Article *NIMHANS Journal*

A New Orientation to the Therapeutics of Psychiatric Disorders

Volume: 14 Issue: 04 October 1996 Page: 249-261

N Pradhan, - *Department of Psychopharmacology, National Institute of Mental Health & Neuro Sciences, Bangalore 560 029, India*

Abstract

In the context of advances in our knowledge of cellular and molecular neurobiology, the therapeutics of psychiatric disorders demands a new orientation. It is surprising that despite considerable advances in neurobiology, our comprehension of neural basis of behaviour, and hence abnormal states of mind encountered in clinical psychiatry practice, remains rudimentary. The current pharmacological management of psychiatric disorders are vastly empirical in nature. The neurobiological strategy to understand behavioural problems or deducing the etiology of psychiatric illnesses from the specificity of drug action is as misleading as deducing the etiology of enteric fever from the action of antipyretic drugs. The current successes of broad spectrum drugs in the management of intractable disorders like schizophrenia, has freshened the debate on the role of multiple-interacting neurochemical systems underlying the behavioural dysfunctions. Against this background, this review paper aims to generate a new perspective for psychopharmacology research. The prototype psychiatric disorders and pharmacological agents used in their treatment are discussed. Some of the newer drugs in experimental stages are also included in this topic. This new orientation marks the end of one generation of view that advocated neurochemical specificity of drug action in the treatment of psychiatric illness. This may also herald the beginning of the emergence of a comprehensive, global and holistic view of brain, behaviour and mental illness from the pharmacological view point. The conjectures and hypotheses in this review may form the basis for future development of new therapeutic methods for psychiatric syndromes.

Key words -
Antipsychotics,
Antidepressants,
Mood stabilizers,
Anxiolytics,
Neuroreceptors

It is naively assumed that drug treatment in psychiatric disorders is now based on rational theories of brain functions. This misplaced reason is based on receptor pharmacology and discovery of chemical agents that are relatively specific in their affinity for a given neuroreceptor [1], [2]. We have gained considerable knowledge about the genes responsible for coding specific mRNAs required for synthesis of specific receptor proteins. The structure and configuration of many neuroreceptors have been worked out. The signal transduction mechanism of the receptor-ligand interaction and internal cascading of intracellular Ca^{++} activity had been elucidated in many conditions [1], [3]. The general evolutionary

emergence of pentameric ionotropic receptors and heptameric metobotropic receptor systems and the possible combinations of these two mechanisms have emerged as the most general principles of cell signaling in central nervous system. However, the degree of complexity of human nervous system is by far astronomical to be comprehended in the near future. It is merely not possible to determine the neural substrates and the processes governing the behavioral responses are expected with identical stimuli, given the dynamical state of the brain which is continuously changing with experience. These aspects have been well established from a number of lesions and denervation studies and from the studies focussing on neural plasticity. The neural system under question in a given human behavioral state is more complex than what we have inferred from animal experiments. Therefore, the therapeutic response of psychotropic drugs is bound to be complicated by a number of ontogenic and neurodynamic variables. In this paper, we project these new concepts and attempt to understand the emerging strategies of drug therapy of psychiatric disorders.

Neurotransmitter-receptor pathology and psychiatric disorders

It is clear from the recent developments is psychopharmacology that the advent of psychotropic drugs has altered our perception, understanding and management of psychological illnesses. The psychotropic drugs have also provided the strategy for understanding the chemical circuitry of brain involved in behavioral responses. The psychotropic agents or drugs acting on the central nervous system (CNS) primarily produce their effects by altering i.e. enhancing or blocking the neural transmission. More specifically the drug responses is determined by the number of active binding sites on neuronal membranes. The cellular changes that are brought out by the receptor occupancy are reflected in the gross behavioral change. This relationship of cellular response and behavioral change is one of the knottiest theoretical and scientific issues in neurobiology. It is natural that the receptor occupancy by psychotropic drugs influence behavior directly or indirectly and thus bring about improvement in the functional status of patients [3], [4], [5], [6]. The therapeutic response and thereby the pathology has been attributed to such receptors. This perplexing development in clinical psychiatry of translating preclinical knowledge of the drug action to clinical etiopathology has been attributed to such receptors. This perplexing development in clinical etiopathology of illness or disorders is scientifically incomprehensible in the absence of any direct evidence of neuro-receptor pathology in psychiatric illnesses. This misconception may not be similar to hierarchy jumping errors seen in preclinical sciences in attributing behavioral dimensions to a group cells in CNS. While it is evidently clear that such inferences are not justified, the scene is further complicated by the dynamism of such cellular responses. The receptor population change by continuance of medication [5], [6].There are drastic plastic changes in the neural behavior to chronic medication. It has been grossly overlooked in the past while relying on the acute drug on the preclinical science of drug action in deciphering etiopathology resulted in the era of psychopharmacology where the dopamine pathology of schizophrenia, NE pathology for depression and 5-HT pathology in melancholia and obsessive compulsive disorder gained substantial acceptance in clinical psychiatry. However, it is emphasized here that there is no evidence for involvement of a specific chemical class of neurons in a given syndrome. It is prudent to think that the syndrome is multifactorial and therefore numerous chemical bases are evidently involved [5], [6], [7]. Similarly a drug though primarily influencing transmission of a specific class of neurons may ultimately result in the modification of transmission in multiple classes of neurons.

