ergic function in schizophrenia. Administration of GABA agonists such as baclofen[85] and muscimol does not ameliorate the symptoms[86].

Reduced plasma concentration of tryptophan, the precursor of 5-hydroxy tryptamine (5-HT), have been reported in acute schizophrenics, but the therapeutic effectiveness of administered oral doses of tryptophan, to correct this apparent deficit, has produced equivocal results[87]. A direct investigation of central 5-HT metabolism in schizophrenics was carried out by Joseph *et al.*[88], who measured the concentration of 5-HT, 5-hydroxy indole acetic acid (5-HIAA) and their precursor tryptophan, in three regions of post mortem brain tissue from 23 controls and 15 schizophrenics, reported that there was no generalized change in 5-HT metabolism in the brain of schizophrenics[89]. Investigations of the concentration of homovanillic acid (HVA-the major end product of dopamine metabolism) in the CSF revealed higher levels of HVA in schizophrenics with family history of schizophrenia[89]. Dopamine receptors have been studied extensively in the brain of schizophrenics, and in general there is a consensus that D2 receptors are at increase in the basal ganglia[90]. Post-mortem studies of dopamine receptors in 15 schizophrenic brains and 15 control brains revealed elevated D2 receptor densities in schizophrenic brains[91].

Post mortem studies in patients with schizophrenia have revealed variety of abnormalities in glutamate transmission. For example, an increased cortical expression of N-methyl-D-aspartate (NMDA) receptor units and glutamate reuptake if frontal cortex, decreased cortical glutamate release and altered concentration of glutamate in schizophrenics are evidenced[92] In contrast, lateralized changes in glutamate uptake sites have also been observed in other brain regions including the amygdala[93].

## MANAGEMENT OF SCHIZOPHRENIA

Schizophrenia can be managed by pharmacological intervention, electroconvulsive therapy (ECT), psychosocial treatments like psycho education, group psychotherapy, individual psychotherapy, family therapy and psychosocial psychotherapy[94,95]. Electroconvulsive therapy involves the

induction of a seizure for therapeutic purposes by the administration of a variable frequency electrical stimulus shock via electrodes applied to the scalp. The effects of its use in people with schizophrenia are unclear[96]. Studies of ECT in acute schizophrenia are effective as antipsychotic drugs, while in chronic schizophrenia, it is less promising[97]. ECT can be tried in patients whose response is poor with antipsychotic drugs[98]. Antipsychotic medications should be administered during and following ECT treatment[99]. Patients should first receive the trials of antipsychotic medications and if these medications are ineffective, acutely ill patients can be treated with ECT. Thus, ECT is most offered to persons who have failed to respond to pharmacotherapy, defining a relatively treatment refractory population for ECT[100].

Most psychotherapy, by themselves, has not been shown to be helpful for treating schizophrenia. Therapies directed at improving family interactions, in conjunction with ongoing medication therapy, however can decrease relapse rate in schizophrenia[101]. Psychoeducation educates the family as well as the patient regarding the nature of illness, its course and treatment, which helps in establishing a good relationship between patient and family[102]. Family therapy is aimed to improve communication, reduce conflict and distress between family members and improve family functioning such as to alleviate the problems that led to the disorder in the identified patient. Several or all of the family members take part in the treatment[103]. Individual psychotherapy is supportive in nature and group psychotherapy is used with the intention of bringing about substantial change in symptoms, identifying personal problems, overcome difficulties in interpersonal relationships or to encourage limited adjustments to specific problems including those of disability physical or mental illness[104]. Other psychosocial therapy includes activity therapy, occupational therapy and psychosocial rehabilitation services[105].

**Pharmacological intervention:**

Prior to 1952, there was no generally applicable, effective pharmacological treatment of schizophrenia[106]. Reserpine (*Rauwolfia serpentina* extract) had been used with some limited success in India by Sen and Bose and electroconvulsive therapy (ECT) was important in reducing symptoms in most acutely disturbed cases[107-109]. Lithium, antidepressants and antianxiety drugs have also been used to treat the symptoms of schizophrenia. However these drugs have not proved to be effective alternative to antipsychotic therapy[110] The discovery of phenothiazine, chlorpromazine, in the early 50's may be the most important single contribution to the treatment of psychiatric illness[111]. Antipsychotics were discovered by Delay and Deniker in 1952 and since their introduction, antipsychotics remain the mainstay of drug treatment of schizophrenia[112] The main therapeutic uses of antipsychotic drugs are to reduce hallucinations, delusions, agitation and psychomotor excitement in schizophrenia[113] and psychosis secondary to a medical condition or mania. The antipsychotic drugs used to treat schizophrenia have a wide variety of mechanism of action, but all share the capacity to occupy postsynaptic dopamine receptors in the brain[114]. Antipsychotic drugs can be categorized into typical antipsychotics or dopamine antagonists and atypical antipsychotics or serotonin-dopamine antagonists[115]. (Table 1)

Dopamine (DA) antagonists appear to reduce psychotic symptoms through inhibition of dopamine-to-dopamine

TABLE 1: ANTIPSYCHOTICS USED IN SCHIZOPHRENIA[116-125]

| Category | Drugs |
|---|---|
| Typical antipsychotics | Chlorpromazine<br>Loxapine<br>Penfluridol<br>Fluphenazine<br>Trifluperidol<br>Triflupromazine<br>Haloperidol<br>Thioridazine<br>Trifluoperazine<br>Pimozide<br>Zuclopenthixol<br>Prochlorperazine<br>Flupenthixol |
| Atypical antipsychotics | Clozapine<br>Olanzapine<br>Risperidone<br>Ziprasidone<br>Quetiapine |
| Depot preparations | Fluphenazine decanoate<br>Haloperidol decanoate<br>Flupenthixol decanoate<br>Zuclopenthixol decanoate<br>Penfluridol<br>Pimozide |

binding receptors. X-ray crystallographic data have demonstrated that the molecular configuration of chlorpromazine is similar to that of dopamine, which may explain its ability to block this neurotransmitter's receptors, preferentially D2 receptor sites[126]. The X-ray structures of different antipsychotic drugs have been examined in detail in an attempt to rationalize their structural activity relationship (SAR) with respect to their ability to block DA receptors in the brain. It was found that antipsychotics are able to block DA receptors because of a conformational complementarity between certain portions of these drugs and dopamine[127]. Serotonin-dopamine antagonists also called as newer, novel or more broadly atypical antipsychotics, which have fewer neurological adverse effects than dopamine antagonists and is effective against positive and negative symptoms of schizophrenia. They differ in having effects related to their ratio of dopamine (D2) and serotonin (5-hydroxy tryptamine, 5-HT2) antagonism[128].

**Mechanism of action of antipsychotic drugs:**

The exact mechanism of action of antipsychotics remains unclear. However it is currently believed that the antipsychotic drugs block dopamine (D2) receptors (antidopaminergic activity) which are mainly present in the mesolimbic system, which accounts for the antipsychotic activity while the blockade of D2 receptors in the extrapyramidal systems accounts for the extrapyramidal side effects[129] The newer or atypical antipsychotics particularly act on 5-HT2 receptors[130]. Typical antipsychotics are effective in treating positive symptoms of schizophrenia whereas atypical drugs are effective in treating both positive and negative symptoms with lesser side effects. Clozapine is effective in the management of treatment resistant schizophrenia[131,132].

Sedation is caused by histaminergic blockade, which is maximum for chlorpromazine. Inhibition of the tuberoinfundibular tract is responsible for the endocrinal side effects whereas blockade of noradrenergic, cholinergic receptors accounts for the various adverse effect profiles seen among the drugs[133-135]. The interaction with non-dopaminergic receptors accounts for cardiotoxic, epileptogenic and anticholinergic side effects[136,137]. (Table 2)

**Depot antipsychotics:**

Since schizophrenic patients are notoriously non compliant with antipsychotic medications, due to various reasons such as lack of insight, adverse effects, discontinuation of medications, often leads to relapse of the disease[146,147]. Long acting (depot) preparations of antipsychotics which are given either intramuscular or administered orally are valuable in such cases. Although reduction in relapse and assured compliance are merits of depot preparations, the demerit is, if side effects (e.g. dystonia, neuroleptic malignant syndrome) develop, it is difficult to alter the dose[148].

**Alternate pathways of drug development:**

Phencyclidine (PCP), an antagonist at NMDA subclass of the glutamate receptor complex, can induce both positive and negative symptoms of schizophrenia[149]. This observation has led to the proposal of a glutaminergic deficiency in the pathophysiology of schizophrenia suggesting that

TABLE 2: ADVERSE EFFECTS OF ANTIPSYCHOTICS[138-145]

| System affected | Adverse effects |
|---|---|
| Autonomic nervous system | Dry mouth, constipation, cycloplegia, mydriasis, urinary retention, postural hypotension, impaired ejaculation, ventricular fibrillation and impotence. |
| Extrapyramidal systems | Pseudo parkinsonism, acute dystonia, akathisia, tardive dyskinesia, rabbit syndrome (peri-oral tremor) and neuroleptic malignant syndrome. |
| Metabolic/Endocrinal side effects | Weight gain, galactor-rhoea, gynaecomastia and hypothermia |
| Central nervous system | Seizures, sedation and pseudo depression. |
| Allergic side effects | Cholestatic jaundice and agranulocytosis. |
| Dematological side effects | Contact dermatitis, photosensitivity reac-tions and hyper pigmen-tation. |

glutaminergic drugs might have therapeutic potential in schizophrenia[150]. Disturbances of NMDA receptor mediated glutaminergic transmission may play an important role in the pathophysiology of schizophrenia[151]. The NMDA receptor has a number of binding sites for glutamate, glycine and the polyamine, spermidine. The glycine modulatory site has become the target for drug development. Increasing NMDA transmission by increasing glycine binding has been hypothesized to reduce symptoms of schizophrenia[152]. Several studies using glycine site modulators including glycine, d-serine and cycloserine have shown effectiveness in small scale clinical trials[153]. However, a major difficulty with increasing NMDA neurotransmission is its narrow range of physiological responsivity. If NMDA stimulation is too high, seizures or neurotoxicity can develop[154,155].