Selectivity-specificity

One may ask a simple question whether the selectivity and specificity of neurotransmitter systems are related to the therapeutic response in psychiatric illness. If the assumptions regarding selectivity and specificity are valid for psychiatric or behaviour problems, then there is always the basis that the future drug development in psychiatry should be directed for more specific agents and for more specific disorders. From the preceding arguments it can be inferred that the selectivity and specificity may not contribute to the therapeutic response or pathogenesis of behavioural disorders. It is apparent that psychiatric syndromes are multimodal and a number of neurotransmitters are affected in a defined clinical syndrome. Therefore, broad spectrum drugs are the choice for treatment of psychiatric illness. Evidence can be found from the basis pharmacology of currently advocated treatment regimes where therapeutic agents are targeted to influence multiplicity of receptor systems [1], [2], [3], [4]. The lag between the administration of the drugs and the therapeutic benefits may be the factor that masks the role of a large number of interacting chemical systems in the brain. In other words, the evidences suggest that specific drugs may cause more intractable side effects and result in protractible state of illness. Only certain category of symptoms respond. Other varieties of behaviour not directly linked to the chemical or drug may improve on long run or may not be changed. Therefore, a careful analysis of the therapeutic impact of psychotropic drugs points to this behaviour. Single and specific drugs are not favored for rapid and better improvement of the functional state of the patient [5], [6], [7].

Receptor changes with drug treatment

It is known that drugs influence the chemical profile of the brain in a big way. We may assume that the illness is evolutionary where the syndrome may be a reflection of compensatory chemical state ontogenically emerging out of certain unknown factors (genetic) or stress or interaction of both in any class of illness. This generalization is not reductionist; rather it is holistic. Such a holistic brain view is better in designing a therapeutic strategy. A detailed account of the dynamic drug receptor interaction can be found in previous papers [5], [6], [7]. The therapeutic strategy discussed here is based on the neurobiologic principle of long term drug effects. When a drug is given a class or classes of neurochemicals are altered in the acute effect. As the continuance of the drug administration is prolonged there are many compensatory mechanisms brought about in the brain. Here is an example. Haloperidol is given in schizophrenic disorder and occupies DA2 receptors in many parts of the brain. Its action in SN brings about extrapyramidal reactions and its possible action in meso-cortical DA system accounts for behavioral effects. Haloperidol acutely produces increase in turn over of DA. As DA receptors blocked, we do not see any hyper-dopaminergic state like aggravation of psychotic state. In course of time, the compensatory increased DA turn over comes down and the DA receptors turn to be hypersensitive. In order to circumvent the DA transmission block, the collateral transmission of the other associated chemical that are coupled to DA system is changed, a classic example being the influence on the cholinergic system. Such a dynamical change ultimately settles down to some state. Is not always guaranteed that such an effect is going to yield a beneficial therapeutic state. It is seen that Tradive dyskinesia evolves as a compensatory mechanism of continued DA block. As our understanding of coupled chemical system in brain is poor we have not been able to understand or treat such emergent TD state chronic neuroleptic medication. Similar general statement can be extended to

any such specific drug [1], [2], [5], [6], [7], [8].

Rationale for broad-spectrum drugs or polypharmacy

The use of broad-spectrum drugs arises out of two imperatives:

(1) It is unlikely that in a given behavioral syndrome only one class of neurons are involved. Multiple neurochemicals are likely to be involved in an illness.