The presynaptic dopamine receptors in the prefrontal and cingulate cortex of the dopamine nerve terminals have been reported to inhibit dopamine synthesis and regulate dopamine release and neuronal firing[156]. Neuroleptics produce supersensitivity of presynaptic inhibitory dopamine receptors, which would result in decreased dopamine release[157]. The concept of presynaptic receptor for dopamine that monitors its release by feedback inhibition offers an appealing method for reducing dopaminergic activity[158]. This indicates that there is a potential for clinical use of dopamine agonists at presynaptic receptors as therapeutic agents in schizophrenia. Aripiprazole, a presynaptic dopamine receptor agonist, was found to be effective in positive and negative symptoms with fewer neurological side effects[159]. However, clinical evidence supporting an antischizophrenic effect related to presynaptic receptor stimulation is far from conclusive, ranging from transient improvement in some patients to absolutely no effects. Levodopa, in small doses and bromocriptine in substantial doses, has been used to treat schizophrenia with unimpressive results[160,161]. Although presynaptic DA receptor agonists may be efficacious in the treatment of schizophrenia, they might also potentially increase the risk for exacerbation of psychosis through stimulation of postsynaptic dopaminergic receptors[162].

Alteration in dopamine (DA) and/or cholecystokinin (CCK) transmission in the CNS may be of relevance for schizophrenia, since CCK and dopamine coexist within mesolimbic and mesocortical dopaminergic neurons[163]. This has focused interest on the possible role of CCK in schizophrenia. Several lines of research, indicate a CCK deficit in schizophrenic patients[164,65], and the administration of CCK to schizophrenics appears to have therapeutic implications[166]. Two types of CCK receptors have been identified as CCKA and CCKB, of which CCKB predominates the brain[167]. The administration of CCK-B agonists to rodents resulted in behavioral effects analogous to those of antipsychotic drugs[168]. Matto *et al.*[169] suggested that CCK tetrapeptide, a CCKB receptor agonist in rat diminishes rat exploratory behaviour in the free exploration paradigm. Based on human studies of altered CCK levels in schizophrenia, initial open studies suggested antipsychotic activity following systemic administration of the CCK analogue caerulin[170]. However, controlled, double-blind crossover studies showed no significant effect with systematically administered caerulin[171].

*Unmada* (schizophrenia) is the most elaborately discussed *manasavyadhi* (mental disorders) in ayurveda. Various herbal drugs have been mentioned in ancient ayurvedic literatures for the management of unmada[172]. Some of the clinical studies are reviewed here. Fozedar[173], used the indigenous drug *Acorus calamus* in 75 schizophrenic patients and reported 7 patients showed improvement over 75% and 9 patients showed improvement over 50%. Ramu *et al.*[174] carried out a pilot study using *brahmyadiyoga*, a herbal compound consisting *Centella asiatica, Acorus calamus, Rauwolfia serpentina, Saussurea lappa, Nymphoides macrospermum* and *Nardostachys jatamansi* in 14 patients suffering from chronic schizophrenia and reported improvement in 7 out of 10 patients who completed the course. Dash *et al.*[175] in a preliminary study used a compound formulation of five potent drugs, *Convolvulus pluricaulis, Nardostachys jatamansi, Bacopa monnieri, Withania somnifera, Acorus calamus*, to evaluate its clinical efficacy in patients suffering from *unmada*. The patients were treated for a period of 6 weeks and observed a notable shift of grades of psychotic symptoms and the trial indicated the effectiveness of the compound in *unmada*. Kale[176] used siledin, an herbal compound formulation in 112 schizophrenic patients and reported improvement rate of 59.9% with no serious side effects. There is a need to take up further studies to assess the relative efficacy of various compound preparations as well as individual drugs. Modern drugs are already known to have neurotoxic side effects, especially movement disorders. If herbal drugs are demonstrated to be free from such adverse effects even on long term use, it may open newer vistas in psychopharmacology.