(2) The Drugs also ultimately affect multiple chemical systems even if these are specific in their actions.

The other evidence comes specifically from the current therapy of schizophrenia, i.e. the highly acclaimed drugs in this illness are broad spectrum (clozapine) [1], [2], [8], [9]. The same principle can be extended to the other psychiatric disorders. However, it leads to a very disturbing conclusion that a broad spectrum drug may be an universal agent which is effective for all types of disorders. It appears quite unacceptable and it negates the very concept of syndrome complexes and clinical diagnostic nosology. However, from a global point of view, it is likely that the distinction or classification of psychiatric disorders may be only operational and the diagnostic nosology may not be reflective of the biological reality of brain states. Even if there are apparent differences in various types of psychiatric disorders, the integrative nature of brain may bind desperate chemical systems in some unique way. Though it is difficult to sustain the argument that a single broad spectrum drug should be effective for all types of behaviour dysfunctions, it is expected that multiple drugs given at a time may accelerate recovery. Therefore, broad spectrum drugs are the choice in psychiatric illness. Fine tuning may be essential for certain prominent symptom profiles. This fine tuning may call for introduction of other agents simultaneously at any other point of time. Thus polypharmacy may be the way to deal with behavioral problems. It may be extended to other forms of illness or dysfunction.

Treatment of disorganized psychosis (schizophrenic illness)

Schizopherenia is a familial illness and it is presumed to indicate a genetic predisposition or a vulnerability. Both structural and functional abnormalities are demonstrable in brains of schizophrenic patients. However, the structural pathology may have a number of determinants and the role of chronic medication and a host of other factors contributing to chronicity and hence atropic changes as a consequence cannot be ruled out. Dopamine blockade by neuroleptics discussed later has established a role in ameliorating psychotic symptoms and improvement in social functioning of these subjects. Primary disturbing factors that lead to a heterogeneity in the neurobiological bases can be attributed to the variable course and outcome of the illness [1], [2], [7], [8]. Poor neuroleptic response and negative symptoms have been attributed to the structural pathology of the illness [7].

The discovery of chlorpromazine is linked to augmentation of anesthesia and pre-anesthetic medication. Its use in psychosis is due to Delay and Deniker which changed the psychiatry all over the world. The generic trade name "Largactil" for large action is broad spectrum. In extension of the principle described earlier, it is not surprising that chlorpromazine is still the most widely prescribed of all anti -psychotics. The term 'antipsychotic' though refers to a class of compounds that act on DA

receptors which have been used in treating psychotic symptoms of both organic and or unknown functional type of illness. The psychotic symptoms are not uniquely specific for DA antagonists [1], [2]. A number of other drugs influence psychotic behaviour in a positive therapeutic way even though the primary action of these agents are far away from the DA system. The candidate agents are many such as lithium, carbamazepine, benzodiazepines etc.

The drugs used in the treatment of schizophrenic illness are classified as

1. Phenothiazines

i) With dimethylaminopropyl side chain
   (a) Chlorpromazine,
   (b) Triflupromazine

ii) With piperidine side chain
   (a) Thioridazine,
   (b) Mesoridazine

iii) With piperazine side chain
   (a) Trifluperazine,
   (b) Fluphenzine,
   (c) Prochlorperazine.

2. Butyrophenone derivatives:

(a) Haloperidol,
(b) Trifluperidol

3. Thioxanthine derivatives:

(a) Thiothixene,
(b) Chlorprothixene,
(c) Flupenthixol

4. Diphenyl butylpiperidine:

(a) Pimozide,
(b) penfluridol

5. Indole derivative:

(a) Molindone

6. Atypical Antipsychotics (Newer drugs):

(a) clozapine,
(b) Risperidone,
(c) Remoxipride

7. Miscellaneous compounds:

(a) Reserpine,
(b) Sulpiride,
(c) Oxypertine

The role of other drugs like

1. 5-HT/D2 antagonists:

(a) HP-8373,
(b) Melperone,
(c) Olanzepine,
(d) ORG-5222,
(e) Sertindole etc

2. D1 antagonists:

(a) NO-01-0687,
(b) SCH-39166

3. DA autoreceptor agonists

(a) BHT-920,
(b) CGS-15873A,
(c) 3-PPP etc

4. 5-HT2A antagonists:

(a) Ritanserin,
(b) Amperozide

5. 5-HTe antagonist:

(a) GR-68755C

6. Sigma antagonist:

(a) DUP-734

7. Partial DA agonists:

(a) MER-327,
(b) SDZ-208-911,
(c) SD-208-912

are not clear. Many of these agents are purely experimental. These drugs are not in clinical use. Hence, these cannot be recommended for alternate use in a disorder like schizophrenia.