## CONCLUSIONS

The explosion of interest in biological aspects of schizophrenia in recent years has led to an improvement in

the understanding of the disease process. Traditional antipsychotics were truly breakthrough medications and were the main stay in the treatment of schizophrenia. The introduction of second generation (atypical) antipsychotics has brought an improvement in treatment options. However, the limitations of these drugs were rapidly recognized. Depot preparations have their own demerits. However schizophrenia remains for many patients a chronic and debilitating disorder. Developing an antipsychotic drug with maximum benefits and minimum or no effects on extrapyramidal systems, will be a major break through in the management of schizophrenia.


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## REFERENCES


1. John, M., Clellan, M. and John, S.W., **Psych. Clin. N. Amer.,** 1992, 15, 131.
2. Peter, N.V. and Rene, S.K., **Schizophrenia Bull.,** 1999, 25, 741.
3. Karki, S.D., Bellnier, T.J., Patil, K. and Oretaga, T., **Drug Ben. Trends,** 2001, 13, 7.
4. Mark, O., **J. Nerv. Mental Dis.,** 1985, 183, 421.
5. Girish, K., **Indian J. Psychiat.,** 1999, 41, 100.
6. Combs, J.S., **Psych. Serv.,** 2000, 51, 525.
7. Andreasen, N.C., **Arch. Gen. Psychiat.,** 1990, 47, 615.
8. William, T.C., **Schizophrenia Bull.,** 1987, 13, 1.
9. Robert, W.B. and William, T.C., In; Benjamin, J.S. and Virginia, A.S., Eds., Kaplan and Saddock's Comprehensive Textbook of Psychiatry, 7th Edn., Vol. I, Lippincott Williams and Wilkins, Philadelphia, 2000, 1096.
10. Niraj, A., In; A Short Textbook of Psychiatry, 5th Edn., Jaypee Brothers, New Delhi, 2002, 55.
11. Robert, I.C. and Jerome J.H., In; Student Psychiatry Today: A Comprehensive Textbook, 2nd Edn., Butterworth Heinemann, London, 1995, 126.
12. Michael, G., Dennis, G., Richard, M. and Philip, C., In; Oxford Textbook of Psychiatry, 3rd Edn., Oxford University Press, Oxford, 1996, 246.
13. Kenna, P.J., In; Schizophrenia and Related Syndromes, Psychology Press, Cambridge, 1993, 11.
14. Warner, R. and Girolamo, G., In; Epidemiology of Mental Disorders and Psychosocial Problems: Schizophrenia, WHO, Geneva, 1995, 2.
15. Carpenter, W.T. and Buchanan, R.W., **N. Engl. J. Med.,** 1994, 330, 681.
16. Jablenski, A. and Sartorius, N., **Psychol. Med.,** 1975, 5, 113.
17. Jablenski, A., **Schizophr. Res.,** 1997, 28, 111.
18. Gottesman, I. and Moldin, S., **Clin. Genet.,** 1997, 52, 404.
19. Bradbury, T.N. and Miller, G.A., **Psychiat. Bull.,** 1985, 98, 569.
20. Norman, R.M. and Malla, A.K., **Brit. J. Psychiat.,** 1993, 161, 162.
21. Adams, W. and Kendell, R.E., **Brit. J. Psychiat.,** 1993, 163, 522.
22. Yolken, R.H., **Brain Res. Rev.,** 2000, 31, 193.
23. Geddes, J.R. and Lawrie, S.M., **Brit. J. Psychiat.,** 1995, 167, 786.
24. Seeman, M.V., **Meds. Wom. Health,** 2000, 5, 21.
25. Jones, P.B., Rantakallio, P. and Hartikainen, A., **Amer. J. Psychiat.,** 1998, 155, 355.
26. Kendler, K.S. and Robinette, C.D., **Amer. J. Psychiat.,** 1983, 140, 1551.
27. Kendler, K.S. and Greunberg, A.M., **Arch. Gen. Psychiat.,** 1984, 41, 982.
28. Heston, L.L., **Brit. J. Psychiat.,** 1996, 122, 819.
29. Kety, S.S. and Rosenthal, D., **Behav. Genet.,** 1976, 6, 219.
30. Freeman, H., **Brit. J. Psychiat.,** 1994, 164, 39.
31. Mallet, R., Leff, J., Bhugra, D., Pang, D. and Zhao, J.H., **Soc. Psych. Psych. Epidemiol.,** 2002, 37, 399.
32. Lewis, S.W., Harvey, I., Ron, M., Murray, R. and Reveley, A., **Brit. J. Psychiat.,** 1990, 157, 600.
33. Zornberg, G.L., Buka, S.L. and Tsuang, M.T., **Amer. J. Psychiat.,** 2000, 157, 196.
34. Mc Neil, T.F., Cantor Graae, E., Torrey, E.F., Sjostrom, K, Bowler, A. and Taylor, E., **Acta. Psychiat. Scand.,** 1994, 89, 196.
35. Callaghan, E., Larkin, C., Kinsella, A. and Waddington, J.L., **Brit. J. Psychiat.,** 1990, 157, 578.
36. Kunugi, H., Urushibara, T., Murray, R.M., Nanko, S. and Hirose, T., **Psych. Clin. Neurosci.,** 2003, 57, 271.
37. McGrath, J. and Castle, D., **Aust. N. Z. J. Psychiat.,** 1995, 29, 23.
38. Kaufmann, C.A., Weinberger, Yolken, R.H., Torrey, E.F. and Potkin, S.F., **Lancet,** 1983, 2, 1136.
39. Kirch, D.G., Kaurmann, C.A., Papadopoulous, N.M., Martin, B. and Weinberger, D.R., **Biol. Psychiat.,** 1985, 20, 1039.
40. Rapoport, M.H., McAllister, C.G., Pickar, D., Nelson, D.L. and Paul, S.M., **Arch. Gen. Psychiat.,** 1989, 46, 291.
41. Mednick, S.A., Machon, R.A., Huttunen, M.O. and Bonett, D., **Arch. Gen. Psychiat.,** 1988, 45, 189.
42. Takei, N., Sham, P., Callaghan, E., Murray, G.K., Hare, E.H., Glover, G. and Murray, R.M, **Amer. J. Psychiat.,** 1994, 151, 117.
43. Sham, P.C., Callaghan, E., Takei, N., Murray, G.K., Hare, E.H. and Murray, R.M., **Brit. J. Psychiat.,** 1992, 160, 461.
44. The ICD-10 Classification of Mental and Behavioral Disorders, WHO, Geneva, 1993, 11.
45. Tsuang, M.T., Stone, W.S. and Farone, S.V., **Amer. J. Psychiat.,** 2000, 157, 1041.
46. Verdoux, H. and Van, H., **J. Schiz. Res.,** 54, 12, 59.
47. Carpenter, W.T., **Amer. J. Psychiat.,** 1976, 133, 172.
48. Kirkby, K.C., Hay, D.A., Daniels, B.A., Jones, E.H. and Mowry, B.J., **Aust. N. Z. J. Psychiat.,** 1998, 32, 410.
49. Wing, J.K., Babor, T. and Brugha, T., **Arch. Gen. Psychiat.,** 1990, 47, 589.
50. Andreasen, N.C. and Flaum, M., **Schizophrenia Bull.,** 1991,

17, 29.
51. Brockington, I.F., Wainwright, S. and Kendell, R.E., **Psychol. Med.**, 1979, 9, 91.
52. Tress, K.H., Bellenis, C., Brownlow, J.M., Livingston, G. and Leff, J.P., **Brit. J. Psychiat.**, 1987, 150, 201.
53. Lutzhoft, J.H., Skadhede, S., Fatkenheuer, B., Hafner, H., Loffler, W., Rossler, A. and Maurer, K., **Psychopathol.**, 1995, 28, 131.
54. Endicott, J. and Spitzer, R.L., **Arch. Gen. Psychiat.**, 1978, 35, 837.
55. Grzesiak, M. and Kiejna, A., **Psych. Pol.**, 1999, 33, 519.
56. Andreasen, N.C. and Flaum, M.A., **Arch. Gen. Psychiat.**, 1992, 49, 615.
57. Miller, P.R., Dasher, R., Collins, R., Griffiths, P. and Brown, F., **Psychiat. Res.**, 2001, 105, 255.
58. Kirkby, K.C., Hay, D.A., Daniels, B.A., Jones, I.H. and Mowry, B.J., **Aust. N. Z. J. Psychiat.**, 1998, 32, 410.
59. Harvey, P.D., Lenzenweger, M.F., Keefe, R.S., Pogge, D.L., Serper, M.R. and Mohs, R.C., **Psychiat. Res.**, 1992, 44, 141.
60. Lachar, D., Bailley, S.E., Rhoades, H.M., Espadas, A., Aponte, M., Cowan, K.A., Gummattira, P., Kopecky, C.R. and Wassef, A., **Psychol. Assess.**, 2001, 13, 384.
61. Andreasen, N.C., **Arch. Gen. Psychiat.**, 1979, 36, 131.
62. Andreasen, N.C., **Arch. Gen. Psychiat.**, 1982, 39, 784.
63. Abrams, R. and Taylor, M A., **Amer. J. Psychiat.**, 1976, 135, 226.
64. Andreasen, N.C. and Alliger, R., **Arch. Gen. Psychiat.**, 1995, 52, 341.
65. Andreasen, N.C., **Arch. Gen. Psychiat.**, 1990, 47, 615.
66. Crow, T.J., **Brit. Med. J.**, 1980, 137, 280.
67. Paul, L.M., Robert, A.M. and George, R.B., Eds., In; Priniciples of Pharmacology: Basic Concepts and Clinical Applications, 1st Edn., Chapman and Hall, New York, 1995, 289.
68. Joseph, T.D., Robert, L.T., Gary, C.Y., Gary, R.M., Barbara, G.W. and Michael L.P., Eds., In; Pharmacotherapy: A pathophysiologic Approach, 3rd Edn., Appleton and Lange, Connecticut, 1996, 1293.
69. Brown, R. and Colter, N., **Arch. Gen. Psychiat.**, 1986, 43, 36.
70. Buchsbaum, M.S., Coursey, R.D. and Murphy, D.L., **Schizophr. Bull.**, 1980, 6, 375.
71. Kammen, D.P.V., Marder, S.R., Murphy, D.L. and Bynney, W.E., **Amer. J. Psychiat.**, 1998, 135, 567.
72. Owen, F., Crow T.J. and Frith, C.D., **Brit. J. Psychiat.**, 1983, 151, 514.
73. Stein, L., Wise, C.D. and Baden, M.M., **J. Psychiat. Res.**, 1981, 11, 185.
74. Hartmann, E. and Keller, M., **Lancet**, 1977, 1, 37.
75. Cross, A.J., Crow, T.J. and Killpack, W.S., **Psychopharmacol.**, 1978, 59, 117.
76. Van Kammen, D.P. and Antelman, S., **Life Sci.**, 1984, 34, 1403.
77. Terenius, L., Wahlstorm, A., Lindstorm, L.H. and Widerlov, E., **Neurosci. Lett.**, 1976, 3, 157.
78. Lindstorm, L.H., Widerlov, E., Gunne, L.M., Whalstorm, A.I. and Terrenius, S.L., **Acta Psych. Scand.**, 1979, 57, 153.
79. Naber, D., Pickar, D. and Post, R.M., **Amer. J. Psychiat.**, 1981, 138, 145.
80. Pickar, D., Davis, G.C. and Schulz, S.G., **Amer. J. Psychiat.**, 1981, 138, 160.