All the antipsychotics drugs exert their effect through central dopaminergic neurotransmitter systems. However the newer antipsychotics are broad spectrum. They influence DA, serotonin (5-HT), γ amino butyric acid and neuropeptide systems too. In fact, there is little to choose between one type of drug over another. The symptomatology and clinical profile may be used as a guideline of drug choice.

It is known that DA blockage occurs within a few hours; however, the therapeutic effects takes few days following administration of an antipsychotic drug. It is attributed to delayed inactivation of DA neurons. Before starting any atypical neuroleptic or drugs having potential risks of agranulocytosis (clozapine), one may be clear that the patient is not responding to conventional antipsychotics. On the other hand it is always beneficial to introduce polypharmacy approach that can mimic broad action of an atypical neurolepic. It is therefore prudent to institute combined treatment of drugs that act on multiple neuroreceptor systems [7], [8].

Mechanism of action

It is known that the antipsychotics block dopamine receptor. Specifically the D2 blockade has been implied in the cause of extrapyramidal effects if not truly to the therapeutic response. The search for DA antagonists that would not have SN DA neuron specificity has lead to the emergence of a vast group of heterogeneous compounds that are termed as atypical antipsychotics and seemingly have large action on CNS and on a number of neurotransmitter systems [4], [7], [8]. The acute effects and the chronic effects need to be separated for any understanding of the dynamics of the therapeutic response. These as follows:

Response of dopamine system to neuroleptic administration

Response of dopamine system to neuroleptic administration

Typical refers to neuroleptics which cause EPS and atypical refers to neuroleptics which tend not to cause EPS. The firing rate refers to single cell activity of DA neurons.

The important effect of atypical neuroleptics lies in their ability to increase activity in the TI-DA neurons and their inability to induce depolarization blockade in SN-DA neurons. These agents have marked anticholinergic effects, alpha-1 blocking action, 5-HT2 blockade, high ratio of 5-HT2 to D2 blocking and D1 selective activities. Importantly both D1 and D2 blockade, partial DA agonist action in the striatal, mesolimbic and cortical DA neurons with 5-HT2 blockade are known to determine their superiority over selective D2 antagonists such as haloperidol.

Acute treatment of schizophrenia

The acute pharmacological phase of schizopherenia treatment concerns medication to alleviate exacerbation of positive psychotic symptoms like delusion, hallucinations, thought disorders and agitation. Extreme forms of negative symptoms like withdrawal and mutism may occur in an acute form. Conventional neuroleptics have been effective in the treatment of acute or relapsed psychotic states. The high potency (non-sedating) and low potency (sedating) neuroleptics are equally effective in both agitated or excited and in withdrawn or psychomotor retarded patients. It is known that neuroleptics in doses less than 400-600mg equivalent of CPZ are less superior to placebo than doses above these ranges. High dose neuroleptic medication do not significantly produce accelerated or better response than standard doses [10], [11]. However, it is seen that there are a group of patients who benefit from higher doses. The concept of therapeutic window and blood plasma level is at times misjudged in clinical practice. The term "therapeutic window" is used only by psychiatrists, when it is apparent that the rule holds good for all drugs used in medical practices. At certain level for any drug the therapeutic response will be masked by side effects that are mostly the toxic manifestation. There is no meaning in using such concepts like therapeutic window. However from large number of patient population of varying dosage regimes and plasma levels a statistical optimal level for therapeutic response can be drawn. It is observed that 5-12 ng/ml of plasma haloperidol level equivalent is the optimal drug concentration for therapeutic effects and levels higher than 12 ng/ml do not result in additional benefits [12]. It may be mentioned that a number of drugs such as fluoxetine, betablockers, cimetidine, barbiturates and carbamazepine influence the pharmacokinetics of haloperidol.

Adjunctive treatments

Lithium: Drugs that alter psychomotor activity May be administered simultaneously with neuroleptics in the treatment of acute psychosis. Lithium has been evaluated in the treatment of mania and is termed as an antimanic agent. Careful analysis shows that lithium effects are limited in schizophrenic symptomatology [13]. Only patients having schizo-affective form of illness may find some benefit.