81. Roberts, E., **Res. Prog. Bull.**, 1972, 12, 468.
82. Bird, E.D., Spokes, E.G. and Barnes, J., **Lancet**, 1977, 2, 1157.
83. Gerner, A.H. and Hare, T.A., **Amer. J. Psychiat.**, 1981, 138, 1098.
84. Cross, A.J. and Owen, F., **Biochem. Soc. Trans.**, 1979, 7, 145.
85. Simpson, G.M., Lee, J.H., Shrivastava, R.K. and Branchey, M.M., **Lancet**, 1975, 1, 966.
86. Tamminga, C.A., Crayton, J.W. and Chase, T.N., **Amer. J. Psychiat.**, 1978, 135, 746.
87. Bowers, M.B., **Neuropharmacol.**, 1970, 9, 599.
88. Joseph, M.H., Baker, H.f. and Crow, T.J., **Psychopharmacol.**, 1979, 62, 279.
89. Sedvall, G.C. and Helgodt, B.W., **Arch. Gen. Psychiat.**, 1980, 37, 1113.
90. Owen, F., Crow, T.J., Poulter, M., Cross, A.J., Longden,A. and Riley, G.J., **Lancet**, 1978, 2, 223.
91. Cross, A.J., Crow, T.J., Ferrier, I.N., Johnstone, E.C., McCreadie, R.M., Owen, F., Owen, D.G.C. and Poulter, M., **J. Neural Transm.**, 1983, 18, 265.
92. Harrison, P.J., **Brain**, 1999, 122, 593.
93. Owen, F. and Cross, A.J., In; Kavanagh, D.J., Eds., Schizophrenia: An Overview and Practical Handbook, 1st Edn., Chapman & Hall, London, 1990, 86.
94. Trevor, S.S. and Paul, T., In; Drug Treatment in Psychiatry, 5th Edn., Routledge, London, 1999, 132.
95. Peter, F.B., John, L.W. and Ross, J.B., Eds., In; Schizophrenia and Mood Disorders: The New Drug Therapies in Clinical Practice, 1st Edn., Butterworth Heinemann, Oxford, 1999, 11.
96. Brandon, S., Cowley, P., Mc Donald, C., Neville, P. and Palmer, R., **Brit. J. Psychiat.**, 1985, 146, 177.
97. Taylor, M.A. and Fleminger, J.J., **Lancet**, 1980, 1, 1380.
98. Mc Call, W.V., **Int. J. Neuropsychopharmacol.**, 2001, 4, 315.
99. Chanpattana, W. and Chakrabhand, M.L., **Psychiat. Res.**, 2001, 105, 107.
100. Tang, W.K. and Ungravi, G.S., **Prog. Neuropsychopharmacol. Biol. Psychiat.**, 2003, 27, 373.
101. McClellan, J. M. and Werry, J.S., **Paed. Psychopharmacol.**, 1992, 15, 131.
102. Hogarty, G.E., Anderson, C.M. and Reiss, D.J., **Arch. Gen. Psychiat.**, 1984, 43, 633.
103. Falloon, I.R.H., Boyd, J.L., Mc Gill, C.E., Williamson, M., Razani, J., Moss, H.B., Gilderman, A.M. and Simpson, G.M., **Arch. Gen. Psychiat.**, 1985, 42, 887.
104. Shepherd, M., **Brit. Med. Journal**, 1984, 288, 809.
105. Presley, A.S., Grubb, A.B. and Semple, D., **Acta. Psychiat. Scand.**, 1982, 66, 83.
106. Robert, W.B. and William, T.C., In; Benjamin, J.S. and Virginia, A.S., Eds., Kaplan and Saddock's Comprehensive Textbook of Psychiatry, 7th Edn., Vol. I, Lippincott Williams and Wilkins, Philadelphia, 2000, 1108.
107. Paul, J.H., **Schizophr. Res.**, 1999, 40, 87.
108. Arnold, J.F., **Schizophrenia Bull.**, 1983, 9, 555.
109. Susan, R.D., **Schizophrenia Bull.**, 1983, 9, 504.
110. Kutcher, S.P., In; Child and Adolescent Psychopharmacology, W.B. Saunders company, 1st Edn., Philadelphia, 1997, 223.

111. Nina, R.S. and William, T.C., **Schizophrenia Bull.,** 1983, 9, 500.
112. John, M.K., **Schizophrenia Bull.,** 1983, 19, 287.
113. Arthur, R., **Psychiat. Clin. N. Amer.,** 1993, 16, 351.
114. Berry, S.L. and Masand, P.S., **Anal. Pharmacother.,** 2000, 34, 200.
115. Milner, K.K. and Valkenstein, M., **Psychiat. Serv.,** 2002, 53, 888.
116. Satoskar, R.S., Bhandarkar, S.D., Ainapure, S.S. and Satoskar, R.R., In; Pharmacology and Pharmacotherapeutics, 16th Edn., Popular Prakashan, Mumbai, 1999, 173.
117. Copolov, D.L. and Link, C.G., **Psychol. Med.,** 2000, 30, 95.
118. Madhusoodanan, S., Brenner, R. and Alcantra, A., **J. Ger. Psychiat. Neuro.,** 2000, 13, 28.
119. Douglas, F.L., **Arch. Gen. Psychiat.,** 1990, 47, 23.
120. Suresh, K. and Chittaranjan, A., **Indian J. Psychiat.,** 2001, 43, 78.
121. Stimmel, G.L., Gutierrez, M.A. and Lee, V., **Clin. Ther.,** 2002, 24, 21.
122. Shijit, K., **Amer. J. Psychiat.,** 1999, 156, 286.
123. Herbert, Y.M., **J. Clin. Psychiat.,** 1994, 55, 47.
124. Herbert, Y.M., **J. Clin. Psychiat.,** 1994, 12, 38.
125. Arthur, R., **Arch. Gen. Psychiat.,** 1991, 48, 166.
126. Kinon, B. and Liberman, J., **Psychopharmacol.,** 1996, 124, 2.
127. Horn, A.S., Post, M.L. and Kennard, O., **J. Pharm. Pharmacol.,** 1975, 27, 553.
128. Joel, G.H., Lee, E.L., Perry, B.M., Raymond, W.R. and Alfred, G.G., Eds., In; Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th Edn., Mc Graw-Hill, Newyork, 1996, 399.
129. Herbert, Y.M., **Schizophrenia. Bull.,** 1991, 17, 263.
130. Tamminga, C.A. and Lahti, A.C., **Int. Clin. Psychopharmacol.,** 1996, 11, 73.
131. Remington, G. and Kapur, S., **Psychopharmacol.,** 2000, 148, 120.
132. Worrel, J.A. and Marken, P.A., **Amer. J. Health. Sys.,** 2000, 57, 238.
133. Liu, S.K., Chen, W.J., Chang, C.J. and Lin, H.N., **Neuropsychopharmacol.,** 2000, 22, 311.
134. Pandarakalam, J.P., **Hosp. Med.,** 2000, 61, 10.
135. Schwartz, L., **Drugs**, 1992, 44, 981.
136. Carolyn, M.M., **J. Clin. Psychiat.,** 1995, 56, 94.
137. Thomas, E.H., **Schizophrenia. Bull.,** 1994, 23, 567.
138. Umbricht, D. and Kane, J.M., **Schizophrenia Bull.,** 1996, 22, 475.
139. Ghani, S.O., Ahmed, W. and Marco, L.A., **Anal. Clin. Psychiat.,** 2000, 12, 51.
140. Buckley, N.A. and Sanders, P., **Drug Safety**, 2000, 23, 215.
141. Peter, N. and Rene, S.K., **Schizophrenia. Bull.,** 1999, 25, 741.
142. Larry, T., **Arch. Gen. Psychiat.,** 1980, 37, 293.
143. David, B., **Amer. J. Psychiat.,** 1999, 156, 1686.
144. Perminder, S., **Schizophr. Res.,** 1995, 16, 33.
145. Luke, B., **Psychiat., Bull.,** 1999, 23, 368.
146. Marder, S.R., Van, P.T. and Mintz, L., **J. Arch. Gen. Psychiat.,** 1987, 44, 518.