Propranolol:- Addition of Propranolol up to 400-2,000 mg to standard neuroleptic regimes is found to accentuate treatment respone [14]; however, it is not clear how much is due to elevated neuroleptic level brought about by changes in the pharmacokinetics of the neuroleptic by betablockers. However, betablockers have not found wide acceptance as adjuncts to neuroleptics.

Carbamazepine: CBZ has been tried in refractory cases or in non-responders [15]. CBZ elevated neuroleptic levels. Care must be exercised that CBZ may worsen the psychosis because it may raise neuroleptic levels to toxic ranges. Schizophrenic symptoms having EEG abnormalities may do better with addition of CBZ. However, there is little to suggest, that CBZ alone or in combination with haloperidol drastically changes drug responsiveness in schizophrenia.

Benzodiazepines: Benzodiazepines bring down the discomfort associated with neuroleptic effects like akathisia and restlessness. However, these agents alone have no antipsychotic properties.

Opiates: Opiate agonists in conjunction with neuroleptics are reported to help treatment resistant cases [16]. However, use of adjunctive opiates cannot be justified in schizophrenic illness.

Antidepressive agents: Most antidepressants have structual similarities to a vast number of neuroleptics. The pharmacokinetic interaction results in the elevation of plasma levels of both drugs. However, SSRIs have produced beneficial effects [17].

ECT: Electroconvulsive treatment can alleviate a large spectrum of schizophrenic symptomatology. The seizure phenomena release a number of transmitter substances and also change the blood flow and metabolic state of the brain. The brain metabolic change may prove beneficial for schizophrenic illness. ECT is of significance in schizophrenia with affective or catatonic symptomatology.

Newer neuroleptics: Two drugs remoxipride and risperidone have been tried in schizophrenia along with clozapine [1], [18]. Remoxipride is a substituted benzamide and is a selective D2 blocking agent. It has greater affinity for sigma sites. It is non-sedating with less EPS side effects than conventional neuroleptics. However because of fatal aplastic anemia efects it may not be used again. Risperidone is a benzisozazole compound and is a potent D2 and 5-HT2 antagonist. This drug may have fewer side effects. However, clinical experience with the agent is limited and acceptability of the drug needs greater evaluations on large patient populations.

Maintenance treatment in schizophrenia

It may be realized that schizophrenia is a complex issue and its evolutional nature needs no further emphasis. Its evolution and outcome is largely determined by societal and family environment than by any indigenous state. Therefore, social factors in long range maintenance and prevention of relapse

should not be ignored. Combination low dose maintenance neuroleptic therapy with psychosocial rehabilitation or intervention should be the primary objective. It is meaningless to treat vigorously any schizophrenic symptom after two years of the illness. Even acture exacerbations are environmentally related and should be handled by psychosocial means. Moreover, active neuroleptic medication may hamper the social functioning of the patient. Judicious evaluation of the dose of neuroleptic requirement is one of the unresearched fields in clinical psychiatry. Both conventional and atypical neuroleptics with or without adjunctive medications are beneficial for maintenance [1], [2], [7], [8]. Drug holidays and intermittent therapy and small dosage poly pharmaceutical approach may be essential for restitution of normal or acceptable social functional states.

Treatment of affective illness

The biological studies in affective illness have been more consistent than with schizophrenic illness. The role of neuro-transmitter-neuroendocrine systems determining mood is apparent. However, the unipolar depression remains as an heterogeneous entity. Endogenoulsy determined depressive symptoms can be effectively treated by selective drugs that have mood elevating and mood stabilizing actions. Central catecholamine activity significantly correlates with cortisol levels. Therefore biological significance of CA-HPA axis in depressive illness is understandable [1], [2], [3]. It is likely to be associated with the disturbances in other neurotransmitter systems. The possible candidates are acetylcholine (ACh) and GABA. The DA system has been implied in both depression and manic symptoms in affective disorders. The serotonin (5-HT) system in mediating depression has been substantiated from physiological role of 5-HT and its deficiency contributing to vegetative symptoms associated with the illness. Further the SSRIs have proven antidepressive effects. A number of neuropeptides like CRF, SRIF and TRH seem to play a significant role in mediating major depression [1], [2], [3]. The studies on manic episodes are few and less consistent in their findings. It is believed that it is the upward swing that creates manic and hypomanic states and mood stabilizing drugs which are not specifically potent antipsychotics or antidepressants are most efficacious in this condition. The treatment of affective psychosis is therefore multimodal. It has been rather difficult to assess the drug responsiveness in major depression.