147. Johnson, D.A.W., **J. Clin. Psychiat.,** 1984, 5, 13.
148. Hogarty, G.E., Schooler, N. and Ulrich, R.F., **Arch. Gen. Psychiat.,** 1979, 36, 1283.
149. Kapur, S. and Seeman, P., **Mol. Psychiat.,** 2002, 7, 837.
150. Carlsson, A., **Neuropsychopharmacol.,** 1988, 1, 179.
151. Levy, U.H., Javitt, D.C., Ermilov, M., Mordel, C., Silipo, G. and Lichtenstein, M., **Arch. Gen Psychiat.,** 1999, 56, 29.
152. Banerjee, S.P., Zuck, L.G., Yablonsky, E. and Lidsky, T.I., **Neuroreport**, 1995, 15, 2500.
153. Javitt, D.C., **Curr. Opin. Investig. Drugs,** 2002, 3, 1067.
154. Gerlach, J., **Schizophrenia. Bull.,** 1991, 17, 289.
155. Farber, N.B., Newcomer, J.W. and Olney, J.W., **Arch. Gen. Psychiat.,** 1999, 56, 13.
156. Meltzer, H.Y., **Schizophrenia. Bull.,** 1991, 17, 273.
157. Nowak, J.Z., Arbilla, S., Galzin, A.M. and Langer, S.Z., **J. Pharmacol. Exp. Ther.,** 1983, 226, 558.
158. Clark, D., Hjort, S. and Carlsson, A., **J. Neur. Trans.,** 1985, 62, 171.
159. Keck, P.E. and Mc Elroy, S.C., **Expert Opin. Investig. Drugs,** 2003, 12, 655.
160. Cutler, N.R., Jeste, D.V., Karoum, F. and Wyatt, R.J., **Life Sci.,** 1982, 30, 753.
161. Ferrier, I.N., Johnstone, E.C., and Crow, T.J., **Brit. J. Psychiat.,** 1984, 144, 341.
162. Ozdemir, V., Fourie, J. and Ozdener, F., **Curr. Opin. Investig. Drugs**, 2002, 3, 113.
163. Dasgupta, S., Li, X.M., Jansson, A., Finnman, U.B., Matsui, T., Rinken, A., Arenas, E., Agnati, L.F. and Fuxe, K., **Brain Res. Mol. Brain Res.,** 1996, 36, 292.
164. Wang, Z., Wassink, T., Andreasen, N.C. and Crowe, R.R., **Amer. J. Med. Genet.,** 2002, 114, 479.
165. Garner, D.L., Beinfeld, M.C. and Yao, J.K., **Psychopharmacol.,** 1990, 26, 377.
166. Nair, N.P., Bloom, D.M. and Nestoros, J.N., **Prog. Neuropsychopharmacol. Biol. Psychiat.,** 1982, 6, 509.
167. Tullio, P., Delarge, J. and Pirotte, B., **Curr. Med. Chem.,** 1999, 6, 433.
168. Bourin, M., Malinge, M., Vasar, E. and Bradwejn, K., **J. Fundam. Clin. Pharmacol.,** 1996, 10, 116.
169. Matto, V., Harro, J. and Allikmets, L., **J. Physiol. Pharmacol.,** 1997, 48, 239.
170. Stoessl, A.J., **J. Psychopharmacol.,** 1989, 3, 99.
171. Crawley, J.N., **Trends Pharmacol. Sci.,** 1991, 12, 232.
172. Ramu, M.G. and Venkataram, B.S., **Anc. Sci. Life,** 1985, 4, 165.
173. Fozedar, N.G., Doongaji, Bagadia, V.N. and Vahia, N.S., **Indian J. Psychiat.,** 1962, 4, 8.
174. Ramu, M.G., Senapati, H.M., Mukundan, H., Janakiramaiah, N., Shankara, M.R., Chaturveda and Narasimha murty, N.S., **Anc. Sci. Life,** 1983, 2, 205.
175. Dash, S.C., Tripathi, S.N. and Singh, R.N., **Anc. Sci. Life,** 1983, 3, 79.
176. Kale, B.S., **Indian J. Psychiat.,** 1961, 3, 260.