Treatment of bipolar illness by mood stabilizing agents

The biological basis of mania has been poorly investigated and it has received scant attention than the depressive illness. The mood stabilizers are a group of drugs that have proven efficacy in cyclic dysfunction which are closely controlled by fluctuating neuroendocrine humoral systems. Bipolarity in affective psychosis reflects alternating attacks of mania/hypomania with depression. Recurrent manic episodes are common in young patients who may eventually develop depressive illness or bipolarity in a later age. The bipolar disorders can be successfully prevented by mood stabilising drugs. It appears that the bipolar illness may be a different disease than unipolar disorder which remains as an heterogeneous entity. The maintenance and prophylaxis with lithium and or mood stabilizers like carbamazepine has considerably altered the course and outcome of this group of disorders which was

not envisaged 50 years back. About 80% of the subjects can be effectively treated with absolute normal state of living and social activity, the only requirement being drug compliance and monitoring of therapeutic drug compliance and monitoring of therapeutic drug level. It is cautioned that these drugs bring about change in the mood. The loss of a positive self-assertive feeling, self-confidence and feeling of happiness are the main causes of poor drug compliance. This calls for adequate psychological support and other non-pharmaceutical mode of intervention as adjustive therapies. The mood stabilizing drugs that have found application in treatment of bipolar disorders both as in acute management and prophylaxis are lithium, carbamazepine and valproic acid. The relapse rate is inversely related to duration of lithium prophylaxis in bipolar disorders [1], [2]. Follow up studies show that with lithium for initial 1-2 years may not show complete amelioration of cycles and fall mood stabilizing effects come only after initial 2 years of treatment. The long term benefits of CBZ and valproate in the prophylaxis of bipolar disorders is awaited.

Treatment of depression

Great strides have been made in the treatment of depression for past decade due to the ability to rationally develop medications to mechanisms of action. Major benefits of new generation of antidepressants has been tolerability and safety. However, these agents have not changed remission rate as compared to conventional TCA and MAOI. Substantial number of patients fail to respond to single drug therapy. The basis of pharmacotherapy of depression may be seen from the target mechanism of the antidepressants and drug can be visualized as

(1) Mixed NE and 5-HT reuptake inhibitors (TCAs, venlafaxine)
(2) Serotonin selective reuptake inhibitors (SSRIs) (Fluoxetine, sertraline, paroxetine)
(3) Mixed serotonin effects with 5-HT2 antagonism (Phenyl Piperazine like trazadone)
(4) Mixed NE/DA reuptake inhibitors (Aminoketones like bupropion)
(5) Monoamine-Oxidase Inhibitors (Irreversible-phenelzine, tranylcypromine, Reversible-moclobemide).

Also data suggest antidepressant activity of benzodiazepines, psychostimulants and azaspirone (e.g. buspirone) in some category of depressive patients. (Detailed guidelines for treatment of depression can be found in a series of papers published by Preskorn et al from 1989-93 in Journal of Clinical Psychiatry) [19], [20], [21]. Here we develop a strategy that may guide in choosing a specific drug for particular patient based on the preclinical effect and mechanism of action of these agents. The selection of SSRIs and TCA should be based upon the prominence of symptoms. If mood and vegetative symptoms are in the forefroont one may start with an SSRI; if agitation or retardation are prominent TCA may be the first drug of choice. In certain ways in clinical practice one may switch over from TCA to SSRIs or vice versa. Sometimes the SSRIs may be combined with TCA for augmenting antidepressive effects. It is not clear whether SSRI-TCA cotherapy is the manifestation of pharmacodynamic mode of action or a pharmacokinetic strategy. Other augmenting agents which have been tried are lithium, reserpine, and neuroleptics. Other less common augmenting agents are psychostimulants, reserpine, estrogens and monoamineagonists. Sleep alteration or sleep deprivation can be one mode of augmenting antidepressive effects of TCA and or SSRIs. The use of MAOI is uncommon in our country; however, potential risks of hypertensive crisis and malignant hypothermia

may be kept in mind when MAOI are combined with TCA or SSRIs. Further, ECT may be a cheaper and safer mode of treating non-responding depressives than trials of alternate pharmacotherapies. Among the novel class of antidepressants the single most largest class of drugs has been the SSRIs. Several of these agents namely fluoxetine, sertraline and paroxetine are used in clinical practice. Other non-uptake inhibiting but serotonergic drugs do possess antidepressive effects. These are

(a) 5-HTA partial agonists. (buspirone, gepirone, ipsapirone and flesinoxan),
(2) 5-HT2C partial agonoistschlorophenylpiperazine (additional antagonists effects at 5-HT2 A and 5-HT3 sites),
(3) 5HT2A/2C antagonist (ritanserin, etoperidone and nefazodone), and
(4) the enhancer of 5-HT uptake (tianeptine). MAO(A) is involved in catabolism of 5-HT, hence a search for selective MAO(A) inhibitor has produced novel compounds like moclobemide, brofarmomine and clorgyline.

More than 13 indentified serotonin receptors have been indentified. Some may have even opposing effects and other multiple neurotransmitters (dopamine, γ -aminobutyric acid, norepinephrine, and neuropeptides) are also modulated by serotonin. It is therefore not surprising to find that 5-HT1A agonists and 2-HT2C antagonists are antidepressive agents. Apart from psychostimulants, drugs that affect DA system possess antidepressive actions. Amineptine which is an atypical tricyclic drug selectively prevents reuptake of DA and is clinically available as an antidepressant. Another compound in this category is medifoxamine. Though NE hypothesis of depression have been in the forefront for past three decades, no selective NE reuptake inhibitor has been found to be clinically antidepressant. The compounds of this category are tomoxetine (a benzenepropanamine), viloxazine (a morpholine) and loferamine (a tricyclic). Drugs that are classified as adrenergic (α 1 agonist) (modafanil and adrafinil) have been found to possess antidepressive property. It can be stated that the search for better and safer antidepressive drugs has just begun. With time it may be possible to develop more selective antidepressive agents. However, at the same time compounds which have broad spectrum activity on dopaminergic, serotonergic and cholinergic transmission (Minaprine) are essential for an effective management of the depressive symptomatology. It may be mentioned that drugs that are classified as antidepressants are also effective in other disorders like obsessive-compulsive disorders, panic disorders and soical phobia.

Treatment of anxiety disorders

Anxiety disorders are the most ill understood facets of biological psychiatry. On the one hand, issues related to anxiety are determined by personality, characteriological or social antecedents; on the other hand, investigations have needlessly focused on the biological disturbances of genetic and neuro-receptor hypotheses. Heterogeneity of anxiety and anxiety related disorders make the distinction between anxiolytics and antidepressants difficult. Further, it is not uncommon to see depression or anxiety as co-morbidity of many other physical psychological problems. Under these circumstances clinical judgment is more vital in deciding the therapy than any necessary pharmacological guideline. However, over the past few years it has been possible to find pharmacological distinctiveness of various anxiety disorders. Generalised anxiety disorder (GAD) is possibly determined by a number or neurotransmitter systems and gradual refractoriness and placebo effect predominates the

pharmacotherapy of this condition. Psychosocial modes of intervention should be the first choice in these conditions rather than falling into the trap of long term anxiolytics medication. Principally the GABA and 5-HT system may contribute to the manifest anxiety. Consequently, the two classes of drugs, benzodiazepines [1], [2], [22] and azapirones (buspirones) [1], [2], [23] have found clinical use in GAD. These two classes of drugs have two distinct mechanism of action on brain. In addition to the widely used BZ group of drugs, GAD can be treated by azapirone (5-HT1A partial agonist); SSRIs have a limited role in this condition. BZs remain as the main armament in the treatment of acute anxiety and GAD and even disorders. Azapirones are less effective in the treatment of panic disorders. Though benzodiazepines are extensively used in our country for GAD, the azapirones in comparison to BZ carry less risk of tolerance and habituation. Psychosocial and personality factors are a greater significance than pharmacotherapy in this condition. The panic disorder are better treated by SSRIs.

1.Bloom F E, Kupfer D J, *eds. Psychopharmacology (The 4th Generation of progress) New York: Raven press*1995

2.Baldessarini R J, Drugs and the treatment of psychiatric disorders
In: Gilman A G, Rall T W, Nies A S, Taylor P, eds. The Pharmacological Basis of Therapeutics. 8th ed
Page: 383-435, 1991

3.Kandel E R, Steven A S, Schwartz J H, Synaptic transmission
In: Kandel E R, Schwartz J H, Jessel T M eds. Principles of Neural Science. Third Edition. London: Pr
Page: 123-34, 1991

4.Watson S, Girdlestone D, *eds. Trends in Pharmocological Sciences, (Receptor and Ionchannel Nomenclature Supplement,1995). Holland: Elsevier Science Limited*1995

5.Pradhan N, Moro S, Srinivasan A S, Effect of chronic imipramine and haloperidol treatment on apomorphine induced motility in rats
Drugs Development Research Page: 18: 113-9, 1980

6.Pradhan N, Neuroleptic responsiveness: Concept and Predictors. In: Pharmacotherapy of Schizophrenia
Proceedings of the Rhone-poulence Symposium on Psychopharmacology of Schizophrenia. SCARF,
Page: 1-15, 1990

7.Pradhan N, Pharmacological probes in understanding receptor function
In: Tandon P N, Bijalani V, Wadhwa S, eds. Lectures in Neurobiology. Wiley Eastern Limited
Page: 34-47, 1990

8.Baldessarini R, Frankenburg R F, Clozapine: a novel antipsychotic agent
New England Journal of Medicine Page: 324: 746-54, 1991

9.Kane J, Honigfeld G, Singer J, Meltzer H Y, The Clozaril Collaborative Study Group. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine
Archives of General Psychiatry Page: 45: 789-96, 1988

10.Rifkin A, Siris S, Drug treatment of acute Schizophrenia - In: Meltzer HY
ed. Psychopharmacology: the third generation of progress. New York: Raven Press Page: 1095-1101, 1987

11.Neborsky R, Janowsky D, Munson E, Depry D, Rapid treatment of acute psychotic symptoms with high and low dose haloperidol
Archives of General Psychiatry Page: 38: 195-9, 1981

12.Van Putten T, Marder S R, Wirshing WC, Aravagiri M, Chabert N, Neuroleptic plasma levels
Schizophrenia Bulletin Page: 17: 197-216, 1991

13.Small J G, Kellams J J, Milsteein V, Moore J, Placebo-controlled study of lithium combined with neuroloptics in chronic schizophrenic patients

American Journal of Psychiatry Page: 132 (12): 1315-7, 1975
14.Pugh C R, Steinert J, Priest R G, Propranolol in schizophrenia: a double blind, placebo controlled trial of propranolol as an adjunct to neuroleptic medication
British Journal of Psychiatry Page: 143: 151-5, 1983
15.Kidron R, Auerbuch I, Klein E, Belmaker R H, Carbamazepine-induced reduction of blood levels of haloperidol in chronic schizophrenia
Biological Psychiatry Page: 20: 219-22, 1985
16.Brizer D A, Kartman N, Sweeney J, Millman R B, Effect of methodone plus neuroleptics on treatment resistant chronic paranoid schizophrenia
American Journal of Psychiatry Page: 142: 1106-7, 1985
17.Ames D, Wishing W C, Marder S M, Yuwiler A, Brammer G L, Fluoxetine and haloperidol stabilized schizophrenic
New research programs and abstracts. APA 146th Annual Meeting, San Francisco Page: NR 66, 76, May 1993
18.King D J, Blomqvist M, Copper S J, Doherty M M, Mitchell M J, Montgomery R C, Placebo controlled trial of remoxipride in the prevention of relapse in chronic schizophrenia
Psychopharmacology Page: 107: 175-9, 1992
19.Preskorn S, Tricyclic antidepressants : the whys and hows of therapeutic drug monitoring
Journal of Clinical Psychiatry Page: 50 (Suppl): 34-42, 1980
20.Preskorn S, Burke M, Somatic therapy for major depressive disorder: selection of an antidepressant
Journal of Clinical Psychiatry Page: 53 (9 Suppl): 5-18, 1992
21.Preskorn S, Pharmacokinetics Of antidepressants: the why and how are they are relevant to treatment
Journal of Clinical Psychiatry Page: 54 (9, Suppl): 14-34, 1993
22.Rickels K, Case W G, Downing R W, Fridman R, One-year follow-up of anxious patients treated with diazepam
Journal of Clinical Psychopharmacology Page: 6: 32-6, 1986
23.Rickels K, Schweizer E, The clinical course and long-term management of generalized anxiety disorder
Journal of Clinical Psychopharmacology Page: 10: 101S-110S, 1990